Endometrial Cancer

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Endometrial cancer is the leading cause of gynecologic cancer in the United States. Etiologically, endometrial carcinoma usually results from unopposed estrogen stimulation of the endometrium, although non–estrogen-related forms occur as well. The most common presentation of endometrial cancer is postmenopausal bleeding. A variety of diagnostic modalities are available to aid in the detection of the disease, each with its own strengths and limitations. These modalities include endometrial biopsy, ultrasonography, saline infusion sonography, and hysteroscopy. A definitive diagnosis requires pathologic confirmation via endometrial biopsy or dilatation and curettage. Surgical staging of endometrial cancer will dictate how physicians manage the condition. For most women, staging and initial treatment are accomplished with total hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washings. Surgery, radiation, and chemotherapy play a role in treatment, depending on tumor stage and grade. At present, there are no recommendations for screening the general population. (*Am Fam Physician.* 2009;80(10):1075-1080, 1087-1088. Copyright © 2009 American Academy of Family Physicians.)
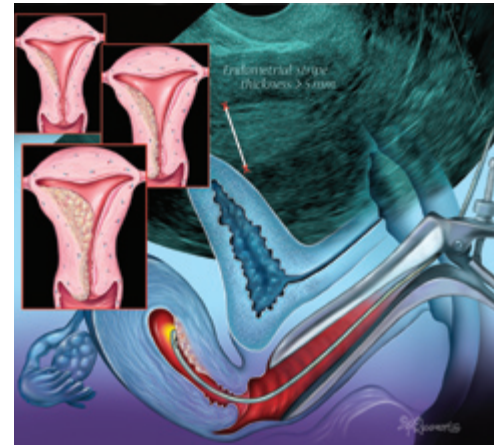
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▶ **Patient information:** A handout on endometrial cancer, written by the authors of this article, is provided on page 1087.

ACF This article exemplifies the AAFP 2009 Annual Clinical Focus on management of chronic illness.

Endometrial cancer is currently the most common gynecologic malignancy in the United States and the fourth most common cancer among women. The American Cancer Society estimates that there will be 42,160 new cases of uterine cancer in 2009 and 7,780 related deaths.[1] Ninety percent of cases occur in women older than 50 years, and the median age at diagnosis is 62 years.[2] Endometrial cancer is more common among white women than black women, yet mortality rates are higher in the latter. The overall annual mortality rate in the United States has increased more than 100 percent during the past two decades and is currently four deaths per 100,000 women per year.[1,3]

Pathogenesis

Endometrial cancer is characterized by neoplasia of the glandular elements of the endometrium and is classified as type I or type II based on histologic properties. Type I, also called the endometrioid type because of its histologic similarity to the endometrium, accounts for more than 75 percent of cases.[4]

Most type I tumors occur in the setting of unopposed estrogen stimulation, leading to endometrial hyperplasia. Previously, hyperplasia was thought to progress along a continuum that led to endometrial cancer. Recent studies show that although some hyperplasias do progress to adenocarcinoma, others coexist with endometrial cancer.[5] The probability of endometrial hyperplasia progressing to adenocarcinoma is greater in patients who have a higher degree of cytologic atypia, as described by the World Health Organization classification system.[5] Simple hyperplasia without cellular atypia has a 1 percent probability of progressing to carcinoma if left untreated; with cellular atypia, the probability is 8 percent.[5] Complex hyperplasia without cellular atypia has a 3 percent probability of progressing; with cellular atypia, the probability is 29 percent.[5]

Unlike type I tumors, type II lesions are not related to estrogen exposure or endometrial hyperplasia. These tumors manifest later in life, are typically diagnosed at a more advanced stage, and carry a poorer prognosis. Type II tumors include serous, clear cell,

mucinous, squamous, and adenosquamous carcinomas, in addition to other less common varieties.

