

EPIDEMIOLOGY OF UTERINE CORPUS CANCERS

Louise A. Brinton, James V. Lacey, Jr., Susan S. Devesa, and Mark E. Sherman

MAJOR CONTROVERSIES

- How much do uterine corpus cancer rates vary geographically and what are the reasons underlying these differences?
- What demographic factors might play a role in the etiology of uterine corpus cancer?
- What factors might explain the observed geographic variation in mortality among whites in the United States?
- Have uterine corpus cancer rates changed over time?
- What factors are associated with survival?
- What factors explain the increased risk of endometrial cancer associated with nulliparity and the decreased risk relating to multiparity?
- What menstrual and reproductive factors other than parity relate to endometrial cancer risk?
- What patterns of oral contraceptive use are most strongly related to decreases in endometrial cancer risk?
- What aspects of exogenous hormone use lead to an increased risk of endometrial cancer?
- Can the adverse effects of estrogens be counteracted by the addition of progestins, and, if so, what is the most effective means by which progestins should be administered?
- What other therapeutic agents affect the risk of endometrial cancer?
- To what extent do body mass and physical activity independently affect risk?
- Which constituents of diet are related to risk?
- Does alcohol consumption affect endometrial cancer risk?
- Does cigarette smoking affect the risk of endometrial cancer, and, if so, what might be the underlying biologic mechanism?
- Do observed relationships with prior medical conditions persist after adjustment for effects of concomitant obesity?
- To what extent do familial factors affect the risk of endometrial cancer?
- Is there a role for environmental factors in the etiology of endometrial cancer?
- How much is known about the natural history of endometrial cancer precursors?
- What is the best system for classifying endometrial cancer precursors?
- What is the epidemiology of endometrial precursors?
- What are the risk factors for endometrial precursors?
- How do endogenous hormones relate to risk?
- Is obesity associated with endometrial cancer independently of endogenous hormones?
- Does the perimenopause represent a crucial period for endometrial cancer?
- What molecular markers might elucidate endometrial carcinogenesis?
- Is there more than one model for endometrial carcinogenesis?

The study of the epidemiology of uterine corpus cancers presents many challenges. Although a large number of factors seem to be strongly predictive of risk (Table 14-1), many of them are highly correlated, requiring a cautious interpretation of causal associations. This issue, along with unclear biologic mechanisms underlying many of the identified risk factors, has led to a number of controversies regarding the epidemiology of the disease. This chapter highlights these controversies and elaborates on additional research that might be useful in increasing the understanding of carcinogenic processes. Information is reviewed relating to the descriptive epidemiology of the disease, known risk factors, and biologic mechanisms mediating these factors.

INCIDENCE, MORTALITY, AND SURVIVAL

According to data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program,^{1,2} an estimated 40,100 cases of cancers of the corpus uteri and cancers of the uterus, not otherwise specified (NOS)—hereafter referred to as uterine corpus cancers—were expected to be diagnosed nationally during 2003. Based on data from 1996 to 1998, the lifetime risk among U. S. women of being diagnosed with uterine corpus cancer is 2.7%, and the lifetime risk of dying from uterine corpus cancer is 0.5%.¹

Globally, uterine corpus cancer accounted for about 42,000 deaths in 1990,³ of which 27,500 occurred in developed countries and 14,400 in developing countries.⁴ About 6,800 deaths due to this cancer were expected to occur among American women during 2003.²

Table 14-1. Risk Factors for Uterine Corpus Cancer

Factors Influencing Risk	Estimated Relative Risk*
Older age	2-3
Residency in North America or Northern Europe	3-18
Higher level of education or income	1.5-2
White race	2
Nulliparity	3
History of infertility	2-3
Menstrual irregularities	1.5
Late age at natural menopause	2-3
Early age at menarche	1.5-2
Long-term use or high dosages of menopausal estrogens	10-20
Long-term use of combination oral contraceptives	0.3-0.5
High cumulative doses of tamoxifen	3-7
Obesity	2-5
Stein-Leventhal disease or estrogen-producing tumor	>5
History of diabetes, hypertension, gallbladder disease, or thyroid disease	1.3-3
Cigarette smoking	0.5

*Relative risks depend on the study and referent group employed.

There is considerable variation in uterine corpus cancer rates, both between and within countries. This has led to questions as to how much of the variation might be explained by reporting differences and the extent to which rates change when individuals migrate from low-incidence to high-incidence areas. Ethnic and racial differences in occurrence have also been noted, raising questions as to probable causes for this variation.

How much do uterine corpus cancer rates vary geographically and what are the reasons underlying these differences?

Internationally, estimated 1990 mortality rates (deaths per 100,000 woman-years, age-adjusted, world standard) varied more than eightfold, from less than 0.4 in China to 4.1 in eastern Europe and the Caribbean and 4.9 in Micronesia/Polynesia.⁴ Rates were also low (less than 1) in other parts of Asia and in Africa. Rates in western Europe and North America ranged between 2 and 3 per 100,000. Mortality rates have declined since at least the 1960s in many countries, with narrowing of the international differences.⁵

In contrast to mortality data, which generally exist at the national level because death certificates are legal documents, incidence data from population-based cancer registries are not as widely available. Data from several dozen well-run registries around the world for 1988 to 1992 suggest that incidence rates (age-adjusted, world standard) varied more than threefold.⁶ Rates were lowest in parts of China, Japan, India, and Costa Rica (less than 6); intermediate in the Caribbean, Spain, and the United Kingdom; and highest in western Europe, Canada, and North America (Fig. 14-1).⁶ The highest rate, 18.4, occurred among U.S. whites. Geographic variation was apparent within many countries, but within-country differences were considerably smaller than those between countries. Rates in urban areas generally exceeded those in neighboring rural areas.⁷

What demographic factors might play a role in the etiology of uterine corpus cancer?

The risk of developing uterine corpus cancer increases rapidly with age during childbearing years (Fig. 14-2). After menopause, rates continue to increase, but at a less rapid pace. Incidence rates for uterine corpus adenocarcinomas are higher among whites than blacks at virtually all ages, with rates twice as high during the perimenopausal years (age 45 to 54). Women of upper socioeconomic status have an elevated risk of uterine corpus cancer.^{8,9} It remains unclear the extent to which this relationship is explained by other risk factors correlated with affluence (e.g., overnutrition, use of estrogen replacement therapy). In contrast to the higher incidence rates among whites,

