Appendix 1. Uterine Cancer Evidence Review Conference Attendees

Attendee Role	Attendee Name(s)
Evidence review expert panelist	Rebecca Brooks, MD
	Arjeme D Cavens, MD
	Kathryn Huber-Keener, MD, PhD
	Dana Marie Scott, MD
	Sangini S. Sheth, MD, MPH
	Sara Whetstone, MD, MHS
	Brett Worly, MD, MBA, FACOG
Stakeholder organization representative	Jeffrey Quinlan, MD, FAAFP (American Academy of Family Physicians)
	Robert A. Smith, PhD (American Cancer Society)
	Amy L. Davis, DO, MS, FACP, FAAHPM, FASAM (American College of Physicians)
	Eloise Chapman-Davis, MD (American Society of Clinical Oncology)
	Mowita Kensinger, MHS, PA-C, RDMS (Association of Physician Assistants in Obstetrics and Gynecology)
	Nancy Lee, MD (Black Women's Health Imperative)
	Wenora Johnson (Facing Our Risk of Cancer Empowered)

Jennifer Mueller, MD (Foundation for Women's Cancer)

Marcela Gaitán, MPH, MA (National Alliance for Hispanic Health)

Raymonde Charles Y. Uy, MD, MBA (National Association of Community Health Centers)

Julia Skapik, MD, MPH (National Association of Community Health Centers)

Samantha Ritter, MPH (National Association of County and City Health Officials)

Nadeem R. Abu-Rustum, MD (National Comprehensive Cancer Network)

Scout, MA, PhD (National LGBT Cancer Network)

Edith P Mitchell, MD, MACP, FCPP, FRCP (National Medical Association)

Mary Charlton, PhD (National Rural Health Association)

Erica Bednar, MS, MPH, CGC (National Society of Genetic Counselors)

Karen Crider, MSN, WHNP-BC (Nurse Practitioners in Women’s Health)

	Carolyn Aldigé (Prevent Cancer Foundation)
Advisory group member	William Burke, MD
	David Chelmow, MD
ACOG staff	Christopher M. Zahn, MD
	Nancy O'Reilly, MHS
	Julia O'Hara, MPH
	Jessica Butler, MPH
	Elizabeth York, MPH
	Carrie Snead, MA
CDC representative and cooperative agreement technical monitor	Temeika L. Fairley, PhD
Consultant	Dana Trevas (Shea & Trevas, Inc.)
Observer	Lisa C. Richardson, MD, MPH (CDC)
	Ally Moehring (CDC)

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

Uterine Cancer Literature Review
Appendix 2. Uterine Cancer Epidemiology

Primary Reviewer: Rebecca Brooks, MD
Secondary Reviewer: Brett Worly, MD

INTRODUCTION

This document addresses the epidemiology of uterine cancer, specifically endometrial cancer (endometrioid, serous, clear cell, and carcinosarcoma) and uterine stromal tumors (leiomyosarcoma, endometrial stromal sarcoma, and others).

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases using a search strategy based on the question, What is the epidemiology of uterine cancer? All identified articles were categorized by level of evidence. Relevant guidelines from ACOG, the American College of Radiology, the American Society for Reproductive Medicine, the European Society for Medical Oncology, the National Comprehensive Cancer Network, the National Institute for Health and Care Excellence, the Society of Gynecologic Oncology, and the U.S. Preventive Services Task Force were also identified and prioritized. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of selected articles. The bibliographies of included articles were reviewed to identify other relevant works not identified by the primary search.

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

In an effort to streamline data retrieval, systematic reviews and meta-analyses were prioritized. The individual source studies included in such articles were not separately included unless their inclusion 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 search was organized according to the histologic variants of uterine cancer. Originally, 1,345 results were identified for endometrioid endometrial cancer. Of these, 319 studies were identified initially pertaining to endometrioid histology. Studies were assessed based on their title and abstract for further review. The results identified 7 level I RCTs; 4 level I systematic reviews and meta-analyses; 192 level II studies, of which 2 were further reviewed and excluded; 8 level III reviews, of which 2 were relevant but excluded; and 6 studies with level of evidence not otherwise specified, of which 2 were excluded. An additional three studies were identified by the reviewer while evaluating references and via PubMed and were included.

Chelmow D, Brooks R, Cavens A, Cavens A, Huber-Keener K Scott DM, et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.

For serous cancers, 231 studies were initially identified. All of the seven level I RCTs pertained to ovarian cancer and were excluded. Of 185 level II RCTs identified, 16 were relevant to epidemiology or prognosis; the rest were treatment related, and 1 of these 16 was included. Of four level III reviews, two were further evaluated, and neither was included. Of 33 studies for which the level of evidence was not specified, 4 were further evaluated, and 1 was included. One additional study was identified through reference review.

A review of the clear cell carcinoma literature yielded 5 level I RCTs, 2 level I systematic reviews or meta-analyses, 28 level II articles, and 6 articles for which the level of evidence was not specified, none of which were relevant to the topic of epidemiology. Of two level III reviews, one was further evaluated.

Initially, 113 references were identified for uterine carcinosarcoma. Of these, two level I RCTs were excluded because they were focused on treatment, and two level II RCTs were not relevant. Of 90 level III studies, 9 were deemed relevant and further evaluated, of which 4 were included.

A total of 127 references were identified for uterine leiomyosarcoma. Of these, one level I RCT and two level I systematic reviews or meta-analyses were excluded. Of 87 level II studies identified, 7 were relevant and further evaluated, and 4 of these were included. Of the 8 level III reviews, 2 were further investigated and included. Of 29 studies for which the level of evidence was not specified, 3 were evaluated, and 1 was included.

For endometrial stroma sarcoma, 125 references were identified. Of these, two level I RCTs and one level I systematic review or meta-analysis were excluded as not relevant. Only 1 of 6 level III reviews and 3 of 32 studies for which the level of evidence was not specified were further evaluated and included. Of 84 level II studies, 3 were further investigated, and 2 of these were included.

Following the Evidence Review Conference of the Uterine Cancer Advisory Group, Expert Panel, and organizational representatives, an additional 10 references were included to incorporate updated data from The Cancer Genome Atlas (TCGA) describing molecular characterization of endometrial cancer. These references were identified through a literature search and on the basis of the primary reviewer's knowledge.

Summary of Data: Epidemiology

Uterine cancer is the most common gynecologic malignancy affecting women in the United States.[1,2] It is estimated that in 2020, there would be 65,620 new cases of uterine cancer, and 12,590 women would die of this disease.[2] Uterine cancer is the fourth most common cancer and accounts for 7% of cancers affecting women, but it is usually diagnosed at an early stage, and therefore falls to sixth place for mortality and is responsible for 4% of female cancer-related deaths.[2] Most women with endometrial cancer have stage I disease confined to the uterus at diagnosis, with local or regional disease in 21% and distant disease in 8%.[1] Uterine cancers can be divided into endometrial cancers affecting the epithelial lining within the uterus and much less common mesenchymal or stromal malignancies, which account for only 3% of uterine cancers (see Box 1).[1]

Box 1. Uterine Cancer Types

Epithelial Precancers

- Epithelial intraepithelial neoplasia (aka complex atypical hyperplasia)
- Epithelial intraepithelial carcinoma

Epithelial (endometrial) cancers

- Endometrioid carcinoma

Serous carcinoma
Clear cell carcinoma
Carcinosarcoma
Undifferentiated carcinoma
Dedifferentiated carcinoma
Mixed histologies

Mesenchymal cancers (aka uterine sarcomas)

Leiomyosarcoma
Low-grade endometrial stromal sarcoma
High-grade endometrial stromal sarcoma
Undifferentiated stromal sarcoma

Endometrial Malignancies

Although endometrial cancer affects premenopausal and postmenopausal women, the median age of diagnosis is around 63 years of age in the United States.[3] It is most commonly diagnosed in women between ages 55 and 64.[3] The incidence of uterine cancer has been steadily increasing. While some of this increase may be related to rising rates of obesity, the incidence of high-risk histologies, which are not typically related to obesity, has also been steadily increasing. Death rates from uterine cancer have also increased over the past decade.[4] In fact, the mortality rate is increasing faster than the incidence rate, potentially because of the higher incidence of high-risk histologies, advanced stage of disease at diagnosis, and diagnoses in older women, who usually have a worse prognosis.[1,5,6] Table 1 summarizes the staging and related 5-year survival rates for endometrial cancers (all histologies combined) based on National Cancer Institute data.

Table 1. Endometrial Cancer Stage and 5-Year Survival Rates (All Types)*

Stage	Description	5-Year Survival Rate (%)†
IA	Cancer confined to endometrium or <50% myometrial invasion	90.3
IB	>50% myometrial invasion	80.0
II	Cervical stromal invasion	80.5
IIIA	Uterine serosal or adnexal involvement	68.5
IIIB	Vaginal or parametrial involvement	53.1
IIIC1	Pelvic lymph node involvement	58.3
IIIC2	Para-aortic lymph node involvement	51.2
IVA	Invasion into bladder or bowel mucosa	22.0
IVB	Distant metastases, including abdominal	21.1

*Data from Lewin SN, Herzog TJ, Barrena Medel NI, Deutsch I, Burke WM, Sun X, Wright JD. Comparative performance of the 2009 International Federation of Gynecology and Obstetrics' staging system for uterine corpus cancer. Obstet Gynecol 2010;116:1141–49. doi: 10.1097/AOG.0b013e3181f39849

†Data from the Surveillance, Epidemiology, and End Results database for patients undergoing lymphadenectomy for endometrial cancer, using the 2009 International Federation of Gynecology and Obstetrics' staging system.

Traditionally, endometrial cancers have been classified as type 1 (estrogen-driven, low-grade [ie, grade 1 or 2] endometrioid cancers), which accounts for approximately 65–80% of cases and usually has a good prognosis, or type 2 (grade 3 endometrioid, serous, and clear cell carcinomas and carcinosarcoma), which has a worse prognosis.[7,8] Rates of type 1 cancer are highest in White women in Western populations, while type 2 cancers disproportionately affect non-Hispanic Black women.[4] Endometrial cancer rates are also increasing significantly in Hispanic women under age 50.[9] The lower-grade endometrioid cancers often arise in younger patients and are thought to be estrogen-driven, often linked with obesity, anovulation, exogenous or endogenous estrogen, diabetes, and granulosa cell cancers.[10] Low-grade endometrial cancers are usually diagnosed at an early stage (80% are diagnosed at stage I), and the prognosis is usually excellent, with 5-year survival rates approximating 80–90% for patients with stage I disease. Recurrences, if they occur, are often local and have a high salvage rate if limited to the vagina or pelvis.[10] Grade 3 endometrioid carcinomas behave more like the high-risk histologies, with 5-year survival rates of approximately 76% if disease is limited to the uterus.[8,11]

While there are important distinctions between serous carcinoma, clear cell carcinoma, carcinosarcoma, and undifferentiated/dedifferentiated cancers, they are often grouped together because of their aggressive behavior and relatively poor prognosis compared with their type 1 counterparts.[1] Increasing age is linked to a higher risk of type 2 carcinoma. In one study, type 2 cancer was found in 22% of women over age 75, compared with only 3% of cases found in women younger than 45.[12]

Uterine serous carcinoma is the most common high-risk histology, accounting for 10% of endometrial cancer cases but up to 40% of deaths.[13] It is more likely to present with disease outside the uterus at diagnosis, invade into lymph vessels and other structures, and involve lymph node metastases at diagnosis.[13] These tumors demonstrate the loss of p53, and human epidermal growth factor receptor 2 (*HER2*) overexpression in up to 62% of cases; *HER2* has been used as a therapeutic target, resulting in improved outcomes.[13] The prognosis is poor compared with type 1 disease even if it is caught early, with only 50–80% of women with stage I uterine serous carcinoma alive at 5 years after diagnosis.[14] Survival is also worse for patients with more advanced stage disease, with 5-year survival rates of 36% for stage III uterine serous carcinoma, compared with 50% for grade 3 endometroid cancer and 69–80% for grade 1 or 2 endometrioid cancer.[15]

Clear cell carcinoma is the least common type 2 endometrial malignancy, accounting for 1–6% of endometrial carcinoma, and demonstrates molecular similarities to clear cell carcinomas of other sites, including the ovary and kidney.[16] Patients are often older and have more advanced disease at diagnosis, similar to uterine serous carcinoma. Clear cell carcinoma does not respond as well as uterine serous carcinoma to chemotherapy and is associated with a relatively poor prognosis, with a 5-year survival rate of 75% for stage I and only 49% for stage III disease.[15]

Carcinosarcoma is made up of malignant epithelial and sarcomatous components and was originally considered a mesenchymal tumor. It is now widely believed that the epithelial component drives the behavior of the cancer, and it has therefore been reclassified as an endometrial malignancy. Carcinosarcoma is a rare and very aggressive malignancy, accounting for 4% of uterine cancers and 6–17% of type 2 endometrial cancers, with an incidence of less than 2 per 100,000 women annually.[17,18] Compared with patients with grade 3 endometrioid carcinoma, patients with carcinosarcoma tend to be older, non-White, and present with more advanced disease.[19] More than 40% of patients have advanced stage disease at diagnosis, and the disease recurs in more than half, which is almost always fatal.[20] Interestingly, the incidence of carcinosarcoma increased from 1973 to 2013, especially among Black women.[18] Undifferentiated cancers are another rare, highly aggressive subtype of

endometrial cancer, with a poor prognosis.[21] Table 2 summarizes the characteristics of high-grade endometrial cancers.

Histology/ Type	Percentage of Endometrial Cancer	Characteristics	Molecular Features	5-year Survival Rate		Comments
Serous[22]	10%[13]	Older patients, extrauterine disease at diagnosis common[13]	p53 mutations, some human epidermal growth factor receptor 2 expression [22]	Stage I: 50–80%[15]	Stage III: 36%[15]	40% of endometrial cancer related deaths[13]
Clear cell[22]	5–10%[15]	Older patients[15]	napsin A+, ER -, ARID1A[22]	Stage I: 75%[15]	Stage III: 49%[15]	Relatively chemoresis-tant[15]
Carcinosarcoma[22]	4%[17]	Older patients, more non-Whites, advanced disease at diagnosis common[19]	p53 mutations common[22]	Stage I: 60%[19]	Stage III: 22%[19]	Biphasic tumor[19]
Endometrioid[22]	20%*	>50% solid components[22]	Genomic profile similar to serous[22]	Stage I: 76%[19]	Stage III: 45%[19]	—
Undifferentiated/ dedifferentiated[22]	2%[22]	Lack any differentiation[22]	PAX8-, SMARCA4[22]	Poor[22]	—	Rare[22]

Table 2. Summary of High-Grade Endometrial Cancer Characteristics

*Data from Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. Cancer 1987;60(8 Suppl):2035–41. doi: 10.1002/1097-0142(19901015)60:8+<2035::aid-cncr2820601515>3.0.co;2-8

Although the type 1/type 2 classification system originally described in 1983 has been a useful framework for categorizing endometrial cancer, it does not account well for grade 3 endometrioid cancers, tumors with mixed histologies, and some other cases with molecular alterations that may lead to a worse prognosis and may not fit cleanly into the two-type system.[23] Additionally, although early-stage, low-risk type 1 endometrial cancer typically can be observed, and patients with metastatic disease clearly benefit from treatment, recent trends have shifted toward better risk-stratification systems beyond the historic type 1/type 2 classification.[10]

Greater understanding of and appreciation for the molecular alterations leading to endometrial cancer have also affected endometrial cancer care. The landmark TCGA 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 (see Table 3):[24]

- The ultramutated/DNA polymerase epsilon (*POLE*) mutated group is characterized by mutations in the *POLE* gene, which is involved in DNA replication and repair. These tumors account for 7% of endometrial cancer cases, have a stable number of genomic copies, are usually of endometrioid histology, and have a high number of somatic mutations.[24] Histologically, they often demonstrate an abundance of tumor-infiltrating lymphocytes. Although some tumors may demonstrate more concerning features, such as high grade and lymph vascular space invasion, the prognosis is typically excellent, with recurrences rare, including in high-grade disease.[25]
- The microsatellite instability hypermutated group is characterized by a high mutational burden, high tumor-infiltrating lymphocytes, and a defect in mismatch repair proteins *MLH1*, *PMS2*, *MSH2*, or *MSH6* (as a result of either somatic or germline mutations such as Lynch syndrome).[26] These tumors may be more radiosensitive, and patients may be candidates for immunotherapy.[1]
- The copy number low group is characterized by relative genomic stability and moderate mutational load, often with mutations in the *PI3K/Akt* and *Wnt/catenin beta1* pathway such as *PTEN*. These tumors are often endometrioid, often have estrogen or progesterone receptor expression, and have a high likelihood of response to hormonal therapy.
- The copy number high (serous-like) group is characterized by a high rate of somatic copy number alterations and a high mutational burden, similar to ovarian cancer.[24] Mutations in *p53* are very common (92%), and mutations in *HER2* and homologous recombination deficiency are also seen. These patients are likely to benefit from chemotherapy.[24]

Molecular-based classification of endometrial cancer is the future of endometrial cancer care, as it is increasingly being used to inform treatment decisions.[22] The use of molecular-based classification to guide adjuvant treatment recommendations is being evaluated in ongoing clinical trials in Europe and Canada.[27]

Table 3. TCGA Endometrial Cancer Classification*

TCGA Class	Percentage of Cases	Prognosis	Potential Treatment Options
Ultramutated/DNA polymerase epsilon	7	Excellent, recurrences rare	Observation may be reasonable; ongoing clinical trials are using this classification for treatment selection.[27]
Microsatellite instability hypermutated	28	Intermediate	Radiation is beneficial; these patients are candidates for immunotherapy if cancer is recurrent.[1]
Copy number low	39	Intermediate to good	These patients are highly likely to respond to hormonal therapy; *PI3K/mTOR* inhibitors are an option for metastatic disease.[1]
Copy number high (serous-like)	26	Poor	Chemotherapy, human epidermal growth factor receptor 2-targeted therapy if positive.[13,24]

*Data from Cancer Genome Atlas Research Network.[24]

Uterine Sarcoma

Uterine leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated uterine sarcoma are the three main types of uterine mesenchymal tumors (or sarcomas). Of these, leiomyosarcoma is the most common, accounting for approximately 63–70% of sarcomas, followed by endometrial stromal sarcoma, which accounts for 21%.[1,28] The incidence of uterine leiomyosarcoma is 0.36 per 100,000 years of life in women, and it is twice as common in Black women.[28] Other rare stromal malignancies include adenosarcoma, rhabdomyosarcoma, and malignant perivascular epithelioid tumors.[1]

Uterine leiomyosarcoma is an aggressive uterine malignancy. Prognosis is poor and directly correlated with stage; tumor size and mitotic rate affect the prognosis for uterine-confined disease.[29] In extremely rare cases, uterine leiomyosarcoma is found unexpectedly during treatment for a presumed fibroid. The diagnosis of an unexpected sarcoma at the time of morcellation occurs only 0.08–0.4% of the time, contributing to controversy about the role of morcellation for suspected fibroids.[30,31] Patients who present with uterine leiomyosarcoma are usually over the age of 40, and the incidence increases significantly after age 50.[28,31,32] The disease behavior and prognosis of uterine leiomyosarcoma are similar to those of primary leiomyosarcoma of the retroperitoneum, extremity, and trunk.[33] Early hematogenous spread is common, resulting in high rates of both local recurrence and recurrence to distant metastatic sites. Lymph node metastases are uncommon, and routine lymphadenectomy is not part of surgical staging, unlike with endometrial malignancies. The 5-year survival rate for stage I disease is only 55%; for stage IV disease, it falls to 21.7%.[34]

Endometrial stromal tumors are rare; they account for only 1% of uterine malignancies and less than 10% of uterine sarcomas.[35] Histologically, endometrial stromal sarcomas appear to resemble proliferative-phase endometrial stromal cells.[1] In 2003, the World Health Organization changed the nomenclature to distinguish low-grade endometrial stroma sarcoma, which has a recurrence-free survival rate of approximately 90%, from undifferentiated endometrial sarcoma, which carries a poor prognosis regardless of stage and only accounts for 6% of uterine sarcomas.[35-38] Low-grade endometrial stromal sarcoma often exhibits a more indolent course.[39] Stage I disease is found at diagnosis in 60% of patients. Low-grade endometrial sarcoma demonstrates myometrial or vascular invasion or both, with finger-like projections that invade into nearby structures, vessels, and lymphatics, with lymph node metastases found in 25–29% of patients.[40] Many low-grade endometrial stromal cancers are hormone-receptor positive, and hormone therapy is often a mainstay of treatment.

DISCUSSION

Endometrial cancer is the most common gynecologic malignancy and has historically been separated into type 1 estrogen-dependent and type 2 high-risk subtypes (including grade 3 endometrioid, clear cell, and serous carcinomas and carcinosarcoma). Newer molecular-based classification centered on the TCGA findings has provided increased insight about the pathogenesis of endometrial cancer, which may inform treatment decisions and will likely influence the future of endometrial cancer care. While the incidence of endometrial cancer is rising, the mortality rate is increasing even faster, likely because of a higher rate of high-risk disease and an aging population at risk for more aggressive disease behavior. Leiomyosarcoma is the most common uterine sarcoma, associated with a high rate of hematogenous metastases and relatively poor prognosis, even if diagnosed at an early stage. Endometrial stromal sarcomas are relatively rare and not well understood, especially those that are high grade. Opportunity for further characterization, including molecular pathways, exists for rare uterine tumors.

GAPS

The prevalence of endometrial cancer is relatively well understood. However, current gaps still exist, including:

- An understanding of mortality differences between Black and White women
- An understanding of why Black women are disproportionately affected by high-grade endometrial cancer
- More robust survival statistics by stage, grade, and histology for the different uterine cancers

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Uterine neoplasms Version 1.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Retrieved December 7, 2020.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30. doi: 10.3322/caac.21590
3. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer. Available at: https://seer.cancer.gov/statfacts/html/corp.html. Retrieved December 12, 2020.
4. Clarke MA, Devesa SS, Harvey SV, Wentzensen N. Hysterectomy-corrected uterine corpus cancer incidence trends and differences in relative survival reveal racial disparities and rising rates of nonendometrioid cancers. J Clin Oncol 2019;37(22):1895–1908. doi: 10.1200/JCO.19.00151
5. Ueda SM, Kapp DS, Cheung MK, Shin JY, Osann K, Husain A, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008;198(2)218.e1–6. doi: 10.1016/j.ajog.2007.08.075
6. Wright JD, Lewin SN, Barrena Medel NI, Sun X, Burke WM, Deutsch I, et al. Endometrial cancer in the oldest old: tumor characteristics, patterns of care, and outcome. Gynecol Oncol 2011;122(1):69–74. doi: 10.1016/j.ygyno.2011.02.040
7. Mang C, Birkenmaier A, Cathomas G, Humburg J. Endometrioid endometrial adenocarcinoma: an increase of G3 cancers? Arch Gynecol Obstet 2017;295(6):1435–40. doi: 10.1007/s00404-017-4370-4
8. Voss MA, Ganesan R, Ludeman L, McCarthy K, Gornall R, Schaller G, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer—a clinical and pathological evaluation. Gynecol Oncol 2012;124(1):15–20. doi: 10.1016/j.ygyno.2011.07.030
9. Temkin SM, Kohn EC, Penberthy L, Cronin KA, Rubinsak L, Dickie LA, et al. Hysterectomy-corrected rates of endometrial cancer among women younger than age 50 in the United States. Cancer Causes Control 2018;29(4–5):427–33. doi: 10.1007/s10552-018-1018-z
10. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations. Gynecol Oncol 2021;160(3):817–26. doi: 10.1016/j.ygyno.2020.12.021
11. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol 2004;95(3):593–6. doi: 10.1016/j.ygyno.2004.08.019
12. Lachance JA, Everett EN, Greer B, Mandel L, Swisher E, Tamimi H, et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol 2006;101(3):470–5. doi: 10.1016/j.ygyno.2005.11.009

13. Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol 2010;22(1):21–9. doi: 10.1097/GCO.0b013e328334d8a3
14. Boruta DM II, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;115(1):142–53. doi: 10.1016/j.ygyno.2009.06.011
15. McGunigal M, Liu J, Kalir T, Chadha M, Gupta V. Survival differences among uterine papillary serous, clear cell and grade 3 endometrioid adenocarcinoma endometrial cancers: a National Cancer Database analysis. Int J Gynecol Cancer 2017;27(1):85–92. doi: 10.1097/IGC.0000000000000844
16. Olawaiye B, Boruta DM II. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;113(2):277–83. doi: 10.1016/j.ygyno.2009.02.003
17. Schiavone MB, Zivanovic O, Zhou Q, Leitao MM Jr, Levine DA, Soslow RA, et al. Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. Ann Surg Oncol 2016;23(1):196–202. doi: 10.1245/s10434-015-4612-2
18. Matsuo K, Ross MS, Machida H, Blake EA, Roman LD. Trends of uterine carcinosarcoma in the United States. J Gynecol Oncol 2018;29(2):e22. doi: 10.3802/jgo.2018.29.e22
19. Bansal N, Herzog TJ, Seshan VE, Schiff PB, Burke WM, Cohen CJ, et al. Uterine carcinosarcomas and grade 3 endometrioid cancers: evidence for distinct tumor behavior. Obstet Gynecol 2008;112(1):64–70. doi: 10.1097/AOG.0b013e318176157c
20. Harano K, Hirakawa A, Yunokawa M, Nakamura T, Satoh T, Nishikawa T, et al. Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. Int J Clin Oncol 2016;21(1):168–76. doi: 10.1007/s10147-015-0859-7
21. AlHilli M, Elson P, Rybicki L, Amarnath S, Yang B, Michener CM, et al. Undifferentiated endometrial carcinoma: a National Cancer Database analysis of prognostic factors and treatment outcomes. Int J Gynecol Cancer 2019;29(7):1126–33. doi: 10.1136/ijgc-2019-000465
22. Murali R, Delair DF, Bean SM, Abu-Rustum NR, Soslow RA. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Natl Compr Canc Netw 2018;16(2):201–9. doi: 10.6004/jnccn.2017.7066
23. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983;15(1):10–7. doi: 10.1016/0090-8258(83)90111-7
24. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73. doi: 10.1038/nature12113. Erratum in: Nature. 2013 Aug 8;500(7461):242.
25. Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. J Natl Cancer Inst 2015;107(1):402. doi: 10.1093/jnci/dju402
26. McConechy MK, Talhouk A, Li-Chang HH, Leung S, Huntsman DG, Gilks CB, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol 2015;137(2):306–10. doi: 10.1016/j.ygyno.2015.01.541
27. van den Heerik ASVM, Horeweg N, Nout RA, Lutgens LCHW, 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(12):2002–7. doi: 10.1136/ijgc-2020-001929

28. Ricci S, Stone RL, Fader AN. Uterine leiomyosarcoma: epidemiology, contemporary treatment strategies and the impact of uterine morcellation. Gynecol Oncol 2017;145(1):208–16. doi: 10.1016/j.ygyno.2017.02.019
29. Rauh-Hain JA, Oduyebo T, Diver EJ, Guseh SH, George S, Muto MG, et al. Uterine leiomyosarcoma: an updated series. Int J Gynecol Cancer 2013;23(6):1036–43. doi: 10.1097/IGC.0b013e31829590dc
30. Vercellini P, Cribiù FM, Bosari S, Scarfone G, Bolis G, Aimi G, et al. Prevalence of unexpected leiomyosarcoma at myomectomy: a descriptive study. Am J Obstet Gynecol 2016;214(2):292–4. doi: 10.1016/j.ajog.2015.09.092
31. Cui RR, Wright JD. Risk of occult uterine sarcoma in presumed uterine fibroids. Clin Obstet Gynecol 2016;59(1):103–18. doi: 10.1097/GRF.0000000000000163
32. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. Int J Gynecol Cancer 2016;26(6):1098–104. doi: 10.1097/IGC.0000000000000720
33. Worhunsky DJ, Gupta M, Gholami S, Tran TB, Ganjoo KN, van de Rijn M, et al. Leiomyosarcoma: one disease or distinct biologic entities based on site of origin? J Surg Oncol 2015;111(7):808–12. doi: 10.1002/jso.23904
34. Zivanovic O, Jacks LM, Iasonos A, Leitao MM Jr, Soslow RA, Veras E, et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. Cancer 2012;118(3):660–9. doi: 10.1002/cncr.26333
35. Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer 2008;99(8):1210–5. doi: 10.1038/sj.bjc.6604527
36. Feng W, Hua K, Gudlaugsson E, Yu Y, Zhou X, Baak JPA. Prognostic indicators in WHO 2003 low-grade endometrial stromal sarcoma. Histopathology 2013;62:675–87. doi: 10.1111/j.1365-2559.2011.04115.x
37. Tanner EJ, Garg K, Leitao MM Jr, Soslow RA, Hensley ML. High grade undifferentiated uterine sarcoma: surgery, treatment, and survival outcomes. Gynecol Oncol 2012;127(1):27–31. doi: 10.1016/j.ygyno.2012.06.030
38. Philip CA, Pautier P, Duffaud F, Ray-Coquard I. High-grade undifferentiated sarcomas of the uterus: diagnosis, outcomes, and new treatment approaches. Curr Oncol Rep 2014;16(10):405. doi: 10.1007/s11912-014-0405-1
39. Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systemic review. Obstet Gynecol 2013;122(3):676–83. doi: 10.1097/AOG.0b013e3182a189ac
40. Thomas MB, Keeney GL, Podratz KC, Dowdy SC. Endometrial stromal sarcoma: treatment and patterns of recurrence. Int J Gynecol Cancer 2009;19(2):253–6. doi: 10.1111/IGC.0b013e3181999c5f

Uterine Cancer Literature Review
Appendix 3. Uterine Cancer Risk Factors

Primary Reviewer: Kathryn Huber-Keener, MD, PhD
Secondary Reviewer: Dana M. Scott, MD, FACOG

INTRODUCTION

This document focuses on the risk factors that can lead to the development of uterine cancer, including age, hormonal factors, genetic predisposition, lifestyle, and prior health concerns. The majority of risk factors reviewed in this document have high levels of evidence; other risks with lower levels of evidence are included because they are frequently the subject of questions from practitioners regarding uterine cancer. The PICO format was used to direct the literature search:

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

This review specifically addresses the following questions:

1. **What age factors are risk factors for uterine cancer? How strong are these risks (quantitate magnitude of risk, broken down by type of cancer when possible)?**
   P/O: Impact of age on endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma, and uterine cancer incidence (ie, 18–50 years, 50–75 years, >75 years)
   P/O: Premenopausal impact on endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma, and uterine cancer incidence
   P/O: Postmenopausal impact on endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma, and uterine cancer incidence

2. **What lifestyle factors are risk factors for uterine cancer? How strong are these risks?**
   P: Adults with a uterus (ie, women, transgender men) with a potential lifestyle risk factor (obesity, high-fat diet, sedentary lifestyle, alcohol use, smoking)
   O: Relative risk (RR) or odds ratio (OR) of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma) or incidence of uterine cancer

3. **What hormonal factors are risk factors for uterine cancer? How strong are these risks?**
   P: Adults with a uterus and lifetime exposure to estrogenic hormones (estrogen therapy, total number of menstrual cycles, tamoxifen, or menopausal hormonal therapy) or testosterone, age at menarche, age at menopause, infertility, tamoxifen use versus no tamoxifen use
   O: RR or OR of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma) or incidence of uterine cancer

4. **What family health history factors are risk factors for uterine cancer? How strong are these risks?**
   P: Adults with a uterus and a known genetic mutation (Lynch syndrome, Cowden disease [*PTEN* carriers], *BRCA1* mutation carriers, Li-Fraumeni [*TP53* carriers], Peutz-Jehgers [*TK11* carriers], retinoblastoma [*RB1* double mutants]) or a family history of uterine cancer or associated cancers without an identified genetic mutation

O: RR or OR of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma) or incidence of uterine cancer

5. **What prior health history factors are risk factors for uterine cancer? How strong are these risks?**
   P: Patients with a known prior health history (breast cancer, ovarian cancer, polycystic ovarian syndrome [PCOS], prior pelvic radiation therapy, type 2 diabetes, endometrial hyperplasia, endometrial polyp, smooth muscle tumor of uncertain malignant potential tumors)
   O: RR or OR of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma) or incidence of uterine cancer

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases for all relevant references addressing the questions identified. All identified articles were categorized by level of evidence. Relevant guidelines 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 Society of Gynecologic Oncology, and the U.S. Preventive Services Task Force were also evaluated. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of selected articles. The bibliographies of included articles were reviewed to identify other relevant works not identified by the primary search.

Inclusion criteria were major society or health service guidelines, systematic reviews, meta-analyses, cohort studies, case-control studies, and randomized control trials (RCTs) published in the year 2000 or later. Only articles available in English were included. Case reports, case series, and articles unavailable in English were excluded. Also excluded were studies conducted outside of countries designated by the United Nations as very high on its Human Development Index (see the United Nations Human Development Index: http://hdr.undp.org/en/composite/HDI).

RESULTS AND DISCUSSION

The literature review returned 2,310 results. There were 171 level I reviews (143 systematic reviews or meta-analyses and 28 RCTs), 1,160 level II studies, and 209 level III articles (5 guidelines and 204 reviews). Another 769 papers were reviewed addressing risk (360 that did not meet the criteria for a higher level of evidence and 409 from PubMed that were not previously included). Of the 2,280 results, following review of the title and abstract, 366 papers met criteria and were included in the review, whereas 1,944 studies did not meet criteria, were duplicates, or were included previously in the larger reviews. For this review, 100 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.

What age factors are risk factors for uterine cancer? How strong are these risks (quantitate magnitude of risk, broken down by type of cancer when possible)?

Endometrial cancer affects 3% of women in the United States. Because of its high prevalence, the impact of age on endometrial cancer has been well studied. In Western countries, endometrial cancer is diagnosed most often among women ages 50 to 65 years and is significantly more common in postmenopausal than premenopausal women.[1] Only 5% of endometrial cancers occur before age 40, and only 15% are diagnosed before age 50.[2] In young women, endometrial cancer may be caused by different mechanisms, driven by risk factors such as the

presence of anovulation, diabetes, nulliparity, and increased body mass index (BMI).[3,4,5,6] More than 75% of women diagnosed with endometrial cancer before the age of 25 are obese, with a BMI of 30 or greater.[7] Additional factors that contribute to premenopausal endometrial cancer before the age of 50 are a lack of oral contraceptive use and age over 30 years at time of first parity.[5,6] (Appendix 4, Prevention and Risk Reduction for Uterine Cancer, covers the evidence around oral contraceptive use and discusses other risk-reducing interventions.)

Other types of uterine cancer include leiomyosarcoma, endometrial sarcoma, and choriocarcinoma. Choriocarcinoma, a malignant transformation of trophoblastic cells, is most often associated with delivery, although it can occur remote from pregnancy. It usually occurs in premenopausal women, but is more common in women who were older than 40 at their last delivery.[4] Other risks for choriocarcinoma will not be discussed in this document as it is considered gestational trophoblastic disease or neoplasia of the placental tissue rather than the uterus itself. Leiomyosarcomas have the highest incidence between ages 45 and 49 in the perimenopausal period but the majority occur in the postmenopausal period. Endometrial stroma sarcomas have a larger age span of highest incidence, with most occurring between ages 45 and 59.[8]

What lifestyle factors are risk factors for uterine cancer? How strong are these risks?

Lifestyle plays a large role in women's risk for uterine cancer. Many lifestyle risk factors can combine to significantly increase uterine cancer risk. While there are a plethora of studies examining lifestyle factors for endometrial cancer risk, little is known about the effect of lifestyle on uterine sarcomas.

