Cancer Progress and Priorities: Uterine Cancer
Ashley S. Felix and Louise A. Brinton

Background
Uterine corpus cancer is the most common invasive gynecologic cancer among U.S. women. Studies of endometrial cancers, which comprise approximately 90% of all uterine cancers, have identified numerous risk factors, many of which appear to reflect high levels of estrogens in the absence of sufficient progesterone. Recent advances have indicated that the disease is etiologically heterogeneous, consisting of at least two major subgroups. This heterogeneity extends to important racial differences in both incidence and survival, possibly partially attributable to genetic factors.

Descriptive Epidemiology
Uterine cancer incidence is highest in North America and Northern Europe, intermediate in Southern Europe and temperate South America, and lowest in Southern and Eastern Asia and most of Africa (Fig. 1; ref. 1). This likely reflects prevalence differences in risk factors, including obesity and reproductive patterns. In the United States, uterine cancer is the fourth most frequently diagnosed cancer, with estimates of 63,230 diagnoses in 2018 (lifetime risk of 1 out of every 40 women; ref. 2). The average annual age-adjusted incidence of uterine cancer from the Surveillance, Epidemiology and End Results Program (SEER) was 25.7 per 100,000 women between 2010 and 2014 (3). The disease is rare before the age of 45 years, but risk rises sharply among women of all races in their late 40s to middle 60s (Fig. 2). Worldwide, uterine cancer ranked in 2012 as the sixth most common cancer, with 319,600 estimated cases (4).

Dramatic changes in the incidence of uterine cancers have occurred over time. A marked increase in U.S. incidence peaked around 1975, a trend later linked with the widespread use of menopausal estrogens in the late 1960s and early 1970s (Fig. 3). After a subsequent period of steady or declining incidence rates in many countries, endometrial cancer is again on the rise, mirroring increases in obesity prevalence (4, 5).

In the United States, age-adjusted mortality is 4.6 per 100,000 women, whereas in Europe, mortality rates between 2 and 4 per 100,000 (refs. 3, 6; Fig. 4). Similar to recent incidence increases, endometrial cancer mortality rates are also on the rise (4, 7). Overall, 5-year survival is approximately 82%, which represents a marked increase since the 1960s when it was 60% (8, 9). The distribution of uterine cancer stage, a strong prognostic factor, has remained stable (8, 10–12). Five-year survival is 95.3% for localized, 67.5% for regional, and 16.9% for distant-stage diseases (9).

Disparities
Historically, endometrial cancer incidence was lower among black compared with white women; however, that gap has narrowed significantly over time (13–17). Moreover, once hysterectomy rates are taken into account, incidence in blacks surpasses that of whites (18). Although the associations for established endometrial cancer risk factors among black and white women are similar (19), prevalence differences may partially explain the markedly higher incidence increases among blacks. Endometrial cancer mortality is twice as high among black compared with white women (8.1 vs. 4.2 per 100,000 women) and has been attributed to aggressive clinical characteristics, lower socioeconomic status, higher prevalence of comorbid conditions, poor patient–provider interactions, and inferior treatment (20). Although less frequently studied, Asian and Hispanic women have lower risks of endometrial cancer compared with white women; however, 5-year survival is the same or better (17, 21).

Risk Factors

Metabolic factors
A strong risk factor for endometrial cancer is obesity, accounting for 40% to 50% of all U.S. cases (refs. 22, 23; see Table 1 and Fig. 5). Overall body size appears to be more important than body fat distribution (24). Women with obesity-associated diseases such as diabetes (25, 26), hypertension (27), and polycystic ovary syndrome (28) are also at elevated risk, although obesity may contribute to these relationships. Metabolic syndrome has also been associated with significant risk elevations, although to a lesser extent than obesity (29).

Reproductive factors
Nulliparous women are at substantially higher risks than parous women (30, 31), with infertility additionally contributing to risk (32). Other established reproductive risk factors include young ages at menarche and/or old ages at menopause (30, 33), potentially reflecting increased numbers of lifetime ovulatory cycles (34). Breastfeeding has also recently emerged as a possible protective factor (35, 36).

Contraceptives
The use of combination oral contraceptives has been linked with marked risk reductions which persist for more than 30 years after discontinuation. Intrauterine devices also appear to reduce endometrial cancer risk (37, 38).
Figure 1.
Age-standardized incidence rates for corpus uteri cancer. Figure 1 shows age-standardized incidence rates for corpus uteri cancer using data from GLOBOCAN, 2012. Uterine cancer incidence is highest in North America and Northern Europe, intermediate in Southern Europe and temperate South America, and lowest in Southern and Eastern Asia and most of Africa.