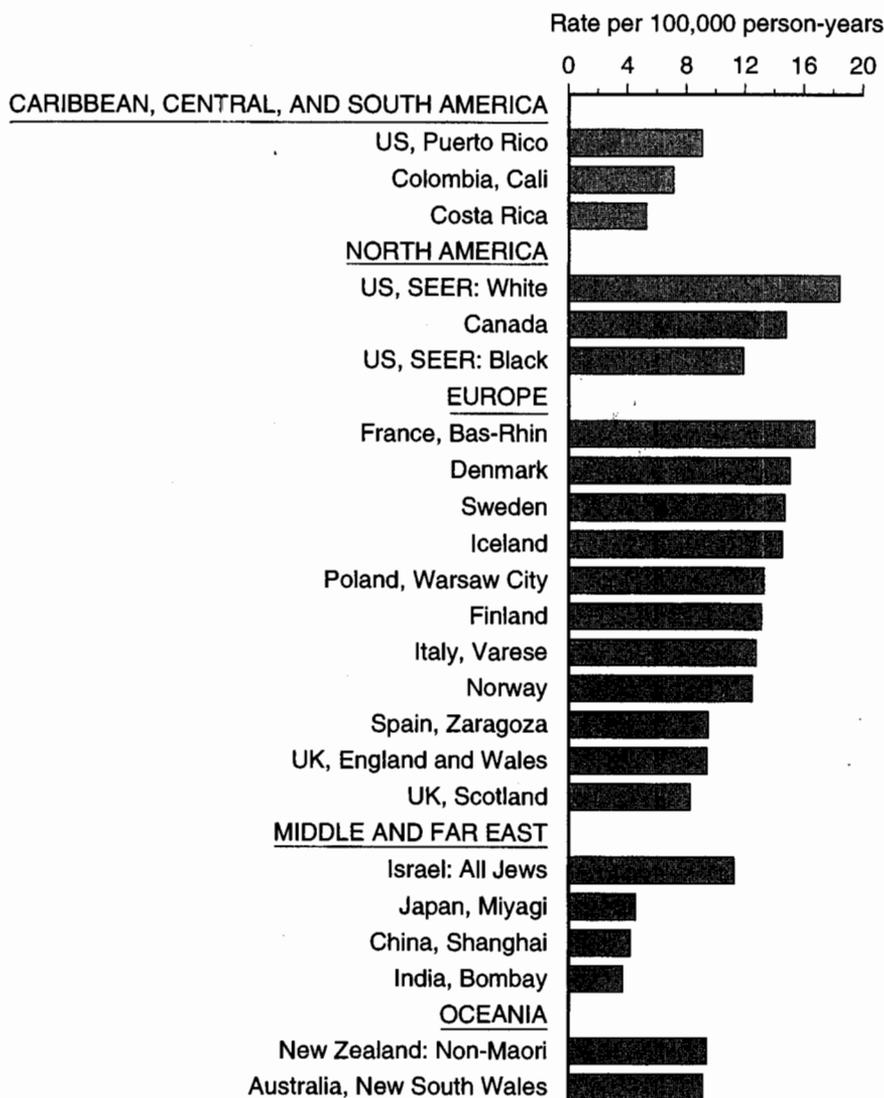


Figure 14-1. International variation in incidence rates (age-adjusted world standard population) of cancer of the corpus uteri and cancer of the uterus, not otherwise specified (NOS) among women, 1988-1992. (Data from Parkin DM, Whelan SL, Ferlay J, et al: *Cancer Incidence in Five Continents, Vol VII*. Lyon, IARC Scientific Publishers, 1997.)

mortality rates are higher among blacks over all age groups.

Within the United States between 1988 to 1992, uterine corpus cancer incidence rates were highest among non-Hispanic white and Hawaiian women (Table 14-2).⁶ Rates for blacks, Asians, and Hispanics were one half to two thirds those for non-Hispanic whites, and Korean women were at notably low risk. Rates in New Mexico were similar among Hispanic and American Indian women and were lower than among Hispanics in Los Angeles or San Francisco.

The rate of uterine corpus cancer among Chinese women living in Shanghai was only 60% of the rate among Chinese women in Hong Kong or Singapore, whereas the rates among Chinese women in Hawaii and San Francisco were more than twice as high (Table 14-3).⁶ Similarly, Japanese women in San Francisco and Hawaii had rates triple those in Japan. Within Israel, women born in Africa or Asia were at considerably reduced risk compared with those born in Israel, Europe, or America.

What factors might explain the observed geographic variation in mortality among whites in the United States?

Considerable geographic variation in uterine corpus cancer mortality rates has been reported within the United States, with notably high rates in parts of the northeast and low rates across the south.¹⁰ Figure 14-3 presents the ranked mortality rates by state economic area for white women during the period 1970 to 1998. The age-adjusted (1970 U.S. standard) rates varied more than threefold, ranging from 1.6 to 5.4 per 100,000 woman-years; the rate was higher than 4 in many areas of the Northeast and Midwest and 3 or lower across the South and mountain states. The regional excess of uterine corpus cancer across the Northeast has been evident for more than four decades.¹¹ The North-South differences have become more pronounced over time as mortality rates have declined more rapidly in many areas of the south. National data on survival rates among uterine corpus

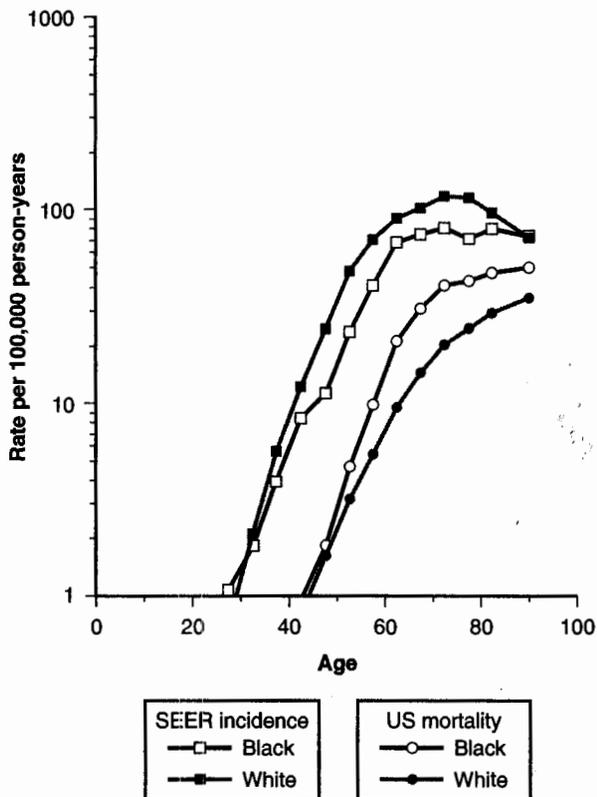


Figure 14-2. Age-specific incidence of cancer of the corpus uteri and cancer of the uterus, not otherwise specified (NOS) in the Surveillance, Epidemiology and End Results (SEER) database and mortality rates among women in the United States, by race, 1990-1998. (Data from Ries LA, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda: National Cancer Institute, 2001.)

cancer patients are not available, but it is unlikely that geographic variations in survival greatly influence the mortality patterns. Explanations for the geographic patterns are unclear, but they may relate to differences in reproductive behavior, socioeconomic status, and access to medical care, as has been found for breast cancer.¹²

Have uterine corpus cancer rates changed over time?

From the 1950s to the 1990s, age-adjusted uterine corpus cancer mortality rates declined among white and nonwhite women in the United States.¹³ During the last two decades of the 20th century, uterine corpus cancer mortality rates continued to decrease, with rates among blacks 60% to 90% higher than those among whites¹ (Fig. 14-4). In 1998, the mortality rates were 5.7 and 3.1 per 100,000 woman-years among blacks and whites, respectively. In contrast, age-adjusted incidence rates consistently have been higher among whites than blacks. Rates peaked during the early 1970s, especially among whites, with the white/black rate ratios exceeding 2; the peaks were related to trends in the use of unopposed estrogens.¹⁴ Rates subsequently declined,

especially among whites during the 1980s, and have been relatively stable since. During the 1990s, incidence was about 40% higher among whites than among blacks.

As shown in Table 14-4, uterine corpus cancer is most commonly diagnosed at localized stages, with recent incidence rates of 17.2 and 8.5 among whites and blacks, respectively. The declines in invasive incidence from 1975-1978 to 1995-1998 were driven by decreases in the rates of localized disease. Rates of localized-stage disease declined at all ages younger than 70 years but increased among older women. Rates of regional-stage disease increased somewhat, and rates of distant disease did not change greatly.

Trends in uterine corpus cancer incidence have varied internationally, including increases in many regions with historically low rates, whereas mortality rates generally have declined.¹⁵

What factors are associated with survival?

The 5-year relative survival rates among women diagnosed with uterine corpus cancer have not changed greatly since the mid-1970s, with rates consistently higher among whites compared with blacks.¹ Based on more than 14,000 cases diagnosed between 1992 and 1997, 75% of uterine corpus cancers among white women were diagnosed at a localized stage, and 13% at a regional stage (Table 14-5). The stage distribution among black women was not as favorable, with localized and regional stages accounting for 52% and 22% of cases, respectively. The proportion of cases diagnosed at a distant stage was considerably higher among black women than white women—18% versus 8%, respectively. Survival rates varied markedly by stage at diagnosis: 83% or more for women with localized disease versus 28% or less for women with distant spread. The more favorable prognosis among whites compared with blacks persisted for patients within each stage category, perhaps because of differences in extent of disease within stage category, tumor aggressiveness, or aggressiveness or effectiveness of treatment. Some support for true biologic variation by racial ethnicity derives from one analysis that showed moderate racial differences in tumor grade remaining even after control for most recognized risk factors.¹⁶

RISK FACTORS

The majority of epidemiologic studies have focused on defining the epidemiology of endometrial adenocarcinomas rather than on the rarer cancers, such as sarcomas and synchronous tumors of the endometrium and ovary, whose epidemiology is less clear. A number of risk factors have been identified for endometrial cancer, although in many cases the inter-relationship between factors and the mediating biologic mechanisms are incompletely understood. Most of the controversies center on these two issues.