Risk Factors

The risk factors that have been identified for endometrial cancer pertain to the endometrioid (type I) form and are associated with increased exposure to unopposed estrogen. *Table 1* lists recognized risk factors for endometrial cancer and their conferred relative risk.[6-8]

Screening

Multiple studies have determined that there is no benefit to screening the general population for endometrial cancer.[9] Screening of large populations is likely to identify early asymptomatic carcinomas. However, universal screening is not recommended because prognosis does not change with earlier diagnosis. In contrast, women with hereditary nonpolyposis colorectal cancer (HNPCC) are at high risk of endometrial cancer. Therefore, the American Cancer Society recommends offering annual screening with endometrial biopsy beginning at 35 years of age for women who have or are at risk of developing HNPCC.[10]

History

Ninety percent of women with endometrial cancer will present with abnormal vaginal

Table 1. Risk Factors for Endometrial Cancer and Their Associated Relative Risk

Factor	Relative risk
Long-term use of high-dosage, unopposed menopausal estrogens	10 to 20
High cumulative doses of tamoxifen	3 to 7
Estrogen-producing tumor	> 5
Obesity	
BMI 30 to 34 kg per m^2	1.7*
BMI 35 to 39 kg per m^2	4.3*
BMI ≥ 40 kg per m^2	6.4*
Nulliparity	3
Diabetes, hypertension, thyroid or gallbladder disease	1.3 to 3
Older age	2 to 3
History of infertility	2 to 3
Late age at natural menopause (older than 52 years)	2 to 3
Early age at menarche (younger than 12 years)	1.5 to 2
Menstrual irregularities	1.5
White race	2
Long-term use of high dosages of combination oral contraceptives	0.3 to 0.5 (decreased risk)
Cigarette smoking	0.5 (decreased risk)

BMI = body mass index.

*—Compared with women who have a BMI of 20 to 24 kg per m^2.

Adapted with permission from Gershenson D, McGuire WP, Gore M, Quinn MA, Thomas G. Gynecologic Cancer: Controversies in Management. Philadelphia, Pa.: Elsevier Churchill Livingstone; 2004, with additional information from references 6 and 7.

bleeding or abnormal discharge.[6] Therefore, any woman presenting with these symptoms should be carefully assessed.[6-8]

When considering endometrial evaluation, it is helpful to begin by considering the age and menopausal status of the woman. The majority of cases of endometrial cancer occur in postmenopausal women. Thus, any postmenopausal woman who reports any amount of vaginal bleeding or vaginal discharge should receive further evaluation. Of note, for postmenopausal women on continuous hormone therapy, irregular bleeding is not uncommon in the first six months of therapy. Any bleeding that begins or continues after the first six months requires further evaluation.[11] Additionally, women on cyclic hormone therapy should be evaluated for any unscheduled bleeding.[12]

Irregular menses is a common concern in women of reproductive age. However, there is a marked increase in the incidence of endometrial cancer after 35 years of age. Therefore, the American College of Obstetricians and Gynecologists (ACOG) recommends endometrial assessment to exclude cancer in any woman older than 35 years with suspected anovulatory uterine bleeding.[4] Anovulatory bleeding can encompass a range of patterns, including spotting, metrorrhagia, and menorrhagia. Additionally, women younger than 35 years who continue to have abnormal vaginal bleeding despite medical treatment, or who have prolonged exposure to unopposed estrogen, should be considered for further evaluation to exclude endometrial cancer. Options for endometrial assessment are discussed in detail below.

Physical Examination

The evaluation of a woman with abnormal vaginal bleeding should include a focused physical examination with calculation of the body mass index, and a thorough pelvic examination. The pelvic examination should include visual inspection to evaluate for any sources of bleeding (i.e., cervical, vaginal, rectal, urethral). The uterus and adnexa should be palpated for uterine size and position, as well as for any suspicious masses.

Laboratory Evaluation

Basic laboratory studies in the evaluation of a patient with abnormal uterine bleeding and suspected endometrial cancer may include urine pregnancy test, complete blood count, Papanicolaou (Pap) smear, and testing for sexually transmitted infections. If suggested by the history or physical examination, other causes of abnormal vaginal bleeding may be investigated. Some examples include thyroid dysfunction (thyroid-stimulating hormone);

liver disease [liver function tests, prothrombin time (PT), partial thromboplastin time (PTT)]; or bleeding diathesis (PT/PTT, platelets, testing for von Willebrand disease).

The Pap smear is not designed to be a screening test for endometrial cancer. However, occasionally the physician will obtain Pap smear results that suggest an endometrial pathology, such as benign endometrial cells, atypical glandular cells (AGC), or atypical endometrial cells.