Obesity and Weight

Obesity (BMI ≥ 30 kg/m²) has long been implicated as a risk factor for endometrial cancer, in particular a woman's current size as opposed to her size at a younger age, especially for premenopausal women.[9,10] In a systematic review of nine case-control studies, overweight women (BMI ≥ 25) had a pooled OR for endometrial cancer of 3.85 (95% confidence interval [CI]: 2.53–5.84), while obese women (BMI ≥ 30) had an even larger pooled OR of 5.25 (95% CI: 4.00–6.90), and extremely obese women (BMI ≥ 40) had an OR of 19.79 (95% CI: 11.18–35.03).[11] Another systematic review and meta-analysis from 2014 showed that overweight women (BMI 25–29) had an RR of endometrial cancer of 1.32 (95% CI: 1.16–1.50), while obese women (BMI ≥ 30) had an RR of 2.54 (95% CI: 2.11–3.06).[12] In a 2015 meta-analysis of 40 studies involving 32,281,242 participants that looked at the effect of different BMI ranges on endometrial cancer, overweight patients had an RR of 1.34 (95% CI: 1.20–1.48) and an OR of 1.43 (95% CI: 1.30–1.56), while obese patients had an RR of 2.54 (95% CI: 2.27–2.81) and an OR of 3.33 (95% CI: 2.87–3.79).[13] A pool-analysis of three case-control hospital studies in Italy and Switzerland revealed that women with a BMI of 35 or higher had an OR of 5.73 (95% CI: 4.28–7.68). When that analysis looked at the OR for BMI ranges of less than 18.5, 18.5 to less than 25, 25 to less than 30, 30 to less than 35, and 35 or higher, the OR increased for increments of BMI of 1 (OR: 1.10, 95% CI: 1.09–1.12) and increments of 5 (OR: 1.63, 95% CI: 1.52–1.750).[14] Together, these large meta-analyses provide strong evidence for the increased risk of endometrial cancer with increasing BMI.

Uterine sarcoma risk also appears to be associated with BMI. One team examined pooled data from the Epidemiology of Endometrial Cancer Consortium, which reported that obesity increased endometrial stromal sarcoma, resulting in an OR of 1.74 (95% CI: 1.03–2.93), whereas this effect was not seen for uterine leiomyosarcoma.[15]

Diet

A broad range of dietary factors have been examined for their impact on endometrial cancer risk. The literature review did not find any high-level evidence for the impact of diet on sarcomas of the uterus.

Glycemic Index (GI) and Glycemic Load (GL)

A particularly large number of studies have looked at the effect of GI, GL, and dietary carbohydrates on endometrial cancer risk, as epidemiology studies have implicated diabetes in increasing uterine cancer risk. GI is a score assigned to food based on how significantly it increases blood sugar, while GL measures the rise in blood sugar based on the number of carbohydrates in one serving of that food. GL is felt to be a better indicator than GI of how a food will affect blood sugar. A meta-analysis by Mulholland et al revealed that women who consumed high GLs (a measure of carbohydrate quality and quantity) had an RR of endometrial cancer of 1.20 (95% CI: 1.06–1.37), which was further increased in obese (BMI ≥ 30) women (RR: 1.54, 95% CI: 1.18–2.03).[16] An updated meta-analysis with additional United States and Italian data again showed no effect of GL, while high GI was associated with an increased risk of endometrial cancer (RR: 1.19, 95% CI: 1.06–1.34).[17] A similar result was seen with another meta-analysis that included the Australian National Endometrial Cancer study; it found that high GI intake was associated with an RR of 1.21 for endometrial cancer (95% CI: 1.09–1.33).[18] A 2014 U.S. prospective study (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) found conflicting results, revealing an inverse relationship between GL and endometrial cancer risk (hazard ratio [HR]: 0.63, 95% CI: 0.46–0.84). That study used a questionnaire, so the authors proposed that the finding might have resulted from underreported energy consumption, which is common in overweight and obese patients, or from confounding factors of other dietary patterns.[19] In general, the data appear to support that high GI, but not GL, significantly increases endometrial cancer risk.

Soy and Isoflavones

Dietary soy has been studied frequently, as it contains a high concentration of isoflavones, also known as plant phytoestrogens, which have been proposed to increase hormone-driven cancers because of their similarity to human estrogen. Phytoestrogens are commonly consumed in a regular diet and used in supplements to alleviate postmenopausal vasomotor symptoms. The results of studies have been contrary to the original hypothesis and mechanism, as the majority of studies have shown a decreased risk of endometrial cancer with soy intake. When examining isoflavone soy protein supplementation, an RCT revealed that women who consumed soy daily over a 3-year period had no significant difference in endometrial hyperplasia or endometrial cancer than those who did not, but they did show a trend toward an inverse correlation.[20] A meta-analysis of seven epidemiologic studies revealed an OR of 0.70 for endometrial cancer in women with the highest soy intake (95% CI: 0.57–0.86),[21] which was corroborated by additional meta-analyses in both non-Asian and Asian populations.[22,23] In the United States, specifically, a case-control study of 500 White, Latina, and African American women diagnosed with endometrial cancer showed that women with the highest-quartile intake of dietary isoflavones had an OR of 0.59 (95% CI: 0.37–0.93).[24] The proposed mechanism for the decrease in endometrial cancer risk is that phytoestrogens competitively bind estrogen receptors without causing a strong estrogenic response, blocking biological estrogen from inducing cell growth and proliferation.

Fat

The impact of dietary fat on endometrial cancer has been studied, with various findings. The Women's Health Initiative (WHI) Dietary Modification RCT examined the effects of low-fat diet on cancers. It found no association between consumption of a low-fat diet over 8 years and endometrial cancer.[25] A large meta-analysis in 2015 by Wu et al of 14 epidemiological studies found no significant effect on endometrial cancer risk related to dose-response dietary saturated, monosaturated, and polyunsaturated fatty acid consumption.[26] A 2016 meta-analysis of 7 cohort and 14 case-control studies found a dose-response effect of saturated fat on endometrial cancer risk (OR: 1.3, 95% CI: 1.0–1.7); the authors proposed that this finding was driven by the addition of a large case-control study accounting for about 10% of the weight in the analysis and the correction of saturated fat intake with energy intake.[27] Consumption of fatty fish (eg, salmon and herring), which contains omega-3 fatty acids, was inversely associated with endometrial cancer risk in Swedish women eating the highest amount of fatty fish (a median of two servings per week) (OR: 0.6, 95% CI: 0.5–0.8; $P = .0002$).[28] A 2017 meta-analysis of 16 studies revealed a null association with overall fish intake. However, when that analysis looked at subgroups, total fish intake in European studies showed an inverse relationship with endometrial cancer (RR: 0.9, 95% CI: 0.84–0.97), as did consumption of fish high in omega-3 fatty acids, with an RR of 0.79 to 0.85, depending on the type of omega-3 (eicosapentaenoic acid: 95% CI: 0.61–1.04, docosahexaenoic acid: 95% CI: 0.64–1.11), while studies performed in Asia showed a higher risk of endometrial cancer with fish consumption (RR: 1.15, 95% CI: 1.10–1.21). The authors proposed that the geographic differences might be secondary to fish preparation methods, because Asian countries are more likely to deep fry or salt-dry their fish.[29] Overall, the evidence supports that saturated fat can increase the risk of endometrial cancer, while omega-3 fatty acid consumption can decrease the risk.

Caffeine/Coffee

Coffee intake has been examined for endometrial cancer risk because it is known to contain antioxidants. A 2007 meta-analysis of coffee drinkers versus non-coffee-drinkers reported a decreased risk of endometrial cancer (RR: 0.8, 95% CI: 0.68–0.94), which was dose-dependent, with the heavy coffee drinkers (from two to seven cups per day, depending on the study) receiving additional benefit (RR: 0.64, 95% CI: 0.48–0.86).[30] This finding was supported by a 2012 meta-analysis of 16 studies that revealed a pooled RR of 0.71 for endometrial cancer among those with the highest coffee intake (95% CI: 0.62–0.81); the meta-analysis also showed a dose-dependent, inverse relationship between coffee consumption and endometrial cancer risk.[31] This decrease in endometrial cancer risk was seen in both premenopausal women (RR: 0.80, 95% CI: 0.72– 0.89) and postmenopausal women (RR: 0.76, 95% CI: 0.69–0.83) in a 2017 meta-analysis.[32] Interestingly, a meta-analysis looking at dose-response of coffee consumption found that women consuming decaffeinated coffee also had a lower risk of endometrial cancer (RR: 0.77, 95% CI: 0.63–0.94), although they had less benefit than caffeinated coffee drinkers (RR: 0.66, 95% CI: 0.52-0.84).[33] These findings challenge the thought that caffeine itself decreases endometrial cancer risk. Generally, coffee-drinking appears to decrease endometrial cancer risk.

General diet

Studies have commonly looked at a variety of dietary factors and patterns in endometrial cancer risk, with varying results. One 2007 meta-analysis showed that consumption of vegetables appears to decrease endometrial cancer risk modestly (RR: 0.71, 95% CI: 0.55–0.91), while fruit does not.[34] However, a 2018 meta-analysis showed conflicting results of vegetable fiber intake between case-control and the overall analysis.[35] While there is some evidence that vegetable intake decreases endometrial cancer, it is more likely that overall diet plays a larger role.

A pooled case-control study found that women who adhered to a Mediterranean diet (high in vegetables, fruits, nuts, cereals, legumes, and fish and low in dairy and meat products) had an OR of 0.43 of endometrial cancer (95% CI: 0.34–0.56).[36] The finding was thought to be secondary to foods rich in phytochemicals, fiber, unsaturated fatty acids, and antioxidants. This dietary approach was supported by the largest dietary meta-analysis to date, performed by Si et al in 2017, which included 27 studies comparing a healthy diet (high in vegetables, fruits, whole grains, olive oil, fish, poultry, and low-fat dairy) with a Western-style diet (high in red meat and processed meat, refined grains, sweets, high-fat dairy, and potatoes and low in fruits and vegetables). That study found that women who reported the highest adherence to a healthy diet had a decreased risk of endometrial cancer (OR: 0.74, 95% CI: 0.62–0.88; $P = .0008$).[37] This finding was supported by another meta-analysis in 2020.[38]

Together, the literature shows that a healthy diet, and a Mediterranean diet in particular, is associated with decreased risk of endometrial cancer. Healthy diets often include soy and isoflavones, coffee, omega-3 fatty acids, and low-saturated fats along with fruits and vegetables, which all have evidence for reducing overall risk of endometrial cancer.

Smoking

While smoking has usually been found to increase the incidence of other cancers, there is evidence that the risk of endometrial cancer decreases in women who smoke. A meta-analysis by Zhou et al looked at 10 prospective studies and 24 case-control studies of ever-smokers. It showed an inverse relationship between smoking and endometrial cancer, with a reduced RR of 0.81 (95% CI: 0.74–0.88) in the prospective studies and an OR of 0.72 (95% CI: 0.66–0.79) in the case-control studies. The findings held true for current and former smokers. Interestingly, the risk reduction was seen only in postmenopausal women in the meta-analysis, and the inverse association between smoking and endometrial cancer was the strongest in the US population. Risk reduction was greatest in postmenopausal women who smoked and used hormone therapy (HT; RR: 0.45, 95% CI: 0.29–0.70) versus nonusers (RR: 0.65, 95% CI: 0.51–0.84). Overall, the studies included showed various effects of smoking on endometrial cancer in premenopausal women, increasing risk in some, decreasing in others, and ultimately having no significant effect in the meta-analysis.[39] A pooled case-control study showed that postmenopausal women who were obese had a further increased risk reduction with current smoking (OR: 0.47, 95% CI: 0.27–0.81).[40] The data support the idea that smoking decreases the risk of endometrial cancer and is particularly significant in women with higher BMI.

Alcohol

Overall, alcohol consumption has not been shown to be a significant risk factor for any type of uterine cancer, although there have been some mixed results based on amount of alcohol consumption. In a meta-analysis of 20 case-control studies and 7 cohort studies totaling 13,120 cases across North America Europe, and Asia, nondrinkers and low drinkers had the same risk as drinkers. Even heavy drinkers (> 14 drinks per week) did not have a significant increase in endometrial cancer risk (RR: 1.12, 95% CI: 0.87–1.45).[41] These results were corroborated by other meta-analyses that showed that neither dose nor type of alcohol was associated with endometrial cancer risk.[37,42,43]

Physical Activity

High levels of physical activity have been hypothesized to help decrease the risk of many types of cancer, secondary to decreased overall inflammation, decreased insulin resistance, and decreased sex steroids, regardless of whether weight loss occurs. A 2015 meta-analysis of 33 studies revealed a reduced risk of endometrial cancer (RR: 0.69, 95% CI: 0.52–0.91) in overweight and obese women with high levels of activity but no reduction in risk for normal-weight women.[44] Another large meta-analysis in 2020 of 80 publications showed an association between higher lifetime physical activity and reduced endometrial cancer risk (RR: 0.77, 95% CI: 0.67–0.88); the risk reduction did not change when adjusted for BMI.[45] The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, which randomized women at high risk for breast cancer to tamoxifen versus placebo, was able to look at the impact of behavioral factors on uterine cancer incidence; it showed no increase in endometrial cancer risk with smoking or alcohol use, but found a 70% greater risk of endometrial cancer among women with low or no activity (P = .026, HR: 1.73, 95% CI: 1.07–2.80).[3] There is strong evidence that high levels of physical activity reduce endometrial cancer risk, with particularly potent effects for women who are obese.

What hormonal factors are risk factors for uterine cancer? How strong are these risks?

As the majority of uterine cancers are hormonally driven, there has been great interest in investigating hormonal factors and their role in uterine cancer risk. Studies have examined lifetime length of exposure to endogenous hormones and exogenous hormones. Anovulation and the use of tamoxifen have also been examined, as these have been shown to lead to overgrowth of the endometrium.

Endogenous Hormone Exposure

Exposure to endogenous hormones varies depending on the age of menarche, age of menopause, parity, timing of parity, and the interval between births. It has been hypothesized that longer and more continuous exposure to normal physiologic, postpuberty, and premenopausal endogenous hormones could increase the risk of uterine cancer, especially endometrial cancer. A 2015 meta-analysis of eight studies examined the role of the age of menarche in endometrial cancer risk; it found that women who underwent menarche in the oldest category had a small but statistically significant decreased risk of endometrial cancer (RR: 0.96, 95% CI: 0.94–0.98) when compared with the youngest category.[46] A similar finding was reported by the Epidemiology of Endometrial Cancer Consortium, which pooled data to examine risk factors for uterine sarcomas. That study revealed that older age of menarche (≥15 years vs <11 years) was inversely associated with uterine sarcoma risk (OR: 0.70, 95% CI: 0.34–1.44).[15]

Age of menopause in relation to endometrial cancer has been controversial. However, the largest study—a meta-analysis of 18 articles in 2019—revealed an RR of endometrial cancer of 1.89 (95% CI: 1.58–2.26) for women with the highest age of menopause compared with the lowest. The association of endometrial cancer risk with age of menopause became positive among women who reached menopause after age 46.5 years.[47]

The idea that earlier menarche and late menopause are positive risk factors for endometrial cancer is also supported by a population-based, case-control study by Xu et al, which primarily showed that pregnancy decreases endometrial cancer risk, and the risk decreases further with more pregnancies.[48] A large cohort study using the Swedish Cancer Registry assessed the effect of the age of parity or first birth on endometrial cancer risk; it broke down subjects by age (grouped into 5-year intervals). The study revealed that increasing age of parity increased endometrial cancer risk substantially; women ages 35–39 at first parity had the highest risk (RR: 9.14, 95% CI: 3.33–25.05) when compared with women who gave birth before age 19.[49] A pooled analysis

of 17 studies reported a pooled OR per 5-year increase in age at last birth of 0.87 (95% CI: 0.85–0.90); women age 40 or older at the time of their last birth had a 44% decreased risk of endometrial cancer.[50] These data together show that women who have had longer, uninterrupted exposure to endogenous female hormones have a higher risk of endometrial cancer. The data for uterine sarcoma risk are minimal, but there is evidence to support that the risk of uterine sarcoma is decreased with older age of menarche.

Exposure to higher levels of endogenous testosterone has been investigated because of the potential role of androgen receptors in some types of endometrial cancer and the potential for the endometrium to aromatize testosterone into estradiol. The European Prospective Investigation into Cancer and Nutrition designed a prospective, nested, case-control study examining circulating levels of sex hormones in postmenopausal women (247 incident endometrial cancers and 481 controls).[51] This 2008 study revealed an endometrial cancer OR of 2.05 (95% CI: 1.23–3.42) for women with the highest versus lowest tertile of free testosterone levels, which was attenuated somewhat but not fully by BMI (OR: 1.74, 95% CI: 1.02–2.96). When adjusted for estrone and estradiol levels, the association between free testosterone and endometrial cancer risk was no longer significant. These results were similar to a 2019 WHI study (OR: 1.91, 95% CI: 1.12–3.24), with a similar attenuation when adjusted for estrogen levels.[52] A 2016 prospective, case-control study nested within three large cohorts (161 cases and 303 controls) examined circulating androgens and the risk of endometrial cancer in both premenopausal and postmenopausal women; this study also showed that women age 55 or older at diagnosis had a BMI-adjusted endometrial cancer OR of 2.08 (95% CI: 1.25–3.44, $P = .005$) for a doubling in testosterone levels, which was not seen in younger, premenopausal women.[53] One of the proposed mechanisms for this increased risk is the possible increased peripheral production of estrogens from testosterone in the postmenopausal years.

Testosterone Therapy

Less is known about the impact of testosterone therapy on endometrial cancer risk. A study of the endometrium in transgender men following androgen therapy showed either endometrial atrophy or inactivity in the hysterectomy specimens of all 32 patients.[54] Another study showed that at least 45% of patients treated with testosterone had endometrial atrophy.[55] Testosterone therapy's effect on the endometrium has also been studied in postmenopausal cisgender women who used testosterone for a year to boost libido without estrogen; these women had more bleeding episodes, which were found to be secondary to atrophy, with no cases of hyperplasia or carcinoma.[56] While there are theoretical risks about the conversion to estrogen, there is minimal evidence that testosterone has a stimulatory effect on the endometrium.

Infertility

Infertility is difficult to study in relation to the risk of cancer, as the cause of infertility is multifactorial in nature, and anovulation, low BMI, obesity, and other health conditions all play a role in the inability to conceive. A review article on risk factors for endometrial cancer reported on a pooled analysis of 14 studies and showed an elevated risk of endometrial cancer in women reporting infertility (OR: 1.76, 95% CI: 1.65–2.00), but there was no attempt to elucidate a cause.[57] Fertility drugs have been proposed to increase uterine cancer, as many are hormonal. In 2016, the American Society for Reproductive Medicine reported no significant relationship between infertility treatment and endometrial cancers, labeling the evidence as grade B.[58] Little is known about the impact of infertility on uterine sarcomas, although one cohort study of 29,700 patients in an in vitro fertilization clinic reported four uterine sarcomas among infertile women who did not undergo in vitro fertilization, which was a larger number than expected.[59] There is some evidence that infertility may increase

endometrial cancer and uterine sarcomas, but more research is needed to determine the relationship between cancer and infertility itself versus confounding factors.

Hormone Therapy

As HT became more popular in the 1990s, there was great interest in studying its effects on endometrial cancer risk, because the endometrium is known to be responsive to female hormones. A systematic review of 28 studies found an increased risk of endometrial cancer with estrogen alone; the review did not show the data from the included RCTs, as the results had very large confidence intervals.[60] The review reported on a meta-analysis from 1995 that showed an RR of 2.3 for unopposed estrogen HT users versus never-users (95% CI: 2.1–2.5), which increased with 10 years of use to an RR of 9.5 and persisted for at least 5 years with an RR of 2.3.[61] The systematic review included a study in which 55% of users of unopposed estrogen discontinued treatment because of endometrial hyperplasia at 3 years.[60] The Mayo Clinic Rochester Epidemiology Project case-control study reported an endometrial cancer OR of 2.18 (95% CI: 1.07–4.45) for women who used unopposed estrogen for more than 6 months when compared with nonusers; there was no increased risk with combined HT in that population.[62] Therefore, the evidence of increased endometrial cancer risk with estrogen-only HT became convincing enough that this regimen is rarely used today in women with a uterus.

Progestin medications were added to the estrogen regimens to protect the endometrium. Numerous regimens have been used over the years, with the current most common regimens being continuous versus sequential 10-day regimens of progesterone. Combined HT risk has been examined, comparing sequential and continuous regimens, to determine the effects on endometrial cancer risk. In this context, "sequential" or "cyclic" combined HT includes monthly HT, in which progestins are taken at least 7 days per month, and long-interval cyclic HT, in which progestin is taken for at least 7 days every 3 months. Examination of the WHI RCT data revealed fewer endometrial cancers in postmenopausal women (ages 50–79) taking combined continuous HT than in those taking placebo (HR: 0.65, 95% CI: 0.48–0.89).[63] A review of HT and cancer risks included a case-control study of women who used sequential HT (progestins <7 days/month) as opposed to continuous combined HT and had an RR of endometrial cancer of 1.87 ($P = .0004$). Women who used unopposed estrogen in this study had an RR of endometrial cancer of 2.17 ($P < .0001$) compared with those using continuous combined HT.[64] A systematic review by Tempfer et al of 31 publications showed a decreased risk of endometrial cancer in patients taking continuous combined HT compared with never-users of HT, with HR ranging from 0.24 to 0.71. Endometrial cancer was significantly increased with sequential, combined HT use in 6 of 12 studies (OR/HR: 1.38–4.35); these sequential studies included both monthly and long-interval sequential progestin use, with increased endometrial cancer risk if progestins were not used at least 10 days each month compared with continuous HT and never-users. Estrogen-only users had an increased risk similar to the risk with sequential HT, with 9 of 12 studies having ORs or HRs of 1.45 to 4.46.[65] Because of these findings, long-interval progestin regimens are not endorsed today.

The method of delivery of combined HT has also been studied. A randomized, multicenter, clinical trial examined the effects of continuous combined HT, comparing delivery of estrogen and progestin through a transdermal patch with an oral combined pill for 96 weeks. Neither group of women had any cases of endometrial cancer or hyperplasia, indicating that both delivery methods worked well for protection of the endometrium through combined hormone treatment.[66] There is some evidence that micronized progesterone may not provide enough endometrial protection; a French cohort study of 65,630 women reported an HR of 2.66 (95% CI: 1.87–3.77) in women who used micronized progesterone for more than 5 years, compared with never-users. No increased risk of endometrial cancer with combined HT with other progestin derivatives was

seen.[67] A review by Pinkerton et al on the effect of vaginal estrogen used for genitourinary symptoms of menopause on endometrial cancer risk referenced the WHI cohort study and showed no statistically different levels of endometrial cancer in vaginal estrogen users.[68] There are some conflicting data reported in the review, but overall, the authors report relative safety of vaginal estrogen in terms of endometrial cancer risk.

BMI has been shown to modify the risk of endometrial cancer with HT use significantly. A meta-analysis of 24 studies revealed that combined HT was protective in women with increased BMIs. Never-users of HT had an RR per 5 kg/m^2 of 1.90 (95% CI: 1.57–2.31) for endometrial cancer, compared with an RR of 1.18 per 5 kg/m^2 (95% CI: 1.06–1.31) for women who used HT. For women with extreme obesity (BMI = 42), the RR was 20.70 (95% CI: 8.28–51.84) for never-users of HT compared with HT users.[69] Overall, combined HT, especially in a continuous fashion, has strong evidence for decreasing endometrial cancer risk, with larger decreases in risk associated with increasing BMI.

Tamoxifen Use

Tamoxifen use appears to increase endometrial cancer risk, although other factors affect the magnitude of the risk. This increased risk is not surprising, as tamoxifen stimulates the endometrium as an estrogen receptor agonist in the uterine cavity. A meta-analysis of extended-use tamoxifen (10 years rather than 5 years) increased the RR of endometrial cancer to 2.29 (95% CI: 1.6–3.28).[70] The risk of endometrial cancer in women younger than 50 who took tamoxifen for 5 years was low (RR: 1.19, 95% CI: 0.53–2.65; P = .6) compared with those who took a placebo, according to three breast cancer prevention trials.[71] In a Markov model of 5 years of tamoxifen use on survival among 50-year-old postmenopausal women, the associated gain in life expectancy was 1–4 months shorter in women with a uterus. If the risk of endometrial cancer was modeled for 5 years after ending tamoxifen treatment, use of tamoxifen led to losses or decreased gains in life expectancy, only showing gains of 1 additional year of life in the women at the highest risk for breast cancer.[72]

In terms of uterine sarcoma risk, the National Surgical Adjuvant Breast and Bowel Project trials showed an increase in uterine sarcomas among women taking 5 years of tamoxifen, with 10% of total uterine malignancies being sarcomas, compared with a normal incidence of one to two cases per 100,000; 9 of the 12 sarcomas were carcinosarcomas.[73] An examination of the National Cancer Institute's Surveillance, Epidemiology, and End Results program incidence data showed that women treated with tamoxifen had an observed-to-expected rate of malignant mixed Mullerian tumors of 4.62 (95% CI: 1.85–2.32).[74] This finding identified enough of a risk of uterine sarcoma that the U.S. Food and Drug Administration issued a "black box" warning for tamoxifen in 2002.[75] Although tamoxifen has significant benefits for breast cancer treatment and prevention, the evidence supports an increased risk of endometrial cancer and uterine sarcoma with its use. Therefore, judicial use is recommended.

What family health history factors are risk factors for uterine cancer? How strong are these risks?

The literature review assessed the main genetic cancer syndromes associated with a higher risk of uterine cancer and whether there is evidence for an increased risk in women with a family history of uterine cancer without a known mutation. While the review identified numerous polymorphisms proposed to be associated with uterine cancer,[76] there was not enough evidence to report on the incidence of uterine cancer other than in the known genetic predisposition syndromes. However, the body of evidence is likely to expand as more studies in genetics and more pedigrees are performed, thanks to decreased costs and increased access to genetic testing.

Genetic Susceptibility

NCCN provides the most up-to-date reviews on genetic cancer risk for uterine cancer.[77,78,79] NCCN reported that 5% of patients with endometrial cancer have germline genetic mutations, and these cancers tend to occur 10–20 years before sporadic cancer.[77] Therefore, screening for genetic mutations should be considered in women younger than 50 at diagnosis in particular and offered to all women with endometrial cancer. NCCN recommends universally offering tumor testing for defective DNA mismatch repair (MMR) immunohistochemistry along with microsatellite instability (MSI) testing of all endometrial cancers and endometrial sarcomas. Screening is not usually recommended for carcinosarcomas (considered high-grade epithelial tumors).

LYNCH SYNDROME

Lynch syndrome is caused by germline mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*). Table 1 describes the risk of endometrial cancer associated with each of the gene mutations of Lynch syndrome.[78] Families with this cancer predisposition syndrome were originally identified by the Bethesda and Amsterdam criteria, which have been revised over the years and now include family history of colorectal/gastrointestinal tract, endometrial, ovarian, pancreatic, urinary tract, and brain cancers.

Table 1. Lynch Syndrome and Risk of Endometrial Cancer

Gene	Average Age (y)	Lifetime Risk of Endometrial Cancer†	NCCN Recommendations*
MLH1	49	34–54%	• Endometrial biopsy every 1–2 y at age 30–35 • Consider hysterectomy when childbearing is complete
MSH2/EPCAM	47–48	21–57%	
MSH6	53–55	16–49%	
PSM2	49–50	13–26%	

*Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ line PMS2 mutations. Gastroenterology. 2008;135:419-28

Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome. J Clin Oncol 2018;36:2961-2968.

Suerink M, et al. An Alternative Approach to Establishing LJnbiased Colorectal Cancer Risk Estimation in Lynch Syndrome. Genet Med, 2019; 21 ;2706-2712.

Moller P, Seppala TT, Bernstein l, et al. Cancer risk and survival in path MMR carriers by gene and gender up to 75 years of age: a repolt from the Prospective Lynch Syndrome Database. Gut 2018;67:1306-1316.

Moller P, Seppala T, Bernstein l, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2017;66:464-472

Dominguez-Valentin M, Sampson J, Seppälä T, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15-25.

†National Comprehensive Cancer Network. Genetic/familial high-risk assessment: Colorectal, version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Updated 2020. Accessed December 3, 2020.

In a meta-analysis by Coletta et al, BMI and weight changes were not found to be associated with increased risk of endometrial cancer among those with Lynch syndrome, but multivitamin use did decrease endometrial cancer risk. This finding that BMI is not associated with increased risk of endometrial cancer in people with Lynch syndrome directly opposes the finding that high BMI increases the risk of endometrial cancer in the general population.[80]

Cowden Syndrome

Cowden syndrome involves increased risk of endometrial cancer, colon cancer, and thyroid cancer. The major criteria include breast cancer, endometrial cancer, follicular thyroid cancer, gastrointestinal hamartomas, macrocephaly (>97th percentile), Lhermitte-Duclos disease, macular pigmentation of glans of penis, and multiple mucocutaneous lesions. There are numerous minor criteria. Before the availability of genetic testing, the diagnosis of Cowden syndrome required a combination of major and minor criteria. Overall, women with pathogenic variants or mutations of PTEN have a 5–10% lifetime risk of endometrial cancer.[81] To manage the endometrial cancer risk among these women, NCCN recommends consideration of endometrial biopsy every 1–2 years starting at age 35. Routine transvaginal ultrasonography is not recommended as a screening tool in premenopausal women. Women with Cowden syndrome might want to consider a hysterectomy upon completion of childbearing.[79]

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome has been identified in families with hamartomatous polyps of the entire gastrointestinal tract along with pigmented macules of the mucous membranes. Patients with Peutz-Jeghers syndrome are at increased risk of gastrointestinal tract cancers and cancers of the female organs, including the uterus. NCCN reports that the risk of uterine cancer risk with a pathogenic variant of *STK11* is 9%[82] and recommends a yearly pelvic exam and Pap test starting at ages 18–20 years, mostly because of the risk of benign sex cord/Sertoli cell tumors and cervical adenoma malignum.[78] The type of uterine cancer usually associated with Peutz-Jeghers syndrome is endometrial carcinoma.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a rare disorder linked to a pathogenic mutation in the tumor suppressor gene TP53 that confers almost a 100% risk of cancer in affected patients. It is associated with soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, gastrointestinal cancers, adrenocortical cancer, brain tumors, and hematologic cancers. There is no defined risk of uterine cancer according to NCCN.[79] However, there is a 15% lifetime risk of sarcomas, including leiomyosarcoma. No studies look specifically at the risk of endometrial cancer in Li-Fraumeni syndrome, but the definition of Li-Fraumeni syndrome has expanded as genetic testing has increased. With the consideration of additional cancers as "core indicators" of Li-Fraumeni syndrome, future research might better quantify risk. While there are no specific recommendations for uterine cancer screening with Li-Fraumeni syndrome, NCCN recommends that patients undergo annual whole-body MRI starting at diagnosis.[79]

BRCA1 and *BRCA2* Pathogenic Variants

There is a paucity of data on whether *BRCA1* and *BRCA2* pathogenic variant carriers have an increased risk of serous uterine cancer. A small study involving 22 Jewish patients diagnosed with uterine serous cancer found

that 27% had a germline mutation in *BRCA1* or *BRCA2*, which is greater than the 1-in-40 prevalence of the gene.[83] A retrospective study of 199 Ashkenazi Jewish patients with endometrial cancer showed no increased risk of endometrial cancer with any of the three founder *BRCA* mutations.[84] NCCN reports that limited data suggest a slightly increased risk of serous uterine cancer among women with *BRCA1* pathogenic variants.[79] NCCN recommends further evaluation of this risk and that providers discuss risks and benefits of hysterectomy at the time of a risk-reducing bilateral salpingo-oophorectomy, mostly secondary to the reduced breast cancer risk of estrogen-only HT as compared with combined HT. The SGO stated that there is no clear increased risk of uterine serous cancer with *BRCA1*.[2] At this time, there is insufficient evidence to support an increased risk of *BRCA1* or *BRCA2* pathogenic variants with uterine cancer risk, although the association will be better elucidated as genetic studies become more common.

RETINOBLASTOMA

Survivors of retinoblastoma have an excess of second malignancies, frequently sarcomas. These malignancies includes leiomyosarcoma, the most common type of sarcoma in retinoblastoma survivors. Patients with a hereditary *RB1* mutation have a higher risk of uterine leiomyosarcoma specifically. In a cohort study involving 525 women with hereditary retinoblastoma and 762 women with nonhereditary retinoblastoma, an excess risk of leiomyosarcoma of 3.9 per 10,000 women was found in those with hereditary retinoblastoma, which increased with age. These women had a cumulative risk of uterine leiomyosarcoma of 3.2% (95% CI: 1.0–8.0). The average age of diagnosis was 41.4 years, while in the general population, uterine leiomyosarcomas tend to appear between ages 50 and 70.[85]

Family History of Endometrial Cancer

A systematic review and meta-analysis of 16 studies revealed an increased risk of endometrial cancer for those with a first-degree relative with a history of endometrial cancer; these women had a pooled RR of 1.82 (95% CI: 1.65–1.98). Three of the studies included attempted to exclude Lynch syndrome families (on the basis of clinical criteria and MMR/MSI), yet all three still reported a significant association with a family history of endometrial cancer but not those with colorectal cancer. There was also no association of family history of breast, ovarian, or cervical cancer with endometrial cancer risk.[86]

What prior health history factors are risk factors for uterine cancer? How strong are these risks?

Prior health history plays a significant role in uterine cancer risk. A history of ovarian cancer has been examined as a risk factor, but there is no clear evidence that it is associated with increased risk of uterine cancer except in women who have a hereditary mutation.

Diabetes and Hypertension Risk

Diabetes mellitus and hypertension are often studied together, as patients often have both conditions. Diabetes is frequently a confounder of studies, so it is often examined as an independent variable in disease, including uterine cancer. A large 2014 meta-analysis and systematic review of 24 studies that examined the incidence of endometrial cancer found that women with diabetes had an RR of endometrial cancer of 1.89 (95% CI: 1.46–2.45) compared with women without diabetes.[87] This finding added to an earlier meta-analysis of 16 studies in which 12 studies showed an increased risk of endometrial cancer in women with diabetes (summary RR: 2.10, 95% CI: 1.75–2.53).[88] This meta-analysis included three studies examining the effect of type 1 diabetes on

endometrial cancer risk and found a summary RR of 3.15 (95% CI: 1.07-9.29).[88] A 2019 systematic review and meta-analysis reported that 14 out of 22 studies showed a statistically significant increased risk of diabetes with endometrial cancer risk (RR: 1.72, 95% CI: 1.48–2.01).[89] A 2015 systematic review and meta-analysis by Hernandez et al of 25 studies looking at insulin resistance found that women with endometrial cancer had higher fasting insulin levels in 13 of those studies (mean difference: 33.94 pmol/L, 95% CI: 15.04–52.85); C-peptide levels were also higher in women with endometrial cancer (mean difference: 0.14 nmol/L, 95% CI: 0.08–0.21).[90] In summary, there is strong evidence that diabetes increases endometrial cancer risk.

Uterine sarcoma risk is also associated with diabetes. Felix et al examined data from the Epidemiology of Endometrial Cancer Consortium and reported that a diagnosis of diabetes increased endometrial stromal sarcoma risk (OR: 2.28, 95% CI: 1.02–5.12).[15]

Hypertension as an independent risk factor for endometrial cancer was studied in a systematic review and meta-analysis of 25 papers, which found a summary RR of 1.61 (95% CI: 1.41–1.85); this study also examined confounding factors such as age, smoking, diabetes, BMI, HT, and reproductive factors and still found that hypertension was associated with endometrial cancer risk.[91] Hypertension is often studied in conjunction with diabetes. The effect of diabetes and hypertension on the odds of endometrial polyps containing premalignant or malignant changes was examined in a meta-analysis of 10 studies; it found women with diabetes had an OR of 2.43 (95% CI: 1.51–3.91) and women with hypertension had an OR of 2.36 (95% CI: 1.16–4.81).[92] In general, both diabetes and hypertension increase endometrial cancer risk, and there is some evidence that diabetes increases endometrial stromal sarcoma.