Figure 2.
Age-specific uterine cancer incidence rates. Figure 2 shows age-specific uterine cancer incidence rates among non-Hispanic white, Hispanic white, black, American Indian/Alaskan Native, and Asian/Pacific Islander U.S. women using data from the SEER Program (SEER-18, 2003-2014).
Elevated endometrial cancer risks have been noted among women with a first-degree family history of endometrial cancer (75, 76). This could reflect familial obesity (genetic or environment) or inherited risk, such as Lynch syndrome, an autosomal-dominant cancer predisposition syndrome attributed to germline mutations in one of several mismatch repair genes. Specific mutations have been estimated to result in cumulative lifetime endometrial cancer risks ranging between 12% and 61% (77–81), with MSH6 showing the highest risks (ref. 82; Table 1). However, the higher range estimates may reflect reliance on data from clinical cancer genetic cohorts that are biased to include patients with family histories of cancer. Although Lynch syndrome is associated with a high cumulative lifetime risk of endometrial cancer, the relative rarity of the condition translates to an attributable fraction of only 5%.

The genome-wide association study approach has identified 17 risk loci for endometrial cancer, including 9 recently identified loci (83), which are modestly associated with risk (ORs, 0.8–1.4). Some risk loci are significant only for endometrioid cancers. Few rare variants have been identified through exome-wide association studies (84), but candidate gene studies (85, 86) have identified a number of SNPs in genes that may possibly affect risk.