According to the Bethesda System, benign endometrial cells are reported on Pap tests in all women 40 years and older. Benign endometrial cells are unlikely to represent serious pathology in asymptomatic premenopausal women at low risk of endometrial cancer.[13] All postmenopausal women with benign endometrial cells on Pap smear, regardless of symptoms, require further evaluation. All women with AGC or atypical endometrial cells require further evaluation of the cervix, endocervix, and endometrium.[13]

Diagnostic Studies

When a woman presents with abnormal bleeding, two questions must be answered: Is endometrial evaluation indicated to rule out endometrial cancer? If so, what diagnostic modalities should be used? Discussion is ongoing about the optimal sequence and combination of procedures for evaluation. A variety of options exist, each with its own strengths and limitations.

ENDOMETRIAL BIOPSY

Traditionally, dilatation and curettage was the primary means of evaluating the endometrium. The development of newer office-based sampling techniques, specifically the Pipelle device, has simplified this evaluation. The sensitivity of the Pipelle in detecting endometrial cancer has been calculated as high as 99 percent in postmenopausal women and 91 percent in premenopausal women.[14] However, blind endometrial sampling techniques, such as the Pipelle, are most useful when the abnormality is global, rather than focal (i.e., endometrial polyp or focal hyperplasia).[15,16] Further evaluation is warranted in the following circumstances: failure to obtain an adequate specimen; inconsistencies between biopsy and imaging; and persistence of symptoms despite a benign biopsy result.[17,18]

ULTRASONOGRAPHY

Endovaginal and transabdominal ultrasonography of the uterus can be helpful when evaluating a patient with abnormal vaginal bleeding. In the premenopausal woman, ultrasonography may reveal a variety of

structural abnormalities of the uterus and endometrium. In the postmenopausal woman, endovaginal ultrasonography has been used to assess endometrial thickness in an attempt to identify women who need further invasive testing.

The Nordic multicenter study evaluated the predictive value of endometrial thickness to exclude endometrial abnormalities in postmenopausal women.[19] Endometrial thickness of less than 4 mm had a negative predictive value of 100 percent for endometrial cancer.[19] A recent ACOG Committee Opinion reviews the use of transvaginal ultrasonography in the evaluation of postmenopausal bleeding.[20] The opinion clarifies that endometrial biopsy or transvaginal ultrasonography may be used in the initial evaluation of postmenopausal bleeding, and both tests may not be necessary. The opinion further concludes that "when an endometrial thickness less than or equal to 4 mm is found, endometrial sampling is not required."[20] When the endometrium cannot be reliably assessed by ultrasonography in women with postmenopausal bleeding because of marked obesity, myomas, or other anatomic limitations, an alternative method of evaluation is necessary.[20]

SALINE INFUSION SONOGRAPHY

In saline infusion sonography (also known as sonohysterography), sterile saline is instilled into the uterine cavity before ultrasound evaluation to allow for more precise visualization of the endometrial structures. Saline infusion sonography is often used as a second step in the evaluation of abnormal bleeding. It is particularly useful when ultrasonography suggests a focal lesion, when endometrial biopsy is nondiagnostic, or when abnormal bleeding persists despite normal initial workup. If a focal lesion is noted on saline infusion sonography, hysteroscopy with directed biopsy is traditionally indicated. However, newer techniques are being developed that combine saline infusion hysterography with endometrial sampling under direct visualization, with highly accurate results.[16] Saline infusion sonography should not be performed if endometrial biopsy detects malignant cells or when ultrasonography suggests endometrial cancer because of concerns of peritoneal spread.[21]

HYSTEROSCOPY

Hysteroscopy is direct endoscopic visualization of the endometrial cavity. A recent review indicates that hysteroscopy is highly accurate in diagnosing endometrial cancer and moderately accurate in diagnosing other endometrial conditions in women with abnormal bleeding.[22]

Treatment and Prognosis
ENDOMETRIAL HYPERPLASIA

Treatment of endometrial hyperplasia depends largely on the presence or absence of cellular atypia, as well as the patient's desire for future fertility.

