
Endometrial Cancer: Part 1— Epidemiology, Diagnosis and Work-Up

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The vast majority of endometrial cancer patients are postmenopausal women. Prolonged or excessive uninterrupted estrogen exposure has been linked to most of the risk factors associated with the disease, and the addition of progestational agents to postmenopausal estrogen replacement regimens substantially reduces risk.

Carcinoma of the endometrium is the most common malignancy of the female genital tract, with an estimated 37,400 new cases and 6,400 deaths from the disease in 1999.¹ Seventy-five percent of endometrial cancer patients are postmenopausal women (median age, 63); only 5% of cases occur in women under the age of 40.² Survival rates of 75% are expected for women with the disease, which is confined to the uterus in 75% of patients.

Treatment of patients with endometrial carcinoma has undergone extensive changes over the past 25 years, ranging from clinical staging and preoperative radiation therapy to surgical staging and individualized postoperative adjuvant radiation therapy for patients at risk for recurrence.

In Part 1 of this article, epidemiology, work-up and diagnosis related to endometrial carcinomas will be reviewed. The discussion will be limited to epithelial endometrial carcinomas, and will not include uterine soft tissue sarcomas.

Epidemiology

Estrogen and progesterone. Prolonged or excessive uninterrupted exposure to estrogen has been linked to most of the risk

factors associated with endometrial hyperplasia or cancer (Table 1).³ The high rate of endometrial cancer in Western societies might be associated with the higher levels of animal fats in the diet and the higher prevalence of obesity in these cultures. High levels of dietary fats might be carcinogenic⁴ and have been associated with various types of cancer.

Obesity, especially morbid obesity, has been associated with an increased risk of death from malignancy.⁴ Endogenous estrogens rise in obese postmenopausal women through the conversion of androstenedione to the weak estrogen estrone.⁵ Morbid obesity (>23 kg overweight) increases the risk of endometrial cancer tenfold.³ Both diabetes and hypertension are associated with obesity and endometrial carcinoma; however, Sholf and Newcomb⁶ showed that diabetes mellitus increased the risk of endometrial cancer approximately threefold in obese patients, while this increased risk was not seen in nonobese diabetic patients.

Because pregnancy is predominantly a progestational state, nulliparity is associated with prolonged, uninterrupted estrogen exposure and increases the risk of endometrial cancer two- to fivefold.³ Late menopause and early menarche lead to a

2.4-times higher relative risk of endometrial cancer.³ Exogenous exposure via uninterrupted estrogen without concurrent progestational agents for treatment of the menopausal syndrome has been recognized as a risk factor for the development of endometrial cancer since the 1970s.⁷ An eightfold increase in relative risk has been associated with ingestion of unopposed exogenous estrogen; the relationship is dose- and duration-dependent, with those at greatest risk taking standard or relatively high doses of estrogen for more than 5 years.⁸

The addition of progestational agents substantially reduces the risk of endometrial cancer. In addition, studies have shown differences in endometrial cancer risk with different progestin regimens. Two large, population-based, case-controlled studies^{8,9} produced similar results. In these studies women taking unopposed estrogen had a sixfold increased risk of developing endometrial cancer, compared to nonusers of estrogen. Women on cyclic progestins (<10 days/month) were at greater risk for the disease than were nonusers of hormones (Pike and colleagues⁸ reported a relative risk of 1.87, and Weiderpass et al⁹ reported a relative risk of 2.9), but to a much lesser degree

than those on unopposed estrogen (relative risk 8.0)⁹. Women on progestins for at least 10 days showed no elevated risk of disease in the study conducted by Weiderpass et al,⁹ while Pike et al⁸ reported an elevated risk of 2.9 in these women.

Although, as illustrated by the findings described above, duration of therapy in relation to the development of endometrial cancer is somewhat controversial, it is clear that the addition of progestins reduces risk, compared to that seen with estrogens alone. In the studies cited above, continuous progestational regimens were not associated with an increase in endometrial cancer risk (1.07: CI 0.8-1.4),⁸ or were actually protective, with a risk reduction of 80% (0.2: CI 0.1-0.8).⁹

Selective estrogen receptor modulators (SERMs): Tamoxifen and raloxifene. Tamoxifen is a synthetic estrogen agonist/antagonist with stimulatory effects on the endometrium and inhibitory effects on the breast. Tamoxifen reduces breast cancer incidence and recurrence in patients with cancer or at risk for the disease,¹⁰⁻¹² but the agent's association with endometrial cancer is well established and was first described by Killackey et al in 1985.¹³ This relationship has been confirmed in multiple large, prospective trials in which tamoxifen use was shown to increase endometrial cancer incidence 2.2- to 7.5-fold in various studies¹⁰⁻¹²; these effects were most pronounced in postmenopausal patients, and the distribution of disease stage and grade was similar to that in patients not treated with tamoxifen. Endometrial cancer screening for patients on tamoxifen has been suggested, but no clinical benefit has been noted from routine ultrasound or biopsy screening. It is recommended that patients on tamoxifen be followed with annual gynecologic exams that include a Pap smear and pelvic exam, a careful history and thorough evaluation for abnormal bleeding.¹⁴

Preclinical trial findings suggest that

raloxifene might have limited effects on the endometrium. While findings from the Multiple Outcomes of Raloxifene Evaluation (MORE) study¹⁵ showed no increased risk of endometrial cancers in the raloxifene-treated patients (RR, 0.8: 95% CI, 0.2-2.7), definitive data on this SERM's effects on the endometrium await the maturation of ongoing randomized trials.