Table 14-2. Variation in Incidence of Uterine Corpus Cancer* by Racial and Ethnic Group Among U.S. Women (SEER Data, 1988-1992)

	Los Angeles		San Francisco		Hawaii		Connecticut		Seattle		Detroit		Atlanta		New Mexico		Iowa		Utah	
	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Non-Hispanic White ¹	3326	20.3	1783	19.0	142	15.8	2295	18.9	2233	19.7	2246	19.8	713	15.4	497	16.1	2048	17.9	845	19.2
Hispanic White	617	11.6	155	13.7	-	-	-	-	-	-	-	-	-	-	139	9.7	-	-	-	-
Filipino	74	11.4	49	9.7	52	11.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Black	335	11.0	160	12.4	-	-	95	13.7	-	-	362	12.0	163	11.1	-	-	-	-	-	-
Japanese	44	8.1	33	16.5	170	14.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chinese	48	7.3	96	11.9	35	14.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Korean	11	2.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hawaiian	-	-	-	-	91	20.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
American Indian	-	-	-	-	-	-	-	-	-	-	-	-	-	-	25	9.6	-	-	-	-

SEER, Surveillance, Epidemiology and End Results program; -, data not available.

*Includes cancers of the corpus uteri and cancers of the uterus, not otherwise specified (NOS); table shows numbers of cases and incidence rates per 100,000 woman-years, age-adjusted using the world standard.

¹Includes all whites in Hawaii, Connecticut, Detroit, and Atlanta, and all women in Seattle, Iowa, and Utah.

From Ries LA, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda: National Cancer Institute, 2001.

Table 14-3. Variation in Incidence of Uterine Corpus Cancer* by Racial and Ethnic Group and Country of Residence, 1988-1992

Group and Place	No. of Cases	Rate
Chinese		
China, Shanghai	1022	4.3
Singapore: Chinese	366	7.0
Hong Kong	1081	7.3
US, Los Angeles: Chinese	48	7.3
US, San Francisco: Chinese	96	11.9
US, Hawaii: Chinese	35	14.3
Japanese		
Japan, Osaka	1372	4.2
Japan, Miyagi	395	4.6
US, Los Angeles: Japanese	44	8.1
US, Hawaii: Japanese	170	14.7
US, San Francisco: Japanese	33	16.5
Israeli		
Israel: Jews born in Africa or Asia	290	7.9
Israel: Jews born in America or Europe	812	13.4
Israel: Jews born in Israel	209	15.3

*Includes cancers of the corpus uteri and cancers of the uterus, not otherwise specified (NOS); table shows number of cases and incidence rates per 100,000 woman-years, age-adjusted using the world standard. From Parkin DM, Whelan SL, Ferlay J, et al: Cancer Incidence in Five Continents, Vol. VII. Lyon, IARC Scientific Publishers, 1997.

What factors explain the increased risk of endometrial cancer associated with nulliparity and the decreased risk relating to multiparity?

Nulliparity is a recognized risk factor for endometrial cancer. Most studies demonstrate a twofold to threefold higher risk for nulliparous women compared with parous women.^{8,17-19} The association of endometrial

cancer with nulliparity has been suggested to reflect prolonged periods of infertility. The hypothesis that infertility is a risk factor for endometrial cancer is supported by studies showing higher risks for married nulliparous women than for unmarried women.^{8,9} One study that specifically evaluated infertility as a risk factor for endometrial cancer found a 3.5-fold increased risk for women who reported an inability to get pregnant lasting 3 years or longer.¹⁸ In another study, nulliparous women who sought advice for infertility were at an almost eightfold excess risk compared with nulliparous women without an infertility problem.¹⁷ In a follow-up study from Israel, infertile women were found to have an approximately fourfold increased risk compared with the general population.²⁰ In that study, women with progesterone deficiencies were at particularly high risk. This finding was noteworthy, given that the means of classifying causes of infertility was based on relatively crude measures. Several ongoing studies that are using well-defined endocrinologic parameters to classify categories of infertility should be even more informative in terms of distinguishing patients who are at high risk for endometrial cancer.

Several biologic alterations linked to infertility have been associated with endometrial cancer risk, including anovulatory menstrual cycles (prolonged exposure to estrogens without sufficient progesterone); high serum levels of androstenedione (i.e., excess androstenedione available for conversion to estrone); and the absence of monthly sloughing of the endometrial lining (residual tissue that may become hyperplastic). Another factor that may be important because of its effect on the amount of free estrogens is the level of serum sex hormone-binding globulin, which has been found to be lower in nulliparous than in parous women.²¹

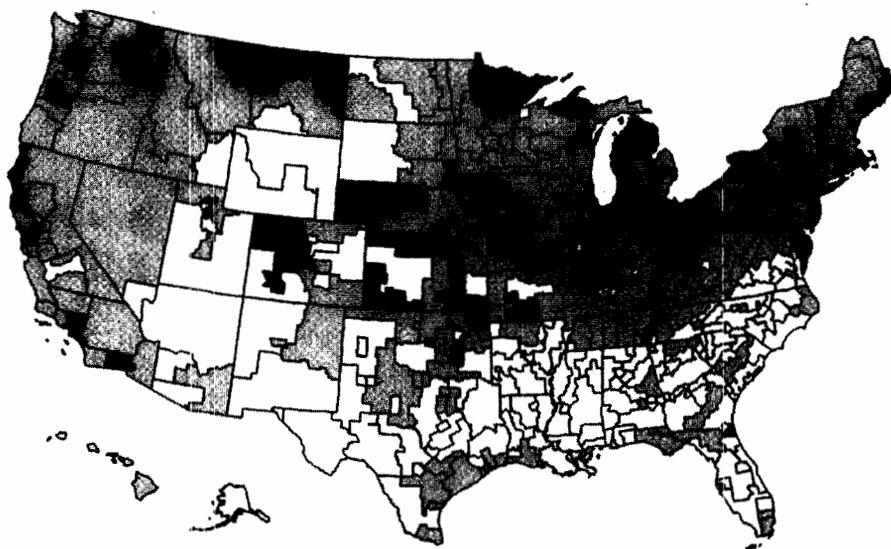
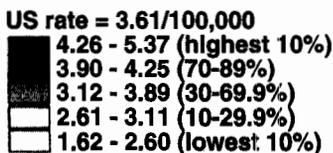


Figure 14-3. Cancer mortality rates among white women for cancer of the corpus uteri and cancer of the uterus, not otherwise specified (NOS), by state economic area (age-adjusted 1970 U.S. population. Updated from <http://www3.Cancer.gov/atlasplus/>, 1970-1998.