Metabolic Syndrome

Metabolic syndrome is a group of risk factors that increase the risks for cardiovascular atherosclerotic disease and type 2 diabetes. These risk factors include abdominal obesity, dyslipidemia, impaired glucose metabolism, and increased blood pressure. Several meta-analyses looked specifically at the risk of endometrial cancer in women who met the criteria for metabolic syndrome. A systematic review and meta-analysis by Esposito et al of six studies showed that women with metabolic syndrome had an RR of 1.89 (95% CI: 1.34–2.67), but that analysis had significant heterogeneity among the studies, partially because of differences in the definition of metabolic syndrome.[93] In a 2019 systematic review of eight articles, the authors determined that there was too much variability in the definition of metabolic syndrome to calculate a true RR.[94] Thus, although metabolic syndrome likely increases the risk of endometrial cancer, high-level evidence does not exist to support such an assertation.

Polycystic Ovarian Syndrome

PCOS is diagnosed in women with two of the three Rotterdam criteria: oligomenorrhea/amenorrhea, hyperandrogenemia, and polycystic ovaries on ultrasonography. While there are numerous smaller studies on the impact of PCOS on endometrial cancer risk, both alone and in conjunction with other risk factors, one systematic review compared 14 studies. The final meta-analysis found five studies meeting criteria that showed that women with PCOS had an increased risk of endometrial cancer (OR: 2.89, 95% CI: 1.52–5.48).[95] The increased risk of endometrial cancer with PCOS is thought to be secondary to anovulation, which prolongs exposure to unopposed estrogen, leading to hyperplasia.

Pelvic Radiation

The literature review found one study that evaluated the National Cancer Institute's Surveillance, Epidemiology, and End Results database for women who developed endometrial cancer after receiving pelvic radiation for cervical, vulvar, vaginal, colon, rectal, anal, and urinary system cancers. The study compared the results with those of women who had one of these cancers but did not receive pelvic radiation. In total, the study found 205 radiation-associated endometrial cancers and 1,001 sporadic endometrial cancers. Radiation-associated endometrial cancers were found slightly earlier, at age 65, compared with the mean age of 68 (P = .007). The OR for developing radiation-induced endometrial cancer was three times as likely in African American women (P < .001). More than 75% of lesions in the radiation-induced endometrial cancers were nonendometrioid, with the most common histology being endometrial sarcomas (26.3%). Sarcomas were four times as likely in those with radiation-induced cancer than sporadic cancer, and clear cell/papillary serous cancers were twice as likely (P < .001). On average, radiation-induced endometrial cancers were more likely to be poorly differentiated, higher-grade cancers.[96]

Uterine Pathology

Uterine pathology with hyperplasia and endometrial polyps has been shown to significantly increase uterine cancer risk, while the presence of leiomyomas has not. Menopausal status affects the risk of uterine cancer associated with uterine pathology. A systematic review and meta-analysis by Lee et al of 17 studies found that postmenopausal women had a higher risk (5.4%) than reproductive-age women (1.7%) of polyps being premalignant or malignant (RR: 3.86, 95% CI: 2.92–5.11). Symptomatic postmenopausal women had an elevated risk of endometrial neoplasia when compared with asymptomatic postmenopausal women (RR: 3.36, 95% CI 1.45–7.80).[97] The finding that postmenopausal women are at higher risk for polyps containing malignancy than premenopausal women is supported by a 2019 systematic review and meta-analysis of 51 studies; premenopausal women had a 1.12% risk of polyps containing malignancy while postmenopausal women had a 4.93% risk (chi-square difference: 397.21, P < .0001).[98]

Another systematic review and meta-analysis of 37 studies showed that menopausal status prevalence ratio (prevalence ratio: 1.67, 95% CI: 1.48–1.89), age older than 60 years (prevalence ratio: 2.41, 95% CI: 1.84–3.16), and tamoxifen use (prevalence ratio: 1.53, 95% CI: 1.06–2.21) increased risk of malignancy within an endometrial polyp. However, history of breast cancer and the size of the endometrial polyp were not associated with endometrial cancer risk within the polyp.[99] Endometrial thickness is also related to risk of endometrial cancer in postmenopausal women, as it is evidence of probable hyperplasia or an existing malignancy. A meta-analysis revealed that in asymptomatic postmenopausal women with an endometrial thickness of 11 mm or more, the RR of endometrial cancer or hyperplasia with atypia was 2.59 (95% CI: 1.66–4.05).[100] Interestingly, in a small study of 27 women, pyometra was associated with underlying malignancy in 22.2% of cases.[101]

The risk of uterine cancer with hyperplasia has been examined multiple times over the years along with attempts at different grading systems for hyperplasia. The 1994 World Health Organization (WHO) criteria use the classifications of simple and complex, atypical and nonatypical, which are a subjective evaluation of cytologic atypia. The newer International Endometrial Collaborative Group classification (2000) uses the designation of benign endometrial hyperplasia versus endometrial intraepithelial neoplasia (EIN), which is considered a premalignant lesion. EIN criteria are more stringent and can be obtained using objective computerized analysis (D-score) or subjective analysis. Evaluation of the two classification systems was performed in a systematic review and meta-analysis by Raffone et al. The meta-analysis included 12 studies using the WHO system, which found a pooled RR for progression to cancer of 8.74 (95% CI: 6.66–11.47). The

EIN subjective criteria yielded a pooled RR of 19.37 (95% CI 5.86–64.01), and the D-score criteria resulted in a pooled RR of 29.22 (95% CI 13.24–64.51). The differences between the D-score and WHO subgroup were significant, while the other differences were not. This study showed that the EIN D-score better predicted risk of cancer than the WHO system.[102]

When the traditional WHO criteria are applied, atypical hyperplasia has been shown to be associated with high rates of occult endometrial cancer or progression to endometrial cancer. In a meta-analysis of concurrent endometrial cancer in women with atypical hyperplasia, 32.6% of women with atypical hyperplasia were found to have occult endometrial cancer (95% CI: 24.1– 42.4). Six studies in the meta-analysis assessed the risk of developing endometrial cancer in the future; together, they found an incidence rate of endometrial cancer in women with atypical hyperplasia of 82.3 per 1,000 person–years (95% CI: 39.3–172.6), equivalent to 8.2% per year.[103] Complex versus simple nonatypical hyperplasia was examined in a meta-analysis of 12 studies, revealing that women with complex nonatypical hyperplasia had an OR of 6.02 of occult cancer (95% CI: 2.35–15.42) and a pooled rate of coexistent cancer of 0.124 (95% CI: 0.084–0.181). Simple nonatypical hyperplasia had a rate of 0.020 of coexistent cancer (95% CI: 0.010–0.038).[104]

No significantly consistent increased risk of uterine cancer has been found with endometriosis[105] or adenomyosis[106] among articles reviewed in meta-analyses. Uterine leiomyomas or fibroids do not carry a high risk of cancer. A review article on the risk of leiomyosarcoma at the time of morcellation of fibroids reported that the U.S. Food and Drug Administration determined that the risk of any uterine occult cancers in women undergoing hysterectomy or myomectomy ranged from 1 in 225 to 1 in 580, and the risk of leiomyosarcoma ranged from 1 in 495 to 1 in 1,100.[107]

The evidence supports the increased rate of endometrial cancer with endometrial polyps and hyperplasia, although the amount of risk varies according to other confounding factors. This review did not find any high-level studies examining the effect of uterine pathology on sarcoma risk. Smooth muscle tumors of uncertain malignant potential were ultimately not included in the review, as they are, by definition, rare tumors that are classified between benign leiomyoma and malignant leiomyosarcomas and, therefore, have a possibility of recurring as leiomyosarcoma.

History of Breast or Ovarian Cancer

This review did not reveal any high-level evidence for increased risk of uterine cancer in women with a history of ovarian cancer who did not have a genetic predisposition syndrome, but there was some evidence for increased risk of uterine cancer with a history of breast cancer. In a review of breast cancer in patients with type 2 endometrial carcinoma, 9.7–32% of women had a personal history of breast cancer, and 29% had a family history of breast cancer. However, these findings are likely multifactorial, as pathogenic germline mutations and tamoxifen use could be confounding factors.[108] In a 2006 retrospective, population-based, multicenter study of 52,109 women with uterine corpus cancer, 1,922 had breast cancer; women with a history of breast cancer had higher rates of uterine papillary serous carcinoma (9.4% vs 6.3%; $P < .001$) and sarcoma (10.3% vs. 8.4%; $P < .001$).[109] However, another systematic review and meta-analysis of 37 studies reported that history of breast cancer and the size of the endometrial polyps were not associated with endometrial cancer risk within the polyp.[99] Thus, there is evidence that a history of breast cancer slightly increases the risk of uterine cancer, but the risk may be higher for developing type 2 endometrial carcinomas.

RESEARCH GAPS

- Significant evidence exists only for topics that have been researched for decades.
- There is limited information about the impact of lifestyle or prior health risks on genetic uterine cancer risk.
- Because of the rarity of endometrial stromal sarcomas and leiomyosarcomas, most studies focused on endometrial cancer risk.
- The literature lacks information on metabolic syndrome, infertility, and history of breast cancer as independent risk factors.

SUMMARY OF RISKS BY LEVEL OF EVIDENCE

In summary, numerous risk factors are associated with endometrial and uterine sarcoma risk. Some are modifiable, such as diet, exercise, BMI, type 2 diabetes, and HT, while others, such as a genetic cancer predisposition or timing of length of reproductive years, cannot be modified. There is strong evidence that certain factors, such as diabetes, obesity, and HT, increase the risk of endometrial cancer, but more research is needed about the risk factors for most uterine sarcomas. The findings are summarized here by evidence level.

Level I Evidence: RCTs, Systematic Reviews, and Meta-Analyses

- Age older than 50 increases endometrial and sarcoma cancer risk.
- Obesity increases endometrial cancer risk.
- High GI intake increases endometrial cancer risk.
- Soy and isoflavone intake decreases endometrial cancer risk.
- High saturated fat intake increases endometrial risk, and high omega-3 fatty acid consumption decreases endometrial cancer risk.
- Coffee consumption decreases endometrial cancer risk, as does a healthy diet high in vegetables, fruits, whole grains, olive oil, fish, poultry, and low-fat dairy.
- Smoking decreases endometrial cancer risk.
- Alcohol has no effect on endometrial cancer risk.
- Unopposed estrogen therapy increases endometrial cancer risk, and continuous HT and sequential HT (more than 7 days of progesterone monthly) decreases endometrial cancer. Women with higher BMIs have an additional benefit from HT in decreasing endometrial cancer risk.
- High levels of physical activity decrease endometrial cancer risk, with increased benefits in obese women.
- Women with the genetic cancer predispositions of Lynch syndrome, Cowden syndrome, and Peutz-Jeghers syndrome have an increased risk of endometrial cancer, and women with Li-Fraumeni syndrome have an increased risk of sarcomas.
- A family history of endometrial cancer in a first-degree relative increases the risk of endometrial cancer.
- Diabetes, hypertension, and metabolic syndrome increase the risk of endometrial cancer, and diabetes also increases the risk of uterine sarcomas.
- PCOS increases the risk of endometrial cancer.
- Uterine polyps and hyperplasia are associated with increased endometrial cancer risk, especially in postmenopausal women.

Level II Evidence

- Obesity increases uterine sarcoma risk.
- Early menarche, late menopause, nulliparity, and increased age of parity all increase endometrial cancer.

- Older age of menarche decreases uterine sarcoma risk.
- Infertility treatment has no effect on endometrial cancer risk.
- Women with a history of retinoblastoma have an increased risk of leiomyosarcoma.
- Pelvic radiation for other cancers increases the risk of both endometrial cancer and uterine sarcomas.

Level III or Individual Article Evidence

- Infertility may be associated with a small increase in uterine sarcomas.
- Carriers of *BRCA1* and *BRCA2* pathogenic variants may have a small increased risk of uterine serous carcinomas.

REFERENCES

1. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2001;15(3):341–54. doi: 10.1053/beog.2000.0180
2. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134(2):385–92. doi: 10.1016/j.ygyno.2014.05.018
3. Okamura Y, Saito F, Takaishi K, Motohara T, Honda R, Ohba T, et al. Polycystic ovary syndrome: early diagnosis and intervention are necessary for fertility preservation in young women with endometrial cancer under 35 years of age. Reprod Med Biol 2016;16(1):67–71. doi: 10.1002/rmb2.12012
4. Niwa K, Imai A, Hashimoto M, Yokoyama Y, Mori H, Matsuda Y, et al. A case-control study of uterine endometrial cancer of pre- and post-menopausal women. Oncol Rep 2000;7(1):89–93.
5. Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS, et al. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol 2000;182(1 Pt 1):23–9. doi: 10.1016/s0002-9378(00)70486-8
6. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 2005;105(3):575–80. doi: 10.1097/01.AOG.0000154151.14516.f7
7. Rosen MW, Tasset J, Kobernik EK, Smith YR, Johnston C, Quint EH. Risk factors for endometrial cancer or hyperplasia in adolescents and women 25 years old or younger. J Pediatr Adolesc Gynecol 2019;32(5):546–49. doi: 10.1016/j.jpag.2019.06.004
8. Koivisto-Korander R, Martinsen JI, Weiderpass E, Leminen A, Pukkala E. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. Maturitas 2012;72(1):56-60. doi: 10.1016/j.maturitas.2012.01.021
9. Yang TYO, Cairns BJ, Allen N, Sweetland S, Reeves GK, Beral V, et al. Postmenopausal endometrial cancer risk and body size in early life and middle age: prospective cohort study. Br J Cancer 2012;107(1):169–75. doi: 10.1038/bjc.2012.229
10. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control 2000;11(2):185–92. doi: 10.1023/a:1008946825313
11. Wise MR, Jordan V, Lagas A, Showell M, Wong N, Lensen S, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. Am J Obstet Gynecol 2016;214(6):689.e1–17.
12. Zhang Y, Liu H, Yang S, Zhang J, Qian L, Chen X. Overweight, obesity and endometrial cancer risk: results from a systematic review and meta-analysis. Int J Biol Markers 2014;29(1):e21–9. doi: 10.5301/jbm.5000047
13. Jenabi E, Poorolajal J. The effect of body mass index on endometrial cancer: a meta-analysis. Public Health 2015;129(7):872–80. doi: 10.1016/j.puhe.2015.04.017

14. Rota M, Rumi F, Bagnardi V, Dal Maso L, Zuchetto A, Levi F, et al. Modelling body mass index and endometrial cancer risk in a pooled-analysis of three case-control studies. BJOG 2016;123(2):285–92. doi: 10.1111/1471-0528.13717
15. Felix AS, Cook LS, Gaudet MM, Rohan TE, Schouten LJ, Setiawan VW, et al. The etiology of uterine sarcomas: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium. Br J Cancer 2013;108(3):727–34. doi: 10.1038/bjc.2013.2
16. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis. Br J Cancer 2008;99(3):434–41. doi: 10.1038/sj.bjc.6604496
17. Galeone C, Augustin LSA, Filomeno M, Malerba S, Zucchetto A, Pelucchi C, et al. Dietary glycemic index, glycemic load, and the risk of endometrial cancer: a case-control study and meta-analysis. Eur J Cancer Prev 2013;22(1):38–45. doi: 10.1097/CEJ.0b013e328354d378
18. Nagle CM, Olsen CM, Ibiebele TI, Spurdle AB, Webb PM, Australian National Endometrial Cancer Study Group; Australian Ovarian Cancer Study Group. Glycemic index, glycemic load and endometrial cancer risk: results from the Australian National Endometrial Cancer study and an updated systematic review and meta-analysis. Eur J Nutr 2013;52(2):705–15. doi: 10.1007/s00394-012-0376-7
19. Coleman HG, Kitahara CM, Murray LJ, Dodd KW, Black A, Stolzenberg-Solomon RZ, et al. Dietary carbohydrate intake, glycemic index, and glycemic load and endometrial cancer risk: a prospective cohort study. Am J Epidemiol 2014;179(1):75–84. doi: 10.1093/aje/kwt222
20. Quaas AM, Kono N, Mack WJ, Hodis HN, Felix JC, Paulson RJ, et al. Effect of isoflavone soy protein supplementation on endometrial thickness, hyperplasia, and endometrial cancer risk in postmenopausal women: a randomized controlled trial. Menopause 2013;20(8):840–4. doi: 10.1097/gme.0b013e3182804353
21. Myung SK, Ju W, Choi HJ, Kim SC, Korean Meta-Analysis (KORMA) Study Group. Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis. BJOG 2009;116(13):1697–705. doi: 10.1111/j.1471-0528.2009.02322.x
22. Zhang GQ, Chen JL, Liu Q, Zhang Y, Zeng H, Zhao Y. Soy intake is associated with lower endometrial cancer risk: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2015;94(50):e2281. doi: 10.1097/MD.0000000000002281
23. Zhong XS, Ge J, Chen SW, Xiong YQ, Ma SJ, Chen Q. Association between dietary isoflavones in soy and legumes and endometrial cancer: a systematic review and meta-analysis. J Acad Nutr Diet 2018;118(4), 637–51. doi: 10.1016/j.jand.2016.09.036
24. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. J Natl Cancer Inst 2003;95(15):1158–64. doi: 10.1093/jnci/djg015
25. Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson G.L, Beresford SAA, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2007;99(20):1534–43. doi: 10.1093/jnci/djm159
26. Wu QJ, Gong TT, Wang YZ. Dietary fatty acids intake and endometrial cancer risk: a dose-response meta-analysis of epidemiological studies. Oncotarget 2015;6(34):36081–97. doi: 10.18632/oncotarget.5555
27. Zhao J, Lyu C, Gao J, Du L, Shan B, Zhang H, et al. Dietary fat intake and endometrial cancer risk: a dose response meta-analysis. Medicine (Baltimore) 2016;95(27):e4121. doi: 10.1097/MD.0000000000004121
28. Terry P, Wolk A, Vainio H, Weiderpass E. Fatty fish consumption lowers the risk of endometrial cancer: a nationwide case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 2002;11(1):143–45.
29. Hou R, Yao SS, Liu J, Wang LL, Wu L, Jiang L. Dietary n-3 polyunsaturated fatty acids, fish consumption, and endometrial cancer risk: a meta-analysis of epidemiological studies. Oncotarget 2017;8(53):91684–93. doi: 10.18632/oncotarget.18295.

30. Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, et al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol 2009;200(2):130–5. doi: 10.1016/j.ajog.2008.10.032
31. Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. Int J Cancer 2012;131(7):1700–10. doi: 10.1002/ijc.27408
32. Lafranconi A, Micek A, Galvano F, Rossetti S, del Pup L, Berretta M, et al. Coffee decreases the risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Nutrients 2017;9(11):1223. doi: 10.3390/nu9111223
33. Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep 2015;5:13410. doi: 10.1038/srep13410
34. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: a systematic literature review and meta-analysis. Nutr Cancer 2007;58(1):6–21. doi: 10.1080/01635580701307929
35. Chen K, Zhao Q, Li X, Zhao J, Li P, Lin S, et al. Dietary fiber intake and endometrial cancer risk: a systematic review and meta-analysis. Nutrients 2018;10(7):945. doi: 10.3390/nu10070945
36. Filomeno M, Bosetti C, Bidoli E, Levi F, Serraino D, Montella M, et al. Mediterranean diet and risk of endometrial cancer: a pooled analysis of three Italian case-control studies. Br J Cancer 2015;112(11):1816–21. doi: 10.1038/bjc.2015.153
37. Si CJ, Shu L, Zheng PF, Zhang XY, Yu XL, Gao W, et al. Dietary patterns and endometrial cancer: a meta-analysis. Eur J Cancer Prev 2017;26(4):336–45. doi: 10.1097/CEJ.0000000000000266
38. Alizadeh S, Djafarian K, Alizadeh M, Shab-Bidar S. The relation of healthy and western dietary patterns to the risk of endometrial and ovarian cancers: a systematic review and meta-analysis. Int J Vitam Nutr Res 2020;90(3–4):365–75. doi: 10.1024/0300-9831/a00051
39. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med 2008;121(6):501–8.e3. doi: 10.1016/j.amjmed.2008.01.044
40. Polesel J, Serraino D, Zucchetto A, Lucenteforte E, Dal Maso L, Levi F, et al. Cigarette smoking and endometrial cancer risk: the modifying effect of obesity. Eur J Cancer Prev 2009;18(6):476-4–81. doi: 10.1097/CEJ.0b013e32832f9bc4
41. Turati F, Gallus S, Tavani A, Tramacere I, Polesel J, Talamini R, et al. Alcohol and endometrial cancer risk: a case-control study and a meta-analysis. Cancer Causes Control 2010;21(8):1285–96. doi: 10.1007/s10552-010-9556-z
42. Sun Q, Xu L, Zhou B, Wang Y, Jing Y, Wang B. Alcohol consumption and the risk of endometrial cancer: a meta-analysis. Asia Pac J Clin Nutr 2011;20(1):125–33.
43. Zhou Q, Guo P, Li H, Chen XD. Does alcohol consumption modify the risk of endometrial cancer? A dose-response meta-analysis of prospective studies. Arch Gynecol Obstet 2017;295(2):467–79. doi: 10.1007/s00404-016-4263-y
44. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol 2015;30(5):397–412. doi: 10.1007/s10654-015-0017-6
45. Hidayat K, Zhou HJ, Shi BM. Influence of physical activity at a young age and lifetime physical activity on the risks of 3 obesity-related cancers: systematic review and meta-analysis of observational studies. Nutr Rev 2020;78(1):1–18. doi: 10.1093/nutrit/nuz024
46. Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 2015;5:14051. doi: 10.1038/srep14051
47. Wu Y, Sun W, Liu H, Zhang D. Age at menopause and risk of developing endometrial cancer: a meta-analysis. Biomed Res Int 2019;2019:8584130. doi: 10.1155/2019/8584130

48. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, Dai Q, et al. Menstrual and reproductive factors and endometrial cancer risk: results from a population-based case-control study in urban Shanghai. *Int J Cancer* 2004;108(4):613–9. doi: 10.1002/ijc.11598
49. Mogren I, Stenlund H, Högberg U. Long-term impact of reproductive factors on the risk of cervical, endometrial, ovarian and breast cancer. Acta Oncol 2001;40(7):849–54. doi: 10.1080/02841860152703481
50. Setiawan VW, Pike MC, Karageorgi S, Deming SL, Anderson K, Bernstein L, et al. Age at last birth in relation to risk of endometrial cancer: pooled analysis in the Epidemiology of Endometrial Cancer Consortium. Am J Epidemiol 2012;176(4):269–78. doi: 10.1093/aje/kws129
51. Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2008;15(2):485–97. doi: 10.1677/ERC-07-0064
52. Michels KA, Brinton LA, Wentzensen N, Pan K, Chen C, Anderson GL, et al. Postmenopausal androgen metabolism and endometrial cancer risk in the Women's Health Initiative Observational Study. JNCI Cancer Spectr 2019;3(3):pkz029. doi: 10.1093/jncics/pkz029
53. Clendenen TV, Hertzmark K, Koenig KL, Lundin E, Rinaldi S, Johnson T, et al. Premenopausal circulating androgens and risk of endometrial cancer: results of a prospective study. *Horm Cancer* 2016;7(3):178–87. doi: 10.1007/s12672-016-0258-1
54. Miller N, Bédard YC, Cooter NB, Shaul DL. Histological changes in the genital tract in transsexual women following androgen therapy. Histopathology 1986;10(7):661–69. doi: 10.1111/j.1365-2559.1986.tb02520.x
55. Gooren LJ. Management of female-to-male transgender persons: medical and surgical management, life expectancy. Curr Opin Endocrinol Diabetes Obes 2014;21(3):233–8. doi: 10.1097/MED.0000000000000064
56. Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008;359(19):2005–17. doi: 10.1056/NEJMoa0707302
57. Ignatov A, Ortmann O. Endocrine risk factors of endometrial cancer: polycystic ovary syndrome, oral contraceptives, infertility, tamoxifen. Cancers (Basel) 2020;12(7):1766. doi: 10.3390/cancers12071766
58. Practice Committee of the American Society for Reproductive Medicine. Fertility drugs and cancer: a guideline. Fertil Steril 2016;106(7):1617–26. doi: 10.1016/j.fertnstert.2016.08.035
59. Venn A, Jones P, Quinn M, Healy D. Characteristics of ovarian and uterine cancers in a cohort of in vitro fertilization patients. Gynecol Oncol 2001;82(1):64–8. doi: 10.1006/gyno.2001.6209
60. Sjogren LL, Morch LS, Lokkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. Maturitas 2016;91:25–35. doi: 10.1016/j.maturitas.2016.05.013
61. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995;85(2):304–13. doi: 10.1016/0029-7844(94)00383-O
62. Beard CM, Hartmann LC, Keeney GL, Crowson CS, Malkasian GD, O'Brien PC, et al. Endometrial cancer in Olmsted County, MN: trends in incidence, risk factors and survival. Ann Epidemiol 2000;10(2):97–105. doi: 10.1016/s1047-2797(99)00039-3
63. Constantine GD, Kessler G, Graham S, Goldstein SR. Increased incidence of endometrial cancer following the Women's Health Initiative: an assessment of risk factors. *J Womens Health (Larchmt)* 2019;28(2):237–43. doi: 10.1089/jwh.2018.6956
64. Mahavni V, Sood AK. Hormone replacement therapy and cancer risk. Curr Opin Oncol 2001;13(5):384–9. doi: 10.1097/00001622-200109000-00012
65. Tempfer CB, Hilal Z, Kern P, Juhasz-Boess I, Rezniczek GA. Menopausal hormone therapy and risk of endometrial cancer: a systematic review. Cancers (Basel) 2020;12(8):2195. doi: 10.3390/cancers12082195

66. Samsioe G, Boschitsch E, Concin H, De Geyter C, Ehrenborg A, Heikkinen J, et al. Endometrial safety, overall safety and tolerability of transdermal continuous combined hormone replacement therapy over 96 weeks: a randomized open-label study. Climacteric 2006;9(5):368–79. doi: 10.1080/13697130600953661
67. Fournier A, Dossus L, Mesrine S, Vilier A, Boutron-Ruault MC, Clavel-Chapelon F, et al. Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992–2008. Am J Epidemiol 2014;180(5):508–17. doi: 10.1093/aje/kwu146
68. Pinkerton JV, Kaunitz AM, Manson JE. Vaginal estrogen in the treatment of genitourinary syndrome of menopause and risk of endometrial cancer: an assessment of recent studies provides reassurance. Menopause 2017;24(12):1329–32. doi: 10.1097/GME.0000000000000996
69. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19(12):3119–30. doi: 10.1158/1055-9965.EPI-10-0832
70. Fleming CA, Heneghan HM, O'Brien D, McCartan DP, McDermott EW, Prichard RS. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. Br J Surg 2018;105(9):1098–106. doi: 10.1002/bjs.10899
71. Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, Sestak I, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer Treat Rev 2012;38(4):318–28. doi: 10.1016/j.ctrv.2011.06.009
72. Col NF, Goldberg RJ, Orr RK, Erban JK, Fortin JM, Chlebowski RT. Survival impact of tamoxifen use for breast cancer risk reduction: projections from a patient-specific Markov model. Med Decis Making 2002;22(5):386–93. doi: 10.1177/027298902236942
73. Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol 2002;20(11):2758–60. doi: 10.1200/JCO.2002.20.11.2758
74. Curtis RE, Freedman DM, Sherman ME, Fraumeni JF Jr. Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. J Natl Cancer Inst 2004;96(1):70–4. doi: 10.1093/jnci/djh007
75. Gottlieb S. Tamoxifen may increase risk of uterine sarcoma. BMJ 2002;325(7354):7. doi: 10.1136/bmj.325.7354.7/a
76. Meyer LA, Westin SN, Lu KH, Milam MR. Genetic polymorphisms and endometrial cancer risk. Expert Rev Anticancer Ther 2008;8(7):1159–67. doi: 10.1586/14737140.8.7.1159
77. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Uterine neoplasms Version 1.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Retrieved December 7, 2020.
78. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Colorectal. Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Retrieved December 3, 2020.
79. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Retrieved December 3, 2020.
80. Coletta AM, Peterson SK, Gatus LA, Krause KJ, Schembre SM, Gilchrist SC, et al. Energy balance related lifestyle factors and risk of endometrial and colorectal cancer among individuals with Lynch syndrome: a systematic review. Fam Cancer 2019;18(4):399–420. doi: 10.1007/s10689-019-00135-7
81. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Couns 2009;18(1):13–27. doi: 10.1007/s10897-008-9187-7
82. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology 2000;119:1447–53. doi: 10.1053/gast.2000.20228

83. Biron-Shental T, Drucker L, Altaras M, Bernheim J, Fishman A. High incidence of BRCA1-2 germline mutations, previous breast cancer and familial cancer history in Jewish patients with uterine serous papillary carcinoma. Eur J Surg Oncol 2006;32(10):1097–100. doi: 10.1016/j.ejso.2006.03.032
84. Levine DA, Lin O, Barakat RR, Robson ME, McDermott D, Cohen L, et al. Risk of endometrial carcinoma associated with BRCA mutation. Gynecol Oncol 2001;80(3):395–8. doi: 10.1006/gyno.2000.6082
85. Francis JH, Kleinerman RA, Seddon JM, Abramson DH. Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. Gynecol Oncol 2012;124(2):254–9. doi: 10.1016/j.ygyno.2011.10.019
86. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol 2015;125(1):89-98. doi: 10.1097/AOG.0000000000000563
87. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol 2014;135(1):163–71. doi: 10.1016/j.ygyno.2014.07.095
88. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007;50(7):1365–74. doi: 10.1007/s00125-007-0681-5
89. Saed L, Varse F, Baradaran HR, Moradi Y, Khateri S, Friberg E, et al. The effect of diabetes on the risk of endometrial cancer: an updated a systematic review and meta-analysis. BMC Cancer 2019;19(1):527. doi: 10.1186/s12885-019-5748-4
90. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR. Insulin resistance and endometrial cancer risk: a systematic review and meta-analysis. Eur J Cancer 2015;51(18):2747–58. doi: 10.1016/j.ejca.2015.08.031
91. Aune D, Sen A, Vatten LJ. Corrigendum: Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. Sci Rep 2018;8:46961. doi: 10.1038/srep46961
92. Pergialiotis V, Prodromidou A, Siotos C, Frountzas M, Perrea D, Vlachos GD. Systemic hypertension and diabetes mellitus as predictors of malignancy among women with endometrial polyps: a meta-analysis of observational studies. Menopause 2016;23(6):691–7. doi: 10.1097/GME.0000000000000602
93. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Giugliano D. Metabolic syndrome and endometrial cancer: a meta-analysis. Endocrine 2014;45(1):28–36. doi: 10.1007/s12020-013-9973-3
94. Adambekov S, Yi Y, Fabio A, Miljkovic I, Edwards RP, Lopa S, et al. Metabolic syndrome in endometrial cancer patients: systematic review. Metab Syndr Relat Disord 2019;17(5):241–9. doi: 10.1089/met.2018.0106
95. Haoula Z, Salman M, Atiomo W. Evaluating the association between endometrial cancer and polycystic ovary syndrome. Hum Reprod 2012;27(5):1327–31. doi: 10.1093/humrep/des042
96. Kumar S, Shah JP, Bryant CS, Seward S, Ali-Fehmi R, Morris RT, et al. Radiation-associated endometrial cancer. Obstet Gynecol 2009;113(2 Pt 1):319–25. doi: 10.1097/AOG.0b013e3181954c5b
97. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. Obstet Gynecol 2010;116(5):1197–1205. doi: 10.1097/AOG.0b013e3181f74864
98. Uglietti A, Buggio L, Farella M, Chiaffarino F, Dridi D, Vercellini P, et al. The risk of malignancy in uterine polyps: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2019;237:48–56. doi: 10.1016/j.ejogrb.2019.04.009
99. Sasaki LMP, Andrade KRC, Figueiredo ACMG, Wanderley MdS, Pereira MG. Factors associated with malignancy in hysteroscopically resected endometrial polyps: a systematic review and meta-analysis. J Minim Invasive Gynecol 2018;25(5):777–85. doi: 10.1016/j.jmig.2018.02.004
100. Alcazar JL, Bonilla L, Marucco J, Padilla AI, Chacon E, Manzour N, et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥11 mm: a systematic review and meta-analysis. J Clin Ultrasound 2018;46(9):565–70. doi: 10.1002/jcu.22631

101. Chan LY, Lau TK, Wong SF, Yuen PM. Pyometra. What is its clinical significance? J Reprod Med 2001;46(11):952–6.
102. Raffone A, Travaglino A, Saccone G, Insabato L, Mollo A, de Placido G, et al. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet 2019;299(5):1233–42. doi: 10.1007/s00404-019-05103-1
103. Doherty MT, Sanni OB, Coleman HG, Cardwell CR, McCluggage WG, Quinn D, et al. Concurrent and future risk of endometrial cancer in women with endometrial hyperplasia: a systematic review and meta-analysis. PLoS One 2020;15(4):e0232231. doi: 10.1371/journal.pone.0232231
104. Travaglino A, Raffone A, Saccone G, D'Alessandro P, Arduino B, de Placido G, et al. Significant risk of occult cancer in complex non-atypical endometrial hyperplasia. Arch Gynecol Obstet 2019;300(5):1147–54. doi: 10.1007/s00404-019-05299-2
105. Li J, Liu R, Tang S, Feng F, Liu C, Wang L, et al. Impact of endometriosis on risk of ovarian, endometrial and cervical cancers: a meta-analysis. Arch Gynecol Obstet 2019;299(1):35–46. doi: 10.1007/s00404-018-4968-1
106. Yuan H, Zhang S. Malignant transformation of adenomyosis: literature review and meta-analysis. Arch Gynecol Obstet 2019;299(1):47–53. doi: 10.1007/s00404-018-4991-2
107. Odejinmi F, Aref-Adib M, Liou N, Sideris M, Mallick R. Rethinking the issue of power morcellation of uterine fibroids: Is morcellation the real problem or is this another symptom of disparity in healthcare provision? In Vivo 2019;33(5):1393–401. doi: 10.21873/invivo.11616
108. Fadare O. Is there an association between type II endometrial carcinomas and breast cancers? A critical appraisal. Womens Health (Lond Engl) 2013;9(4):315–7. doi: 10.2217/whe.13.27
109. Chan JK, Manuel MR, Cheung MK, Osann K, Husain A, Teng NN, et al. Breast cancer followed by corpus cancer: Is there a higher risk for aggressive histologic subtypes? Gynecol Oncol 2006;102(3):508–12. doi: 10.1016/j.ygyno.2006.01.014

Uterine Cancer Literature Review
Appendix 4. Prevention and Risk Reduction for Uterine Cancer

Primary Reviewer: Dana M. Scott, MD, FACOG
Secondary Reviewer: Kathryn Huber-Keener, MD, PhD

INTRODUCTION

This document summarizes prevention of uterine cancer. The following questions were addressed:

1. **Which high-risk patient groups benefit from risk-reducing strategies?**
2. **What strategies are recommended to reduce risk of uterine cancer in these groups (attempt to quantify magnitude of risk reduction)?**

The PICO format was used to direct the literature search:

P (Patient, problem, or population): Adult with a uterus (ie, women and transgender men)
I (Intervention): Presence or absence of certain preventive strategies (lifestyle modifications, progestin administration, hysterectomy, metformin administration, or chemoprevention)
C (Comparison, control, or comparator): One preventive strategy versus another preventive strategy or regular care or no strategy
O (Outcome[s]): Relative risk (RR) or odds ratio (OR) of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma) or incidence of uterine cancer

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases using a search strategy based on the PICO criteria. All identified articles were categorized by level of evidence. Relevant guidelines 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 Society of Gynecologic Oncology, and the U.S. Preventive Services Task Force were also identified. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of selected articles. The bibliographies of included articles were reviewed to identify other relevant works not identified by the primary search.