Age and race. The incidence of endometrial cancer increases with age, with 12 per 100,000 women diagnosed with the disease at age 40, and 84 per 100,000 at age 60. Advanced age also is associated with poor outcome; multiple causative factors are possible, including more advanced disease stage and grade, and delay of initial treatment in older patients.

The incidence of endometrial cancer is also higher in Caucasians than in African-Americans. In addition, between 1973 and 1996, the incidence of the disease decreased by 26.5% in Caucasians and increased by 15.3% in African-Americans. These effects are thought to be associated with exogenous estrogen exposure.¹⁶

African-Americans tend to have a lower incidence of hormonally related (good prognosis) tumors; therefore, the relative percentage of higher-risk histologic subtypes tends to lead to worse outcomes in this patient group. There is, however, controversy about whether African-American race alone is an independent risk factor for worse endometrial cancer outcomes. Though controversial, similar outcomes for African-Americans and Caucasians are reported by many authors when similar histologic subtypes and stages are compared; however, findings from at least two recent studies suggest that race alone, controlled for disease stage and other histopathologic factors, is associated with worse

prognoses in African-American women.^{17,18}

Diagnosis and Work-Up

The most common presentation for endometrial cancer is postmenopausal or abnormal premenopausal uterine bleeding. Uterine bleeding with advancing age is strongly associated with the presence of cancer (Table 2),¹⁹ and a pelvic exam, Pap

Table 1.
Endometrial Carcinoma Risk Factors*

Characteristic	Increased Risk
Obesity	
>30 lbs	3 x
>50 lbs	10 x
Nulliparity	2 x
Late menopause	2.4 x
"Bloody" menopause	4 x
Diabetes mellitus	2.8 x
Hypertension	1.5 x
Unopposed estrogen use	9.5 x
Complex atypical hyperplasia	29 x

*Reprinted with permission. Barakat RR, Park RC, Grigsby PW, et al. Corpus: Epithelial tumors. In: Hoskins WJ, Perez CA, Young RC, editors. *Principles and practice of gynecologic oncology, 2nd ed.* Philadelphia: Lippincott-Raven Publishers, 1997:860.

Table 2.
Frequency of Endometrial Carcinoma by Age Group in Women with Postmenopausal Bleeding*

Age Group	Corpus Cancer		
	Total Cases	No.	Percent
<50	34	0	0.0
50-59	161	15	9.3
60-69	92	15	16.3
70-79	43	12	27.9
>80	5	3	60.0

*Reprinted with permission. Hawwa ZM, Nahhas WA, Copenhaver EH. Postmenopausal bleeding. *Lahey Clinic Foundation Bulletin* 1970;19:61. In: Morrow P, Curtin JP, Townsend DE, editors. *Synopsis of gynecologic oncology, 4th ed.* New York: Churchill Livingstone, 1993:159.

smear, uterine biopsy and endocervical curettage are performed to evaluate for cervical or uterine pathology. In-office endometrial biopsy findings correlate with those of operative dilatation and curettage (D&C) in 90-95% of cases.²⁰ If the biopsy is inadequate, fractional D&C is recommended. Endometrial pathology is rare with an endometrial thickness <5 mm (by ultrasound), and ultrasound evaluations can be useful when an in-office biopsy cannot be performed.²¹ D&C, however, remains the gold standard for diagnosis²²; numerous reports illustrate that, while rare, endometrial cancer can be found when endometrial thickness is <5 mm.

Operative hysteroscopy can be helpful in the diagnosis of abnormal bleeding of an unknown origin but should be reserved for patients who have continued bleeding despite a negative biopsy. Hysteroscopy should not be used in the primary evaluation of postmenopausal bleeding because of the risk of dissemination of malignant cells through the fallopian tubes and into the peritoneal cavity; increased incidence of malignant peritoneal cytology and at least one abdominal recurrence in an otherwise low-risk patient have been reported.^{23,24}

Endocervical biopsy should be included in initial evaluation to identify patients with cervical involvement and to differentiate between endocervical and endometrial cancers. Endocervical involvement has been associated with higher rates of nodal and adnexal metastases. If endocervical disease is present, the surgeon should prepare to perform pelvic and para-aortic node sampling at the time of hysterectomy.

Once the diagnosis has been established, with disease apparently limited to the uterus, attempts should be made to identify patients at high risk for occult lymphatic spread. Grade-3 malignancy, clear cell and serous histologic subtypes, deep myometrial invasion, cervical stromal invasion and lymph-vascular space invasion are the primary pathologic risk factors for occult metastatic disease. Se-

rum CA-125 evaluation and transvaginal ultrasound are effective, inexpensive tests for detecting high-risk features. CA-125 levels >20 U/ml have been associated with deep invasion into the myometrium, with a sensitivity of 69.0%, a specificity of 74%, a positive predictive value of 59% and a negative predictive value of 82%.²⁵ Transvaginal pelvic ultrasound can reliably determine the depth of myometrial invasion in approximately 80% of cases.²⁶ The combination of preoperative tumor grading, endocervical curettage, and CA-125 and transvaginal ultrasound findings should help the clinician identify patients who require pelvic and para-aortic lymph node sampling at the time of hysterectomy. ■

Part 2 of this article will address prognosis and treatment.

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