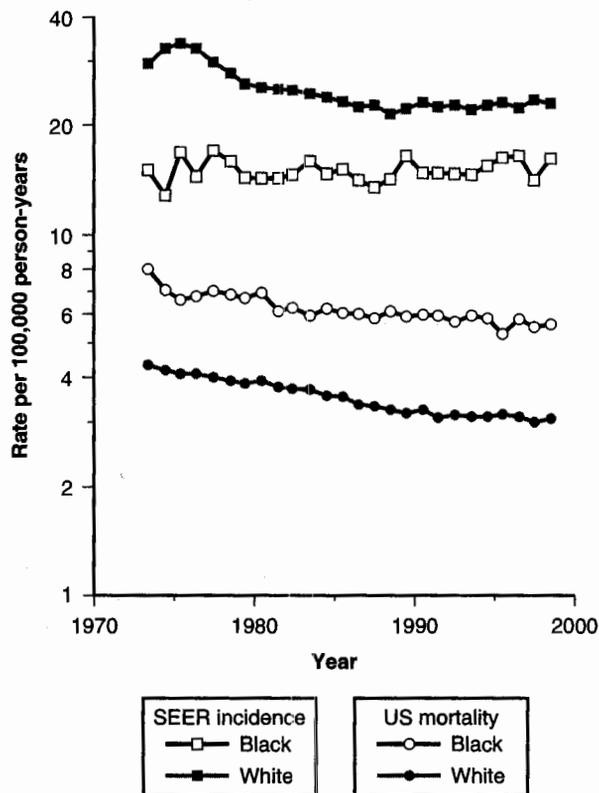


Figure 14-4. Trends in cancer of the corpus uteri and cancer of the uterus, not otherwise specified (NOS) in the Surveillance, Epidemiology and End Results (SEER) (age-adjusted 1970 U.S. population) database and mortality rates incidence among women in the United States by race, 1973-1998. (Data from Ries LA, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda: National Cancer Institute, 2001.)

What menstrual and reproductive factors other than parity relate to endometrial cancer risk?

Most studies find that among parous women there is decreasing risk of endometrial cancer with increasing number of births. The age at which a woman has her first liveborn child does not appear to relate to endometrial cancer risk.^{8,17,18} However, several recent studies suggest that a last birth occurring late in reproductive life may reduce the risk.^{22,23} Although this may reflect unique hormone profiles of women who are able to conceive at older ages, it is also plausible that births at an older age may afford protection by mechanically clearing malignantly transformed cells from the uterine lining. This hypothesis is consistent with observations that the risk of endometrial cancer increases with time since the most recent pregnancy.^{22,23} Further support for this hypothesis derives from several studies that have shown reductions in risk among users of intrauterine devices.²⁴⁻²⁶ However, it is also possible that these devices may affect risk by causing structural or biochemical changes that alter the sensitivity of the endometrium to circulating hormones.

The relationship of risk to breast-feeding remains controversial. Although a number of studies have

failed to show any relationship,^{8,9,17} more recent studies suggest that prolonged lactation may offer some protection.^{27,28} In one of these investigations, however, the reduced risk did not persist into the age range when endometrial cancer becomes common.²⁸

Early age at menarche was found to be related to increased endometrial cancer risk in several studies, although the associations were generally rather weak and trends inconsistent.^{8,9,17,18} Several studies found stronger effects of age at menarche among younger women, although this has not been consistently demonstrated.¹⁸ The extent to which these relationships reflect increased exposure to ovarian hormones or other correlates of early menarche (e.g., increased body weight) is unresolved.

Most studies have indicated that the age at menopause is directly related to the risk of developing endometrial cancer.⁸ About 70% of all women diagnosed with endometrial cancer are postmenopausal. Most studies support the estimate of MacMahon²⁹ that there is about a twofold increased risk associated with natural menopause after the age of 52 years, compared with menopause before 49 years of age. Elwood and colleagues⁶ hypothesized that the effect of late age at menopause on risk may reflect prolonged exposure of the uterus to estrogen stimulation in the presence of anovulatory (progesterone-deficient) cycles. The interrelationships among menstrual factors, age, and weight are complex, and the biologic mechanisms of these variables operating in the pathogenesis of endometrial cancer are subject to substantial speculation.

Use of oral contraceptives is clearly related to risk (see later discussion), but whether other means of controlling reproduction affect risk remains less clear. As elaborated previously, use of an intrauterine device may be associated with a reduced risk of endometrial cancer. Several studies have suggested that tubal sterilization may result in endogenous hormone alterations. However, a recent study failed to find an association of this procedure with endometrial cancer risk.³⁰

What patterns of oral contraceptive use are most strongly related to decreases in endometrial cancer risk?

Users of combination oral contraceptives have been found to experience approximately half the risk for endometrial cancer of nonusers, and long-term users in most studies experience even further reductions in risk.³¹⁻³⁴ Kaufman and associates³⁴ showed that the reduced risk persisted for at least 5 years after discontinuation, but Weiss and Sayvets³³ found that the protective effect waned within 3 years. In several studies, the greatest reduction in risk was associated with pills containing high progestin doses, although this finding was not confirmed elsewhere.^{32,35} A number of studies have claimed that the protective effect of the pill appears to be greatest among nulliparous women.^{18,31} In other studies, the protection has been limited to nonobese women or to those who have not been exposed to noncontraceptive estrogens.^{18,33}

Table 14-4. Incidence Trends of Uterine Corpus Cancer* by Race, Stage, and Age (SEER Data, 1975-1978 and 1995-1998)

Population and Type	1975-1978		1995-1998		Change in Rate	
	No. of Cases	Rate	No. of Cases	Rate	Actual	Percent
Whites by Stage						
In situ	970	2.6	245	0.5	-2.1	-79.8
Invasive						
Total	12,194	31.1	11,382	22.9	-8.1	-26.2
Localized	9,821	25.2	8,324	17.2	-8.1	-32.0
Regional	921	2.3	1,612	3.1	0.8	35.4
Distant	677	1.7	831	1.6	-0.1	-3.0
Unstaged	775	1.9	615	1.0	-0.8	-44.8
Blacks by Stage						
In situ	25	0.7	10	0.2	-0.5	-73.5
Invasive						
Total	517	16.2	814	15.7	-0.4	-2.6
Localized	310	9.5	443	8.5	-0.9	-9.9
Regional	73	2.4	179	3.5	1.1	44.2
Distant	74	2.3	124	2.5	0.2	6.5
Unstaged	60	2.0	68	1.2	-0.7	-36.5
Localized Stage among Whites by Age Group (yr)						
30-39	202	4.5	194	2.9	-1.7	-37.0
40-49	758	20.0	818	13.4	-6.6	-33.0
50-59	3,557	90.4	1,960	48.6	-41.8	-46.2
60-69	3,330	112.1	2,214	71.5	-40.7	-36.3
70-79	1,459	75.1	2,185	80.1	5.0	6.7
80+	488	46.6	936	54.8	8.1	17.4

SEER, Surveillance, Epidemiology and End Results program.

*Includes cancers of the corpus uteri and cancers of the uterus, not otherwise specified (NOS); table shows number of cases and incidence rates per 100,000 woman-years, age-adjusted using the 1970 U.S. standard.

From Ries LA, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda: National Cancer Institute, 2001.

In contrast to combination oral contraceptives, several studies have shown an increased risk of endometrial cancer among women who had previously used Oracon, a sequential preparation that combined dimethisterone (a weak progestogen) with a

large dose of a potent estrogen (ethinyl estradiol).^{18,33} The risk associated with the use of other sequential oral contraceptives remains unclear, mainly because these drugs are no longer marketed.

Table 14-5. Distribution of Uterine Corpus Cancer* and 5-Year Relative Survival Rates by Stage at Diagnosis among White and Black Women (SEER Data, 1992-1997)

	White	Black
Cases (N)	14,369	1,019
Stage at Diagnosis (%)		
Total	100	100
Localized	75	52
Regional	13	22
Distant	8	18
Unstaged	4	9
5-Year Relative Survival Rate (%)		
Total	85.8	58.9
Localized	96.9	82.9
Regional	65.1	42.7
Distant	27.7	13.1
Unstaged	47.6	48.9

SEER, Surveillance, Epidemiology and End Results program.

*Includes cancers of the corpus uteri and cancers of the uterus, not otherwise specified (NOS).

From Ries LA, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda: National Cancer Institute, 2001.

What aspects of exogenous hormone use lead to an increased risk of endometrial cancer?