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

In an effort to streamline resources, systematic reviews and meta-analyses were prioritized. The individual source studies included in such articles were not included separately 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 search identified 12 guidelines from major professional societies and health services, of which 9 were excluded. Three additional relevant guidelines were included after reviewing references of included articles. One of the included NCCN guidelines was updated during creation of this manuscript, and the most up-to-date version was included. In total, six guidelines were included in this review.

The literature search identified 442 results. There were 75 level I studies (47 RCTs and 28 systematic reviews and meta-analyses), 164 level II studies, and 5 level III studies. There were 71 studies that did not meet criteria for level III or higher, and 63 additional studies were identified through PubMed that were not indexed in Ovid. Reviewers removed 29 duplicates, and 317 articles were excluded after review of the title and abstract. An additional 62 articles were excluded after full manuscript review. Another 8 articles were identified after reviewing references of the included articles.

Summary of Data

Which high-risk patient groups benefit from risk-reducing strategies?

Endometrial cancer is the most common gynecologic cancer among women in the United States.[1] There are multiple populations at particularly elevated risk, including those with a genetic predisposition for uterine cancer, women with obesity, women with unopposed estrogen, and women taking tamoxifen.[2] Despite these known risk factors, few clear guidelines describe the target populations for risk-reducing strategies.

Women with Lynch syndrome have a significantly elevated lifetime risk of endometrial cancer of up to 60%.[3] There is evidence of benefit from both risk-reducing surgery and chemoprevention in this population.[3] Cowden syndrome (also called *PTEN* hamartoma tumor syndrome) may be associated with a 5–10% lifetime risk of endometrial cancer, though the exact risk estimate is undetermined.[4] Carriers of a *BRCA 1* mutation may have a small increased risk of serous uterine cancer.[4] Peutz-Jegher syndrome (pathogenic *STK11* variants) is associated with a 9% lifetime risk of uterine cancer.[3] There are few data supporting risk-reducing strategies in these populations.

Obesity is a known risk factor for endometrial cancer, but there is a paucity of data on intentional weight loss as a preventive strategy.[1,2,5] Nevertheless, this population is a frequent target for risk reduction. A risk prediction model has been proposed to help identify those who would benefit most from prevention.[6] This model calculates a risk score based on a patient's anthropometric measurements, reproductive history, insulin resistance, and genetic and familial factors, and risk-reduction strategies are suggested based on the score. If such a model were validated, appropriate risk stratification and identification of effective risk reduction strategies may improve.[6] (Appendix 3, Uterine Cancer Risk Factors, addresses genetic predisposition and other risk factors in more depth.)

What strategies are recommended to reduce risk of uterine cancer in these groups (attempt to quantify magnitude of risk reduction)?

Lifestyle Modifications

Given the association of obesity with endometrial cancer, a multitude of studies have targeted lifestyle modifications as a potential preventive measure. Common dietary factors studied include animal-based versus

plant-based diets, dietary fiber intake, glycemic index, and isoflavonic phytoestrogens. A 2008 systematic review evaluating six systematic reviews and meta-analyses of lifestyle modifications available at the time noted conflicting results of common dietary and activity interventions.[7] However, there does appear to be a greater likelihood of endometrial cancer risk reduction with higher adherence to cancer prevention guidelines for healthy lifestyle.[8]

High-fat diets, particularly those containing high levels of animal-based proteins, are potentially associated with an increased risk of endometrial cancer. Data primarily come from case-control studies, with few prospective studies identified in the literature search. Elevated risk of endometrial cancer is seen in those with high consumption compared with low consumption of meat (OR: 1.26, 95% confidence interval [CI]: 1.03–1.54), particularly red meat (OR: 1.51, 95% CI: 1.19–1.93).[7,9] A population-based case-control study in China noted similar effects of dietary animal-derived iron intake (adjusted OR: 1.9, 95% CI: 1.4–2.7), particularly in women who were postmenopausal, overweight, or obese.[10] Conversely, high intake of fruits and vegetables appears to have a protective effect (fruits: OR: 0.97, 95% CI: 0.92–1.02; vegetables: OR: 0.71, 95% CI: 0.55–0.91; cruciferous vegetables: OR: 0.85, 95% CI: 0.74–0.97).[7,11] However, more recent data from the large, prospective, population-based National Institutes of Health-AARP Diet and Health cohort study did not show a protective effect from fruit and vegetable intake.[12] Risk was unaffected even when controlling for other risk factors and stratifying by amount of fruit and vegetable intake. Similarly, the Women's Health Initiative Dietary Modification RCT did not show any difference in endometrial cancer risk among those assigned to a diet of reduced total fat intake and increased intake of vegetables, fruits, and grains.[13]

Rather than focus on intake of specific foods, a large, retrospective, case-control study in Italy evaluated the effect of an anti-inflammatory diet on endometrial cancer risk. Pro-inflammatory diets contain higher amounts of saturated fats, carbohydrates, and protein, while anti-inflammatory diets contain more polyunsaturated fats, flavonoids, and other micronutrients. The study found an increased risk of endometrial cancer among women with the most pro-inflammatory diet compared with those with the most anti-inflammatory diet (OR: 1.46, 95% CI: 1.02–2.11).[14]

Isoflavones are phytoestrogens found in high concentration in soy and legumes that act similarly to selective estrogen receptor modulators.[7] It has been suggested that isoflavones may decrease endometrial cancer risk. One systematic review reported a decreased risk of endometrial cancer among women without obesity who had high consumption of isoflavones compared with women with obesity and lower consumption.[7] The most recent meta-analysis of three prospective cohorts and 10 population-based case-control studies also suggested a weak inverse correlation between isoflavone consumption and endometrial cancer (OR: 0.81, 95% CI: 0.74–0.89).[15] Although the inverse correlation remained in subgroup analysis of case-control studies (OR: 0.81, 95% CI: 0.73–0.90), there was no association in subgroup analysis of the prospective cohorts (OR: 0.81, 95% CI: 0.66–1.00).[15] One double-blind RCT involving isoflavones was identified, and it showed no significant change in endometrial thickness, endometrial hyperplasia, or endometrial cancer among postmenopausal women randomized to consume a soy protein supplement daily for 3 years when compared with those who consumed a placebo.[16] There was a slight trend towards an inverse correlation with endometrial thickness.

Dietary fiber may be inversely associated with endometrial cancer. A dose-response meta-analysis of one case-cohort and nine case-control studies noted a risk estimate of 0.82 (95% CI: 0.75–0.90) per 5g/1,000 kcal of dietary fiber intake.[17] No association was seen in the only prospective study included in the analysis. A large,

population-based, prospective cohort study evaluating dietary energy density, glycemic index, and glycemic load found no association with endometrial cancer risk.[18]

Multiple retrospective studies have suggested a significant reduction of endometrial cancer risk with increased physical activity.[7] This interaction is biologically plausible, in that physical activity reduces serum estradiol by increasing sex hormone-binding globulin. Physical activity can also prevent weight gain and improve hyperinsulinemia, both of which are associated with endometrial cancer. Multiple prospective studies have confirmed the protective role of physical activity. In a meta-analysis of eight prospective cohort studies, women with the most recreational physical activity had a significantly decreased risk of endometrial cancer (pooled RR: 0.73, 95% CI: 0.58–0.93) compared with those who had the least activity.[19] This association persisted even when adjusting for body mass index (pooled RR: 0.78, 95% CI: 0.63–0.95).[19] A more recent meta-analysis confirmed these results (highest vs lowest lifetime physical activity: RR: 0.77, 95% CI: 0.67–0.88).[20] Importantly, prolonged sedentary behavior is associated with an increased risk of endometrial cancer (sitting ≥ 9 hours vs < 3 hours per day: RR: 1.45, 95% CI: 1.10–1.92).[19] This negative effect of sedentary behavior is even seen among women who participate in recreational physical activity, though to a lesser degree.

Bariatric Surgery

Bariatric surgery is an effective weight-loss intervention for patients with obesity who do not respond to medical treatment, and it is associated with a reduction in cardiovascular disease, myocardial infarction, stroke, and death.[21] A meta-analysis of three large, retrospective cohort studies revealed a significantly decreased risk of endometrial cancer after bariatric surgery (pooled RR: 0.43, 95% CI: 0.26–0.72).[21] Two prospective cohorts showed a reduction in circulating endometrial cancer biomarkers (hemoglobin A1c, homeostatic model assessment for insulin resistance, interleukin-1Rα, C-reactive protein, and interleukin-6) and an increase in reproductive biomarkers (sex hormone-binding globulin, luteinizing hormone, and follicle stimulating hormone) after bariatric surgery.[22,23] One prospective cohort also noted improvements on endometrial biopsy after bariatric surgery, including decreased *Ki-67* (biomarker of endometrial proliferation), *pAKT* (oncogenic signaling), and estrogen and progesterone receptor status.[22] While cancer rate was not evaluated directly, these two prospective studies support the protective effect of bariatric surgery on endometrial cancer risk from a biologic standpoint.

Progestins

The levonorgestrel intrauterine system (LNG-IUS) is used in fertility-sparing treatment for select cases of endometrial hyperplasia and malignancy and is therefore of interest as a risk-reducing agent in women at high risk.[24,25] A systematic review and meta-analysis of nine case-control studies and one cohort study noted a significant reduction in endometrial cancer among ever-users of an intrauterine device (IUD; adjusted, pooled OR: 0.6, 95% CI: 0.4–0.7).[26] Most studies did not report the IUD type, though it is likely that predominantly nonhormonal IUDs were included based on the study dates and locations. The proposed mechanism for the risk reduction with nonhormonal IUDs is an induced sterile inflammatory response within the uterine cavity, resulting in increased immune cells.[26] The Norwegian Women and Cancer Study, a large, prospective, population-based cohort, demonstrated a profound reduction in endometrial cancer risk among those who used the LNG-IUS. Compared with never-users, ever-users of the LNG-IUS had significantly lower risk of endometrial cancer (RR: 0.22, 95% CI: 0.13–0.40), even when adjusted for age, body mass index, physical activity, and other risk factors (RR: 0.34, 95% CI: 0.18–0.65).[27]

No studies evaluated the LNG-IUS as a risk-reducing agent in women with obesity or a genetic predisposition to uterine cancer. A cost-effectiveness analysis of the LNG-IUS for endometrial cancer prevention in women with obesity used modified Markov modeling and assumed risk reductions based on available literature.[28] It determined that the LNG-IUS would be a potentially cost-effective preventive agent if the risk reduction lasts after removal, if risk reduction is 68% or higher, or if the device cost decreases.[28] A recent Cochrane review of four RCTs found the LNG-IUS reduced the risk of endometrial polyps and endometrial hyperplasia among women taking tamoxifen for adjuvant breast cancer treatment (OR: 0.22, 95% CI: 0.13–0.39; OR: 0.13, 95% CI: 0.03–0.67, respectively).[29] However, incidence of endometrial cancer was low among all studies (six reported cases), and none of the studies were powered to evaluate endometrial cancer risk.[29] Among high-risk women with Lynch syndrome, a 3-month course of depot medroxyprogesterone acetate decreased endometrial proliferation based on measurements of *Ki-67* expression and endometrial histology, though rates of endometrial cancer were not evaluated.[30]

Oral Contraceptives

Use of combined oral contraceptives (COCs) is associated with a decreased risk of endometrial cancer.[25,31] A 2010 systematic review of 15 case-control and cohort studies showed a significant reduction in endometrial cancer risk with COC use across most studies.[32] The protective effect increased with longer duration of use and persisted for more than 10 years after discontinuation.[32] A 2013 meta-analysis of three case-control and four cohort studies also showed a significant reduction in endometrial cancer with ever-use of COCs (OR: 0.57, 95% CI: 0.43–0.77), but significant heterogeneity was noted.[33] More recently, the Danish Sex Hormone Register Study, a large, retrospective, population-based cohort, found a significant reduction in endometrial cancer among current or recent users of COCs (RR: 0.57, 95% CI: 0.43–0.75).[34] The magnitude of risk reduction increased with increasing duration of use, and the reduction persisted for more than 10 years after last use (RR: 0.57, 95% CI: 0.36–0.89).[34] A prospective U.S. population-based cohort also noted endometrial cancer risk reduction among COC users compared to never-users, and the risk reduction was higher among long-term users (1–4 years: hazard ratio [HR]: 0.79, 95% CI: 0.70–0.90; 5–9 years: HR: 0.84, 95% CI: 0.73–0.97; 10+ years: HR: 0.66, 95% CI: 0.56–0.78).[35] Similar results were noted specifically among Black U.S. women, with endometrial cancer risk inversely related to duration of use (1–4 years: incidence rate ratio [IRR]: 0.98, 95% CI: 0.71–1.35; 5–9 years: IRR: 0.74, 95% CI: 0.48–1.13; 10+ years: IRR: 0.45, 95% CI: 0.27–0.74).[36] Use of COCs for 5 or more years before first full-term pregnancy is associated with decreased endometrial cancer risk, even if this was a woman's only COC use.[37]

Among high-risk women with Lynch syndrome, retrospective data suggest a decreased risk of endometrial cancer with hormonal contraception use (HR: 0.39, 95% CI: 0.23–0.64).[3] Short-term COC use significantly decreased endometrial proliferation, based on a decrease in endometrial *Ki-67* expression and histologic examination showing inactive or secretory glands on endometrial biopsy.[30] While this result suggests a mechanism for decreased risk, endometrial cancer rates were not specifically evaluated.

Tubal Ligation

A population-based Danish cohort study of 65,232 women showed a decreased risk of endometrial cancer among women who had undergone tubal sterilization (standardized incidence ratio: 0.66, 95% CI: 0.5–1.0).[38] There was a nonsignificant trend toward risk reduction with long-term follow-up. A Swedish population-based cohort study of 5,385,186 women similarly showed a decreased risk of endometrial cancer after tubal sterilization (HR: 0.73, 95% CI: 0.65–0.83) that persisted for at least 10 years.[39] Additionally, decreased endometrial cancer mortality was seen in women who developed endometrial cancer after tubal sterilization.

The mechanism of risk reduction is unclear, and the literature search did not identify any specific recommendations for tubal sterilization as a preventive strategy for endometrial cancer.

Hysterectomy

Prophylactic hysterectomy is a definitive risk reduction option for women with Lynch syndrome who have completed childbearing, although recommendations are predominantly based on expert opinion.[2,3,25,31,40] A retrospective multicenter study of women with Lynch syndrome found a significant reduction in endometrial cancer incidence among those who had undergone hysterectomy after a follow-up of 7 years (33% among 210 women without hysterectomy compared with zero among 61 women with hysterectomy).[41] Surgical morbidity was low. Prophylactic hysterectomy has not been associated with decreased endometrial cancer mortality.[3] The NCCN recommends consideration of risk-reducing hysterectomy for Lynch syndrome patients, but it does not describe optimal timing.[3] ACOG recommends discussing risk-reducing hysterectomy when a patient is in the early to mid-40s because of the increased risk of endometrial cancer with increasing age (2–4% risk by age 40, 8–17% risk by age 50).[31] Both guidelines recommend individualizing the timing of hysterectomy based on the patient's reproductive goals, family history, and specific Lynch syndrome gene mutation.[3,31]

The risk of serous-type uterine cancer among *BRCA 1* mutation carriers remains controversial.[4,2,40] A prospective, multicenter cohort of 1,083 *BRCA* mutation carriers undergoing risk-reducing bilateral salpingo-oophorectomy (BSO) without hysterectomy demonstrated an elevated risk of serous or serous-like uterine cancer among *BRCA 1* mutation carriers (4 observed, 0.18 expected; observed-to-expected ratio: 22.2, 95% CI: 6.1–56.9; $p<0.01$).[42] There was no increased risk of endometrioid or sarcoma subtypes. Another prospective multicenter cohort of 438 *BRCA 1* mutation carriers, which controlled for tamoxifen use, did not observe an increased risk of serous uterine cancer (three observed uterine cancer cases [all endometrioid subtype], 1.04 expected; observed-to-expected ratio: 2.87, 95% CI: 0.59–8.43; $P = 0.18$).[43] The NCCN guidelines state that the risks and benefits of concomitant hysterectomy at the time of risk-reducing BSO may be discussed with *BRCA 1* mutation carriers, but further clarification of the magnitude of risk of serous uterine cancer is needed.[4] A modified Markov modeling cost analysis using a 3.5% lifetime risk of serous uterine cancer among *BRCA 1* mutation carriers suggests that hysterectomy at the time of risk-reducing BSO is a cost-effective prophylactic strategy.[44]

The literature search found no data evaluating risk-reducing hysterectomy among women with Cowden syndrome. Because of the elevated risk of endometrial cancer, however, the NCCN and SGO recommend discussion of risks and benefits of hysterectomy on an individualized basis, although it does not indicate a recommended age range for surgery.[2,4] Others suggest discussing hysterectomy before age 50.[40] No recommendations regarding risk-reducing hysterectomy were identified for women with Peutz-Jegher syndrome (pathogenic *STK11* variants).

Metformin

Metformin has been proposed as an endometrial cancer risk-reducing agent because of the association of obesity, polycystic ovary syndrome, and type 2 diabetes mellitus with endometrial cancer. A small prospective study of metformin and lifestyle modifications showed minor improvements in serum biomarkers for endometrial cancer, though the study results were limited by small sample size and short follow-up.[45] A recent meta-analysis of seven studies evaluating endometrial cancer risk did not show an association between metformin use and endometrial cancer (OR: 1.05, 95% CI: 0.82–1.35).[46] A population-based, nested, case-control study also showed no difference in endometrial cancer based on metformin use (OR: 1.5, 95% CI: 0.9–

2.4).[47] Use of multiple diabetes medications was associated with a significantly increased risk of endometrial cancer, suggesting the degree of insulin resistance may drive endometrial cancer risk rather than exposure to a specific diabetes medication.[47]

Aspirin

Aspirin inhibits cyclooxygenase and decreases serum prostaglandin, which may theoretically decrease the risk of endometrial cancer. A systematic review and meta-analysis of 13 studies showed a decreased risk of endometrial cancer with aspirin use (RR: 0.93, 95% CI: 0.88–0.99).[48] In subgroup analysis, this reduction was seen only in women with obesity (pooled RR: 0.83, 95% CI: 0.69–0.99) and for type I endometrial cancer (pooled RR: 0.89, 95% CI: 0.82–0.96).[48]

Bisphosphonates

Bisphosphonates have been proposed to have an antitumor effect based on experimental studies and have been associated with a reduced risk of breast cancer. Given that endometrial cancer is also somewhat hormonally mediated, a potential impact on endometrial cancer has been suggested. A recent meta-analysis of seven studies noted a reduction in endometrial cancer risk among women who had ever used bisphosphonates compared with never-users (RR: 0.73, 95% CI: 0.58–0.93).[49] Risk reduction was more pronounced among postmenopausal women (RR: 0.52, 95% CI: 0.34–0.93).[49] Longer duration of use increased the risk reduction, and no risk reduction was seen in women using bisphosphonates for less than 1 year.[49]

DISCUSSION

Numerous studies have evaluated potential risk reduction strategies for uterine cancer. A strength of this literature review is the large number of high-level studies available, including systematic reviews and meta-analyses for most interventions. While there were many retrospective studies supporting the efficacy of potential interventions, few prospective studies were identified. Many of the interventions, particularly lifestyle modifications, are vague and inconsistently defined across studies. Additionally, the potential for confounding variables is present in many of the studies. Many studies looked at risk reduction in relation to obesity, but few studies included specifically addressed risk reduction in other high-risk populations, such as those with Lynch syndrome and other genetic predispositions. Finally, most of the studies addressed endometrial cancer specifically, with very few studies addressing reduction of other types of uterine cancer.

Research Gaps

- Many of the lifestyle modifications are not clearly defined across studies. Further clarification and definition of specific lifestyle modifications would improve the ability to study outcomes and counsel patients.
- While progestins and COCs have been associated with decreased risk of endometrial cancer overall, further research is necessary to demonstrate a similar effect in patients with Lynch syndrome.
- Further research investigating the ideal timing of risk-reducing hysterectomy in Lynch syndrome patients is necessary.
- The literature search primarily revealed information about prevention of endometrial cancer, specifically. Future studies should evaluate prevention of other types of uterine cancer as well.

Summary

The findings are summarized here by evidence level.

Level I Evidence: RCTs, Systematic Reviews, and Meta-Analyses

- Consumption of meat, particularly red meat, is associated with increased endometrial cancer risk in retrospective studies.
- Data are controversial regarding the effect of fruit and vegetable intake on endometrial cancer risk. Retrospective studies suggest an inverse correlation, but a prospective cohort and an RCT did not confirm the relationship.
- High consumption of isoflavones is associated with small decreased endometrial cancer risk in retrospective studies.
- Dietary fiber intake may be inversely associated with endometrial cancer. There seems to be a dose-response effect in retrospective studies.
- Physical activity is associated with a significantly decreased risk of endometrial cancer.
- Sedentary behavior is associated with an increased risk of endometrial cancer, even among those who participate in recreational physical activity.
- Bariatric surgery is associated with a significant decrease in endometrial cancer risk, endometrial cancer biomarkers, and endometrial proliferation.
- Use of any IUD (inert, copper-bearing, or hormonal) is associated with decreased risk of endometrial cancer.
- Metformin use is not associated with a reduction in endometrial cancer risk.
- Aspirin is associated with a decreased risk of endometrial cancer, particularly in women with obesity and for type I endometrial cancer.
- Bisphosphonate use for 1 year or longer is associated with a reduced risk of endometrial cancer, with a more significant risk reduction among postmenopausal women.

Level II Evidence

- Anti-inflammatory diets are associated with decreased endometrial cancer risk in retrospective studies.
- Use of an LNG-IUS is associated with a significant reduction in endometrial cancer risk.
- Use of COCs is associated with a significant decrease in endometrial cancer risk.
- Use of COCs or depot medroxyprogesterone acetate reduces endometrial proliferation in women with Lynch syndrome.
- Hysterectomy decreases the risk of uterine cancer among Lynch syndrome patients, but is not associated with decreased endometrial cancer mortality.
- Tubal sterilization is associated with a decreased risk of endometrial cancer and improved endometrial cancer mortality.

Level III or Individual Article Evidence

- Risk-reducing hysterectomy should be discussed with Lynch syndrome patients by their early to mid-40s. Timing should be individualized based on family history, reproductive plans, and specific Lynch syndrome gene mutation.
- Data regarding serous uterine cancer risk among *BRCA 1* mutation carriers is controversial, but the risks and benefits of concomitant hysterectomy at the time of risk-reducing BSO may be discussed.
- Risks and benefits of risk-reducing hysterectomy should be discussed with Cowden syndrome patients on an individualized basis.

REFERENCES

Chelmow D, Brooks R, Cavens A, Cavens A, Huber-Keener K Scott DM, et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2022;139.

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

1. PDQ Screening and Prevention Editorial Board. Endometrial cancer prevention (PDQ®): health professional version. Available at https://www.cancer.gov/types/uterine/hp/endometrial-prevention-pdq. Retrieved December 2, 2020.

2. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations. Gynecol Oncol 2021;160(3):817–26. doi: 10.1016/j.ygyno.2020.12.021

3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Colorectal. Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Retrieved December 3, 2020.

4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Retrieved December 3, 2020.

5. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 2003;27(12):1447–52. doi: 10.1038/sj.ijo.0802437

6. Kitson SJ, Evans DG, Crosbie EJ. Identifying high-risk women for endometrial cancer prevention strategies: proposal of an endometrial cancer risk prediction model. Cancer Prev Res (Phila) 2017;10(1):1–13. doi: 10.1158/1940-6207.CAPR-16-0224

7. Linkov F, Edwards R, Balk J, Yurkovetsky Z, Stadterman B, Lokshin A, et al. Endometrial hyperplasia, endometrial cancer and prevention: gaps in existing research of modifiable risk factors. Eur J Cancer 2008;44(12):1632–44. doi: 10.1016/j.ejca.2008.05.001

8. Sun H, Chang Q, Liu YS, Jiang YT, Gong TT, Ma XX, et al. Adherence to cancer prevention guidelines and endometrial cancer risk: evidence from a systematic review and dose-response meta-analysis of prospective studies. Cancer Res Treat 2021;53(1):223–32. doi: 10.4143/crt.2020.546

9. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. Cancer Causes Control, 2007;18(9):967–88. doi: 10.1007/s10552-007-9038-0

10. Kallianpur AR, Lee SA, Xu WH, Zheng W, Gao YT, Cai H, et al. Dietary iron intake and risk of endometrial cancer: a population-based case-control study in Shanghai, China. Nutr Cancer 2010;62(1):40–50. doi: 10.1080/01635580903191544

11. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: a systematic literature review and meta-analysis. Nutr Cancer 2007;58(1):6–21. doi: 10.1080/01635580701307929

12. Kabat GC, Park Y, Hollenbeck AR, Schatzkin A, Rohan TE. Intake of fruits and vegetables, and risk of endometrial cancer in the NIH-AARP Diet and Health Study. Cancer Epidemiol 2010;34(5):568–73. doi: 10.1016/j.canep.2010.06.005

13. Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson G.L, Beresford SAA, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2007;99(20):1534–43. doi: 10.1093/jnci/djm159

14. Shivappa N, Hébert JR, Zucchetto A, Montella M, Serraino D, La Vecchia Cet al. Dietary inflammatory index and endometrial cancer risk in an Italian case-control study. Br J Nutr 2016;115(1):138–46. doi: 10.1017/S0007114515004171

15. Zhong XS, Ge J, Chen SW, Xiong YQ, Ma SJ, Chen Q. Association between dietary isoflavones in soy and legumes and endometrial cancer: a systematic review and meta-analysis. J Acad Nutr Diet 2018;118(4), 637–51. doi: 10.1016/j.jand.2016.09.036

16. Quaas AM, Kono N, Mack WJ, Hodis HN, Felix JC, Paulson RJ, et al. Effect of isoflavone soy protein supplementation on endometrial thickness, hyperplasia, and endometrial cancer risk in postmenopausal women: a randomized controlled trial. Menopause 2013;20(8):840–4. doi: 10.1097/gme.0b013e3182804353

17. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Association between dietary fiber and endometrial cancer: a dose-response meta-analysis. Am J Clin Nutr 2007;86(6):1730–37. doi: 10.1093/ajcn/86.5.1730

18. Hartman TJ, McCullough ML, Hodge JM, Gaudet MM, Wang Y, Gapstur SM. Dietary energy density, glycemic load, glycemic index, and risk for endometrial cancer in the CPS-II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2018;27(1):113–15. doi: 10.1158/1055-9965.EPI-17-0964

19. Moore S.C, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. Br J Cancer 2010;103(7), 933–8. doi: 10.1038/sj.bjc.6605902

20. Hidayat K, Zhou HJ, Shi BM. Influence of physical activity at a young age and lifetime physical activity on the risks of 3 obesity-related cancers: systematic review and meta-analysis of observational studies. Nutr Rev 2020;78(1):1–18. doi: 10.1093/nutrit/nuz024

21. Upala S, Sanguankeo A. Bariatric surgery and risk of postoperative endometrial cancer: a systematic review and meta-analysis. Surg Obes Relat Dis 2015;11(4):949–55. doi: 10.1016/j.soard.2014.09.024

22. MacKintosh ML, Derbyshire AE, McVey RJ, Bolton J, Nickkho-Amiry M, Higgins C.L, et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. Int J Cancer 2019;144(3):641–50. doi: 10.1002/ijc.31913

23. Linkov F, Goughnour SL, Ma T, Xu Z, Edwards RP, Lokshin AE, et al. Changes in inflammatory endometrial cancer risk biomarkers in individuals undergoing surgical weight loss. Gynecol Oncol 2017;147(1):133–38. doi: 10.1016/j.ygyno.2017.07.144

24. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations, part II. Gynecol Oncol 2021;160(3):827–34. doi: 10.1016/j.ygyno.2020.12.024

25. Chen LM, Blank SV, Burton E, Glass K, Penick E, Woodard T. Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine evidence-based review. Fertil Steril 2019;112(6):1034–42. doi: 10.1016/j.fertnstert.2019.07.1349

26. Curtis KM, Marchbanks PA, Peterson HB. Neoplasia with use of intrauterine devices. Contraception 2007;75(6 Suppl):S60–9. doi: 10.1016/j.contraception.2007.01.002

27. Jareid M, Thalabard JC, Aarflot M, Bøvelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer: results from the NOWAC study. Gynecol Oncol 2018;149(1):127–32. doi: 10.1016/j.ygyno.2018.02.006

28. Dottino JA, Hasselblad V, Secord AA, Myers ER, Chino J, Havrilesky LJ. Levonorgestrel intrauterine device as an endometrial cancer prevention strategy in obese women: a cost-effectiveness analysis. Obstet Gynecol 2016;128(4):747–53. doi: 10.1097/AOG.0000000000001616

29. Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database of Syst Rev 2015;2015(12):CD007245. doi: 10.1002/14651858.CD007245.pub3

30. Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, et al. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res 2013;6(8):774–81. doi: 10.1158/1940-6207.CAPR-13-0020

31. American College of Obstetricians and Gynecologists and the Society of Gynecology Oncology. Lynch syndrome. ACOG Practice Bulletin No. 147. Obstet Gynecol 2014;124(5):1042–54. doi: 10.1097/01/AOG/0000456325.50739/72

32. Mueck AO, Seeger H,Rabe T. Hormonal contraception and risk of endometrial cancer: a systematic review. Endocr Relat Cancer 2010;17(4):R263–71. doi: 10.1677/ERC-10-0076

33. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 2013;22(11):1931–43. doi: 10.1158/1055-9965.EPI-13-0298

34. Iversen L, Fielding S, Lidegaard Ø, Hannaford PC. Contemporary hormonal contraception and risk of endometrial cancer in women younger than age 50: a retrospective cohort study of Danish women. Contraception 2020;102(3):152–58. doi: 10.1016/j.contraception.2020.06.008

35. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. JAMA Oncol 2018;4(4):516–21. doi: 10.1001/jamaoncol.2017.4942

36. Sponholtz TR, Palmer JR, Rosenberg LA, Hatch EE, Adams-Campbell LL, Wise LA. Exogenous hormone use and endometrial cancer in U.S. Black women. Cancer Epidemiol Biomarkers Prev 2018;27(5):558–65. doi: 10.1158/1055-9965.EPI-17-0722

37. Cook LS, Dong Y, Round P, Huang X, Magliocco AM, Friedenreich CM. Hormone contraception before the first birth and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 2014;23(2):356–61. doi: 10.1158/1055-9965.EPI-13-0943

38. Kjaer SK, Mellemkjaer L, Brinton LA, Johansen C, Gridley G, Olsen JH. Tubal sterilization and risk of ovarian, endometrial and cervical cancer: a Danish population-based follow-up study of more than 65 000 sterilized women. Inter J Epidemiol 2004;33(3):596–602. doi: 10.1093/ije/dyh046

39. Falconer H, Yin L, Altman D. Association between tubal ligation and endometrial cancer risk: a Swedish population-based cohort study. Int J Cancer 2018;143(1):16–21. doi: 10.1002/ijc.31287

40. Piszczek C, Ma J, Gould CH, Tseng P. Cancer risk-reducing opportunities in gynecologic surgery. J Minim Invasive Gynecol 2018;25(7):1179–93. doi: 10.1016/j.jmig.2017.10.025

41. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354(3):261–9. doi: 10.1056/NEJMoa052627.

42. Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol 2016;2(11):1434–40. doi: 10.1001/jamaoncol.2016.1820

43. Lee YC, Milne RL, Lheureux S, Friedlander M, McLachlan SA, Martin KL, et al. Risk of uterine cancer for BRCA1 and BRCA2 mutation carriers. Eur J Cancer 2017;84:114–20. doi: S0959-8049(17)31112-7

44. Havrilesky LJ, Moss HA, Chino J, Myers ER, Kauff ND. Mortality reduction and cost-effectiveness of performing hysterectomy at the time of risk-reducing salpingo-oophorectomy for prophylaxis against serous/serous-like uterine cancers in BRCA1 mutation carriers. Gynecol Oncol 2017;145(3):549–54. doi: 10.1016/j.ygyno.2017.03.025

45. Yates MS, Coletta AM, Zhang Q, Schmandt RE, Medepalli M, Nebgen D, et al. Prospective randomized biomarker study of metformin and lifestyle intervention for prevention in obese women at increased risk for endometrial cancer. Cancer Prev Res (Phila) 2018;11(8):477–90. doi: 10.1158/1940-6207.CAPR-17-0398

46. Chu D, Wu J, Wang K, Zhao M, Wang C, Li L, et al. Effect of metformin use on the risk and prognosis of endometrial cancer: a systematic review and meta-analysis. BMC Cancer 2018;18(1):438. doi: 10.1186/s12885-018-4334-5

47. Kwon JS, Albert AYK, Gill S, Hutcheon JA. Diabetic pharmacotherapy and endometrial cancer risk within a publicly funded health care system. J Obstet Gynaecol Can 2017;39(1):42–48. doi: 10.1016/j.jogc.2016.09.078

48. Zhang D, Bai B, Xi Y, Zhao Y. Can aspirin reduce the risk of endometrial cancer?: a systematic review and meta-analysis of observational studies. Int J Gynecol Cancer 2016;26(6):1111–20. doi: 10.1097/IGC.0000000000000731

49. Zhang XS, Zhang YM, Li B, Fan B, Zhao Y, Yang SJ. Risk reduction of endometrial and ovarian cancer after bisphosphonates use: a meta-analysis. Gynecol Oncol 2018;150(3):509–14. doi: 10.1016/j.ygyno.2018.06.012

Uterine Cancer Literature Review
Appendix 5. Screening for Uterine Cancer

Primary Reviewer: Arjeme Cavens, MD
Secondary Reviewer: Rebecca Brooks, MD

INTRODUCTION

This document summarizes the currently available evidence regarding screening for endometrial cancer in asymptomatic patients. The PICO format was used to direct the literature search:

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

This review specifically addresses the following questions:

1. **What is the evidence against screening asymptomatic women at usual risk for endometrial cancer?**
   P: Adult patients with a uterus, at average risk, without abnormal uterine bleeding
   I: Endometrial cancer screening (transvaginal ultrasonography, endometrial biopsy, dilation and curettage, or hysteroscopy)
   C: Screening vs no screening
   O: Relative risk (RR) or odds ratio (OR) of uterine cancer (endometrial cancer, leiomyosarcoma, endometrial stromal sarcoma), incidence of uterine cancer, stage at diagnosis, or survival rate

2. **Are there high-risk subgroups of women who would benefit from screening for endometrial cancer? How should screening be performed in these women?**
   P: Adult patients with a uterus with Cowden syndrome, Lynch Syndrome, tamoxifen use, *BRCA* mutation carriers, family history of endometrial cancer, polycystic ovary syndrome (PCOS), Li-Fraumeni syndrome, Peutz-Jeghers syndrome, or obesity
   I: Endometrial cancer screening (transvaginal or pelvic ultrasonography, endometrial sampling [endometrial biopsy, dilation and curettage], or hysteroscopy)
   C: Screening vs no screening, one screening method vs another
   O: RR or OR of endometrial cancer, incidence, stage at diagnosis, or survival rate

3. **How can high-risk women be identified?**
   P: Adult patients with a uterus without Cowden syndrome, Lynch Syndrome, tamoxifen use, *BRCA* mutation, family history of endometrial cancer, PCOS, granulosa cell tumors, Li-Fraumeni syndrome, or Peutz-Jeghers syndrome
   I: Assessment of menstrual history, assessment of family history, or genetic testing
   C: One assessment measure vs another vs no assessment or usual care
   O: RR or OR of endometrial cancer, incidence, stage at diagnosis, survival rate, or diagnosis of endometrial hyperplasia

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed (for references not indexed in Ovid) databases. The literature search

was supplemented by identification of pertinent studies referenced in the identified papers. A manual search identified other guidelines and resources from professional societies and health service organizations within the United States. These additional resources were included if they met the inclusion and exclusion criteria. A single investigator reviewed the title and abstracts of all identified articles and guidelines, then examined the full text of those articles that were relevant to the proposed questions.