Because of its benign course, endometrial hyperplasia without atypia is usually treated with hormonal intervention. Hyperplasia develops in the presence of unopposed estrogen. Therefore, the administration of a progestin is usually sufficient to counteract the effects of unopposed estrogen. Medroxyprogesterone acetate (Provera), 10 mg daily for 10 to 14 days per month, replicates the natural presence of progesterone in an ovulatory woman. Megestrol (Megace), 40 mg daily on a continuous basis, is also commonly administered.[2]

Endometrial hyperplasia with cellular atypia is considered a precancerous lesion with a 29 percent risk of developing into endometrial cancer.[23] Endometrial cancer is a concurrent condition in 42.6 percent of women who have been diagnosed with atypical endometrial hyperplasia by endometrial biopsy.[24] If a woman has completed childbearing, a hysterectomy should be recommended to rule out the presence of adenocarcinoma, as well as to prevent its future development. If the patient desires to retain fertility, a thorough evaluation of the endometrium should be performed to rule out a coexisting cancer. If no cancer is present, the patient may undergo high-dose progesterone therapy in an attempt to reverse the condition. This treatment option has also been described for women with well-differentiated adenocarcinomas.[25,26] If treatment is successful, the patient may attempt pregnancy with close follow-up. After the patient has completed childbearing, a hysterectomy must be considered because of possible recurrence of atypical endometrial hyperplasia or endometrial cancer.

ENDOMETRIAL CANCER

The staging of endometrial cancer is surgically based *(Table 2)*.[27,28] Preoperative evaluation should include physical examination and chest radiography. The uterine size, potential extrauterine tumor involvement, and presence of comorbidities should be assessed on examination.[6] Other testing may include Pap smear, transvaginal ultrasonography, cancer antigen 125 level, or magnetic resonance imaging if extrauterine metastases are suspected.[21] From a primary care perspective, the preoperative evaluation should also focus on optimizing medical comorbidities that could complicate the course of treatment.

In the absence of obvious extrauterine metastases, staging and initial treatment are accomplished with total hysterectomy, bilateral salpingo-oophorectomy, and

Table 2. Staging for Endometrial Cancer

Stages	Description	Treatment	Five-year survival (%)
I	Tumor limited to uterine corpus	Hysterectomy Bilateral salpingo-oophorectomy Pelvic washings Presence of risk factors (see text) Pelvic and para-aortic lymph node dissection	
IA	Tumor limited to endometrium		90.8
IB	< 50 percent myometrial invasion		91.1
IC	≥ 50 percent myometrial invasion	Radiation	85.4
II	Tumor invades cervix and uterine corpus	Hysterectomy Bilateral salpingo-oophorectomy Pelvic washings Pelvic and para-aortic lymph node dissection Radiation	
IIA	Endocervical gland involvement		83.3
IIB	Invasion of cervical stroma		74.2
III	Local and/or regional spread	Hysterectomy Bilateral salpingo-oophorectomy Pelvic washings Pelvic and para-aortic lymph node dissection Radiation	
IIIA	Positive peritoneal cytology, serosal involvement, and/or adnexal involvement		66.2
IIIB	Tumor involves vagina		49.9
IIIC	Metastases to pelvic and/or para-aortic lymph nodes	Systemic adjuvant therapy	57.3
IV	Intra-abdominal or extra-abdominal metastases	Surgery and tumor debulking Systemic adjuvant therapy	
IVA	Invasion of bladder or bowel mucosa		25.5
IVB	Distant metastases (including intra-abdominal and inguinal lymph node spread)		20.1

Information from references 27 and 28.

peritoneal washings. Based on risk factors such as extent of myometrial invasion and tumor grade, pelvic and para-aortic lymph node dissection should be performed as a prognostic indicator and a treatment strategy. With more advanced stages of disease, tumor debulking is indicated to improve treatment outcomes.[29]

Radiation therapy via external beam radiotherapy or brachytherapy is an effective treatment for endometrial cancer. In stage I disease, the use of radiation therapy is beneficial for patient subgroups determined by age, tumor grade, depth of myometrial invasion, and lymphovascular space involvement.[30] In more advanced disease, radiation therapy is useful in women with lymph node involvement and regional spread. It also effectively controls local recurrence of disease.

Systemic therapy with high-dose progestins or chemotherapy may benefit patients with metastatic disease.[21] Progestins alone or in combination with tamoxifen have shown increased progression-free and overall survival rates. Doxorubicin (Adriamycin) and paclitaxel (Taxol), in addition to the use of a platinum-based agent, have also demonstrated improved survival in women with advanced or recurrent disease.[2]

Prevention
Control or prevention of risk factors such as obesity, diabetes, and hypertension could play a role in the primary prevention of endometrial cancer. However, there are no outcomes studies or recommendations from major medical organizations about the effectiveness of this approach.

Women with an intact uterus who take estrogens for hormone therapy should also take a progestin to reduce their risk of endometrial hyperplasia and endometrial cancer.

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Author disclosure: Nothing to disclose.

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