Although it is well known that use of estrogen replacement therapy is associated with a 2-fold to 12-fold elevation in risk of endometrial cancer,³⁶⁻³⁹ many aspects of the relationship remain less clear. In most investigations, the increased risk did not become apparent until the drugs had been used for at least 2 to 3 years, and longer use of estrogen was generally associated with higher risk.^{9,36,37,40} The highest relative risks, reaching 10 to 20, have been observed after 10 years of use, but it is not clear whether there is any additional increase after 15 years. In most studies, cessation of use appears to be associated with a relatively rapid decrease in risk, although a number of studies suggest that elevated risks may continue for some time after discontinuation, possibly for as long as 15 years.^{36,37,39,41-43}

All doses of estrogen appear to increase risk, with some evidence that higher doses are associated with greater elevations in risk. Of note is a study showing that even 0.3 mg of unopposed equine estrogen can result in a significant increase in risk.⁴⁴ Fewer studies

have focused on differences in risk according to cyclic versus continuous regimens of use or whether effects vary with the use of oral synthetic versus conjugated estrogens. However, from the limited data available, it appears that these differences in modes of administration are less important predictors than several other measures of use, notably duration of use and interval since last use.⁴⁵ Unresolved is whether use of estrogen patches, creams, or injections can affect risk; given the relationships of risk with even low-dose estrogens, it is plausible that these regimens may confer some increase in risk.

From a number of studies, it appears that estrogen effects are strongest among women who are thin, nondiabetic, or normotensive.^{36,41,42,46} These findings suggest that estrogen metabolism differs in these groups of women or that risk is already high enough in obese, hypertensive, or diabetic women that exposure to exogenous estrogens has only a small additional effect.

An interesting observation is that tumors associated with estrogen use generally demonstrate favorable characteristics, including earlier stage at diagnosis, lower grade, and fewer instances of myometrial invasion.^{36,47} Estrogen users tend to be younger at diagnosis than patients who have not used estrogen, and the tumors are more frequently accompanied by hyperplasia or adenomyosis.^{48,49} These observations may indicate that some advanced endometrial hyperplasias are being diagnosed as endometrial carcinomas; however, several studies and pathologic reviews have shown that the association of estrogen with endometrial cancer persists. Although the estrogen-associated risk is highest for early-stage cancers, the elevated risks also pertain to later-stage disease.^{43,47} Therefore, misclassification of endometrial hyperplasias as endometrial cancer probably accounts for only a small portion of the elevation in risk associated with estrogen use.

Can the adverse effects of estrogens be counteracted by the addition of progestins, and, if so, what is the most effective means by which progestins should be administered?

Progesterone has been shown to produce regressive changes in endometrial hyperplasia, a presumed precursor of endometrial cancer. In postmenopausal women with simple hyperplasia, administration of medroxyprogesterone acetate (MPA) in a dose of 10 mg/day for 12 days has been shown to result in conversion of the endometrium to an atrophic or nonhyperplastic pattern.^{50,51} This is consistent with the clinical recommendation that combined estrogen-progestin therapy be prescribed for all women with intact uteri. As shown in Table 14-6, studies indicate that the excess risk of endometrial cancer can be significantly reduced if progestins are given for at least 10 days each month.^{38,52,53} In several studies, however, subjects who used progestins for fewer than 10 days per month continued to experience some increased risk, with only a slight reduction compared with users of estrogen only.^{40,53,54} The sharp contrast between the effects of less than 10 and more than 10 days of progestin use has led to the suggestion that the extent of endometrial sloughing or of "terminal" differentiation at the completion of the progestin phase may play a critical role in determining risk.⁴⁰ Although it is now generally accepted that progestins must be administered for at least 10 days each month to provide protection against endometrial cancer risk, it remains questionable whether this regimen is sufficient for complete protection, particularly for long-term users.⁵⁵ Few studies have had large numbers of long-term sequential users, and in two studies there was evidence that this pattern of use may result in some persistence of risk.^{38,54} Therefore, further studies of long-term users of this regimen are needed.

Table 14-6. Relative Risks of Endometrial Cancer with Use of Sequential or Continuous Progestins Plus Estrogens in Postmenopausal Women

Study and Year	Progestin Days/Cycle	Duration of Use (yr)	Relative Risk	(95% Confidence Interval)
Weiderpass, 1999 ⁵³	<10	>5	2.9	(1.8-4.6)
	Continuous	>5	0.2	(0.1-0.8)
Beresford, 1997 ⁵⁴	<10	>5	3.7	(1.7-8.2)
	10-21	>5	2.5	(1.1-5.5)
Pike, 1997 ³⁸	Continuous	5	1.4	(1.0-1.9)
	<10	5	1.9	(1.3-2.6)
Jick, 1993	≥10	5	1.1	(0.8-1.4)
	Continuous	5	1.1	(0.8-1.4)
Voigt, 1991	Not specified	>5	1.3	(0.5-3.4)
Persson, 1989 ⁵²	<10	>3	2.4	(0.6-9.3)
	≥10	>3	1.1	(0.4-3.6)
	7-10	3-5	1.2	(0.3-5.5)

Adapted from Archer DF: The effect of the duration of progestin use on the occurrence of endometrial cancer in postmenopausal women. *Menopause* 2001;8:245-251.

Given the lack of resolution of this issue, there has been increased enthusiasm for prescribing estrogens continuously with progestins. Although Weiderpass and coworkers⁵³ in Sweden observed a risk considerably below unity for this regimen, Pike and associates,³⁸ in the United States, found no difference in risk for sequential versus continuous use of progestins. Discrepancies in findings may relate to the use of more potent progestins in Europe.

What other therapeutic agents affect the risk of endometrial cancer?

A number of clinical trials and a population-based case-control study have indicated an increased risk for endometrial cancer among tamoxifen-treated breast cancer patients.⁵⁶⁻⁵⁹ This is consistent with tamoxifen's estrogenic effects on the endometrium. Elevated risks have been observed primarily among women receiving high cumulative doses of therapy, usually in the range of 15 g or more. One recent study documented a poor prognosis among long-term tamoxifen users who developed endometrial cancer, presumably reflecting less favorable histologies and higher stages of disease at diagnosis.⁶⁰ Whether this finding is generalizable to other populations remains unclear.

Increasing use of ovulation induction agents, including clomiphene citrate, has raised concern about potential links with a variety of cancers, including endometrial cancer. Sufficient data are not currently available to determine whether any association exists.⁶¹ One recent report suggested an increased risk of endometrial cancer associated with use of psychotropic medications⁶²; additional confirmatory data on this relationship are needed.

To what extent do body mass and physical activity independently affect risk?

Obesity is a well-recognized risk factor for endometrial cancer, with as much as 25% of the disease possibly explained by this factor.^{17,63-68} Very heavy women appear to have disproportionately high risks. Brinton and coworkers¹⁷ reported a sevenfold excess risk for women weighing 200 pounds or more, compared with those weighing less than 125 pounds. Although studies have demonstrated significant positive trends of endometrial cancer with both weight and various measures of body mass, including Quetelet's index (weight in kilograms divided by the square of the height in meters), height has not been consistently associated with risk. Obesity appears to affect both premenopausal and postmenopausal endometrial cancer, although possibly through different mechanisms.^{9,65,68}

Blitzer and colleagues⁶⁹ found a positive association between endometrial cancer and adolescent obesity and hypothesized that long-standing obesity is a more important risk factor than adult weight. However, in several studies that have examined weight both

during early adulthood and later in life, contemporary weight and weight gain during adulthood appeared to be most predictive of endometrial cancer risk.^{18,66,68,70}

Interest has also focused on determining whether the distribution of body fat predicts endometrial cancer risk. Upper-body fat has been found in several studies to have an effect on endometrial cancer risk independent of body size.^{68,71,72} However, other studies have suggested either no effect of body fat distribution or a more crucial role for central obesity.⁷³⁻⁷⁵ Further investigations on this issue are needed, especially studies that consider intervening effects of endogenous hormones.

Several studies have suggested a protective effect of physical activity on endometrial cancer risk that appears independent of relationships with body weight.^{63,76-79} However, a number of these studies had internal inconsistencies. For instance, in a recent report,⁷⁹ the absence of differences in risk by duration or intensity of physical activity suggested the need for caution before the association is interpreted as causal. A potential relationship is biologically appealing, given that physical activity can result in changes in the menstrual cycle, body fat distribution, and levels of endogenous hormones. The issue therefore deserves attention in future investigations.