Inclusion criteria were major society or health service guidelines, systematic reviews, meta-analyses, cohort studies, case-control studies, and randomized controlled trials published in the year 2000 or later. Only articles available in English were included. Case reports, case series, and articles unavailable in English were excluded. Also excluded were studies conducted outside of countries designated by the United Nations as very high on its Human Development Index (see the United Nations Human Development Index: http://hdr.undp.org/en/composite/HDI).

RESULTS

The primary literature search returned 361 results and 12 guidelines. After title and abstract review, 263 manuscripts were excluded; another 56 were excluded after full review, and duplicates were accounted for. The 12 guidelines from the initial search were excluded, although others were independently identified. A manual secondary review yielded an additional 12 resources (guidelines, professional society publications, and studies) that were reviewed and included. Ultimately, 45 studies and publications were included based on the listed criteria and relevance to presented research questions.

SUMMARY OF DATA

What is the evidence against screening asymptomatic women at usual risk for endometrial cancer?

Ultrasonography

Several studies have sought to assess the feasibility of various testing modalities as tools for endometrial cancer screening. From a meta-analysis including 15 studies reporting on endometrial cancer prevalence, the prevalence in asymptomatic postmenopausal women was found to be 0.62% for carcinoma (range: 0–2.1%), 0.59% for hyperplasia (range: 0–3.5%), and 1.21% for pooled hyperplasia or carcinoma (range: 0–4.3%).[1] The prevalence would be expected to be lower in asymptomatic premenopausal women given the association of age and endometrial cancer risk. Transvaginal ultrasonography has been extensively studied and found to be of limited utility in screening asymptomatic postmenopausal women given its low positive predictive value. A cohort of 1,926 asymptomatic postmenopausal women was studied, of whom 1,792 underwent transvaginal ultrasonography and endometrial aspiration prior to randomization in an osteoporosis prevention trial.[2] Using an endometrial thickness threshold of 6 mm, the positive predictive value for endometrial carcinoma was 2% and the negative predictive value was more than 99% (sensitivity: 16%, specificity: 98%). In this study, however, the positive predictive value may have been underestimated, as half of the women with endometrial thickness more than 6 mm did not undergo sampling.

Breijer et al performed a meta-analysis that included 20 studies with 5,198 women to assess the sensitivity and specificity of endometrial thickness measurement by transvaginal ultrasonography for diagnosing premalignant and malignant endometrial disease in asymptomatic postmenopausal women.[1] Using endometrial thickness thresholds of 5 mm or 6 mm respectively, the sensitivity of ultrasonography for diagnosis of endometrial carcinoma was 0.83 or 0.33, and the specificity was 0.72 or 0.94. In this analysis, as in other studies, the use of

endometrial thickness was not demonstrated to have justifiable utility in screening asymptomatic postmenopausal women for endometrial cancer or atypical hyperplasia.[3]

Endometrial Sampling

Endometrial biopsy and dilation and curettage alone, while used in many studies for histopathologic confirmation, have not been proposed or studied as primary screening mechanisms for asymptomatic populations according to this literature review. Similarly, in this review, sonohysterography and hysteroscopy have been proposed as follow-up studies after abnormal imaging findings in asymptomatic women, but not as initial screening methods in asymptomatic populations.

Cytology

While cervical cytology can yield results that are suspicious for or diagnostic of endometrial cancer, it has not been proposed as a primary screening method for endometrial cancer given its overall insufficient accuracy for this diagnosis. –A retrospective study aimed to compare the accuracy of SurePath liquid-based cytology with conventional Pap testing in the detection of endometrial carcinoma, acknowledging that neither method is designed for the diagnosis of endometrial cancer.[4] This study demonstrated that liquid-based cytology results of endometrial adenocarcinoma had a 73.3% positive predictive value for this diagnosis or a 36.1% positive predictive value if including results of atypical endometrial cells. By comparison, conventional Pap testing had a positive predictive value of 42.3% for a result of endometrial adenocarcinoma or a positive predictive value of 25.8% if atypical endometrial cell results were included. Actual detection rates for endometrial carcinoma by liquid-based cytology and conventional Pap testing among these cohorts were 0.013% and 0.006%, respectively, when corrected for false-positive results.

Though not routinely used in the United States, endometrial cytology is a method for cytologic sampling of the endometrial cavity, using a cytobrush similar to that employed for cervical cytology. A retrospective cohort study in Japan comparing 427 women who were diagnosed with endometrial cancer based on symptoms with 21 women who were diagnosed based on routine endometrial cytology screening demonstrated a difference in depth of tumor invasion between the two cohorts, but did not demonstrate a difference in endometrial cancer grade, lymph node involvement, cervical or adnexal involvement, peritoneal cytology, surgical stage (classified as I/II vs III/IV), or survival.[5]

Mortality Outcomes

Essential to a successful screening modality is the ability to detect cancer at early stages and ultimately decrease cancer-related mortality. In the case of endometrial cancer, detecting treatable premalignant lesions such as epithelial intraepithelial neoplasia could have the additional benefit of decreasing the overall incidence of endometrial cancer. This review yielded no data to support that screening by any method decreases the incidence of endometrial cancer or mortality from endometrial cancer. In a retrospective cohort study, 21 asymptomatic women diagnosed with endometrial cancer (the majority of whom were diagnosed by endometrial cytology used as a screening tool) were compared with 427 symptomatic women diagnosed with endometrial cancer. While these two groups demonstrated different histopathologies and depth of tumor invasion, there was no difference in various measures, most notably 5-year survival rate.[5] Another retrospective study of 190 postmenopausal women demonstrated that asymptomatic women diagnosed with endometrial cancer had no prognostic advantage compared with women diagnosed as a result of postmenopausal bleeding of

less than 8 weeks' duration. The study authors concluded that screening by transvaginal ultrasonography is not justified, as it does not lead to diagnosis at an earlier stage, nor does it confer increased overall or disease-free survival.[6]

Some studies have shown that women who are asymptomatic at diagnosis may have earlier-stage disease, but this finding has not translated into improved survival. Gemer et al studied 1,607 postmenopausal women with endometrial cancer and found that more asymptomatic women had stage IA tumors and fewer needed radiation therapy as adjuvant treatment; however, there was no difference in diagnosis of stage II–IV disease, high-grade histology, 5-year recurrence-free survival rates, disease-specific survival rates, or overall survival.[7] Barak et al found a trend toward improved survival in asymptomatic patients but also did not demonstrate any statistically significant difference in stage I deeply invasive disease or advanced stage disease, grade 3 tumors, or overall survival.[8] A meta-analysis of 2,961 patients (which included the Gemer et al and Barak et al studies) found more stage I tumors in the asymptomatic patient population (RR: 1.19, although with high heterogeneity), but no difference in the proportion of high-grade histology, overall survival, or disease-free survival.[9] Though these three studies compared women whose endometrial cancer was diagnosed based on symptoms with asymptomatic women diagnosed following detection of abnormalities on imaging, it is reasonable to extrapolate these data to the utility of detecting endometrial cancer by screening asymptomatic women.

The American Cancer Society states that there is no indication that screening is warranted for women with no identified risk factors.[10] Neither the National Cancer Institute nor the National Comprehensive Cancer Network (NCCN) makes recommendations for screening in asymptomatic patient populations. ACOG asserts that screening for endometrial cancer is not performed in the general population because of low disease prevalence, early stage at presentation, and the frequency of abnormal uterine bleeding as a presenting symptom.[11,12]

This review did not yield any articles specifically addressing screening for leiomyosarcoma or endometrial stromal sarcoma.

Are there high-risk subgroups of women who would benefit from screening for endometrial cancer? How should screening be performed in these women?

Lynch Syndrome

Women with hereditary nonpolyposis colorectal cancer, or Lynch syndrome, have a 13–57% lifetime risk of developing endometrial cancer, which varies by specific genetic mutation.[13] The utility of different screening approaches has been studied in patients with confirmed or suspected Lynch syndrome, mostly using ultrasonography, endometrial sampling, or both. In one prospective study, women with suspected or proven Lynch syndrome were screened every 1–2 years with transvaginal ultrasonography. This approach failed to detect the two cancers that arose in this cohort of 269 women over 13 years, suggesting that endometrial cancer surveillance by ultrasonography at these intervals might not be beneficial.[14] In contrast, a prospective study evaluated 58 women with Lynch syndrome who underwent both ultrasonography and endometrial biopsy as part of yearly screening evaluations. Two patients in this cohort were diagnosed with cancer. Compared with endometrial biopsy as the reference standard, ultrasonography used to detect endometrial cancer or atypical hyperplasia had 100% sensitivity, 55% specificity, 6% positive predictive value, and 100% negative predictive value.[15] Some studies in patients with Lynch syndrome have demonstrated no added benefit of endometrial sampling compared with screening with ultrasonography alone.[16] Other studies have demonstrated that screening modalities involving endometrial sampling perform better than ultrasonography alone.[17]

A retrospective study of 175 Lynch syndrome patients screened women every 2–3 years with ultrasonography and endometrial biopsy (at 94% and 74% of the 503 visits, respectively).[18] In these patients, 14 endometrial cancers developed, 11 of which were diagnosed based on screening, and 3 of which were interval diagnoses. Ultrasonography detected 4 of the 11 endometrial cancer cases, whereas endometrial biopsy detected 8 cases. Endometrial biopsy also diagnosed more instances of hyperplasia than ultrasonography alone. Another retrospective study demonstrated that the addition of routine endometrial sampling detected more cases of endometrial hyperplasia than the preceding protocol of routine ultrasonography alone with the addition of endometrial sampling only in the setting of abnormal findings.[19]

A retrospective study of 55 women with Lynch syndrome undergoing combined colonoscopy and endometrial biopsy screening also demonstrated superiority of endometrial sampling to sonographic screening, as ultrasonography alone would have missed three out of the four cases of hyperplasia and the single endometrial cancer found within the 111 screening visits that occurred.[20] Detection rates of endometrial cancer were comparable to yearly surveillance in this group, despite the every 1–2-year protocol used, and no interval cancers occurred. These findings suggest that there may be a role for combining colorectal and endometrial cancer screening visits, which allows for patient sedation and likely improved comfort and which yielded an 88% compliance rate in this study.

Outpatient hysteroscopy with endometrial sampling was evaluated in a small prospective study. It demonstrated a sensitivity of 100%, specificity of 89.8%, positive likelihood ratio of 9.8, and negative likelihood ratio of 0 for the detection of atypical hyperplasia or malignancy, statistically outperforming ultrasound screening alone.[21]

There is less evidence regarding whether these various screening modalities translate into decreased endometrial cancer mortality in women with Lynch syndrome. In the study of 175 Lynch mutation carriers screened with ultrasonography and endometrial biopsy every 2–3 years, tumors in the screened population tended to be earlier stage, and there was a trend toward improved survival at 10 years compared with 83 patients with symptom-detected endometrial cancer, but these differences did not reach statistical significance.[18] It is worth noting that consideration of risk-reducing hysterectomy is recommended for patients with Lynch syndrome after childbearing is completed. Screening modalities are intended for use prior to recommended prophylactic hysterectomy; therefore, using mortality alone as an outcome measure of screening utility might be less informative. Furthermore, while fertility maintenance is not a standard endpoint by which to assess the utility of screening modalities, it does represent an important, clinically relevant endpoint. Further investigation is needed to determine whether early detection of endometrial cancer or its precursors leads to an increased ability to employ fertility-sparing treatment in reproductive-aged patients and to preserve natural fertility options in those for whom that remains a priority.

The American Cancer Society recommends that patients with or at high risk for Lynch syndrome be offered annual screening with endometrial biopsy beginning at age 35.[10] This recommendation is based on expert opinion. NCCN asserts:[13]

> Endometrial cancer screening does not have proven benefit in women with [Lynch syndrome]. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 can be considered. Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the

> clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.

ACOG and the Society of Gynecologic Oncology recommend endometrial biopsy every 1–2 years, starting at age 30–35, for women with Lynch syndrome.[11]

Cowden Syndrome

Cowden syndrome is an autosomal dominant condition caused by a mutation in the *PTEN* tumor suppressor gene. Women with Cowden syndrome are thought to have a 5–10% lifetime risk of developing endometrial cancer, with some cases even being reported in adolescence.[22] A review of the literature did not yield any individual studies evaluating nor recommendations for endometrial cancer screening in women with Cowden syndrome.

According to the NCCN:[22]

> Endometrial cancer screening does not have proven benefit in women with [Cowden syndrome or *PTEN* hamartoma tumor syndrome]. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered. Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.

BRCA Mutation Carriers

A review of the literature did not yield any studies evaluating nor recommendations for endometrial cancer screening in *BRCA 1* or *BRCA 2* mutation carriers. The risk of endometrial cancer in *BRCA 1* mutation carriers is 3%.[23] An increased risk of endometrial cancer in *BRCA* mutation carriers higher than that of the baseline population risk has not yet been consistently demonstrated. While some studies have shown a higher risk of serous endometrial cancers in *BRCA 1* carriers, this finding remains controversial.[12,24] (Appendix 3, Uterine Cancer Risk Factors, and Appendix 4, Prevention and Risk Reduction for Uterine Cancer, describe the evidence related to *BRCA* mutations in more detail.)

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is an autosomal dominant condition caused by a mutation in the *TP53* tumor suppressor gene. Although patients with Li-Fraumeni are at increased risk of soft tissue sarcoma, including uterine leiomyosarcoma, this disorder is rare, therefore it is difficult to make evidence-based screening recommendations for this population.[25] A review of the literature did not yield any studies evaluating endometrial cancer screening in individuals with Li-Fraumeni syndrome.

Peutz-Jeghers Syndrome

The lifetime risk of endometrial cancer in women with Peutz-Jeghers syndrome is 9%.[26,27] A review of the literature did not yield any studies evaluating nor specific recommendations for endometrial cancer screening in individuals with Peutz-Jeghers syndrome (although NCCN recommends pelvic examination and Pap test annually given the risk of cervical cancer).[13,26]

Family History of Endometrial Cancer

A family history of endometrial cancer can raise one's risk of this diagnosis two- to threefold. A review of the literature did not reveal any studies evaluating endometrial cancer screening in individuals with a family history of endometrial cancer aside from studies of patients with known or suspected Lynch syndrome.

Tamoxifen Users

Women with a history of tamoxifen use have an increased risk of developing both endometrial cancer and benign endometrial polyps, a risk which increases with total duration of tamoxifen use.[28] The absolute risk for endometrial cancer, above that of the general population, is 0.7 per 1,000 in unscreened populations, and 1.7 per 1,000 in screened populations.[29] The rationale against screening for endometrial cancer in tamoxifen users mirrors that for the general population: endometrial cancer often presents with early symptoms and progresses slowly, and there is concern about potential harms and unnecessary procedures resulting from screening this patient population. A prospective study assessed 304 premenopausal and postmenopausal women using tamoxifen who underwent baseline endometrial biopsy followed by yearly ultrasonography.[30] In this population, 32% of ultrasonography findings required further evaluation, and 80% of these were ultimately revealed as benign polyps. Using an endometrial thickness cutoff of 9 mm, there was a 63% sensitivity, 28% specificity, and 1.4% positive predictive value for the detection of endometrial cancer. Of note, all of the cancers detected in this study occurred in subjects who presented with symptoms. The use of color Doppler increased sensitivity, but the study ultimately reported a 56% false-positive rate.

Another prospective study evaluated 107 postmenopausal women who had baseline ultrasonography prior to tamoxifen initiation, followed by ultrasonography and endometrial biopsy after 1 year of use.[31] No cancers occurred in this study population, but 69% of participants had abnormalities detected on 1-year ultrasonography; of these, 20% had benign polyps, and 72% had endometrial atrophy. These studies and others demonstrate that routine ultrasonography has limited utility as a screening modality in this population and leads to many unnecessary, invasive evaluations. Furthermore, up to 50% of tamoxifen users may have an endometrial thickness of 8 mm after 3 years of use;[29] even with endometrial thickness of 5 mm or more, up to 80% may have no pathologic lesions.[32] As of yet, there is no universally accepted threshold for normal endometrial thickness in tamoxifen users.

Hysteroscopy has also been studied as a screening tool in tamoxifen users. One study looked at 84 postmenopausal and 31 premenopausal women using tamoxifen who underwent baseline hysteroscopy followed by annual hysteroscopy, with additional tissue sampling as needed based on the findings.[28] No histopathological abnormalities were identified within the first 2 years of tamoxifen use, but thereafter, 4.3% (n = 5) developed complex hyperplasia, and one patient who did not return for screening until 6 years after tamoxifen initiation developed endometrial cancer (0.86%). This literature review did not find any comparison of hysteroscopy with other modalities or reference standards as a screening tool for tamoxifen users, although hysteroscopy has been assessed in comparison with other modalities (such as endometrial sampling) for its use in evaluating abnormal findings.

This review found no studies demonstrating the effect of screening tamoxifen users on endometrial cancer-related mortality. The review found no studies of saline infusion sonography or biopsy for surveillance in women on tamoxifen.

This review did not find evidence-based guidelines recommending screening prior to tamoxifen initiation in breast cancer patients, nor any regarding the management of pretreatment imaging results. It has been demonstrated that postmenopausal women with endometrial polyps at baseline are more likely to develop atypical lesions after tamoxifen exposure. In one study, 510 postmenopausal women with breast cancer underwent transvaginal ultrasonography prior to tamoxifen initiation and also hysteroscopy with endometrial biopsy for any endometrial thickness greater than 5 mm.[33] Identified polyps were resected, and all women were screened yearly. Among these women, those with baseline lesions were more likely to develop atypical lesions during the follow-up period compared with those without initial lesions (11.7% vs 0.7%). Women with breast cancer have a high baseline prevalence of asymptomatic endometrial polyps and obese women with estrogen-receptor-positive endometrial cancer are more likely to have baseline endometrial polyps (RR: 2.24) than non-obese women, and the difference is most pronounced in postmenopausal obese women.[34]

To date, ACOG does not recommend routine endometrial surveillance in women using tamoxifen but states there may be a role for pretreatment screening of postmenopausal women with ultrasonography or sonohysterography before initiation of tamoxifen therapy.[35] Patients should be counseled about warning symptoms and the significance of irregular bleeding while taking tamoxifen. The National Cancer Institute notes that routine ultrasound surveillance in asymptomatic women using tamoxifen is not useful.[36] The American Cancer Society states that there is no indication that screening for endometrial cancer should be recommended for women at increased risk for endometrial cancer because of history of tamoxifen therapy.[10]

Polycystic Ovary Syndrome

PCOS can be associated with an increased risk of endometrial cancer (OR: 4.0),[37] but this risk seems to be attenuated when adjustments are made for body mass index. The literature review did not yield any studies evaluating endometrial cancer screening specific to women with PCOS.

Obesity

Obesity has been shown in multiple studies to be associated with an increased risk of endometrial cancer and premalignant endometrial lesions, as well as endometrial cancer-related mortality.[38,39,40] A review of the literature did not yield any studies specifically evaluating endometrial cancer screening in obese women. The American Cancer Society states that there is no indication that screening for endometrial cancer should be recommended for women at increased risk for endometrial cancer because of history of obesity.[10]

How can high-risk women be identified?

Women who do not have a diagnosed genetic mutation that puts them at high risk for endometrial cancer (eg, Lynch syndrome) but do have a family aggregation of colorectal or endometrial cancer should undergo genetic consultation.[41] A personal and family history should be obtained from all patients to identify patterns that are concerning for other heritable genetic conditions and that may confer an increased risk of endometrial cancer, warranting genetic consultation or testing. Some data suggest that women diagnosed with colorectal cancer

under the age of 50 have a substantially increased risk of developing uterine cancer, while other data do not support this relationship to age.[42,43] This evidence review did not find any data to support differential screening practices on the basis of this factor alone, although it remains important information to elicit and consider as part of individualized patient assessment.

Several other risk factors and combinations of risk factors increase a woman's risk of endometrial cancer above the baseline population risk. These include lifestyle factors, family history, reproductive factors, hormone exposure, medication exposure, and genetic factors. There are few data to guide the calculation or use of a woman's risk profile based on these factors. Risk prediction models have been proposed to stratify the population into low-, medium-, and high-risk categories, which could aid in the use of screening or prevention strategies in higher-risk individuals,[44] but such models have not yet been validated. Studies are also underway to incorporate serum biomarkers and data from genome-wide association studies into such approaches. These methods, however, are still in their infancy and will require more investigation before offering reliable information that that can be used to mitigate risk or affect cancer incidence and mortality.

Although the literature review addressed asymptomatic individuals, risk profiles are under development to assess the RR of endometrial cancer in symptomatic women (ie, those with premenopausal abnormal uterine bleeding or postmenopausal bleeding). In one prospective study, such risk has been shown to be mitigated by age, hormone therapy, parity, obesity, type 2 diabetes, and recurrence of postmenopausal bleeding.[45] These risk stratification tools have yet to be validated but may prove useful in identifying which symptomatic women are at highest risk of endometrial cancer and in developing investigational protocols accordingly. This review found no studies of the effects of such tools on endometrial cancer incidence or mortality.

DISCUSSION

Strengths

This literature review identified studies with levels I through III evidence, and the scope of literature represented geographically variable populations. There were professional society guidelines available for some of the questions posed.

Weaknesses

- The majority of the primary literature was level II and III evidence, comprising mostly retrospective cohort studies. There were no data from randomized, controlled trials to assess screening in the populations of interest.
- Given the lack of standardized definitions for normal versus abnormal endometrial thickness for premenopausal or asymptomatic postmenopausal women and tamoxifen users, studies assessing the use of ultrasonography as a screening modality varied with regard to the thresholds used for endometrial thickness.
- While there seems to be a large sample of literature assessing the ability of modalities to evaluate or diagnose symptomatic premenopausal and postmenopausal women, most of the literature that addressed screening of asymptomatic individuals at usual risk for endometrial cancer studied postmenopausal populations.
- Although dilation and curettage is still seen as the gold standard diagnostic tool, studies used varying reference standards for "confirming" cases of endometrial cancer, and none employed routine dilation and curettage to this end.

- Many studies used the endpoint of cancer or atypical hyperplasia (a more prevalent combined outcome). While it is plausible that identification of hyperplasia may lead to a lower incidence of endometrial carcinoma, per the results of this review, that principle remains to be supported with evidence, and again, further study is needed to demonstrate a favorable effect on mortality.
- The available data on Lynch syndrome vary with regard to population inclusion criteria. Some studies specifically assess populations with confirmatory genetic testing, while others utilize Amsterdam II criteria or suspicious family histories without specific genetic testing, limiting the generalizability of some of these data.
- Even in cases for which professional society guidelines are available, the recommendations are based on expert opinion and acknowledge the lack of data demonstrating concrete benefits for screening in particular populations.
- Few studies assessed long-term outcomes such as reduced mortality, which is ultimately the goal of implementing screening processes.

Research Gaps

There would be benefit from further research addressing the following:

- More prospective data assessing survival benefit in screened versus unscreened individuals
- More data regarding screening in premenopausal women
- Further exploration of endometrial cancer risk and screening related to women with breast cancer and tamoxifen use, which could be undertaken in women without breast cancer who use tamoxifen for preventive purposes
- Better defining levels of endometrial cancer risk (eg, Lynch syndrome is considered to pose a high risk, but there are no definitions of relative or absolute risk that qualify as low, intermediate, or high risk)
- Further survival outcome data

To this end, it is important to maximize the registration of screening programs or studies, or the inclusion of findings in national databases, to provide more data for further investigation.[15]

REFERENCES

1. Breijer MC, Peeters JAH, Opmeer BC, Clark TJ, Verheijen RHM, Mol BWJ, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012;40(6):621–29. doi: 10.1002/uog.12306
2. Fleischer AC, Wheeler JE, Lindsay I, Hendrix SL, Grabill S, Kravitz B, et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol 2001;184(2):70–5. doi: 10.1067/mob.2001.111088
3. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Clinical usefulness of endometrial screening by ultrasound in asymptomatic postmenopausal women. Maturitas 2004;48(4):421–4. doi: 10.1016/j.maturitas.2003.10.006
4. Patel C, Ullal A, Roberts M, Brady J, Birch P, Bulmer JN, et al. Endometrial carcinoma detected with SurePath liquid-based cervical cytology: comparison with conventional cytology. Cytopathology 2009;20(6):380–7. doi: 10.1111/j.1365-2303.2008.00621.x
5. Jobo T, Arai T, Sato R, Kuramoto H. Clinicopathologic relevance of asymptomatic endometrial carcinoma. Acta Cytol 2003;47(4):611–15. doi: 10.1159/000326577

6. Gerber B, Krause A, Müller H, Reimer T, Külz T, Kundt G, et al. Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding. Eur J Cancer 2001;37(1):64–71. doi: 10.1016/s0959-8049(00)00356-7
7. Gemer O, Segev Y, Helpman L, Hag-Yahia N, Eitan R, Raban O, et al. Is there a survival advantage in diagnosing endometrial cancer in asymptomatic postmenopausal patients? An Israeli Gynecology Oncology Group study. Am J Obstet Gynecol 2018;219(2):181.e1–e6. doi: 10.1016/j.ajog.2018.05.013
8. Barak F, Kalichman L, Gdalevich M, Milgrom R, Laitman Y, Piura B, et al. The influence of early diagnosis of endometrioid endometrial cancer on disease stage and survival. Arch Gynecol Obstet 2013;288(6):1361–4. doi: 10.1007/s00404-013-2898-5
9. Segev Y, Dain-Sagi L, Lavie O, Sagi S, Gemer O. Is there a survival advantage in diagnosing endometrial cancer in asymptomatic patients? A systemic review and meta-analysis. J Obstet Gynaecol Can 2020;42(4):481–7.e2. doi: 10.1016/j.jogc.2019.04.020
10. Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, 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;51(1):38–75. doi: 10.3322/canjclin.51.1.38
11. American College of Obstetricians and Gynecologists and the Society of Gynecology Oncology. Lynch syndrome. ACOG Practice Bulletin No. 147. Obstet Gynecol 2014;124(5):1042–54. doi: 10.1097/01/AOG/0000456325.50739/72
12. American College of Obstetricians and Gynecologists. Endometrial cancer. Practice Bulletin No. 149. Obstet Gynecol 2015;125(4):1006–26. doi: 10.1097/01.AOG.0000462977.61229.de
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Colorectal. Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Retrieved December 3, 2020.
14. Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HFA, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer 2002;94(6):1708–12. doi: 10.1002/cncr.10380
15. Lecuru F, Huchon C, Metzger U, Bats AS, Le Frere-Belda MA, Olschwang S, et al. Contribution of ultrasonography to endometrial cancer screening in patients with hereditary nonpolyposis colorectal cancer/Lynch syndrome. Int J Gynecol Cancer 2010;20(4):583–7. doi: 10.1111/IGC.0b013e3181d7283a
16. Helder-Woolderink JM, De Bock GH, Sijmons RH, Hollema H, Mourits MJE. The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome. Gynecol Oncol 2013;131(2):304–8. doi: 10.1016/j.ygyno.2013.05.032
17. Tzortzatos G, Andersson E, Soller M, Askmalm MS, Zagoras T, Georgii-Hemming P, et al. The gynecological surveillance of women with Lynch syndrome in Sweden. Gynecol Oncol 2015;138(3):717–22. doi: 10.1016/j.ygyno.2015.07.016
18. Renkonen-Sinisalo L, Bützow R, Leminen A, Lehtovirta P, Mecklin JP, Järvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120(4):821–4. doi:10.1002/ijc.22446
19. Gerritzen LHM, Hoogerbrugge N, Oei ALM, Nagengast FM, van Ham MAPC, Massuger LFAG, et al. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. Fam Cancer 2009;8(4):391–7. doi: 10.1007/s10689-009-9252-x
20. Nebgen DR, Lu KH, Rimes S, Keeler E, Broaddus R, Munsell MF, et al. Combined colonoscopy and endometrial biopsy cancer screening results in women with Lynch syndrome. Gynecol Oncol 2014;135(1):85–9. doi: 10.1016/j.ygyno.2014.08.017

21. Manchanda R, Saridogan E, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, et al. Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS). Arch Gynecol Obstet 2012;286(6):1555–62. doi: 10.1007/s00404-012-2492-2
22. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Retrieved December 3, 2020.
23. Saule C, Mouret-Fourme E, Briaux A, Becette V, Rouzier R, Houdayer C, et al. Risk of serous endometrial carcinoma in women with pathogenic BRCA1/2 variant after risk-reducing salpingo-oophorectomy. J Natl Cancer Inst 2018;110(2):10.1093/jnci/djx159. doi: 10.1093/jnci/djx159
24. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M, Salom E, Gehrig P. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134(2):385–92. doi:10.1016/j.ygyno.2014.05.018
25. Hensley ML, Barrette BA, Baumann K, Gaffney D, Hamilton AL, Kim JW, et al. Gynecologic Cancer InterGroup (GCIG) consensus review: uterine and ovarian leiomyosarcomas. Int J Gynecol Cancer 2014;24(9 Suppl 3):S61–6. doi: 10.1097/IGC.0000000000000261
26. Vellone VG, Paudice M, Varesco L. Hereditary non-BRCA gynecological tumors. Minerva Ginecol 2016;68(5):579–86.
27. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJP, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res 2006;12(10):3209–15. doi: 10.1158/1078-0432.CCR-06-0083
28. Zarbo G, Caruso G, Zammitti M, Caruso S, Zarbo R. The effects of tamoxifen therapy on the endometrium. Eur J Gynaecol Oncol 2000;21(1):86–8.
29. Neven P, Vergote I. Tamoxifen, screening and new oestrogen receptor modulators. Best Pract Res Clin Obstet Gynaecol 2001;15(3):365–80. doi: 10.1053/beog.2001.0182
30. Fung MFK, Reid A, Faught W, Le T, Chenier C, Verma S, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003;91(1):154–9. doi: 10.1016/s0090-8258(03)00441-4
31. Kazerooni T, Ghaffarpasand F, Mosalaei A, Kazerooni Y. The value of transvaginal ultrasonography in the endometrial evaluation of breast cancer patients using tamoxifen. Med Princ Pract 2010;19(3):222–7. doi: 10.1159/000285296 .
32. Marchesoni D, Driul L, Fabiani G, Di Loreto C, Cataldi P, Mozzanega B. Endometrial histologic changes in post-menopausal breast cancer patients using tamoxifen. Int J Gynaecol Obstet 2001;75(3):257–62. doi: 10.1016/s0020-7292(01)00476-3
33. Berlière M, Radikov G, Galant C, Piette P, Marbaix E, Donnez J. Identification of women at high risk of developing endometrial cancer on tamoxifen. Eur J Cancer 2000;36(Suppl 4):S35–6. doi: 10.1016/s0959-8049(00)00217-3
34. Lubian Lopez DM, Lopez FO, Molina LGB, Novo PB, Solis EP, Almagro DM, et al. Endometrial polyps in obese asymptomatic pre and postmenopausal patients with breast cancer: is screening necessary? Gynecol Oncol 2014;133(1):56–62. doi: 10.1016/j.ygyno.2013.12.029
35. American College of Obstetricians and Gynecologists. Tamoxifen and uterine cancer. ACOG Committee Opinion No. 601. Obstet Gynecol 2014;123(6):1394–7. doi: 10.1097/01.AOG.0000450757.18294.cf
36. PDQ Screening and Prevention Editorial Board. Endometrial cancer screening (PDQ®): health professional version. Available at https://www.cancer.gov/types/uterine/hp/endometrial-screening-pdq. Retrieved December 2, 2020.
37. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM, Australian Ovarian Cancer Study Group and Australian National Endometrial Cancer Study Group. Polycystic ovary syndrome increases the risk

of endometrial cancer in women aged less than 50 years: an Australian case-control study. Cancer Causes Control 2010;21(12):2303–8. doi: 10.1007/s10552-010-9658-7
38. Viola AS, Gouveia D, Andrade L, Aldrighi JM, Viola CFM, Bahamondes L. Prevalence of endometrial cancer and hyperplasia in non-symptomatic overweight and obese women. Aust N Z J Obstet Gynaecol 2008;48(2):207–13. doi: 10.1111/j.1479-828X.2008.00845.x
39. Renaud MC, Le T, SOGC-GOC-SCC Policy and Practice Guidelines Committee, special contributors. Epidemiology and investigations for suspected endometrial cancer. J Obstet Gynaecol Can 2013;35(4):380–1. doi: 10.1016/S1701-2163(15)30970-1
40. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician 2016;93(6):468–74.
41. Bohiltea RE, Ancar V, Cirstoiu MM, Radoi V, Bohiltea LC, Furtunescu F. Project for the National Program of Early Diagnosis of Endometrial Cancer Part I. J Med Life 2015;8(3):305–14.
42. Matsuo K, Mandelbaum RS, Machida H, Yoshihara K, Muggia FM, Roman LD, et al. Decreasing trends of secondary primary colorectal cancer among women with uterine cancer: a population-based analysis. J Clin Med 2019;8(5):714. doi: 10.3390/jcm8050714
43. Chang WC, Muo CH, Liang JA, Sung FC, Kao CH. Gynecological malignancy risk in colorectal cancer survivors: a population-based cohort study. Eur J Oncol Nurs 2015;19(5):473–8.
44. Kitson SJ, Evans DG, Crosbie EJ. Identifying High-Risk Women for Endometrial Cancer Prevention Strategies: Proposal of an Endometrial Cancer Risk Prediction Model. *Cancer Prev Res (Phila).* 2017;10(1):1-13. doi: 10.1016/j.ejon.2015.02.006
45. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med 2018;178(9):1210–22. doi: 10.1001/jamainternmed.2018.2820

Uterine Cancer Literature Review
Appendix 6. Uterine Cancer Early Diagnosis

Primary Reviewer: Sangini S. Sheth, MD, MPH
Secondary Reviewer: Sara Whetstone, MD, MHS

INTRODUCTION

This document focuses on common presenting symptoms among women diagnosed with uterine precancer or cancer and effective methods of evaluation to facilitate early diagnosis of uterine precancer or cancer. Specifically, this document reviews the evidence about who should undergo evaluation for various clinical situations and evidence-based methods of evaluation (eg, imaging, uterine sampling, or observation). The PICO format was used to direct the literature search:

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

This review specifically addresses the following questions:

1. **What are common presenting symptoms among women diagnosed with uterine cancer or precancer? How predictive are these presenting symptoms of uterine cancer or precancer?**
   P: Adults with uterine cancer (epithelial or mesenchymal or both), with complex atypical hyperplasia or atypical hyperplasia or complex hyperplasia with atypia, or with endometrial intraepithelial hyperplasia (EIN)
   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])
   C: Adults with uterine cancer or precancer with one or more presenting symptoms versus no presenting symptoms
   O: Diagnosis of uterine cancer, accurate prediction of underlying uterine cancer or precancer, incidence, stage at diagnosis, or survival rate

2. **In premenopausal patients with abnormal uterine bleeding, who should undergo evaluation for uterine cancer or precancer? What are the most effective methods of evaluation for uterine cancer or precancer?**
   P: Premenopausal adults with abnormal uterine bleeding
   I: Uterine evaluation (endometrial biopsy, dilation and curettage [D&C], hysteroscopy, transvaginal ultrasonography)
   C: One evaluation method versus another or hysterectomy or observation
   O: Diagnosis of uterine cancer, diagnosis of EIN or precancer, test parameters (sensitivity, specificity, positive predictive value and negative predictive value, or number needed to detect EIN or uterine cancer)

3. **In patients with postmenopausal uterine bleeding, what are the most effective methods of evaluation for uterine cancer or precancer?**
   P: Postmenopausal adults with abnormal uterine bleeding
   I: Uterine evaluation (endometrial biopsy, D&C, hysteroscopy, or transvaginal ultrasonography)
   C: One evaluation method versus another or hysterectomy or observation

Chelmow D, Brooks R, Cavens A, Cavens A, Huber-Keener K Scott DM, et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.