Which constituents of diet are related to risk?

Although obesity has been consistently related to endometrial cancer, epidemiologic studies have only recently evaluated the etiologic role of dietary factors. Geographic differences in disease rates (i.e., high rates in Western and low rates in Eastern societies) suggest that nutrition has a role, especially the high content of animal fat in Western diets.⁸⁰ Armstrong and Doll⁸¹ demonstrated a strong correlation between a country's total fat intake and endometrial cancer incidence.

Although a number of studies have assessed endometrial cancer risk in relation to consumption of dietary fat, the association remains unclear. A clear assessment of risk depends on careful control for effects of both body size and caloric intake (energy). In the case-control study by Potischman and associates,⁸² a relationship with animal fat intake appeared to be relatively independent of other dietary factors. In the case-control study of Goodman and colleagues,⁶³ some of the effect of fat calories appeared to be explained by body size, although the relationship continued to remain significant. Several other case-control studies, however, failed to confirm a relationship with fat intake.^{83,84} In addition, a recent cohort study found just the opposite trend, namely some decrease in risk with relatively high intakes of saturated or animal fat.⁶⁴

More consistent are studies that have shown a possible protective effect of certain nutritional patterns, including reduced risks associated with the consumption of certain micronutrients. For instance, Barbone and associates⁸⁵ found no relationship with either animal or vegetable fat intake but found reduced risks

related to high intake of certain micronutrients (including carotene and nitrate). In line with this result, a European study found reduced risks among women who reported high intake of fruits and vegetables, specifically those containing high levels of β -carotene.⁸⁵ Goodman and colleagues⁶³ found inverse relationships of risk with consumption of cereals, legumes, vegetables, and fruits, particularly those high in lutein. McCann and coworkers⁸⁴ also found evidence for reduced risks among women in the highest quartiles of intake of protein, dietary fiber, phytosterols, vitamin C, folate, α - and β -carotene, lycopene, lutein + zeaxanthin, and vegetables. However, not all studies support relationships with micronutrients, including recently reported results from a large Canadian prospective study.⁶⁴

The quest for protective factors has expanded to include phytoestrogens and consumption of foods high in omega-3 fatty acids, such as fatty fish. Although two studies suggested that consumption of these food items may be beneficial in terms of endometrial cancer risk,^{86,87} additional confirmatory studies are needed.

It is clear that further studies are needed to resolve relationships between dietary factors and endometrial cancer risk. These studies should assess the extent to which dietary associations for endometrial cancer are mediated through modifications in hormone metabolism, because both observational and intervention studies have shown higher levels of plasma estrone, estradiol, and prolactin among women who consume a high-fat or omnivorous diet, compared with a low-fat or vegetarian diet.⁸⁸⁻⁹¹

Does alcohol consumption affect endometrial cancer risk?

In a number of studies, regular consumption of alcoholic beverages has been linked to substantial reductions in endometrial cancer risk.⁹²⁻⁹⁵ Several studies noted more pronounced effects among premenopausal or overweight women, suggesting that an attenuation in endogenous estrogen levels may be responsible for the reduced risk.^{93,95} However, inconsistent findings from other studies emphasize the need for further evaluation of the relationship between alcohol consumption and endometrial cancer risk.⁹⁶⁻⁹⁹

Does cigarette smoking affect the risk of endometrial cancer, and, if so, what might be the underlying biologic mechanism?

A reduced risk of endometrial cancer among smokers has been reported, with current smokers having approximately half the risk of nonsmokers.^{92,98,100-105} In a number of studies, the reduced risk associated with smoking was more pronounced in postmenopausal than in premenopausal women.^{98,101,103} Several reports found that the reduced risk associated with smoking

was most apparent in obese patients.^{101,102,104,105} In a recent investigation,¹⁰⁴ smoking also appeared to reduce risks to a greater extent in diabetics and users of postmenopausal hormones, leading to the suggestion that smoking may exert its effects on risk through an antiestrogenic mechanism. In one investigation, cigarette smoking was not related to changes in estradiol levels but did affect serum androstenedione levels,⁹² a known source of estrogens in postmenopausal women. A number of issues regarding effects of cigarette smoking on endometrial cancer remain unresolved. Most notably, the extent to which there may be mechanistic differences between premenopausal and postmenopausal women is an intriguing research issue worthy of further pursuit.

Do observed relationships with prior medical conditions persist after adjustment for effects of concomitant obesity?

Numerous clinical reports link polycystic ovary syndrome with an increase in the risk of endometrial cancer, particularly among younger women who present with both conditions.¹⁰⁶⁻¹⁰⁸ However, given that obesity is one of the defining features of this condition, the independence of the two conditions is unclear. In a follow-up study at the Mayo Clinic, women with chronic anovulation were found to be at a threefold increased risk for development of endometrial cancer.¹⁰⁹ Case-control studies have usually had difficulties in obtaining appropriate histories of polycystic ovary syndrome, but several studies have reported increased risks of endometrial cancer among patients who report histories of either hirsutism or acne,^{17,110} conditions often associated with hyperandrogenism.

A number of studies have noted a high risk of endometrial cancer among diabetics, but again the issue is whether the association is independent of weight. Two cohort studies^{111,112} and a number of case-control studies^{17,19,113-115} suggest that the relationship persists when analyses are restricted to nonobese women or are adjusted for the effects of weight. However, in several other studies,^{67,116} the effect of diabetes on endometrial cancer risk was apparent only among obese women, suggesting the possible involvement of selected metabolic abnormalities, including hyperinsulinemia. Further research is needed to resolve the association, as well as to elaborate on how specific types of diabetes may be involved.

A variety of other diseases have been suggested as possibly predisposing to endometrial cancer risk, including hypertension, arthritis, thyroid conditions, gallbladder disease, and cholesterolemia. In a number of studies, positive findings may be partially explained by the correlation of the diseases with other factors. Similar to patients with breast cancer, those with previous fractures were found to have a reduced risk of endometrial cancer,^{117,118} presumably reflecting the association of lowered bone density with altered endogenous hormone levels.

To what extent do familial factors affect the risk of endometrial cancer?

Several studies have suggested that a family history of endometrial cancer is a risk factor for the disease.¹¹⁹⁻¹²² Data from a family-cancer database in Sweden¹²⁰ showed that risk was inversely related to age at diagnosis, with a more than 10-fold excess risk among young (<50 years) daughters of mothers with early-onset diseases. In addition, subjects with a family history of colon cancer were at an increased risk for endometrial cancer, an association that is now well recognized and reflects a role for the dominantly inherited hereditary nonpolyposis colorectal cancer gene.¹²³ In contrast, studies do not support an etiologic role in endometrial cancer for inherited mutations in either the *BRCA1* or the *BRCA2* gene.¹²⁴ Several investigations have suggested possible disease associations with more common genetic polymorphisms, including the estrogen receptor, methylenetetrahydrofolate reductase (*MTHFR*), and cytochrome P-450 1A1 (*CYP1A1*) genes,¹²⁵⁻¹²⁷ but confirmatory studies are needed.

Is there a role for environmental factors in the etiology of endometrial cancer?

Geographic variations in rates of endometrial cancer, with high rates in certain industrial areas, have led to the suggestion that environmental agents may affect risk. Given the well-recognized influence of hormones on the disease, there has been particular concern about a potential role for certain endocrine disruptors, including dichlorodiphenyltrichloroethane (DDT). Several studies have addressed this issue by comparing levels of DDE (the active metabolite of DDT) in the sera of cases and controls, finding no significant differences.^{128,129} Electromagnetic fields have also been of interest, given that they can influence hormone levels. A recent study, however, found no relationship between endometrial cancer risk and use of electric blankets or mattress covers.¹³⁰

The fact that increasing numbers of women are entering the workforce has led to questions about how occupational exposures relate to cancer risk. This issue has only recently begun to be explored with respect to endometrial cancer. In one record linkage study in Finland, endometrial cancer was associated with exposure to animal dander and sedentary work.⁹⁸

NATURAL HISTORY AND BIOMARKERS

How much is known about the natural history of endometrial cancer precursors?

The diagnosis of endometrial cancer precursors and carcinoma is usually made on the basis of endometrial biopsy¹³¹ or curettage¹³² performed to determine the cause of abnormal vaginal bleeding. Clinical treatment decisions for endometrial lesions depend on lesion

severity, patient age, medical history, and patient preferences. Women who are postmenopausal or who have completed childbearing often undergo hysterectomy, whereas younger women who have only mild abnormalities and wish to preserve their fertility increasingly choose conservative management with hormone treatment and repeat sampling.^{50,133-135}

The historical acceptance of hysterectomy as first-line therapy¹³⁶ may have minimized the impetus for understanding the natural history of endometrial cancer. The existence of multiple different pathologic classification systems, poor diagnostic reproducibility, and the lack of valid population-based screening methods have further compromised the ability to study endometrial cancer precursors. Nonetheless, the realization that many women have undergone unnecessary hysterectomy for highly reversible lesions and the increasing frequency of delayed childbearing have spurred interest in elucidating the natural history of endometrial cancer precursors through multidisciplinary investigations.

Endometrial hyperplasia: A heterogeneous set of pathologic lesions

Most endometrial carcinomas, specifically those histopathologically classified as endometrioid, seem to develop slowly from morphologically defined precursors. Endometrial hyperplasia includes a heterogeneous set of pathologic lesions ranging from immediate endometrial cancer precursors to mild, highly reversible proliferations. Microscopically, these lesions comprise a continuum of morphologic appearances.¹³⁷ The earliest lesions consist of slightly crowded and dilated endometrial glands composed of cells with nuclei resembling normal proliferative endometrium; advanced lesions are composed of almost back-to-back glands containing markedly abnormal nuclei, an appearance that closely resembles well-differentiated endometrioid carcinoma.

Most hyperplastic lesions represent innocuous glandular proliferations that regress spontaneously or can be induced to regress with progestins and repeated curettage.^{138,139} Occult carcinoma is present in 20% to 45% of women with biopsies diagnosed as endometrial hyperplasia,¹⁴⁰⁻¹⁴² which is usually classified as atypical complex endometrial hyperplasia in the World Health Organization (WHO) classification.

What is the best system for classifying endometrial cancer precursors? Multiple systems have been proposed for classifying endometrial carcinoma precursors.¹⁴³ The WHO classification is based largely on a retrospective pathologic review of biopsies and clinical records of 170 women accessioned between 1940 and 1970 at one U. S. reference laboratory.¹⁴⁴ In the WHO system, simple hyperplasia includes dilated glands with mild crowding, and complex hyperplasia consists of more irregularly shaped glands with more severe crowding. These two categories are further subdivided into atypical and non-atypical groups, based

on the size and appearance of the nuclei of the glandular cells. In the WHO classification, cytologic atypia is considered to represent the best morphologic predictor of progression to carcinoma.¹⁴⁴ The intraobserver and interobserver reproducibilities of the WHO classification are less than ideal, in part because the criteria for assessing glandular crowding and cytologic atypia are relatively imprecise and morphologic distinctions are somewhat subjective.^{145,146}

To improve the diagnostic reproducibility of biopsy interpretation, Bergeron and colleagues¹⁴⁷ proposed a modified WHO classification that collapses atypical hyperplasia and well-differentiated adenocarcinoma into a single category called "endometrioid neoplasia." All other lesions (i.e., non-atypical hyperplasias) are designated simply as "hyperplasia." This classification is predicated on the concept that "endometrial neoplasia" captures all carcinomas or incipient carcinomas (which are treated similarly), rendering further subdivision of the endometrial neoplasia category moot. However, biologic evidence to support this approach is lacking and the cutpoint between endometrial neoplasia and hyperplasia in this system is based on WHO criteria, with the same attendant limitations.

The recent Endometrial Intraepithelial Neoplasia (EIN) system uses morphologic criteria that emerged from retrospective studies using computerized image analysis of endometrial biopsies to identify morphologic features predictive of progression to carcinoma. These features were translated into diagnostic criteria that can be applied with the use of conventional light microscopy: (1) percentage of tissue occupied by glands (i.e., "volume percentage stroma"), (2) heterogeneity in nuclear diameter, and (3) complexity of glandular shape.¹⁴⁸ Microscopically, lesions that measure at least 1 to 2 mm, appear cytologically distinct from surrounding tissue, and display a volume percentage stroma of less than 55% are classified as EIN. Other abnormal proliferative lesions are classified as hyperplasia.

The categories in these three classification systems overlap in complex patterns; which classification best predicts cancer risk and is most reproducible is unclear.^{143,149} Although pathologists achieve better interobserver agreement for severe forms of endometrial hyperplasia, diagnoses of milder lesions are less reproducible.¹⁴⁶ Historically, the crucial diagnostic issue for clinical management has been the tendency for general pathologists to misclassify variants of normal endometrium as hyperplastic, leading to excessive treatment. The optimal surrogate end point for endometrial cancer has not been identified, because the risk of progression for endometrial lesions is not well defined. Most studies that have attempted to define those risks have been small and retrospective and have not used statistical methods to account for follow-up time or possible confounders.^{144,150-152}

What is the epidemiology of endometrial precursors?

Population-based prevalence estimates and incidence rates for endometrial hyperplasia are difficult to

determine because registries usually do not track this diagnosis. One study of 2586 asymptomatic volunteers who were screened for endometrial cancer by direct sampling of the endometrium in combination with a cytologic technique found a similar period prevalence for endometrial hyperplasia and endometrial cancer.¹⁵³ In contrast, a summary of 2662 endometrial curettages performed at 11 Dutch hospitals reported 2182 hyperplasias and 480 carcinomas, indicating that invasive cancer is much less common than hyperplasia. However, only 49 of the hyperplasias were classified as atypical, which suggests that the most severe putative precursors are one tenth as common as carcinoma in clinical practice.¹⁵⁴ In short, the scarce data about the reservoir of endometrial cancer and its precursors in populations limit the ability to understand its natural history and accompanying public health issues.

What are the risk factors for endometrial precursors?

Risk factor data for endometrial precursors are rather limited. One comparison of 109 women with hyperplasia and 111 with endometrial cancer reported that unopposed estrogen and obesity were risk factors for both hyperplasia and cancer; however, parity, age at first birth, age at menopause, and body mass were associated only with cancer.¹⁵⁵ A case-control study of 129 women with endometrial hyperplasia without atypia and 258 controls concluded that higher education, obesity, diabetes, and hormone replacement therapy were risk factors for hyperplasia.¹⁵⁶ A retrospective clinical study of 46 cases of endometrial hyperplasia among premenopausal women found that older age, heavier weight, infertility, nulliparity, and family history of colon cancer were associated with increased risk.¹⁵⁷

Biomarkers of Risk for Endometrial Cancer

How do endogenous hormones relate to risk? Despite the recognition that endometrial cancer is a hormonally responsive tumor, few studies have assessed its relationships with endogenous hormones. To date, only three large epidemiologic studies have assessed associations with circulating estrogens.^{92,158,159} All three studies observed an increased risk of postmenopausal endometrial cancer with increasing levels of estrone after adjustment for other factors, although in one study¹⁵⁸ the association was considerably attenuated after adjustment for body mass. In addition, two studies reported an increased risk with bioavailable (free and albumin-bound) fractions of estradiol and a reduced risk with increasing serum hormone-binding globulin.^{158,159} In one investigation,¹⁵⁸ estrogens appeared to be less predictive of premenopausal disease, suggesting that anovulation or progesterone deficiency might be more predictive of risk.