O: Diagnosis of uterine cancer, diagnosis of EIN or precancer, test parameters (sensitivity, specificity, positive predictive value and negative predictive value, or number needed to detect EIN or uterine cancer)

4. **In asymptomatic patients with an incidental finding of an endometrial polyp or thickened endometrium on transvaginal ultrasonography, who should undergo evaluation for uterine cancer or precancer? What are the most effective methods of evaluation for uterine cancer or precancer?**
   P: Premenopausal versus postmenopausal asymptomatic patients with a uterus and with endometrial polyp or thickened endometrium on transvaginal ultrasound imaging
   I: Uterine evaluation (endometrial biopsy, D&C, or hysteroscopy)
   C: One evaluation method versus another or hysterectomy or observation
   O: Diagnosis of uterine cancer or EIN or precancer

5. **In women with benign endometrial cells on cervical cytology, who should undergo evaluation for uterine cancer or precancer?**
   P: Premenopausal versus postmenopausal patients with endometrial cells on cervical cytology, patients age less than 45 years versus women 45 years and older with endometrial cells on cervical cytology
   I: Uterine evaluation (endometrial biopsy or transvaginal ultrasonography)
   C: One evaluation method versus another or hysterectomy or observation
   O: Diagnosis of uterine cancer or EIN or precancer, sensitivity, specificity, or positive predictive value and negative predictive value of endometrial cells on cervical cytology

6. **What is the appropriate evaluation of women with atypical glandular cells (AGCs) on cervical cytology?**
   P: Patients with AGCs on cervical cytology
   I: Uterine evaluation (endometrial biopsy, D&C, hysteroscopy, or transvaginal ultrasonography)
   C: Patients with one or more other clinical risk factors (eg, age, menopausal status, obesity, anovulatory disorders, tamoxifen, or abnormal bleeding) versus no other clinical risk factors
   O: Diagnosis of uterine cancer or EIN or precancer, sensitivity, specificity, or positive predictive value and negative predictive value of AGCs on cervical cytology

7. **What methods of evaluation are beneficial for early detection in patients with other concerning symptoms (ie, not bleeding or abnormal cervical cytology)?**
   P: Patients with suspected uterine cancer (epithelial or mesenchymal or both) displaying some combination of the following symptoms: abdominal or pelvic pain, abdominal distention, bloating, early satiety, change in bowel or bladder function, fever, weight loss, nausea or vomiting, and infertility
   I: Imaging (transvaginal ultrasonography, pelvic computed tomography [CT], pelvic magnetic resonance imaging [MRI]) or endometrial sampling (endometrial biopsy, D&C, or hysteroscopy)
   C: One evaluation method versus another or observation or no evaluation
   O: Mode of evaluation, uterine cancer diagnosis, or stage of uterine cancer diagnosis

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases for all relevant references. Additional review was carried out to identify relevant guidelines published by ACOG, the American Cancer Society, the National Comprehensive Cancer Network, the Society of Gynecologic Oncology (SGO), the European Society for

Medical Oncology, the National Institute for Health and Care Excellence (NICE), the American College of Radiology, the United States Preventive Services Task Force, and the American Society for Reproductive Medicine. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of selected articles. The bibliographies of included articles were reviewed to identify other relevant works not identified by the primary search.

Inclusion criteria were major society or health service guidelines, systematic reviews, meta-analyses, cohort studies, case-control studies, and randomized controlled trials published in the year 2000 or later. Only articles available in English were included. Low-quality studies, correspondence or editorials, case reports, case series, and articles unavailable in English were excluded. Also excluded were studies conducted outside of countries designated by the United Nations as very high on its Human Development Index (see the United Nations Human Development Index: http://hdr.undp.org/en/composite/HDI).

References were reviewed if they addressed symptoms associated with uterine cancers, methods of evaluation when uterine cancer is suspected, or assessments of who should undergo such evaluations. They were not reviewed if they addressed nonuterine cancers, epidemiology or trends in uterine cancer, experimental tests and procedures, treatment or surveillance for uterine precancer or cancer, imaging or treatment of uterine fibroids, or general evaluation or treatment of abnormal uterine bleeding or if they focused on risk assessment or risk perception.

RESULTS

The literature review found no guidelines specific to early diagnosis of uterine cancer. SGO has published reviews on endometrial and uterine papillary serous cancer that discuss common presenting symptoms and diagnostic evaluation among women with concerning symptoms.[1,2] NICE has published guidance on testing strategies for Lynch syndrome in people with endometrial cancer; it notes that the benefits of gynecologic surveillance in people with Lynch Syndrome is uncertain, but raising awareness of early symptoms of gynecologic cancers in these individuals is likely to lead to early diagnosis.[3] In 2020, ASCCP published updated guidelines on the evaluation of cervical cytology interpreted as AGCs.[4]

The literature review found 807 publications, of which, after review, 61 were included based on the criteria described.

What are common presenting symptoms among women diagnosed with uterine cancer or precancer? How predictive are these presenting symptoms of uterine cancer or precancer?

The most common presenting symptom among women diagnosed with endometrial cancer is postmenopausal bleeding, which is seen in 91% of cases.[1,2,5] Postmenopausal bleeding is defined as any vaginal bleeding occurring after at least 1 year of amenorrhea. The presence of postmenopausal bleeding is not associated with cancer stage. However, the risk of endometrial cancer in women with postmenopausal bleeding varies greatly across studies, ranging from 3% to 25%.[5,6] Postmenopausal bleeding is common, occurring in 10% of women in the first year after menopause,[7] and most often associated with benign causes, such as atrophy or endometrial polyp. In a recent systemic review and meta-analysis, the pooled risk of endometrial cancer in women with postmenopausal bleeding was 9%.[5] The risk of endometrial cancer in women with postmenopausal bleeding increases to 12% when women taking hormone therapy are excluded. Additionally, there is geographic variation in risk of endometrial cancer with postmenopausal bleeding, ranging from 5% in North America to 13% in

Western Europe. Postmenopausal bleeding is therefore sensitive for early detection of endometrial cancer but has low positive predictive value. Also, irregular menstrual cycles are commonly reported by premenopausal women diagnosed with endometrial cancer.[8] Additional symptoms associated with endometrial cancer include abnormal vaginal discharge; in patients with more advanced disease, abdominal or pelvic pain, abdominal distention, early satiety, or change in bowel or bladder function can be seen.[9]

Among mesenchymal uterine cancers or uterine sarcomas, the most common presenting symptoms are similar to those of uterine myomas. They include abnormal uterine bleeding, pelvic mass, and pelvic pain.[10,11]

In the absence of a screening test for any uterine cancer, expert opinion recommendations from ACOG and NICE include educating women with Lynch syndrome and postmenopausal women taking tamoxifen about the risk associated with abnormal vaginal bleeding or spotting and the importance of evaluation to facilitate early diagnosis should such symptoms occur.[3,12] However, a recent Cochrane review determined that there is an absence of evidence on the effectiveness of educational interventions for health care providers and patients that would support promoting early presentation and referral for women with symptoms concerning for endometrial cancer.[13]

In premenopausal patients with abnormal uterine bleeding, who should undergo evaluation for uterine cancer or precancer? What are the most effective methods of evaluation for uterine cancer or precancer?

Who Should Undergo Evaluation

The International Federation of Gynecology and Obstetrics (FIGO) defines abnormal uterine bleeding as nongestational uterine bleeding in the reproductive years that is abnormal in duration, volume, frequency, or regularity and has been present for most of the preceding 6 months.[14] ACOG recommends endometrial sampling for all premenopausal patients with abnormal uterine bleeding who are 45 years of age or older.[15] For women under 45, ACOG recommends performing endometrial sampling in those with risk factors, such as unopposed estrogen exposure (eg, women with obesity or polycystic ovary syndrome), failed medical management, and persistent abnormal uterine bleeding.[15,16] FIGO states, “For those at increased risk, endometrial biopsy is probably warranted.”[17] NICE 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.[18] SGO recommends endometrial sampling if the patient has risk factors or the results of a workup for the bleeding are negative.[2] Among premenopausal breast cancer patients treated with adjuvant tamoxifen, abnormal uterine bleeding should merit endometrial sampling to evaluate for the presence of endometrial cancer or precancer.[19,20]

Methods of Evaluation

Hysteroscopic-guided biopsy is commonly used in the diagnostic evaluation of endometrial cancer, with a sensitivity and negative predictive value of 98% for intrauterine pathology, significantly higher than the diagnostic accuracy of D&C (46% and 7.1%, respectively) when compared with histology at the time of hysterectomy among a mixed population of premenopausal and postmenopausal women.[21]

Office-based endometrial sampling is recommended as a first-line, minimally-invasive, and cost-effective procedure.[9,15,22] Although several devices are available for office sampling, the Pipelle catheter has been shown to be a reliable and accurate method of endometrial sampling in the evaluation of uterine precancer or cancer,

with detection rates of 81% and 99.1%, respectively, in premenopausal women.[9,22] In a recent systematic review and meta-synthesis of literature comparing the Pipelle with other endometrial sampling techniques or instruments in assessing low-risk, premenopausal women with abnormal uterine bleeding, the Pipelle was noted to be comparable to D&C and better than most other sampling devices for histologic sample adequacy. In comparing test performance of Pipelle and D&C with final results from hysterectomy pathology, the sensitivity of Pipelle ranged from 62% to 99.2% and that of D&C ranged from 67% to 100%. Concordance between Pipelle and D&C was 66% to 94%. Endometrial sampling with Pipelle was associated with minimal discomfort.[23] The accuracy of an endometrial biopsy is more limited, however, when an adequate specimen is not obtained or if the endometrial pathology is not global.[15] Additionally, a negative biopsy result indicates that the posttest probability of endometrial cancer is 0.9%.[24] Given these results, the authors concluded that a positive test was more accurate for ruling in disease than a negative test was for ruling out endometrial cancer. In the setting of a negative or benign biopsy result, persistent abnormal uterine bleeding should be further evaluated with a hysteroscopic-guided biopsy.[9]

Office-based hysteroscopy with guided biopsies can also be utilized. No direct comparative effectiveness studies between Pipelle sampling and hysteroscopic-guided biopsy (in the office or operating room) were identified in the literature review. The benefits of office-based hysteroscopy include lower cost, convenience for patient and clinician, faster recovery time, and less time off from work.[15]

A systematic quantitative review to determine the accuracy of hysteroscopic visualization of the endometrial cavity found a large increase in the likelihood of endometrial cancer with a positive hysteroscopic impression (likelihood ratio [LR]: 60.9, 95% confidence interval [CI]: 51.2–72.5) and a moderate decrease in likelihood of endometrial cancer with a negative hysteroscopic impression (LR: 0.15, 95% CI: 0.13–0.18). For the combined outcome of endometrial cancer or hyperplasia, there was a moderate increase in the likelihood with a positive hysteroscopic impression (LR: 10.4, 95% CI: 9.7–11.1) and a small decrease in the likelihood with a negative impression (LR: 0.24, 95% CI 0.22–0.25).[25] The study, however, included women with abnormal premenopausal and postmenopausal bleeding, and results were not reported separately for premenopausal women. The authors concluded that with adequate visualization of the uterine cavity, hysteroscopy is highly accurate and clinically useful for the diagnosis of endometrial cancer in women with abnormal uterine bleeding. Hysteroscopy without biopsy or endometrial sampling is less useful for the exclusion of endometrial cancer, and further evaluation may be warranted with a negative result. In the diagnosis of endometrial hyperplasia or cancer, hysteroscopy without any tissue diagnosis (or sampling) has more limited utility, especially for premenopausal women.

In obtaining diagnostic imaging in premenopausal women with abnormal uterine bleeding, multiple studies have shown saline infusion sonography to be superior to transvaginal ultrasonography in the detection of intracavitary pathology.[26,27] In a prospective, nonblinded, randomized trial comparing accuracy of the two modalities in detection of intrauterine pathology in premenopausal (n = 130) and postmenopausal (n = 67) women with abnormal uterine bleeding, sensitivity and negative predictive value were found to be significantly higher for sonohysterography.[28] There is no clinical utility, however, for measuring the endometrial thickness in premenopausal women with abnormal uterine bleeding.[15,29]

Additional studies are ongoing to determine the diagnostic value of serum markers in the evaluation and early diagnosis of uterine cancer, including the use of combination markers. The risk index for endometrial cancer combines HE4, D-dimer, fibrinogen, and CA199, for example, and has shown some initial promise, with sensitivity of 91.3% and specificity of 70.1% in a single retrospective study.[30] Currently, such markers are not

used routinely to evaluate for uterine cancer or precancer, and thus the major societies recommend the other diagnostic strategies described.

In patients with postmenopausal uterine bleeding, what are the most effective methods of evaluation for uterine cancer or precancer?

There is variation in recommendations on the best diagnostic pathway for women with postmenopausal bleeding. ACOG supports initial evaluation with transvaginal ultrasonography for assessment of endometrial thickness or starting evaluation with endometrial sampling.[31] However, in the setting of insufficient tissue on initial endometrial sampling, transvaginal ultrasonography can be used, and if endometrial sampling is negative in patients with postmenopausal bleeding, hysteroscopy with D&C is recommended for persistent or recurrent bleeding. ACOG recommends using an endometrial thickness of more than 4 mm to prompt endometrial sampling if starting evaluation with transvaginal ultrasonography.[31] Appropriate evaluation for recurrent or persistent postmenopausal bleeding varies.[32]

Pelvic ultrasonography is commonly used for first-line evaluation in patients with postmenopausal bleeding. In a systematic review and meta-analysis including 13 studies, an endometrial thickness cutoff of 5 mm on ultrasonography had a sensitivity and specificity of 90% and 54%, respectively. A cutoff of 3 mm had a sensitivity and specificity of 98% and 35%, resulting in a posttest probability of 0.7% for endometrial cancer, and was thus favored by the authors to rule out endometrial cancer in women with postmenopausal bleeding.[9,32,33] In a systematic review and meta-analysis on the risk of endometrial cancer with postmenopausal bleeding, the authors noted more than double the risk (19%) when an endometrial thickness threshold of more than 4–5 mm was incorporated.[5] In a cost-effectiveness analysis from the United Kingdom, a strategy using transvaginal ultrasonography with a threshold of 5 mm for initial evaluation was the least expensive approach. Transvaginal ultrasonography using a threshold of 4 mm for endometrial sampling and endometrial sampling were similarly cost-effective for initial evaluation.[34] These findings are in line with ACOG's current recommendations, which support either initial evaluation with transvaginal ultrasonography for assessment of endometrial thickness or starting evaluation with endometrial sampling.[31]

In a 2016 systematic review and meta-analysis on the accuracy of endometrial sampling in patients with postmenopausal bleeding for the diagnosis of endometrial cancer and atypical hyperplasia, the weighted failure rate and weighted insufficient rate of endometrial sampling were 11% and 31%, respectively.[35] The reference standard in included studies was either blind D&C (five studies) or hysteroscopy with histology (seven studies). The weighted percentage of women with endometrial cancer or precancer among those with failed or insufficient sampling was 7% (range: 0–18%). The sensitivity of endometrial sampling for the diagnosis of endometrial cancer was 100% with a D&C referent and weighted to 90% using hysteroscopy with histology as a referent; specificity was 99–100%. The weighted sensitivity of endometrial sampling for the diagnosis of atypical hyperplasia or endometrial cancer was 92% with a D&C referent and 82% using hysteroscopy with histology as a referent; specificity was 99–100%. Given the lower sensitivity for diagnosis of atypical hyperplasia and focal abnormalities, further evaluation for focal disease is warranted in the setting of a negative result with endometrial sampling in women with persistent postmenopausal bleeding following a negative blind biopsy, similar to recommendations for premenopausal women with persistent symptoms.[31,35] In addition, cost-effectiveness analysis has demonstrated that endometrial sampling in patients with postmenopausal bleeding using the Pipelle is as effective as but less costly than D&C, even after accounting for sampling failure rate, further supporting initial office-based evaluation.[36]

Data are limited on the diagnostic value of saline infusion sonography in women with postmenopausal bleeding. Although overall sensitivity and specificity of saline infusion sonography in the diagnosis of uterine cavity abnormalities is 95% and 88%, respectively, data specific to postmenopausal women or for the diagnosis of endometrial cancer have not been reported. Additionally, the success rate of saline infusion sonography is significantly lower in postmenopausal women compared with premenopausal women.[32] One study evaluated the diagnostic accuracy of histologic evaluation of intrauterine saline when aspirated following saline infusion sonography evaluation, with positive findings and notably high sensitivity and specificity (86.7% and 100%, respectively) for the diagnosis of endometrial hyperplasia or cancer.[37]

Hysteroscopy is considered to be highly accurate in the diagnosis of endometrial cancer among premenopausal and postmenopausal women with abnormal uterine bleeding when there is adequate visualization of the uterine cavity.[25] Hysteroscopy is less useful for the exclusion of endometrial cancer, and further evaluation may be warranted with a negative result. Hysteroscopy is moderately useful in the diagnosis of endometrial hyperplasia or cancer. Furthermore, studies have shown hysteroscopy to be highly accurate in the diagnosis of intrauterine abnormalities more broadly among postmenopausal women.[32]

Investigations are underway to identify biomarkers that can be used in the prediction or early diagnosis of endometrial cancer in postmenopausal women; however, validated tests have yet to be identified.[38] In addition, adjunct molecular testing with reverse transcriptase-polymerase chain reaction on RNA from endometrial sampling specimens may help to improve the accuracy of office-based endometrial sampling for the diagnosis of endometrial cancer and improve the reliability of negative results.[39] In addition, several studies have attempted to identify additional ultrasound features and scoring systems to improve diagnostic accuracy for endometrial cancer or precancer; however, such technologies require further development, and their clinical utility remains unclear.[40-45]

In asymptomatic patients with an incidental finding of a thickened endometrium or endometrial polyp on transvaginal ultrasonography, who should undergo evaluation for uterine cancer or precancer? What are the most effective methods of evaluation for uterine cancer or precancer?

Among asymptomatic postmenopausal women, a thickened endometrium on transvaginal ultrasonography of 4 mm or more has poor accuracy for the diagnosis of endometrial hyperplasia with atypia or endometrial carcinoma.[46,47] A decisional analysis study based on a theoretical cohort demonstrated that in asymptomatic postmenopausal women, an endometrial thickness of more than 11 mm conferred similar risk for endometrial cancer as a postmenopausal patient with vaginal bleeding and an endometrial thickness of more than 5 mm (6.7% vs 7.3%). For an asymptomatic postmenopausal patient with an endometrial thickness of 11 mm or less, the risk for endometrial cancer is 0.002% compared with a risk of less than 0.07% in a symptomatic postmenopausal patient with an endometrial thickness of 5 mm or less.[48] Similar results were noted in a cohort study in which 488 asymptomatic postmenopausal women underwent hysteroscopy for endometrial thickness of 5 mm or more; 3.1% were diagnosed with EIN and 2.0% with endometrial cancer. Receiver operating characteristic analysis demonstrated that an endometrial thickness of 11 mm would best differentiate patients with benign lesions from those with EIN or malignant lesions.[49] Evaluation methods to consider are similar to those used for symptomatic patients and include endometrial biopsy, endometrial curettage, or hysteroscopy. There are no specific guidelines on the most effective method of evaluation for asymptomatic postmenopausal women with a thickened endometrium.

In a large, retrospective, multicenter study, 1.6% of polyps removed from asymptomatic postmenopausal women were precancerous or cancerous, compared with 6% in symptomatic postmenopausal women.[50] A systematic review and meta-analysis including 37 studies with 21,057 patients showed that among identified endometrial polyps, 3.4% will have precancerous or cancerous lesions.[51] Characteristics associated with a higher risk of precancerous or cancerous lesions in endometrial polyps include postmenopausal status, age 60 years or older, tamoxifen use, obesity, diabetes mellitus, hypertension, and abnormal uterine bleeding (including postmenopausal bleeding).[51] In a more recent and larger systematic review and meta-analysis of 51 studies comprising 35,345 patients, the prevalence of malignant 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%) than symptomatic women (5.14%, $P < 0.001$).[52] An observational multi-institutional cohort study of premenopausal and postmenopausal women undergoing hysteroscopic polypectomy showed that after adjusting for potential correlates, only older age (odds ratio [OR]: 1.08, 95% CI: 1.03–1.14) and abnormal uterine bleeding (OR: 3.53, 95% CI: 1.87–6.65) were associated with increased risk of precancerous and cancerous endometrial polyps.[53] Other similar cohort studies have also shown increased risk with older age (≥ 60 years), menopausal status, or abnormal uterine bleeding.[50,54-56] Based on these studies, the consensus in the literature is for polyp removal in older, postmenopausal women with abnormal uterine bleeding. When further evaluation of endometrial polyps is indicated, it can be done by hysteroscopic resection, blind polyp removal, or endometrial curettage in order to submit a sample for histologic evaluation. ACOG 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.[57] Although rates of malignancy among asymptomatic postmenopausal women are low, there are no clear consensus guidelines on the role of evaluation for asymptomatic postmenopausal women at intermediate risk with an incidental finding of endometrial polyps on transvaginal ultrasound imaging. Little data support evaluation for uterine cancer or precancer among asymptomatic premenopausal patients at low risk with an incidental finding of endometrial polyp.[54]

In women with benign endometrial cells on cervical cytology, who should undergo evaluation for uterine cancer or precancer?

The 2014 Bethesda System for reporting cervical cytology recommends reporting benign-appearing endometrial cells for women 45 years or older (a change from the 2001 Bethesda System, which recommended reporting for women 40 years and older).[58] In addition, the 2014 Bethesda System recommends adding an educational note in the pathology report to specify that endometrial evaluation is recommended in postmenopausal women. The prior 2012 and more recent 2019 ASCCP consensus guidelines also recommend endometrial evaluation only in postmenopausal women, based on evidence of increased risk of endometrial pathology in this group.[4,59]

In one systematic review and meta-analysis of 22 studies reporting on normal endometrial cells from cervical cytology specimens in postmenopausal women or women age 40 or older, the prevalence of normal endometrial cells was 0.7% (95%: CI 0.4–1.4%). The proportion of normal endometrial cells associated with endometrial hyperplasia or endometrial carcinoma was 7% (95% CI: 4–10%); it was 11% (95% CI: 8–14%) for conventional cytology and 2% (95% CI: 1–2%) for liquid-based cytology. Among those with significant endometrial pathology, normal endometrial cells were associated with abnormal uterine bleeding in 79% of women who had follow-up, indicating that many instances of normal endometrial cell cytology results are accompanied by symptoms.[60] A more recent study showed that 2.7% of normal endometrial cells from liquid-based cytology were associated with precancerous or cancerous endometrial lesions.[61] Precancerous or cancerous endometrial lesions were found almost exclusively in women 50 years and older with normal endometrial cells evaluated on day 12 or later of their menstrual cycle or in postmenopausal women. The

authors recommended routine endometrial sampling when normal endometrial cells are identified on cervical cytology in these groups of women. There are no guidelines on the role of endometrial sampling or further evaluation when benign-appearing endometrial cells are identified on cervical cytology of premenopausal women.

What is the appropriate evaluation of women with AGCs on cervical cytology?

ASCCP has published guidelines on the evaluation of women with AGCs on cervical cytology.[4] Its 2019 Risk-Based Management Consensus Guidelines recommend that for AGCs of all subcategories, except atypical endometrial cells, a colposcopy should be performed regardless of the result of human papillomavirus (HPV) testing. Endocervical sampling is recommended at the time of colposcopy, except in pregnancy. Additionally, endometrial sampling is recommended for nonpregnant patients age 35 years and older and for nonpregnant patients younger than 35 if they are at increased risk of precancerous or cancerous endometrial lesions (as indicated, eg, by abnormal uterine bleeding, chronic anovulatory disorders, or obesity). For patients with atypical endometrial cells, initial evaluation with endometrial and endocervical sampling is preferred, but including colposcopy in the initial evaluation is acceptable. Additional evaluation with colposcopy is recommended if the initial evaluation is negative for endometrial pathology and colposcopy was initially deferred.[4] Because AGCs can be associated with benign conditions, adenocarcinomas of the cervix, or cancers of other reproductive tract organs, including the endometrium, thorough evaluation is often warranted. In older women who test negative for HPV, endometrial cancer or precancer must be considered.[4]

In one study of 1,422 patients with AGC cytology, 4% were diagnosed with endometrial cancer, 1.4% with endometrial hyperplasia, and 0.3% with other uterine cancers.[62] Endometrial cancer was identified in AGC subcategories as follows: 5.4% with AGC not otherwise specified, 0.5% with AGC endocervical cells, and 14.6% with AGC endometrial cells. Age 50 years or older was significantly associated with risk of endometrial cancer among women with AGC (OR: 6.07, 95% CI: 3.23–11.4), all cases of which were HPV-negative. A more recent study with 3,709 cases of AGC found similar prevalence of endometrial cancer (5.5%), with increased risk in patients age 50 years or older.[63]

What methods of evaluation are beneficial for early detection in patients with other concerning symptoms (ie, not bleeding or abnormal cervical cytology)?

SGO's Clinical Practice Committee recommends that for patients with symptoms suggestive of endometrial cancer, the standard diagnostic evaluation should include pelvic ultrasonography, office endometrial biopsy, or D&C with or without hysteroscopy. Hysteroscopic-guided biopsy is considered the gold standard for diagnostic evaluation of endometrial cancer.[9] The literature review did not identify any specific papers or guidelines on methods of evaluation of endometrial cancer for specific concerning symptoms other than abnormal bleeding and cervical cytology.

No guidelines or other papers were identified on methods of evaluation beneficial for the early diagnosis of mesenchymal uterine cancers. One study investigated the diagnostic performance of MRI in detection of myomas and adenomyosis of the uterus among women with an enlarged uterus accompanied by gynecologic symptoms or with an asymptomatic pelvic mass who had consented to total abdominal hysterectomy.[64] As part of this study, five uterine sarcomas were diagnosed (3.7%); sensitivity and specificity of MRI for diagnosis of uterine sarcoma was 60% and 99.2%, respectively. The positive and negative predictive value were 75% and 98.5%.

DISCUSSION

Strengths

Several systematic reviews and meta-analyses were available to guide early diagnosis and effective evaluation for uterine cancer and precancer, including the association of endometrial cancer risk with postmenopausal bleeding, polyps, or normal endometrial cells on cytology; the diagnostic accuracy of Pipelle for endometrial sampling; the use hysteroscopic visualization of the endometrial cavity; and transvaginal ultrasound evaluation of women with postmenopausal bleeding for the diagnosis of endometrial cancer or precancer.[5,23,25,33,35,51,60] In addition, expert consensus guidelines on several aspects related to the early diagnosis of uterine cancer or precancer, based on high-quality indirect evidence, are available from ACOG, SGO, and ASCCP.[4,9,31]

Weaknesses and Gaps in Information Pertinent to Making Recommendations

The quality of primary studies and of those included in the systematic reviews and meta-analyses were low to moderate, often based on cross-sectional data or retrospective or prospective cohort studies, with few randomized trials comparing diagnostic strategies. Studies often lacked important variables or did not include heterogenous populations in studies based on age, body mass index, menopausal status, or use of hormone therapy. In addition, pathology variability in the diagnosis of endometrial hyperplasia exists, and endometrial hyperplasia was rarely an independent outcome assessed separately from endometrial cancer. The majority of studies were focused on endometrial cancer or precancer, with very little data identified relevant to other types of uterine cancers.

There are several clinical scenarios for which clear consensus guidelines are not available, including the management of incidental endometrial polyps in asymptomatic postmenopausal women. In addition, the evidence is lacking about when additional testing is warranted if initial evaluation is negative and what the optimal sequence of testing should be, given the availability of multiple testing modalities.

REFERENCES

1. Boruta D II, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;115(1):142–53. doi: 10.1016/j.ygyno.2009.06.011
2. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations. Gynecol Oncol 2021;160(3):817–826. doi: 10.1016/j.ygyno.2020.12.021
3. National Institute for Health and Care Excellence. Testing strategies for Lynch syndrome in people with endometrial cancer. NICE Diagnostics Guidance [DG42] (October 28, 2020). Available at https://www.nice.org.uk/guidance/dg42. Retrieved June 2, 2021.
4. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24(2):102–31. doi: 10.1097/LGT.0000000000000525

5. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med 2018;178(9):1210–22. doi: 10.1001/jamainternmed.2018.2820
6. Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B. Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. Health Technol Assess 2004;8(34):iii–iv, 1–139. doi: 10.3310/hta8340
7. Astrup K, Olivarius NDF. Frequency of spontaneously occurring postmenopausal bleeding in the general population. Acta Obstet Gynecol Scand 2004;83(2):203–07. doi: 10.1111/j.0001-6349.2004.00400.x
8. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 2005;105(3):575–80. doi: 10.1097/01.AOG.0000154151.14516.f7
9. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M, Salom E, Gehrig P. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134(2):385–92. doi: 10.1016/j.ygyno.2014.05.018
10. Lin JF, Slomovitz BM. Uterine sarcoma 2008. Curr Oncol Rep 2008;10(6):512–8. doi: 10.1007/s11912-008-0077-9
11. Nathenson MJ, Ravi V, Fleming N, Wang WL, Conley A. Uterine adenosarcoma: a review. Curr Oncol Rep 2016;18(11):68. doi: 10.1007/s11912-016-0552-7
12. American College of Obstetricians and Gynecologists. Tamoxifen and uterine cancer. ACOG Committee Opinion No. 601. Obstet Gynecol 2014;123(6):1394–7. doi: 10.1097/01.AOG.0000450757.18294.cf
13. Cheewakriangkrai C, Kietpeerakool C, Charoenkwan K, Pattanittum P, John D, Aue-Aungkul A, et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database Syst Rev 2020;3(3):CD013253. doi: 10.1002/14651858.CD013253.pub2
14. Munro MG, Critchley HOD, Fraser IS. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018;143(3):393–408. doi: 10.1002/ijgo.12666
15. American College of Obstetricians and Gynecologists. Diagnosis of abnormal uterine bleeding in reproductive-aged women. Practice Bulletin No. 128. Obstet Gynecol 2012;120(1):197–206. doi: 10.1097/AOG.0b013e318262e320
16. Wise MR, Gill P, Lensen S, Thompson JM, Farquhar CM. Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. Am J Obstet Gynecol 2016;215(5):598.e1–8. doi: 10.1016/j.ajog.2016.06.006
17. Munro MG, Critchley HOD, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet 2011;113(1):3–13. doi: 10.1016/j.ijgo.2010.11.011
18. National Institute for Health and Care Excellence. Heavy menstrual bleeding: assessment and management. NICE Guideline 88 (2018). Available at https://www.nice.org.uk/guidance/ng88. Retrieved May 25, 2021.
19. Lee M, Piao J, Jeon MJ. Risk factors associated with endometrial pathology in premenopausal breast cancer patients treated with tamoxifen. Yonsei Med J 2020;61(4):317–22. doi: 10.3349/ymj.2020.61.4.317

20. Taponeco F, Curcio C, Fasciani A, Giuntini A, Artini PG, Fornaciari G, et al. Indication of hysteroscopy in tamoxifen treated breast cancer patients. J Exp Clin Cancer Res 2002;21(1):37–43.
21. Ceci O, Bettocchi S, Pellegrino A, Impedovo L, Di Venere R, Pansini N. Comparison of hysteroscopic and hysterectomy findings for assessing the diagnostic accuracy of office hysteroscopy. Fertil Steril 2002;78(3):628–31. doi: 10.1016/s0015-0282(02)03246-6
22. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000;89(8):1765–72.
23. Narice BF, Delaney B, Dickson JM. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Family Practice 2018;19(1):135. doi: 10.1186/s12875-018-0817-3
24. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 2002;109(3):313–21. doi: 10.1111/j.1471-0528.2002.01088.x
25. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA 2002;288(13):1610–21. doi: 10.1001/jama.288.13.1610
26. Alborzi S, Parsanezhad ME, Mahmoodian N, Alborzi S, Alborzi M. Sonohysterography versus transvaginal sonography for screening of patients with abnormal uterine bleeding. Int J Gynaecol Obstet 2007;96(1):20–3.
27. de Vries LD, Dijkhuizen FP, Mol BW, Brolmann HA, Moret E, Heintz AP. Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding. J Clin Ultrasound 2000;28(5):217–23. doi: 10.1002/(sici)1097-0096(200006)28:5<217::aid-jcu2>3.0.co;2-b
28. Guven MA, Bese T, Demirkiran F. Comparison of hydrosonography and transvaginal ultrasonography in the detection of intracavitary pathologies in women with abnormal uterine bleeding. Int J Gynecol Cancer 2004;14(1):57–63. doi: 10.1111/j.1048-891x.2004.14105.x
29. Dueholm M, Jensen ML, Laursen H, Kracht P. Can the endometrial thickness as measured by trans-vaginal sonography be used to exclude polyps or hyperplasia in pre-menopausal patients with abnormal uterine bleeding? Acta Obstet Gynecol Scand 2001;80(7):645–51.
30. Ge L, Liu G, Hu K, Huang K, Zhang M, Zhou J, et al. A new risk index combining D-dimer, fibrinogen, HE4, and CA199 differentiates suspecting endometrial cancer from patients with abnormal vaginal bleeding or discharge. Technol Cancer Res Treat 2020;19:1533033819901117. doi: 10.1177/1533033819901117
31. American College of Obstetricians and Gynecologists. The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. ACOG Committee Opinion No. 734. Obstet Gynecol 2018;131(5):e124-e129. doi: 10.1097/AOG.0000000000002631
32. van Hanegem N, Breijer MC, Khan KS, Clark TJ, Burger MPM, Mol BWJ, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. *Maturitas* 2011;68(2):15–64. doi: 10.1016/j.maturitas.2010.11.010
33. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol 2010;116(1):160–67. doi: 10.1097/AOG.0b013e3181e3e7e8