Less well investigated is whether other endogenous hormones are related to endometrial cancer risk. Key and Pike¹⁶⁰ suggested cancer risk is associated with increased cell cycling, which is increased by estrogens

and reduced by progesterone. Although progesterone deficiency could therefore be important, no major epidemiologic studies have assessed relationships with progesterone levels. The recognition that the adrenal cortex is the main source of steroid hormones has also led to an interest in adrenal hormones, such as cortisol, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate. Two large studies showed positive associations of endometrial cancer risk with serum androstenedione levels.^{92,158} In one of these investigations,¹⁵⁸ this association remained after control for estrone levels, leading the investigators to speculate on the importance of aromatase and local conversion of estrone from androstenedione via abnormal endometrial cells.

Other hormone-related biomarkers have only recently been assessed with respect to endometrial cancer, and conclusive relationships are not yet apparent.¹⁵⁹ Of interest, however, are potential relationships with pituitary hormones and insulin-like growth factors.

Is obesity associated with endometrial cancer independently of endogenous hormones? Obesity, which is hypothesized to reflect elevated estrogen levels,¹⁶⁰ seems to represent a key risk factor for both endometrial hyperplasia and carcinoma, but the mechanisms mediating this risk are unclear. One case-control analysis of serum estrogen levels¹⁵⁸ reported that the risk associated with obesity was not entirely mediated by estrogen, especially among premenopausal women.¹⁶¹ This led to interest in a potential role for insulin levels.¹⁶² However, C peptide levels were found to be unrelated to risk.¹⁶³ In another cohort study of postmenopausal women, elevated serum estrogen concentrations appeared to account for the majority of the risk associated with obesity.¹⁵⁹ The relationship of hormones to identified risk factors therefore remains unresolved, supporting the need for further investigations to assess the interrelationships among a variety of risk factors with putative hormone biomarkers.

Does the perimenopause represent a crucial period for endometrial cancer? The "unopposed estrogen" hypothesis, in which exposure to estrogens in the absence of sufficient progestins leads to endometrial proliferation that can develop into endometrial precursors and endometrial cancer, appears to unify the risk and protective factors for endometrial cancer.¹⁶⁴ Key and Pike¹⁶⁰ hypothesized that estrogen levels higher than a certain threshold stimulate endometrial proliferation. In some women, the perimenopause seems to be associated with periodically spiking high levels of unopposed estrogens and anovulatory cycles, which could predispose to cancer development.

What molecular markers might elucidate endometrial carcinogenesis?

Several biomarkers are consistently associated with endometrioid cancer or hyperplasia. Human endometrial tissue expresses two isoforms of the estrogen

receptor (ER- α and ER- β) and two isoforms of the progesterone receptor (PRA and PRB), but the role of these receptors in endometrial carcinogenesis is unclear. Expression of both ER and PR isoforms increases in the proliferative phase of the menstrual cycle,¹⁶⁵ but ER- α expression is stronger than that of ER- β near the time of ovulation. In one study, ER- α was detected in 80% of endometrial carcinomas, and ER- β in 36%, with nearly all of the latter showing coexpression of ER- α .¹⁶⁶ Silencing of the PRB gene via promoter methylation has been found in endometrial cancers but not in normal tissue.¹⁶⁷ Endometrial carcinoma may also be associated with a shift toward production of more carcinogenic estrogen metabolites.¹⁶⁸

Among other markers that have been studied in endometrial tissues, 17 β -hydroxysteroid dehydrogenase type 2, which converts estradiol to the less potent estrone, is expressed in secretory endometrium and in a subset of hyperplasias and cancers.¹⁶⁹ Expression of growth factors such as transforming growth factor- β ,¹⁷⁰ inflammatory markers such as cyclooxygenase-2,¹⁷¹ and proliferation and apoptosis markers such as Ki-67 and Bcl-2¹⁷² suggests other markers of potential interest in endometrial carcinogenesis.

The tumor suppressor gene *PTEN* appears to influence several pathways that mediate apoptosis, cell proliferation, and motility.¹⁷³ *PTEN* mutations have been identified in up to 83% of endometrial cancers in some case series, as well as in a significant percentage of endometrial hyperplasias. In one report, endometrial samples obtained from about 50% of women with abnormal vaginal bleeding contained small foci of histologically normal glands that showed less of *PTEN* expression.¹⁷⁴ Histologically, normal appearing glands that demonstrated loss of *PTEN* expression may persist for over one year¹⁷⁵ and reflect an early predispositional state for the development of endometrial cancer.¹⁷⁶ If the high prevalence of *PTEN* alterations in non-neoplastic endometrium is confirmed, epidemiologic studies will be needed to determine why most of these foci remain quiescent or regress, whereas a minority expand and develop into precursor lesions.

Microsatellite instability, secondary to inactivating germline mutations in mismatch repair genes (*hMLH1*, *hMSH2*), is characteristic of endometrial cancers that develop in women with hereditary nonpolyposis colorectal carcinoma syndrome.¹⁷⁶ Loss of mismatch repair function of these same enzymes as a consequence of promoter methylation has been found in approximately 20% of sporadically occurring endometrial carcinomas.¹⁷⁷

Endometrial carcinogenesis: more than one model?

Bokhman¹⁷⁸ first drew attention to the concept that there may be more than one pathway of endometrial carcinogenesis. Based on clinical data, he proposed that about two thirds of endometrial cancers (designated type I) are indolent neoplasms that are related to usual endometrial cancer risk factors that seem to reflect

excess estrogen exposure, whereas the remainder (designated type II) are aggressive tumors that seem less related to typical hormonal risk factors mediated. Most endometrioid carcinomas represent the archetype of type I tumors, whereas serous carcinomas seem more characteristic of type II neoplasms.¹⁷⁹ Endometrial hyperplasia is considered to be the precursor of most type I tumors, whereas many type II tumors appear to develop from malignant transformation of atrophic endometrial surface epithelium rather than glandular proliferations. The pathologic lesion that reflects malignant surface change has been referred to by different authors as endometrial intraepithelial carcinoma,^{180,181} endometrial carcinoma in situ,¹⁸² and uterine surface carcinoma¹⁸³ and may represent the precursor of some invasive type II tumors. The two types display different patterns of molecular markers: *ras* and *PTEN* mutations and mismatch repair defects characterize type I tumors, whereas *TP53* tumor suppressor gene mutations have been found with high frequency in type II tumors.^{184,185}

Endometrial carcinogenesis: future directions

The development of a refined model of endometrial carcinogenesis that incorporates genetic alterations, established risk factors, protective exposures, and hormonal imbalances, especially in the setting of anovulation, would enhance the understanding of this disease. The modifiable risk factors, particularly exogenous estrogens and increasing weight, might have crucial effects on distinct lesions at particular points in the spectrum from benign endometrium to invasive carcinoma. Continued efforts to better understand precursor lesions and to clarify the role of potential molecular markers should lead to improved efforts to reduce the population burden of endometrial cancer.

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GYNECOLOGIC CANCER

Controversies in Management

David M. Gershenson, MD

Professor and Chairman

Department of Gynecologic Oncology

The University of Texas M.D. Anderson Cancer Center

Houston, Texas

William P. McGuire, MD

Director

Oncology Service Line and Harry and Jeanette Weinberg

Cancer Institute

Franklin Square Hospital Center

Baltimore, Maryland

Martin Gore, PhD, FRCP

Professor of Cancer Medicine

Director

Rare Cancers Division

The Royal Marsden Hospital

London, United Kingdom

Michael A. Quinn,

MB ChB Glas, MGO Melb, MRCP, FRCOG,

FRANZCOG, CGO

Associate Professor

University of Melbourne

Director of Oncology/Dysplasia

Royal Women's Hospital

Melbourne, Australia

Gillian Thomas, MD

Professor of Radiation, Oncology, Obstetrics and Gynecology

Toronto-Sunnybrook Regional Cancer Center

Toronto, Ontario, Canada



ELSEVIER
CHURCHILL
LIVINGSTONE

ELSEVIER
CHURCHILL
LIVINGSTONE

The Curtis Center
170 S Independence Mall W 300E
Philadelphia, Pennsylvania 19106

or

11830 Westline Industrial Drive
St. Louis, Missouri 63146

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