34. Clark TJ, Barton PM, Coomarasamy A, Gupta JK, Khan KS. Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies. BJOG 2006;113(5):502–10. doi: 10.1111/j.1471-0528.2006.00914.x
35. van Hanegem N, Prins MMC, Bongers MY, Opmeer BC, Sahota DS, Mol BWJ, et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2016;197:147–55. doi: 10.1016/j.ejogrb.2015.12.008
36. Yi Y, Bryce CL, Adambekov S, Edwards RP, Goughnour SL, Linkov F. Cost-effectiveness analysis of biopsy strategies for endometrial cancer diagnosis in women with postmenopausal bleeding: Pipelle sampling curette versus dilatation & curettage. Gynecol Oncol 2018;150(1):112–8. doi: 10.1016/j.ygyno.2018.04.565
37. Rotenberg O, Renz M, Reimers L, Doulaveris G, Gebb J, Goldberg GL, et al. Simultaneous endometrial aspiration and sonohysterography for the evaluation of endometrial pathology in women aged 50 years and older. Obstet Gynecol 2015;125(2):414–23. doi: 10.1097/AOG.0000000000000631
38. Tarney CM, Wang G, Bateman NW, Conrads KA, Zhou M, Hood BL, et al. Biomarker panel for early detection of endometrial cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Obstet Gynecol 2019;221(5):472.e1–10. doi: 10.1016/j.ajog.2019.06.005
39. Perez-Sanchez C, Colas E, Cabrera S, Falcon O, Sanchex-del-Rio A, Garcia E, et al. Molecular diagnosis of endometrial cancer from uterine aspirates. Int J Cancer 2013;133(10):2383–91. doi: 10.1002/ijc.28243
40. Dueholm M, Hjorth IMD, Dahl K, Pedersen LK, Ortoft G. Identification of endometrial cancers and atypical hyperplasia: development and validation of a simplified system for ultrasound scoring of endometrial pattern. Maturitas 2019;123:15–24. doi: 10.1016/j.maturitas.2019.01.017
41. Epstein E, Skoog L, Isberg PE, De Smet F, De Moor B, Olofsson PA, et al. An algorithm including results of gray-scale and power Doppler ultrasound examination to predict endometrial malignancy in women with postmenopausal bleeding. Ultrasound Obstet Gynecol 2002;20(4):370–6. doi: 10.1046/j.1469-0705.2002.00800.x
42. Emoto M, Tamura R, Shirota K, Hachisuga T, Kawarabayashi T. Clinical usefulness of color Doppler ultrasound in patients with endometrial hyperplasia and carcinoma. Cancer 2002;94(3):700–6. doi: 10.1002/cncr.10208
43. Samulak D, Wilczak M, Englert-Golon M, Michalska MM. The diagnostic value of evaluating the maximum velocity of blood flow in the uterine arteries of women with postmenopausal bleeding. Arch Gynecolo Obstet 2011;284(5):1175–8. doi: 10.1007/s00404-010-1824-3
44. Michail G, Karahaliou A, Skiadopoulos S, Kalogeropoulou C, Terzis G, Boniatis I, et al. Texture analysis of perimenopausal and post-menopausal endometrial tissue in grayscale transvaginal ultrasonography. Br J Radiol 2007;80(956):609–16. doi: 10.1259/bjr/13992649
45. Alcazar JL, Galvan R. Three-dimensional power Doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium. Am J Obstet Gynecol 2009;200(1):44.e1–6. doi: 10.1016/j.ajog.2008.08.027
46. Yasa C, Dural O, Bastu E, Ugurlucan FG, Nehir A, Iyibozkurt AC. Evaluation of the diagnostic role of transvaginal ultrasound measurements of endometrial thickness to detect endometrial malignancy in asymptomatic postmenopausal women. Arch Gynecol Obstet 2016;294(2):311–6. doi: 10.1007/s00404-016-4054-5
47. Breijer MC, Peeters JAH, Opmeer BC, Clark TJ, Verheijen RHM, Mol BWJ, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women:

a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012;40(6):621–29. doi: 10.1002/uog.12306
48. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol 2004;24(5):558–65. doi: 10.1002/uog.1704
49. Li Z, Lei L. Risk of malignancies among asymptomatic postmenopausal women with thickened endometrium: a cohort study. Medicine (Baltimore) 2019;98(6):e14464. doi: 10.1097/MD.0000000000014464
50. Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, et al. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. Am J Obstet Gynecol 2009;200(3):235.e1–6. doi: 10.1016/j.ajog.2008.09.876
51. Sasaki LMP, Andrade KRC, Figueiredo ACMG, Wanderley MDS, Pereira MG. Factors Associated with malignancy in hysteroscopically resected endometrial polyps: a systematic review and meta-analysis. J Minim Invasive Gynecol 2018;25(5):777–85. doi: 10.1016/j.jmig.2018.02.004
52. Uglietti A, Buggio L, Farella M, Chiaffarino F, Dridi D, Vercellini P, et al. The risk of malignancy in uterine polyps: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2019;237:48–56. doi: 10.1016/j.ejogrb.2019.04.009
53. Litta P, Di Giuseppe J, Moriconi L, Delli Carpini G, Piermartiri MG, Ciavattini A. Predictors of malignancy in endometrial polyps: a multi-institutional cohort study. Eur J Gynaecol Oncol 2014;35(4):382–6.
54. Wethington SL, Herzog TJ, Burke WM, Sun X, Lerner JP, Lewin SN, et al. Risk and predictors of malignancy in women with endometrial polyps. Ann Surg Oncol 2011;18(13):3819–23. doi: 10.1245/s10434-011-1815-z
55. Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, et al. The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol 2004;115(2):206–10. doi: 10.1016/j.ejogrb.2004.02.002
56. Baiocchi G, Manci N, Pazzaglia M, Giannone L, Burnelli L, Giannone E, et al. Malignancy in endometrial polyps: a 12-year experience. Am J Obstet Gynecol 2009;201(5):462.e1–4. doi: 10.1016/j.ajog.2009.05.055
57. American College of Obstetricians and Gynecologists. The use of hysteroscopy for the diagnosis and treatment of intrauterine pathology. ACOG Committee Opinion No. 800. Obstet Gynecol 2020;135(3):e138–48. doi: 10.1097/AOG.0000000000003712
58. Cibas ES, Chelmow D, Waxman AG, Moriarty AT. Endometrial cells: the how and when of reporting. In: Nayar R, Wilbur DC, editors. The Bethesda System for reporting cervical cytology: definitions, criteria, and explanatory notes, 3rd ed. Switzerland: Springer International Publishing; 2015. p. 91–102.
59. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2013;17(5 Suppl 1):S1–27.
60. Canfell K, Kang YJ, Clements M, Moa AM, Beral V. Normal endometrial cells in cervical cytology: systematic review of prevalence and relation to significant endometrial pathology. J Med Screen 2008;15(4):188–98. doi: 10.1258/jms.2008.008069
61. Li Z, Gilbert C, Yang H, Zhao C. Histologic follow-up in patients with Papanicolaou test findings of endometrial cells: results from a large academic women's hospital laboratory. Am J Clin Pathol 2012;138(1):79–84. doi: 10.1309/AJCP07DCKKZFKSDL

62. Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Relationship of atypical glandular cell cytology, age, and human papillomavirus detection to cervical and endometrial cancer risks. Obstet Gynecol 2010;115(2 Pt 1):243–8. doi: 10.1097/AOG.0b013e3181c799a3
63. Pradhan D, Li Z, Ocque R, Patadji S, Zhao C. Clinical significance of atypical glandular cells in Pap tests: an analysis of more than 3000 cases at a large academic women's center. Cancer Cytopathol 2016;124(8):589–95. doi: 10.1002/cncy.21724
64. Stamatopoulos CP, Mikos T, Grimbizis GF, Dimitriadis AS, Efstratiou I, Stamatopoulos P,et al. Value of magnetic resonance imaging in diagnosis of adenomyosis and myomas of the uterus. J Minim Invasive Gynecol 2012;19(5):620–6. doi: 10.1016/j.jmig.2012.06.003

Uterine Cancer Literature Review
Appendix 7. Overview of Diagnosis and Care Coordination for the Primary Care Provider

Primary Reviewer: Rebecca Brooks, MD
Secondary Reviewer: Arjeme Cavens, MD

INTRODUCTION

This document addresses what the primary care provider should know about diagnosis and care coordination for a patient with endometrial cancer. The following primary research question was posed:

> **What are the current major society or health service guidelines for risk assessment, screening, prevention, and survivor care of patients with uterine cancer?**

The PICO format was used to direct the literature search:

P (Patient, problem, or population): Adults at risk for or with a diagnosis of uterine cancer
I (Intervention): Major society or health service guidelines for uterine cancer related to medical history; physical examination; appropriate laboratory, pathology, and imaging tests; consideration of age-related factors; or considerations for referral to gynecologic oncology
C (Comparison, control, or comparator): One guideline versus another
O (Outcome[s]): Survival rate, quality-adjusted life years, receipt of standard care of treatment, or mortality rates

METHODS

The American College of Obstetricians and Gynecologists (ACOG) Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed (for references not indexed in Ovid) databases for all relevant references. All identified articles were categorized by level of evidence. Additional review was carried out to identify relevant guidelines published by ACOG, the American Cancer Society, the National Comprehensive Cancer Network (NCCN), the Society of Gynecologic Oncology, the European Society for Medical Oncology, the National Institute for Health and Care Excellence, the American College of Radiology, the U.S. Preventive Services Task Force, and the American Society for Reproductive Medicine. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of selected articles. The bibliographies of included articles were reviewed to identify other relevant works not identified by the primary search.

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

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

In response to feedback from the Uterine Cancer Evidence Review Conference, a section was added to address what constitutes abnormal vaginal bleeding and how to identify it. Because this feedback came after the ACOG

Chelmow D, Brooks R, Cavens A, Cavens A, Huber-Keener K Scott DM, et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.

literature search was performed, the primary reviewer conducted an independent search using key terms and identified related articles highlighted in PubMed.

RESULTS

Literature Summary

The literature summary prioritized the reviews highlighted by the ACOG team, including high-level reviews and the Society of Gynecologic Oncology and ACOG consensus statements and committee opinions.

An in-depth review was performed of 73 level 1 systematic reviews or meta-analyses provided by ACOG. Forty were excluded based on title or subject. The remaining 33 were further evaluated, of which 16 were relevant and were included. The search also identified 15 level III reviews, of which 4 were relevant and further evaluated. Two of these were included, and two were rejected after review of the abstract or manuscript. One NCCN guideline document was included, totaling 19 references included from the ACOG literature search. An additional 48 relevant studies were identified through author review and prior knowledge of the related literature, including references added based on stakeholder input.

Summary of Data

Diagnosis and Care Coordination for the Primary Care Provider

MEDICAL HISTORY

A thorough medical history is essential when considering risk factors for endometrial cancer, as well as when considering surgical risk and treatment options for patients with a new diagnosis of endometrial cancer. According to the ACOG Committee Opinion, *The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women with Postmenopausal Bleeding*, "Clinical risk factors for endometrial cancer, including but not limited to age, obesity, use of unopposed estrogen, specific medical comorbidities (eg, polycystic ovary syndrome, type 2 diabetes mellitus, atypical glandular cells on screening cervical cytology), and family history of gynecologic malignancy, also should be considered when evaluating postmenopausal bleeding."[1]

This review did not identify major society guidelines regarding what questions to ask when taking a medical history for a patient with newly diagnosed endometrial cancer. Risk factors for endometrial cancer are discussed extensively in Appendix 3, Uterine Cancer Risk Factors. A thorough initial medical history may include questions about risk factors such as obesity, anovulation, diabetes, and polycystic ovarian syndrome (PCOS).[2] Thyroid disorders may also impact bleeding patterns. Medications that affect endometrial cancer risk include unopposed estrogen hormone therapy, which can cause iatrogenic endometrial cancer if given without progesterone, resulting in a 20-fold increased risk of cancer.[3] Medications, including nonsteroidal anti-inflammatory drugs, warfarin, heparin derivatives, direct thrombin inhibitors, and other anticoagulants, and herbal supplements, such as ginseng, gingko, and motherwort, may affect bleeding patterns. Tamoxifen, which is a partial agonist and can be pro-estrogenic to the endometrial lining, may increases the risk in a time-dependent fashion, with an up to fourfold risk of endometrial cancer after 5 years of use.[2] Oral contraceptives, progestins, and levonorgestrel-releasing intrauterine devices (LNG-IUDs) may decrease the risk of endometrial cancer.[4] Recording a patient's reproductive history is also pertinent, as nulliparity, infertility, earlier menarche, and later menopause are known to be risk factors, and multiparity is a protective factor.[5–7]

Other medical comorbidities that may affect surgical risk include cardiovascular disease, history of myocardial infarction, stroke, thromboembolism, and diabetes. It is important to identify patients taking anticoagulants, which can worsen irregular bleeding, as decisions will need to be made about the timing and safety of stopping them. Because the management of uterine cancer is mostly surgical, facilitating updated medical evaluation may be important for risk stratification, surgical decision making, and optimization.

The link between endometrial cancer and obesity is noteworthy. Almost 60% of endometrial cancer in the United States is attributed to obesity, a risk which increases by at least 50% for each 5-point increase in body mass index (BMI).[2] Moreover, premenopausal obese women are more likely to experience chronic anovulation, further increasing their risk of endometrial cancer.[5] Therefore, the threshold may be lower to evaluate for endometrial cancer in young premenopausal women who are obese and have abnormal or anovulatory bleeding patterns given the increased risk for endometrial cancer in this population.[8] The history obtained during patient encounters may elicit bleeding patterns, which might trigger a workup and necessitate intervention. Irregular bleeding and discharge are the most common presenting symptoms in patients with endometrial cancer.[5]

Vaginal Bleeding Patterns. A thorough history of the patterns, frequency, and heaviness of bleeding is critical. According to ACOG, "A medical history should include questions about menstrual bleeding patterns, severity, pain associated with bleeding, and family history."[8] An in-depth review of what constitutes abnormal uterine bleeding is beyond the scope of this review. (See the ACOG Practice Bulletin, *Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women*, and the ACOG Committee Opinion, *The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women with Postmenopausal Bleeding*.) However, key issues are described here.

Premenopausal patients. This review did not identify one consistent definition of what constitutes normal menses, though normal menses usually lasts up to 8 days.[9] Bleeding lasting longer and intermenstrual bleeding may be considered abnormal. Cyclic bleeding, even if heavy, is less likely to be a sign of carcinoma.[10] Variation exists in the definition of normal and abnormal menstrual patterns. The International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Committee has described classifications for causes of abnormal uterine bleeding (See Table 1).[9] ACOG describes slightly different ranges, with a normal menstrual flow lasting 5 days and the normal menstrual cycle lasting 21 to 35 days.[8]

Table 1: Normal and Abnormal Bleeding Patterns in Premenopausal Patients*

Parameter	Normal	Abnormal	☐
Frequency	Absent (no bleeding) = amenorrhea		☐
	Infrequent (>38 days)		☐
	Normal (≥24 and ≤38 days)		☐
	Frequent (<24 days)		☐
Duration	Normal (≤8 days)		☐
	Prolonged (>8 days)		☐
Regularity	Normal or "regular" (shortest to longest cycle variation: ≤7–9 days)		☐

	Irregular (shortest to longest cycle variation: ≥10 days)		☐
Flow volume (patient determined)	Light		☐
	Normal		☐
	Heavy		☐
Intermenstrual bleeding	None		☐
	Random		☐
	Cyclic (predictable)	Early cycle	☐
		Mid cycle	☐
		Late cycle	☐
Unscheduled bleeding on progestin ± estrogen gonadal steroids (birth control pills, rings, patches, or injections)	Not applicable (not on gonadal steroid medication)		☐
	None (on gonadal steroid medication)		☐
	Present		☐

*Reprinted from Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions [published correction appears in Int J Gynaecol Obstet. 2019 Feb;144(2):237]. Int J Gynaecol Obstet 2018;143(3):393-408. doi:10.1002/ijgo.12666

Abnormal uterine bleeding can be further classified as acute or chronic. Chronic nongestational abnormal uterine bleeding consists of uterine bleeding that is abnormal in volume, duration, frequency, or regularity and has been present for 6 months or longer. Acute abnormal uterine bleeding is bleeding that in the clinician's opinion justifies immediate intervention.[9] The acronym PALM-COEIN has been used to describe the causes of abnormal uterine bleeding: PALM refers to structural causes, including polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia; COEIN refers to nonstructural causes, including coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and causes not otherwise classified.[8]

This review did not identify any uniform, data-driven concrete guidelines about when to perform endometrial sampling. According to FIGO, "Selection for endometrial sampling is based on a combination of risk factors for the presence of premalignant or malignant changes, comprising some combination of age, personal, and genetic risk factors, and [transvaginal ultrasound] screening for endometrial echo-complex thickness."[9] Some studies have suggested that endometrial sampling be considered for patients with abnormal uterine bleeding using a typical age cutoff, usually age 45.[11] Because obesity is a major contributor to the risk of precancerous and malignant endometrial conditions, BMI should be considered in deciding whether to sample the endometrium in younger patients.[12] Additionally, prolonged amenorrhea, especially in patients with PCOS, is linked to endometrial cancer risk and may warrant evaluation. According to ACOG, "Endometrial tissue sampling should be performed in patients with abnormal uterine bleeding who are older than 45 years as a first-line test. Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent abnormal uterine bleeding."[8]

Chelmow D, Brooks R, Cavens A, Cavens A, Huber-Keener K Scott DM, et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.

Perimenopausal patients. The transition between a premenopausal and postmenopausal state (also known as perimenopause) varies in time (median: 4–11 years).[13] Perimenopause is characterized by significant variability in age of onset, duration, and bleeding patterns.[10] Many women demonstrate signs of perimenopause in their 40s, though some may have signs in their 30s and others as late as their 50s. During the early menopause transition, consecutive menstrual cycles develop a persistent difference in length of 7 days or more, or the woman may experience one or more skipped cycles. Gradually, longer intervals of amenorrhea occur, typically lasting 60 days or more during the late menopausal transition, eventually reaching menopause. During this time, levels of inhibin B, anti-Müllerian hormone, and estradiol decrease, while levels of follicle-stimulating hormone and the likelihood of hot flashes increase.[14] Because bleeding patterns vary among women in the perimenopausal period, it can be difficult to discern normal from abnormal bleeding. Transvaginal ultrasonography remains the primary imaging test of the uterus for the evaluation of suspected abnormal bleeding.[10] (For an in-depth review of abnormal uterine bleeding in perimenopause, see Goldstein SR, Lumsden MA. Abnormal uterine bleeding in perimenopause. *Climacteric*. 2017;20(5):414–420. doi: 10.1080/13697137.2017.1358921.)

This review did not identify a specific age after which continued menstrual bleeding is considered abnormal. The average age of menopause is 51 years; ongoing normal periods far beyond what is considered within normal age range might warrant further investigation. Hormonal levels, such as serum follicle-stimulating hormone, can also be assessed to understand where a patient falls in the menopausal spectrum.

Postmenopausal patients. Menopause is typically defined as a period of amenorrhea lasting 12 months or longer; bleeding after that point is considered postmenopausal. Although only approximately 10% of postmenopausal bleeding is caused by cancer, and atrophy is a more common cause, postmenopausal bleeding is the most common symptom of endometrial cancer and therefore warrants evaluation.[15,16] The Southern California Permanente Medical Group's Abnormal Uterine Bleeding Working Group suggests that the initial assessment of spontaneous postmenopausal bleeding be performed with either endometrial sampling or ultrasonography, and those patients who have an endometrial thickness less than 4 mm should be observed.[17]

Other Symptoms. Severe fatigue, weakness, palpitations, or dyspnea on exertion could be indicators of related anemia. Pain may reflect local or metastatic disease. Although pelvic cramping similar to that of menstruation is not uncommon, severe sidewall pain, back pain, or sciatica could be symptoms of nodal or other metastatic disease.[18] Early satiety and bloating can be signs of peritoneal carcinomatosis.

FAMILY HISTORY

Patients should be assessed for a family history of endometrial or colon cancer.[8] Although awareness has recently heightened regarding the association between these cancers and Lynch syndrome, prior generations may not have been assessed or screened for Lynch syndrome. Even in the absence of a diagnosis of Lynch syndrome, women with a first-degree family member with endometrial cancer or colorectal cancer are at increased risk of developing endometrial cancer.[19] Cancers related to Lynch syndrome include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestinal cancers. Referral to a genetic counselor or testing for Lynch syndrome should be considered in any patient with the following:[18]

- Personal history of colorectal cancer or endometrial cancer that was diagnosed before age 50
- Personal history of any other cancer related to Lynch syndrome

- Any relative diagnosed with a cancer related to Lynch syndrome before age 50
- Two or more relatives with a cancer related to Lynch syndrome, diagnosed at any age
- A known family history of Lynch syndrome

Women with Lynch syndrome have a lifetime risk of endometrial cancer of 40–60%.[2] The median age of onset is slightly younger for women with *MLH1* or *LSH2* germline mutations (48 years) than those with an *MSH6* mutation (53 years).[20] It is important to identify these patients, as other screening mechanisms may be considered, and risk-reducing surgery after childbearing may be an option. (See Appendix 4, Prevention and Risk Reduction for Uterine Cancer, and Appendix 5, Screening for Uterine Cancer.)

Patient Education

Educating patients on the warning signs of endometrial cancer is crucial for early diagnosis. Patients should be aware that any postmenopausal bleeding deserves immediate evaluation, and they should be empowered to discuss such bleeding with their care provider. A British prospective survey of 142 patients identified a relatively low awareness of symptoms that might indicate endometrial cancer. Although 86.6% of patients presented with vaginal bleeding, almost half reported not being aware that bleeding could be a symptom of cancer. Furthermore, 52% of patients waited more than a month and 12% waited more than 6 months prior to presenting to their primary physician.[21] Unfortunately, a recent meta-analysis of health education interventions with the aim of promoting early presentation and referral for women with symptoms of endometrial cancer failed to demonstrate effectiveness of these interventions.[22] These findings underscore the need for improved patient education.

Physical Examination

A complete physical examination is an important part of initial evaluation for a patient diagnosed with or suspected to have endometrial cancer. Lymph node enlargement in the cervical, supraclavicular, and inguinal regions may be suggestive of metastatic disease. A cardiopulmonary examination may identify abnormalities that may influence surgical risk (such as a murmur, irregular heartbeat, or wheezing); it can also assess for decreased breath sounds suggestive of a pleural effusion. Abdominal examination may reveal surgical scars that may lend information about prior surgical procedures performed. It may also reveal abdominal distention or a fluid wave that may suggest ascites, a pelvic mass, or uterine enlargement.

The pelvic examination is important to evaluate and confirm the source of bleeding, assess the size and mobility of the uterus for surgical planning, assess for disease spread, and evaluate for other synchronous problems.[18] According to the ACOG Practice Bulletin, *Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women*, "A pelvic exam also should be performed as part of the physical examination, and in adults, this should include speculum and bimanual exam. A speculum examination should be performed to assess for cervical or vaginal lesions, with appropriate tissue sampling when abnormalities are noted. A bimanual examination should be performed to assess the size and contour of the uterus."[8]

Evaluation for coexisting cervical dysplasia or cancer using human papillomavirus (HPV)-based testing (either cotesting with cervical cytology or primary HPV testing) may be considered in patients with a recent history of HPV or outdated cervical cancer screening results, in conjunction with U.S. Preventive Services Task Force or American Cancer Society guidelines.[23,24] Although endometrial cancer can cause irregular bleeding, it is possible to have a synchronous cervical cancer, which may affect surgical decision making. Careful evaluation

of the vagina is also important to exclude metastases. A rectal examination is a helpful component of the physical examination. Although beyond the scope of the primary care provider, for patients with bulky cervical involvement, radical hysterectomy or preoperative radiation therapy may be considered.

Appropriate Laboratory, Pathology, and Imaging Tests

Preoperative serum evaluation of CA 125 may be useful in certain situations, especially in patients with serous carcinoma.[25] Elevations of CA 125 have been associated with extrauterine disease, including lymph node involvement in some studies, but not all.[5] It is also reasonable to defer this evaluation to the gynecologic oncologist. A complete blood count should be ordered, and a comprehensive metabolic profile should be considered to evaluate renal function, liver function, and nutritional status to inform decision making.[18]

As endometrial cancer may be the presenting cancer in approximately 50% of patients with Lynch syndrome, a diagnosis of endometrial cancer affords an opportunity to identify patients and family members at risk of endometrial and other cancers.[26,27] Many institutions now reflexively test all patients with endometrial cancer, looking at either the biopsy or hysterectomy specimens with immunohistochemistry for the Lynch-related proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or using polymerase chain reaction to test for microsatellite instability (MSI). NCCN and ACOG support this practice of universal testing.[18,28] According to NCCN guidelines:[18]

> Universal testing of endometrial carcinomas for MMR [mismatch repair] proteins/MSI is recommended.
> - Testing may be performed on the initial biopsy or [dilation and curettage] material or the final hysterectomy specimen.
> - MLH1 loss should be further evaluated for promoter methylation to assess epigenetic process.
> - Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended.
> - For those who are MMR intact/MSI stable or those who have not been screened, but have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing is recommended.

MMR testing also can be potentially informative for treatment options, as immunotherapy is approved as second-line systemic therapy for patients with metastatic disease who are MMR deficient/MSI high.

Obtaining a diagnosis of endometrial cancer preoperatively provides many benefits, such as classification of the histologic subtype for risk stratification and treatment planning. Although frozen section performs relatively well for diagnosing and grading cancer, permanent section has better accuracy, and discrepancy between frozen section and final pathology is not uncommon.[29] A recent systematic review and meta-analysis evaluating intraoperative frozen section in 6,387 women in 35 studies found a pooled sensitivity of 85% (95% confidence interval [CI]: 81–88%) and specificity of 97% (95% CI: 96–98%).[29]

Relevant imaging modalities in the diagnosis and evaluation of endometrial cancer include computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and positron-emission tomography–computed tomography (PET/CT). Ultrasonography is often performed at the time of presentation and is useful for surgical planning in patients with low-grade disease when uterine size cannot be appreciated on examination because of body habitus or other factors. Transvaginal ultrasonography has moderate diagnostic performance for the evaluation of deep myometrial invasion. A recent systematic review and meta-analysis including 24

articles evaluating the utility of transvaginal ultrasonography to identify deep myometrial invasion found a pooled sensitivity of 82% (95% CI: 76–87%), specificity of 81% (95% CI: 76–85%), positive likelihood ratio of 4.3 (95% CI: 3.6–5.3), and negative likelihood ratio of 0.22 (95% CI: 0.16–0.3).[30]

MRI is helpful for assessing for depth of invasion in young patients who desire fertility-sparing treatment, for evaluation of the primary cancer site when it is unclear whether a malignancy is arising from the uterus or cervix, and for assessing for cervical involvement or parametrial extension.[18] Diffusion-weighted MRI has excellent ability to detect deep myometrial invasion, with a sensitivity of 90% and specificity of 89%.[31] A meta-analysis of diffusion-weighted MRI for the preoperative assessment of endometrial cancer invasion found high sensitivity (0.9) and specificity (0.89) for deep myometrial invasion.[31]

CT imaging can be useful in some patients to assess for extrauterine metastatic disease. Candidates include patients with high-risk disease, those with symptom profiles raising suspicion for long-standing disease, and those in whom metastatic disease is suspected. Because high-risk histologies (uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and high-grade endometrioid or undifferentiated carcinoma) more often demonstrate extrauterine disease at diagnosis, imaging with CT of the chest, abdomen, and pelvis and CA 125 evaluation may be considered at diagnosis.[18,32] For low-grade disease, chest X-ray is often sufficient for evaluating for metastatic disease in the absence of other risk factors. Routine CT for low-grade disease is not recommended, as it not cost-effective and rarely affects management.[33]

PET/CT has relatively high specificity for the detection of nodal and other metastases, especially for larger sites of disease.[34] For metastatic lesions larger than 10 mm, the detection rate of PET/CT was 100% compared with only 12% for lesions measuring 4 mm or less.[34] The diagnostic accuracy for lymph node metastases is high, with a sensitivity of 63–72% and specificity of 94–95%, as well as excellent capability for detecting disease recurrence in patients in whom recurrent or metastatic disease is a concern.[35-37] Because CT is frequently sufficient, PET is often reserved for settings in which a lesion is visible but of indeterminate significance, such as in the liver, lung, or lymph nodes, or to evaluate for disease that CT may have missed in the metastatic setting. The decision to use PET may be more appropriately made by the gynecologic oncologist or treating provider.[38]

Special Considerations for Treatment

Treatment decisions should be made after referral to a gynecologic oncologist, but primary care and general gynecology practitioners should be knowledgeable about treatment approaches to facilitate preliminary counseling of patients at the time of diagnosis. Young patients may be candidates for fertility-sparing options. Fertility-sparing treatment is often an option for candidates with low-grade disease and without evidence of deep invasion as assessed by MRI, but only after evaluation by a gynecologic oncologist. Both oral progestins and LNG-IUDs are treatment options for appropriate candidates, with initial response rates of 66–91% of patients with endometrial intraepithelial neoplasia (EIN) and 48–54% of patients with cancer.[39,40]

Total hysterectomy with removal of both fallopian tubes and ovaries is standard surgical treatment. However, two 2016 large database studies demonstrated that ovarian conservation may be reasonable for patients younger than 50 with grade 1–2, early-stage endometrial cancer, without worsening cancer-related survival, and with a decreased risk of cardiovascular events.[41,42] There is a risk of a synchronous ovarian malignancy, especially in patients with Lynch syndrome; therefore, the decision about bilateral salpingo-oophorectomy versus preservation should be individualized.[5]

Elderly patients may be more likely to have high-risk disease, for which preoperative imaging and medical clearance may be indicated. Additionally, for frail patients with poor functional status who are not surgical candidates or do not desire surgical intervention, definitive radiation may be curative.[43,44] Hormonal therapy with oral progestin, LNG-IUD, or alternating progestin and tamoxifen can also be considered in patients with low-grade disease who are not candidates for surgery.[45] Older patients also represent a special population for whom the expected benefits and related toxicity of treatment need to be balanced against a decreased life expectancy and decreased tolerance to stress.[46](See the NCCN guidelines for more information about cancer in older adults: Older adult oncology. Version 1.2020 – February 7, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf.)

Considerations for Referral to a Gynecologic Oncologist

ENDOMETRIAL HYPERPLASIA/EIN GRADING SYSTEMS

Endometrial cancer precursors can be classified using several different nomenclature systems. For decades, endometrial hyperplasia was classified into four categories using the 1994 World Health Organization classification of endometrial hyperplasia, which correlated with the risk of progression to cancer. These categories were simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia.[47] Complex atypical hyperplasia coexists with cancer in approximately 37–48% of patients who undergo hysterectomy for this condition, and therefore consideration of referral to a gynecologic oncologist is justified in these patients.[48] In 2014, the World Health Organization revised its classification system into a two-class EIN diagnostic schema: hyperplasia without atypia (non-neoplastic) and atypical hyperplasia (EIN).[49] EIN is the precursor to type 1 endometrial carcinoma. The two-category classification may result in more agreement among pathologists and differentiates more clearly those entities that are premalignant.[50] Hysteroscopy with image-directed sampling via dilation and curettage may provide the best opportunity to confirm a truly premalignant lesion and exclude a possible underlying endometrial carcinoma.[50,51]

When appropriate, total hysterectomy, including removal of the cervix and without morcellation, provides definitive therapy and excludes a potential underlying cancer. Although the likelihood of a deeply invasive or high-grade cancer that would require surgical staging is low, the risk of having concurrent cancer is 42.6–62.5%, with an approximately 11% chance of deep myometrial invasion.[52,53] Moreover, studies looking at the role of lymph node dissection in patients with a preoperative diagnosis of complex atypical hyperplasia/EIN have demonstrated that the risk of lymph node involvement is approximately 2.5%, and that a lymph node dissection was indicated and affected clinical decision making in 28% of patients who were thought to have only EIN.[54,55] No consensus recommendations address whether all patients with EIN should be referred to a gynecologic oncologist. However, 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.

INDICATIONS FOR REFERRAL

Management decisions for patients with endometrial cancer have important, complex, and subtle nuances that should be carefully considered. According to ACOG:[3]

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.

When possible, accounting for a patient's disease distribution, medical comorbidities, and functional status, surgery is standard treatment for endometrial cancer. Minimally invasive surgical management for endometrial cancer has been shown in two randomized trials to be associated with improved short-term quality of life, fewer complications, and no difference in overall survival when compared with the historic open approach.[56,57] Moreover, risk factors for endometrial cancer, such as obesity and diabetes, also increase the risk of wound infections and other complications that are higher with an open surgical approach.

Lymph node assessment is an important consideration in endometrial cancer. The extent to which to perform a staging lymphadenectomy and in which candidates has been a matter of debate for decades. Identification of nodal metastases allows for tailored chemotherapy and radiation that can be curative, yet two randomized trials failed to demonstrate a survival advantage associated with staging lymphadenectomy, with the caveat that differences in adjuvant treatment administered may have contributed to these findings.[58,59] Additionally, a full staging lymphadenectomy carries with it higher blood loss, longer operative time, the risk of lymphoceles, and the risk of lymphedema, which can be permanent in approximately 30% of patients.[60] Moreover, low-grade, early-stage disease is associated with a very low risk of lymph node involvement, and the risk of lymph node involvement increases with increasing grade, tumor size, depth of invasion, and lymph vascular space invasion.[61]

This spectrum of risk versus benefit has led many gynecologic oncologists to adopt an individualized approach, such as the Mayo Criteria. The utility of these criteria—a tumor size of less than 2 cm, less than 50% myometrial invasion, and grade 1–2 endometrioid histology—were confirmed through a large Gynecologic Oncology Group ancillary study, with a lymph node metastases risk of only 0.8% in this population.[62]

Sentinel lymph node assessment in endometrial cancer has recently evolved as an accurate and refined alternative to full staging. A 2017 multicenter, prospective, cohort study (Determining the Sensitivity of Sentinel Lymph Nodes Identified with Robotic Fluorescence Imaging [FIRES] trial) demonstrated that sentinel lymph node assessment is an alternative to a full staging lymphadenectomy. Injection of indocyanine green into the cervix with near-infrared assessment, followed by complete lymphadenectomy, identified sentinel lymph nodes in 86% of patients, with a sensitivity of 97.2%, a negative predictive value of 99.6%, and a false-negative rate of only 2.8%.[63] Sentinel lymph node assessment also provides other potential advantages for patients. The sentinel lymph nodes are analyzed by ultrastaging, allowing for identification and more thorough assessment of the most at-risk lymph nodes, though the significance of small-volume isolated tumor cells remains unclear.[64] Additionally, the risk of lymphedema is lower with a sentinel lymph node approach compared with full lymphadenectomy.[65] Especially in the era of sentinel lymph node assessment, all patients with proven endometrial carcinoma may benefit from gynecologic oncology referral, because once the hysterectomy has been completed, patients are not candidates for a sentinel lymph node dissection and miss a window of opportunity for this refined approach to staging. Moreover, the decision to perform a second completion staging surgery can be a difficult one, and often a second surgery results in a harder recovery for a patient. Furthermore, approximately 20% of patients with presumed early-stage disease are found to have metastatic disease at the

time of surgery, and management of these patients by a gynecologic oncologist improves cancer related outcomes.[5]

Considerations for Patients with Known or Suspected Uterine Sarcoma

The medical history and physical examinations are similar for the patient with known or suspected uterine sarcoma. Symptoms can be difficult to differentiate from uterine fibroids; they include vaginal bleeding in 56% of patients, increased abdominal girth or a palpable mass in 52%, and pelvic pain or pressure in 22%.[66] 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 and definitively diagnose a uterine sarcoma.[66] MRI may be the best method for characterizing uterine masses concerning for sarcoma.[66] Decision tree algorithm modeling has also been used, combining T2 and T1 signaling, with 77.8% specificity for uterine leiomyosarcoma; however, positive predictive value was 67.74% (CI: 48.63–83.82%), and negative predictive value was only 83.33% (CI: 68.84–93.3%), highlighting the difficulty in accurate preoperative diagnosis based on imaging.[67] Diffusion-weighted MRI and fused PET/MRI are imaging modalities that are evolving and may be applicable for these patients in the future.[68] Given the high risk of metastatic disease to distant sites, CT of the chest, abdomen, and pelvis is recommended at the time of diagnosis.[18] Data on the utility of PET/CT in this setting are limited.[69] In cases of suspected malignancy based on a rapidly growing uterine mass, an enlarging mass in a postmenopausal female, evidence of metastases, concerning characteristics of the mass on imaging, or other concerns, referral to a gynecologic oncologist may be considered.

DISCUSSION

Obtaining a bleeding history to identify any abnormal bleeding patterns that could be suggestive of pathology is crucial to the diagnosis of endometrial cancer. A comprehensive medical history that covers symptoms, medications, reproductive history, and family history is an important first step in evaluating patients with uterine cancer. The pelvic examination is important to assess for locoregional disease, evaluate concerns about distant disease, and plan imaging and management. Patients with low-grade disease usually only need a chest X-ray, while patients with high-grade endometrial cancer or uterine sarcoma benefit from a CT of the chest, abdomen, and pelvis. Ultimately, patients with known or suspected uterine cancer should be offered an expeditious referral to a gynecologic oncologist or other provider with expertise in the management of uterine cancer.

Strengths

There is a vast body of knowledge about the risk factors, diagnostic strategies, and treatment considerations for endometrial cancer patients being evaluated by the primary care provider.

Weaknesses

It is difficult to concisely and comprehensively cover a vast body of literature and synthesize what is most relevant to the primary care physician.

Gaps

- Interventions to promote early presentation and referral for patients with endometrial cancer are lacking and ineffective. Opportunity in this area clearly exists, and the primary care provider is central to this process.
- Limited evidence was identified to address after what age continued vaginal bleeding is abnormal and justifies workup.
- There is a fair amount of ambiguity about what constitutes abnormal uterine bleeding and what justifies evaluation for endometrial hyperplasia and cancer. The decision is often left to the provider.
- Further educational resources for providers and patients may be beneficial.
- Guidelines about a targeted history, examination, and appropriate workup for a patient with newly diagnosed endometrial cancer are lacking.
- This review did not identify clear guidelines for whether all patients with EIN should be referred to a gynecologic oncologist.

REFERENCES

1. American College of Obstetricians and Gynecologists. The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. ACOG Committee Opinion No. 734. Obstet Gynecol 2018;131(5):e124-e129. doi: 10.1097/AOG.0000000000002631
2. Lu KH, Broaddus RR. Endometrial cancer. N Engl J Med 2020;383(21):2053–64. doi: 10.1056/NEJMra1514010
3. American College of Obstetricians and Gynecologists. Endometrial cancer. Practice Bulletin No. 149. Obstet Gynecol 2015;125(4):1006–26. doi: 10.1097/01.AOG.0000462977.61229.de
4. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol 2015;16(9):1061–70. doi: 10.1016/S1470-2045(15)00212-0
5. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations. Gynecol Oncol 2021;160(3):817-826. doi: 10.1016/j.ygyno.2020.12.021.
6. Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 2015;5:14051. doi: 10.1038/srep14051
7. Wu Y, Sun W, Liu H, Zhang D. Age at menopause and risk of developing endometrial cancer: a meta-analysis. Biomed Res Int 2019;2019:8584130. doi: 10.1155/2019/8584130
8. American College of Obstetricians and Gynecologists. Diagnosis of abnormal uterine bleeding in reproductive-aged women. Practice Bulletin No. 128. Obstet Gynecol 2012;120(1):197–206. doi: 10.1097/AOG.0b013e318262e320
9. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions [published erratum appears in Int J Gynaecol Obstet 2019;144(2):237]. Int J Gynaecol Obstet 2018;143(3):393–408. doi: 10.1002/ijgo.12666
10. Goldstein SR, Lumsden MA. Abnormal uterine bleeding in perimenopause. Climacteric 2017;20(5):414–20. doi: 10.1080/13697137.2017.1358921
11. National Institute for Health and Care Excellence. Heavy menstrual bleeding: assessment and management. NICE Guideline 88 (2018). Available at https://www.nice.org.uk/guidance/ng88. Retrieved May 25, 2021.
12. Wise MR, Jordan V, Lagas A, Showell M, Wong N, Lensen S, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. Am J Obstet Gynecol 2016;214(6):689.e1–17. doi: 10.1016/j.ajog.2016.01.175

13. Nicula R, Costin N. Management of endometrial modifications in perimenopausal women. Clujul Med 2015;88(2):101–10. doi: 10.15386/cjmed-421
14. Delamater L, Santoro N. Management of the perimenopause. Clin Obstet Gynecol 2018;61(3):419–32. doi: 10.1097/GRF.0000000000000389
15. Burbos N, Musonda P, Giarenis I, Shiner AM, Giamougiannis P, Morris EP, et al. Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEFAB risk assessment tool. Br J Cancer 2010;102(8):1201–6. doi: 10.1038/sj.bjc.6605620
16. Begum J, Samal R. A clinicopathological evaluation of postmenopausal bleeding and its correlation with risk factors for developing endometrial hyperplasia and cancer: a hospital-based prospective study. J Midlife Health 2019;10(4):179–83. doi: 10.4103/jmh.JMH_136_18
17. Munro MG; Southern California Permanente Medical Group's Abnormal Uterine Bleeding Working Group. Investigation of women with postmenopausal uterine bleeding: clinical practice recommendations. Perm J. 2014;18(1):55–70. doi: 10.7812/TPP/13-072
18. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Uterine neoplasms Version 1.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Retrieved December 7, 2020.
19. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol 2015;125(1):89–98. doi: 10.1097/AOG.0000000000000563
20. Ryan NAJ, Morris J, Green K, Lalloo F, Woodward ER, Hill J, Crosbie EJ, et al. Association of mismatch repair mutation with age at cancer onset in Lynch syndrome: implications for stratified surveillance strategies. JAMA Oncol 2017;3(12):1702–6. doi: 10.1001/jamaoncol.2017.0619
21. Johnson N, Miles T, Bailey D, Tylko-Hill K, Das N, Ahson G, et al. Delays in treating endometrial cancer in the South West of England. Br J Cancer 2011;104(12):1836–9. doi: 10.1038/bjc.2011.173
22. Cheewakriangkrai C, Kietpeerakool C, Charoenkwan K, Pattanittum P, John D, Aue-Aungkul A, et al. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. Cochrane Database Syst Rev 2020;3(3):CD013253. doi: 10.1002/14651858.CD013253.pub2
23. US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;320(7):674–86. doi:10.1001/jama.2018.10897
24. Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020;70:321–46. doi: 10.3322/caac.21628
25. Boruta D II, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;115(1):142–53. doi: 10.1016/j.ygyno.2009.06.011
26. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995;64(6):430–3. doi: 10.1002/ijc.2910640613
27. Dunlop MG, Farrington SM, Carothers AD, Wyllie AH, Sharp L, Burn J, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 1997;6(1):105–10. doi: 10.1093/hmg/6.1.105
28. American College of Obstetricians and Gynecologists and the Society of Gynecology Oncology. Lynch syndrome. ACOG Practice Bulletin No. 147. Obstet Gynecol 2014;124(5):1042–54. doi: 10.1097/01/AOG/0000456325.50739/72

29. Alcazar JL, Dominguez-Piriz J, Juez L, Caparros M, Jurado M. Intraoperative gross examination and intraoperative frozen section in patients with endometrial cancer for detecting deep myometrial invasion: a systematic review and meta-analysis. Int J Gynecol Cancer 2016;26(2):407–15. doi: 10.1097/IGC.0000000000000618
30. Alcazar JL, Orozco R, Corral TMA, Juez L, Utrilla-Layna J, Minguez JA, et al. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2015;46(4):405–13. doi: 10.1002/uog.14905
31. Das SK, Niu XK, Wang JL, Zeng LC, Wang WX, Bhetuwal A, et al. Usefulness of DWI in preoperative assessment of deep myometrial invasion in patients with endometrial carcinoma: a systematic review and meta-analysis. Cancer Imaging 2014;14(1):32. doi: 10.1186/s40644-014-0032-y
32. Olawaiye AB, Leath CA III. Contemporary management of uterine clear cell carcinoma: a Society of Gynecologic Oncology (SGO) review and recommendation. Gynecol Oncol 2019;155(2):365–73. doi: 10.1016/j.ygyno.2019.08.031
33. Bansal N, Herzog TJ, Brunner-Brown A, Wethington SL, Cohen CJ, Burk WM, et al. The utility and cost effectiveness of preoperative computed tomography for patients with uterine malignancies. Gynecol Oncol 2008;111:208–12. doi: 10.1016/j.ygyno.2008.08.001
34. Kitajima K, Murakami K, Yamasaki E, Kaji Y, Sugimura K. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. Eur Radiol 2009;19(6):1529–36. doi: 10.1007/s00330-008-1271-8
35. Bollineni VR, Ytre-Hauge S, Bollineni-Balabay O, Salvesen HB, Haldorsen IS. High diagnostic value of 18F-FDG PET/CT in endometrial cancer: systematic review and meta-analysis of the literature. J Nucl Med 2016;57(6):879–85. doi: 10.2967/jnumed.115.170597
36. Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH. 18F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: a systematic review and meta-analysis. Eur J Radiol 2012;81(11):3511–7. doi: 10.1016/j.ejrad.2012.01.024
37. Hu J, Zhang K, Yan Y, Zang Y, Wang Y, Xue F. Diagnostic accuracy of preoperative 18F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet 2019;300(3):519–29. doi: 10.1007/s00404-019-05207-8
38. Ghooshkhanei H, Treglia G, Sabouri G, Davoodi R, Sadeghi R. Risk stratification and prognosis determination using (18)F-FDG PET imaging in endometrial cancer patients: a systematic review and meta-analysis. Gynecol Oncol 2014;132(3):669–76. doi: 10.1016/j.ygyno.2014.01.039
39. Gunderson CC, Faber AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012;125(2):477–82. doi: 10.1016/j.ygyno.2012.01.003
40. Westin SN, Fellman B, Sun CC, Broaddus RR, Woodall ML, Pal N, et al. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. Am J Obstet Gynecol 2021;224(2):191e1–15. doi: 10.1016/j.ajog.2020.08.032
41. Wright JD, Jorge S, Tergas AI, Hou JY, Burke WM, Huang Y, et al. Utilization and outcomes of ovarian conservation in premenopausal women with endometrial cancer. Obstet Gynecol 2016;127(1):101–8. doi: 10.1097/AOG.0000000000001181
42. Matsuo K, Machida H, Shoupe D, Melamed A, Muderspach LI, Roman LD, et al. Ovarian conservation and overall survival in young women with early-stage low-grade endometrial cancer. Obstet Gynecol 2016;128(4):761–70. doi: 10.1097/AOG.0000000000001647

43. van der Steen-Banasik E, Christiaens M, Shash E, Coens C, Casado A, Herrera FG, et al. Systemic review: radiation therapy alone in medical non-operable endometrial carcinoma. Eur J Cancer 2016;65:172–81. doi: 10.1016/j.ejca.2016.07.005
44. Schwarz JK, Beriwal S, Esthappan J, Erickson B, Feltmate C, Fyles A, et al. Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Brachytherapy 2015;14(5):587–99. doi: 10.1016/j.brachy.2015.06.002
45. Palisoul M, Mutch DG. The clinical management of inoperable endometrial carcinoma. Expert Rev Anticancer Ther 2016;16(5):515–21. doi: 10.1586/14737140.2016.1168699
46. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Older adult oncology Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf. Retrieved December 28, 2020.
47. Scully RE, Bonfiglio TA, Kurman, Silverberg SG, Wilkinson EJ, eds. Uterine corpus. In: Histological typing of female genital tract tumours. 2nd ed. New York: Springer-Verlag; 1994., p. 13–30.
48. Rakha E, Wong SC, Soomro I, Chaudry Z, Sharma A, Deen S, et al. Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature. Am J Surg Pathol 2012;36(11):1683–90. doi: 10.1097/PAS.0b013e31825dd4ff
49. Ordi J, Bergeron C, Hardisson D, McCluggage WG, Hollema H, Felix A, et al. Reproducibility of current classifications of endometrial endometrioid glandular proliferations: further evidence supporting a simplified classification. Histopathology 2014;64(2):284–92. doi: 10.1111/his.12249
50. American College of Obstetricians and Gynecologists. Endometrial intraepithelial neoplasia. Committee Opinion No. 631. Obstet Gynecol 2015;125:1272-8. doi: 10.1097/01.AOG.0000465189.50026.20
51. Bourdel N, Chauvet P, Tognazza E, Pereira B, Botchorishvili R, Canis M. Sampling in atypical endometrial hyperplasia: Which method results in the lowest underestimation of endometrial cancer? A systematic review and meta-analysis. J Minim Invasive Gynecol 2016;23(5):692–701. doi: 10.1016/j.jmig.2016.03.017
52. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ II, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006;106(4):812–9. doi: 10.1002/cncr.21650
53. Karamursel BS, Guven S, Tulunay G, Kucukali T, Ayhan A. Which surgical procedure for patients with atypical endometrial hyperplasia? Int J Gynecol Cancer 2005;15(1):127–31. doi: 10.1111/j.1048-891X.2005.15013.x
54. Touhami O, Grégoire J, Renaud MC, Sebastianelli A, Grondin K, Plante M. The utility of sentinel lymph node mapping in the management of endometrial atypical hyperplasia. Gynecol Oncol 2018;148(3):485–90. doi: 10.1016/j.ygyno.2017.12.026
55. Whyte JS, Gurney EP, Curtin JP, Blank SV. Lymph node dissection in the surgical management of atypical endometrial hyperplasia. Am J Obstet Gynecol 2010;202(2):176.e1-4. doi:10.1016/j.ajog.2009.10.855
56. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study [published erratum appears in J Clin Oncol 2012;30(13):1570]. J Clin Oncol 2012;30(7):695–700. doi: 10.1200/JCO.2011.38.8645
57. Janda M, Gebski V, Davies LC, Forder P, Brand A, Hogg R, et al. Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage i endometrial cancer: a randomized clinical trial. JAMA 2017;317(12):1224–33. doi: 10.1001/jama.2017.2068

58. Panici PB, Basile S, Maneschi F, Lissoni AA, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100(23):1707–16. doi:10.1093/jnci/djn397
59. ASTEC Study Group; Kitchener H, Swart AMC, Qian Q, Amos C, Parmar MKB. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC Trial): a randomised study. Lancet 2009;373(9658):125–36. doi: 10.1016/S0140-6736(08)61766-3
60. Carlson JW, Kauderer J, Hutson A, Carter J, Armer J, Lockwood S, et al. GOG 244—The lymphedema and gynecologic cancer (LEG) study: incidence and risk factors in newly diagnosed patients. Gynecol Oncol 2020;156(2):467–74. doi: 10.1016/j.ygyno.2019.10.009
61. Cohn DE, Horowitz NS, Mutch DG, Kim SM, Manolitsas T, Fowler JM. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002;87(3):243–6. doi: 10.1006/gyno.2002.6825
62. Milam MR, Java J, Walker JL, Metzinger DS, Parker LP, Coleman RL; Gynecologic Oncology Group. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012;119(2 Pt 1):286–92. doi: 10.1097/AOG.0b013e318240de51
63. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 2017;18(3):384–92. doi: 10.1016/S1470-2045(17)30068-2
64. Holloway RW, Abu-Rustum NR, Backes FJ, Boggess JF, Gotlieb WH, Lowery WJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol 2017;146(2):405–15. doi: 10.1016/j.ygyno.2017.05.027
65. Leitao MM Jr, Zhou QC, Gomez-Hidalgo NR, Iasonos A, Baser R, Mezzancello M, et al. Patient-reported outcomes after surgery for endometrial carcinoma: prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy. Gynecol Oncol 2020;156(1):147–53. doi: 10.1016/j.ygyno.2019.11.003
66. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010;116(1):131–9. doi: 10.1016/j.ygyno.2009.09.023
67. Kaganov H, Ades A, Fraser DS. Preoperative magnetic resonance imaging diagnostic features of uterine leiomyosarcomas: a systematic review. Int J Technol Assess Health Care 2018;34(2):172–9. doi: 10.1017/S0266462318000168
68. Dubreuil J, Tordo J, Rubello D, Giammarile F, Skanjeti A. Diffusion-weighted MRI and 18F-FDG-PET/CT imaging: competition or synergy as diagnostic methods to manage sarcoma of the uterus? A systematic review of the literature. Nucl Med Commun 2017;38(1):84–90. doi: 10.1097/MNM.0000000000000612
69. Sadeghi R, Zakavi SR, Hasanzadeh M, Treglia G, Giovanella L, Kadkhodayan S. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography imaging in uterine sarcomas: systematic review and meta-analysis of the literature. Int J Gynecol Cancer 2013;23(8):1349–56. doi: 10.1097/IGC.0b013e3182a20e18

Uterine Cancer Literature Review
Appendix 8. Special Considerations

Primary Reviewer: Brett Worly, MD
Secondary Reviewer: Dana M. Scott, MD, FACOG

INTRODUCTION

Many special considerations are important in caring for endometrial cancer patients. The PICO format was used to direct a literature search:

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

This literature review specifically addresses the following questions:

1. **How are stigma and shame associated with gynecologic abnormalities, symptoms, and cancers?**
   P: Adult women with endometrial cancer
   I: Multiple interventions are possible, including:
   a) Awareness of this problem, so that patients may address it
   b) Treatment or therapy to correct the medical condition
   C: Endometrial cancer patients with stigma or shame versus those without stigma or shame, who have had surgery versus no surgery, who have had a hysterectomy versus no hysterectomy, with pelvic exenteration versus no exenteration, with radiation versus no radiation
   O: Endometrial cancer diagnosis associated with stigma or shame

2. **How can trauma-informed, body-positive/sex-positive, gender-affirming care build rapport and trust with patients to talk about sensitive subjects?**
   P: Adult women with endometrial cancer
   I: Multiple interventions are possible, including:
   a) Trauma-informed approach
   b) Body-positive/sex-positive approach
   c) Gender-affirming care
   C: Endometrial cancer patients with trauma-informed care versus no trauma-informed care, with body-positive/sex-positive care versus without body-positive/sex-positive care, with gender-affirming care versus without gender-affirming care
   O: Endometrial cancer patients with trauma-informed, body-positive/sex-positive, gender-affirming care who build rapport and trust with their providers and discuss sensitive subjects

3. **What are important unique survivorship concerns (fertility preservation, isolation, and sexual health) that need to be considered?**
   P: Adult women with endometrial cancer
   I: Comprehensive care, including:
   a) Fertility preservation
   b) Reducing feelings of isolation
   c) Improving sexual health

C: Endometrial cancer patients with fertility preservation versus without fertility preservation, with a reduction of feelings of isolation versus those with feelings of isolation, with improving sexual health versus poor sexual health

METHODS

Study Population

This review focused on women with past or present endometrial cancer diagnosis. It included topics such as obesity, sexuality, patient-initiated follow-up, quality of life, fertility preservation, feelings of isolation, trauma-informed approach to care, body-positive/sex-positive counseling, gender-affirming care, and shame.

Search Strategy

The American College of Obstetricians and Gynecologists Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases for all relevant references. Additional review was carried out to identify relevant guidelines published by the American College of Obstetricians and Gynecologists, the American Cancer Society, the National Comprehensive Cancer Network, the Society of Gynecologic Oncology, the European Society for Medical Oncology, the National Institute for Health and Care Excellence, the American College of Radiology, the United States Preventive Services Task Force, and the American Society for Reproductive Medicine.

The literature search was supplemented by examining the bibliographies of included studies and finding other notable pertinent works that had not been identified by the primary search. Inclusion criteria were major society or health service guidelines, systematic reviews, meta-analyses, cohort studies, case-control studies, and randomized, controlled trials published in the year 2000 or later. Only articles available in English were included. Case reports, case series, articles unavailable in English, and studies that did not evaluate patients with endometrial cancer were excluded. A single investigator reviewed the title and abstracts of all identified articles. The full text of those articles that met eligibility criteria was then reviewed by the same investigator.

RESULTS

Literature Summary

The literature search returned 1,047 citations. Of those, 928 were excluded after review of the title and abstract, leaving 119 articles. An additional 40 papers were excluded after manuscript review because they were not applicable. The initial search yielded 20 papers pertinent to the topic, which were reviewed in their entirety. An additional 10 papers were found from these articles and added to this review.

Summary of Data

How are stigma and shame associated with gynecologic abnormalities, symptoms, and cancers?

A qualitative study looked at 15 obese (body mass index [BMI] > 40 kg/m^2) women with low-grade endometrial cancer who were either preparing for hysterectomy or had a hysterectomy in the past 6 months. During semistructured phone interviews, 80% of patients identified stigma and shame related to their size and

endometrial cancer. The study population included patients receiving care from a tertiary care academic medical center in Canada. Phone interviews were conducted so that subjects would not be aware of the interviewer's body size. Patients noted that they were unaware of a link between obesity and endometrial cancer (100%, n = 15/15). Most patients (93%) noted that potentially modifiable barriers, including geographic, administrative, financial, and logistical barriers to care, exist for obese endometrial cancer patients, but they believed that good-quality care for obese endometrial cancer patients is an attainable goal.[1]

How can trauma-informed, body-positive/sex-positive, gender-affirming care build rapport and trust with patients to talk about sensitive subjects?

After extensive literature review, no specific data were found regarding trauma-informed care, body-positive/sex-positive care, or gender-affirming care for endometrial cancer patients.

What are important unique survivorship concerns (fertility preservation, isolation, and sexual health) that need to be considered?

FERTILITY PRESERVATION

An increasing number of women of reproductive age are being diagnosed with endometrial cancer and may want to preserve their fertility.[2] 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.[3] Endometrial cancers in this age group are increasing in frequency and are often early-stage, well-differentiated endometrioid-type adenocarcinomas, with rare cases of myometrial invasion or lymph node metastasis.[4,5] The American Society for Reproductive Medicine recommends that patients of reproductive age undergoing potentially gonadotoxic therapies should be informed by their health care provider about fertility preservation and future reproduction prior to the initiation of the treatment. A collaborative, multidisciplinary, team-based approach may be helpful.[3]

Although fertility-sparing techniques limit complete surgical staging, the Society of Gynecologic Oncology and the National Comprehensive Cancer Network identify candidates for fertility-sparing treatment as those who strongly desire fertility, have a well-differentiated tumor (grade 1), no evidence of invasion (stage IA), no contraindications for medical management, and a willingness to accept the risks of nonstandard treatment.[5,6] Dilation and curettage (D&C) is the optimal method to confirm grading and histologic differentiation of endometrial cancer, in combination with contrast-enhanced magnetic resonance imaging to assess cervical, myometrial, adnexal, lymph node, or peritoneal involvement.[5,6]

Progestin treatment is an option for patients with stage 1A, grade 1, minimally invasive endometrial cancer who desire fertility-sparing therapy.[5] Patients who desire fertility preservation should be placed on a continuous progestin-based therapy with megestrol, medroxyprogesterone, or the levonorgestrel intrauterine device (IUD). They should have endometrial sampling by office biopsy or D&C every 3–6 months, with a complete response expected by 6 months. D&C is reserved for patients with symptoms or signs of recurrence. Hysterectomy is recommended once childbearing has been completed.[5-7] Response rates to oral progestin therapy range from 48.2% to 76.2% of patients, with recurrence rates of 35.4–40.6%, a 34.8% pregnancy rate, and a 28% live birth rate.[8,9] Several studies support the use of progestin-releasing IUDs.[5-7]

The studies in this literature review indicate that fertility preservation among endometrial cancer survivors with stage IA, grade 1 endometrioid adenocarcinoma is reasonable for patients with goals of future fertility.[5,6] Careful conversations regarding the risks and benefits of fertility preservation, medications, regimens, dosages, modalities, side effects, chance of recurrence, and chance of successful live birth are all essential.[3]

Isolation

After extensive literature review, no specific data were found regarding isolation among endometrial cancer patients.

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 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 aspects that contribute differently to an endometrial cancer patient's sexual health. Sexual health in an intimate relationship is unique in that it often requires a healthy partner and a strong relationship.[10-12] A cross-sectional cohort study assessed 79 women with gynecologic cancer and 87 healthy controls. In the cancer patient group:

- 59.5% were not sexually active
- 23.4% were inactive because of a lack of partner ($P = 0.172$)
- 40.4% were inactive because of a lack of interest ($P = .044$)
- 27.7% were inactive because of a physical problem ($P = .031$)
- 6.4% were inactive because of general well-being or fatigue ($P = .708$)

The average age of patients in this study was 62 years old.[13]

In a retrospective cohort study of 100 sedentary endometrial cancer survivors that included a physical activity intervention, sexual dysfunction correlated with financial problems and psychological distress, and sexual function and interest were worse among patients with less than a 4-year college degree ($P < .001$). Sexual interest was higher among patients who had a partner ($P = .012$).[14] Aerts et al looked at 84 patients with endometrial cancer, 84 patients with benign gynecologic disease, and 84 healthy controls in a prospective cohort study for 2 years following gynecologic surgery. While only 24% of patients were monitored for the full 2 years of follow-up, 54% of endometrial cancer patients were sexually active, and this number remained stable throughout the study. In subgroup analysis, endometrial cancer patients who underwent laparoscopic surgery or lymph node dissection were no different than patients who had abdominal hysterectomy. Endometrial cancer patients had increased rates of decreased sexual desire ($P < .01$), entry dyspareunia ($P < .01$), and decreased intensity of orgasm ($P < .01$) compared with the healthy control group. The differences in decreased sexual desire and entry dyspareunia persisted for the 2 years of follow-up, and endometrial cancer patients noted decreased sexual arousal throughout the 2-year follow-up period ($P < .01$).[15]

Chemotherapy, radiation, and surgical interventions have been assessed to determine whether these treatments might alter sexual function for endometrial cancer patients. Surgical options for treatment of endometrial cancer include laparoscopy, robotic-assisted surgery, and open surgery, and surgical intervention has not been found to negatively impact sexual function in most studies.[16-19] Damast et al looked at a cohort of 104 endometrial cancer patients being treated in a radiation oncology clinic and found that laparotomy, when compared with minimally

invasive surgery, was associated with decreased sexual function scores on the Female Sexual Function Index, with an effect size of −7.1 (95% CI: −11.2 to −3.1, $P<0.001$). This study also found that 80.77% of endometrial cancer patients had sexual dysfunction.[20]

Rowlands et al performed a cross-sectional study of 395 patients treated for endometrial cancer in the previous 3–5 years and addressed the question of whether surgery, chemotherapy, radiation, or brachytherapy had a negative impact on sexual health. That study found that patients with high levels of sexual well-being were more likely to have surgery without adjuvant therapy or radiation.[19] Other studies contrasted with Rowlands et al, suggesting that vaginal brachytherapy does not increase the risk of sexual dysfunction, although sexual dysfunction prevalence is high overall.[21-25] The Post Operative Radiation Therapy in Endometrial Cancer trial, a randomized, controlled trial of endometrial cancer patients receiving either vaginal brachytherapy or external beam radiation, found no differences in sexual interest, sexual activity, or vaginal dryness, although patients that had vaginal beam radiation were more likely to report having enjoyable sex ($P < .001$).[21] The same trial indicated that sexual activity increased over time, with a low baseline of 15% after surgery and a peak 6 months after treatment at 39% ($P < .001$), without significant differences between the treatment groups.[25] In contrast, Gao et al performed a cross-sectional study of 118 endometrial cancer survivors and found that sexual dysfunction correlated with radiotherapy and increasing age, while improved sexual function correlated with increased time since surgery and consultation to discuss sexual matters with a physician.[26]

Treatment for sexual dysfunction in endometrial cancer survivors requires attention and further research. Brotto et al evaluated the efficacy of cognitive behavioral therapy (CBT) for gynecologic cancer survivors with decreased sexual desire or sexual arousal concerns. Patients were randomly assigned to a CBT group for three 90-minute sessions with a sex therapist or to a wait list for 3 months. While no improvement was noted among patients assigned to the wait list (n = 9), patients in the intervention group (n = 31) had post-CBT improvements in sexual desire, arousal, orgasm, lubrication, and satisfaction and had decreased sexual distress ($P < .01$). In addition, these improvements persisted at 6 months following CBT.[27]

Patients undergoing radiation adjuvant therapy for endometrial cancer sometimes experience the side effect of vaginal stenosis. A prospective cohort study looked at endometrial cancer survivors who also received either external beam radiation (n = 28) or intracavitary radiation (n = 28) and assigned both groups to a home-based vaginal dilator intervention, then monitored progress over 1 year. A 57.1% noncompliance rate was noted at 1 year, and 64.2% of subjects had vaginal stenosis at 1 year. Sexual activity decreased during radiation treatment, but an improvement was noted at the 1-year evaluation ($P < .001$). Despite an increase in sexual activity over the course of the study, sexual enjoyment decreased ($P = .013$). Vaginal dilator use did not improve the vaginal dilator measurement at the conclusion of treatment, but patients with less vaginal stenosis reported increased sexual enjoyment compared with patients with a worse grade of vaginal stenosis ($P = 0.01$).[28]

A cross-sectional study of 112 endometrial cancer survivors evaluated vaginal dilator use and sexual health at a median of 6 years following radiation treatment, and 38% of patients were still using the vaginal dilators. Patients with higher levels of sexual activity and interest were more likely to be using the vaginal dilators ($P < .001$).[29]

In sum, the literature suggests that sexual health is multifaceted. Large studies and high-quality evidence for sexual health in endometrial cancer patients are limited. Patients should be considered on an individual basis, as issues relating to their sexual partner, their personal physical and mental health, education, financial matters, and endometrial cancer surgery and treatment may contribute to sexual function.[12] When sexual dysfunction is

noted for endometrial cancer survivors, treatment options and success rates should be reviewed. Referral to a sexual health specialist may be appropriate. We searched for patient-friendly resources and information to help practitioners address sexual health needs of endometrial cancer patients. The American Cancer Society website provides sexual health education, resources, and talking points to address, with specific guidance for patients with gynecologic cancers (https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/sexuality-for-women-with-cancer.html).[30] The American Society of Clinical Oncology also provides additional guidance for practitioners to address sexual health in cancer patients.[12]

RESEARCH GAPS AND OPPORTUNITIES

- What treatments are most effective for endometrial cancer patients with sexual dysfunction?
- How are stigma and shame associated with gynecologic abnormalities, symptoms, and cancers?
- How can trauma-informed, body-positive/sex-positive, gender-affirming care build rapport and trust with patients to support discussion of sensitive subjects?
- What are important, unique survivorship concerns related to isolation that need to be considered?

REFERENCES

1. Cusimano MC, Simpson AN, Han A, Hayeems R, Bernardini MQ, Robertson D, et al. Barriers to care for women with low-grade endometrial cancer and morbid obesity: a qualitative study. BMJ Open 2019;9(6):e026872. doi: 10.1136/bmjopen-2018-026872
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer. Available at: https://seer.cancer.gov/statfacts/html/corp.html. Retrieved 12/12/2020.
3. American Society for Reproductive Medicine. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril 2018;110(3):380–6. doi: 10.1016/j.fertnstert.2018.05.034
4. Park JY, Nam JH. Progestins in the fertility-sparing treatment and retreatment of patients with primary and recurrent endometrial cancer. Oncologist 2015;20(3):270–8. doi: 10.1634/theoncologist.2013-0445
5. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M, Salom E, Gehrig P. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol 2014;134(2):393–402. doi: 10.1016/j.ygyno.2014.06.003
6. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16(2):170–99. doi: 10.6004/jnccn.2018.0006
7. Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, et al. European Society of Gynecologic Oncology Task Force for Fertility Preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. Int J Gynecol Cancer 2015;25(7):1258–65. doi: 10.1097/IGC.0000000000000493
8. Gunderson CC, Faber AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012;125(2):477–82. doi: 10.1016/j.ygyno.2012.01.003
9. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2012 Oct;207(4):266.e1–12.

10. Cianci S, Rosati A, Capozzi VA, Tarascio M, Uccella S, Palumbo MA, et al. Quality of life and sexual functioning of patient affected by endometrial cancer. Minerva Med 2021;112(1):81–95. doi: 10.23736/S0026-4806.20.07081-0
11. Ferrandina G, Petrillo M, Mantegna G, Fuoco G, Terzano S, Venditti L, et al. Evaluation of quality of life and emotional distress in endometrial cancer patients: a 2-year prospective, longitudinal study. Gynecol Oncol 2014;133(3):518–25. doi: 10.1016/j.ygyno.2014.03.015
12. Katz A. The sounds of silence: sexuality information for cancer patients. J Clin Oncol 2005;23(1):238–41. doi: 10.1200/JCO.2005.05.101
13. Harter P, Schrof I, Karl LM, Hils R, Kullmann V, Traut A, et al. Sexual function, sexual activity and quality of life in women with ovarian and endometrial cancer. Geburtshilfe Frauenheilkd 2013;73(5):428–32. doi: 10.1055/s-0032-1328602
14. Armbruster SD, Song J , Bradford A, Carmack CL, Lu KH, Basen-Engquist KM. Sexual health of endometrial cancer survivors before and after a physical activity intervention: a retrospective cohort analysis. Gynecol Oncol 2016;143(3):589–95. doi: 10.1016/j.ygyno.2016.09.016
15. Aerts L, Enzlin P, Verhaeghe J, Poppe W, Vergote I, Amant F. Sexual functioning in women after surgical treatment for endometrial cancer: a prospective controlled study. J Sex Med 2015;12(1):198–209. doi: 10.1111/jsm.12764
16. Buckingham L, Haggerty A, Graul A, Morgan M, Burger R, Ko E, et al. Sexual function following hysterectomy for endometrial cancer: a five-year follow up investigation. Gynecol Oncol 2019;152(1):139–44. doi: 10.1016/j.ygyno.2018.10.025
17. Carter J, Huang H, Chase DM, Walker JL, Cella D, Wenzel L. Sexual function of patients with endometrial cancer enrolled in the Gynecologic Oncology Group LAP2 Study. Int J Gynecol Cancer 2012;22(9):1624–33. doi: 10.1097/IGC.0b013e31827277fa
18. Ferguson SE, Panzarella T, Lau S, Gien LT, Samouelian V, Giede C, et al. Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer. Gynecol Oncol 2018;149(3):476–83.
19. Rowlands IJ, Lee C, Beesley VL, Webb PM, Australian National Endometrial Cancer Study Group. Predictors of sexual well-being after endometrial cancer: results of a national self-report survey. Support Care Cancer 2014;22(10):2715–23. doi: 10.1007/s00520-014-2263-7
20. Damast S, Alektiar KM, Goldfarb S, Eaton A, Patil S, Mosenkis J, et al. Sexual functioning among endometrial cancer patients treated with adjuvant high-dose-rate intra-vaginal radiation therapy. Int J Radiat Oncol Biol Phys 2012;84(2):e187-93. doi: 10.1016/j.ijrobp.2012.03.030
21. de Boer SM, Nout RA, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, van der Steen-Banasik EM, et al. Long-term impact of endometrial cancer diagnosis and treatment on health-related quality of life and cancer survivorship: results from the randomized PORTEC-2 trial. Int J Radiat Oncol Biol Phys 2015;93(4):797–809. doi: 10.1016/j.ijrobp.2015.08.023
22. Hanlon A, Small W Jr, Strauss J, Lin LL, Hanisch L, Huang L, et al. Dilator use after vaginal brachytherapy for endometrial cancer: a randomized feasibility and adherence study. Cancer Nurs 2018;41(3):200–9. doi: 10.1097/NCC.0000000000000500
23. Damast S, Alektiar K, Eaton A, Gerber NK, Goldfarb S, Patil S, et al. Comparative patient-centered outcomes (health state and adverse sexual symptoms) between adjuvant brachytherapy versus no adjuvant brachytherapy in early stage endometrial cancer. Ann Surg Oncol 2014;21(8):2740–54. doi: 10.1245/s10434-014-3562-4
24. Becker M, Malafy T, Bossart M, Henne K, Gitsch G, Denschlag D. Quality of life and sexual functioning in endometrial cancer survivors. Gynecol Oncol 2011;121(1):169–73. doi: 10.1016/j.ygyno.2010.11.024

25. Nout RA, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, van der Steen-Banasik EM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009;27(21):3547–56. doi: 10.1200/JCO.2008.20.2424
26. Gao H, Xiao M, Bai H, Zhang Z. Sexual function and quality of life among patients with endometrial cancer after surgery. Int J Gynecol Cancer 2017;27(3):608–12. doi: 10.1097/IGC.0000000000000905
27. Brotto LA, Erskine Y, Carey M, Ehlen T, Finlayson S, Heywood M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. Gynecol Oncol 2012;125(2):320-5. doi: 10.1016/j.ygyno.2012.01.035
28. Akbaba S, Oelmann-Avendano JT, Krug D, Arians N, Bostel T, Hoerner-Rieber J, et al. The impact of vaginal dilator use on vaginal stenosis and sexual quality of life in women treated with adjuvant radiotherapy for endometrial cancer. Strahlenther Onkol 2019;195(10):902–12. doi: 10.1007/s00066-019-01466-1
29. Foerster R, Schnetzke L, Bruckner T, Arians N, Rief H, Debus J, et al. Prognostic factors for long-term quality of life after adjuvant radiotherapy in women with endometrial cancer. Strahlenther Onkol 2016;192(12):895–904. doi: 10.1007/s00066-016-1037-1
30. American Cancer Society website: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/sexuality-for-women-with-cancer.html. Accessed 5/3/2021.