Etiologic Heterogeneity

Important heterogeneity has been noted between type I (predominantly endometrioid adenocarcinomas with a hormonally driven etiology) and type II (mainly nonendometrioid malignancies that occur frequently among older and nonwhite women) cancers (see Tables 1 and 2). Several epidemiologic studies have found that type II cancers are less strongly linked to classic risk factors, such as obesity, nulliparity, and hormones (44, 87).
Stronger relationships of hormonal, reproductive, and anthropometric risk factors have been found for endometrioid endometrial cancers compared with serous, clear cell, mucinous, or mixed epithelial tumors (44, 87–91). Furthermore, The Cancer Genome Atlas (TCGA) study has identified four molecular subtypes of endometrial cancer: polymerase ε (POLE) ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high clusters (92).
<table>
<thead>
<tr>
<th>Domain</th>
<th>Factor</th>
<th>Estimated relative risk</th>
<th>Heterogeneity of risk</th>
<th>Comments</th>
<th>Highest level of evidence</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic factors</td>
<td>Obesity</td>
<td>2.0 – 5.0</td>
<td>Association stronger for type I than type II cancers</td>
<td>Each 5 kg/m² increase in BMI is associated with a 62% increased risk</td>
<td>Cohort study</td>
<td>(22, 83)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>2.0</td>
<td>No heterogeneity observed</td>
<td>Association between hypertension and endometrial cancer was weaker, but still significant, among studies with adjustment for BMI</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(27)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1.1 – 1.3</td>
<td>Not examined</td>
<td>Association between hypertension and endometrial cancer was weaker, but still significant, among studies with adjustment for BMI</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(27)</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
<td>1.4 – 2.0</td>
<td>No heterogeneity observed</td>
<td>Adjustment for overweight/obesity does not eliminate increased risks associated with metabolic syndrome factors</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(29, 114)</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
<td>2.8</td>
<td>Not examined</td>
<td>Uncertain extent to which relations are confounded by obesity</td>
<td>Meta-analysis of case-control studies</td>
<td>(28)</td>
</tr>
<tr>
<td>Reproductive factors</td>
<td>Nulliparity</td>
<td>3.0</td>
<td>Association restricted to type I cancers</td>
<td>Further reductions for multiparous women</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(30, 31)</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
<td>1.8</td>
<td>No heterogeneity observed</td>
<td>Even after adjusting for nulliparity, infertile women had increased risk</td>
<td>Pooled analysis of case-control and cohort studies</td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>Young age at menarche</td>
<td>1.5 – 2.0</td>
<td>No heterogeneity observed</td>
<td>4% reduction in risk per 2 years delay in menarcheal age</td>
<td>Meta-analysis of cohort studies</td>
<td>(33, 86)</td>
</tr>
<tr>
<td></td>
<td>Old age at natural menopause</td>
<td>1.5 – 2.2</td>
<td>No heterogeneity observed</td>
<td>Pronounced risks among nonusers of menopausal hormones</td>
<td>Cohort studies</td>
<td>(30, 86)</td>
</tr>
<tr>
<td></td>
<td>Breastfeeding</td>
<td>0.9</td>
<td>No heterogeneity observed</td>
<td>Greater reductions for long-term breastfeeding</td>
<td>Pooled analysis of case-control and cohort studies</td>
<td>(36)</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>Combination oral contraceptives</td>
<td>0.3 – 0.5</td>
<td>No heterogeneity observed</td>
<td>Risk reduction persists for &gt; 30 years</td>
<td>Pooled analysis of case-control and cohort studies</td>
<td>(83, 86)</td>
</tr>
<tr>
<td></td>
<td>Intrauterine device use</td>
<td>0.5 – 0.8</td>
<td>Association stronger for type I than type II cancers</td>
<td>More studies needed on the effects of progestin-releasing devices</td>
<td>Pooled analysis of case-control and cohort studies</td>
<td>(37, 38)</td>
</tr>
<tr>
<td>Menopausal hormone therapy</td>
<td>Menopausal estrogens</td>
<td>10.0 – 20.0</td>
<td>Not examined</td>
<td>Highest risks for long-term and high-dose users of unopposed estrogens</td>
<td>Cohort study</td>
<td>(39)</td>
</tr>
<tr>
<td></td>
<td>Menopausal estrogen plus progestins</td>
<td>0.7</td>
<td>Association stronger for type I than type II cancers</td>
<td>Risk reduction is greatest for obese women</td>
<td>Randomized trial</td>
<td>(39, 42, 43)</td>
</tr>
<tr>
<td>Tamoxifen use</td>
<td>High cumulative doses of tamoxifen</td>
<td>2.2</td>
<td>Nonendometrioid histology subtypes appear to be especially affected by tamoxifen</td>
<td>Endometrial cancer risks highest shortly after exposure</td>
<td>Randomized trial</td>
<td>(44, 45)</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Cigarette smoking</td>
<td>0.5</td>
<td>No heterogeneity observed</td>
<td>Effects of cigarette smoking are particularly strong among postmenopausal women and menopausal hormone users</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(47, 87)</td>
</tr>
<tr>
<td></td>
<td>Moderate-to-vigorous physical activity</td>
<td>0.8</td>
<td>No heterogeneity observed</td>
<td>Inverse relation with physical activity restricted to overweight or obese women</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(49, 50, 90)</td>
</tr>
<tr>
<td>Family history</td>
<td>Family history</td>
<td>1.8</td>
<td>No heterogeneity observed</td>
<td>Association independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(75, 76)</td>
</tr>
<tr>
<td>High penetrance gene mutations</td>
<td>MLH1</td>
<td>18% – 54% lifetime risk</td>
<td>Not examined</td>
<td>Association is independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(77 – 79)</td>
</tr>
<tr>
<td></td>
<td>MSH2</td>
<td>2% – 4% lifetime risk</td>
<td>Not examined</td>
<td>Association is independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(77 – 79)</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td>16% – 51% lifetime risk</td>
<td>Not examined</td>
<td>Association is independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(78, 79)</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>12% lifetime risk</td>
<td>Not examined</td>
<td>Association is independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(80)</td>
</tr>
<tr>
<td></td>
<td>EPCAM</td>
<td>12% lifetime risk</td>
<td>Not examined</td>
<td>Association is independent of Lynch syndrome status</td>
<td>Meta-analysis of case-control and cohort studies</td>
<td>(81)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
### Table 1. Summary of risk factors, candidate genes, and serum biomarkers associated with endometrial cancer risk (Cont’d)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Factor</th>
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<th>Highest level of evidence</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low and moderate penetrance genes</td>
<td></td>
<td>1.1–1.4</td>
<td></td>
<td>Some SNP associations differ according to histology</td>
<td></td>
<td>(86)</td>
</tr>
<tr>
<td>Serum biomarkers</td>
<td>Estradiol and other endogenous estrogens</td>
<td>2.0–6.2</td>
<td></td>
<td>Some support for stronger relations with type I than II cancers</td>
<td></td>
<td>(97)</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td></td>
<td>Not examined</td>
<td>Associations persist after adjustment for body mass and show slightly stronger relations for type I than II cancers</td>
<td></td>
<td>(99)</td>
</tr>
<tr>
<td></td>
<td>C-peptide</td>
<td></td>
<td>Not examined</td>
<td>A lack of information on fasting time since the last meal may have led to misclassification of C-peptide levels</td>
<td></td>
<td>(99)</td>
</tr>
<tr>
<td>Androgen</td>
<td>Postmenopausal: 1.7</td>
<td></td>
<td></td>
<td>Higher circulating levels of androgens are associated with endometrial cancer among postmenopausal women</td>
<td></td>
<td>(93–95, 97, 98)</td>
</tr>
<tr>
<td></td>
<td>Premenopausal: 0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td>SERPINE1: 2.4</td>
<td></td>
<td></td>
<td>No heterogeneity observed although the number of women with type II was small</td>
<td>Endometrial cancer risk was most pronounced among obese women with the highest inflammation score</td>
<td>(102)</td>
</tr>
<tr>
<td></td>
<td>VEGF-A: 2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory cytokines (IL1, IL2): 0.5–0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proinflammatory cytokines (CCL3, IL1B, IL23): 0.5–0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td></td>
<td></td>
<td>Not examined</td>
<td>Inverse associations were strongest among postmenopausal women, nulliparous women, and nonhormone users</td>
<td></td>
<td>(103)</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>2.2</td>
<td>Not examined</td>
<td>Associations were strongest among nonhormone users, diabetic women, and in prospective studies</td>
<td></td>
<td>(103)</td>
</tr>
</tbody>
</table>
comprehensive evaluation of endometrial cancer risk factors according to TCGA subtype has not yet been conducted.

**Biological Underpinnings of Identified Risk Factors**

Estrogens are strongly related to risk (Table 1; refs. 93–95), with one study showing generalized uterotropic activity of both parent estrogens and metabolites (96). Circulating androgens, with one study showing generalized uterotropic activity of both (96). Androgens and estrogens can be produced from the same precursor, DHEA, in adipose tissue (97). Consistent with this potential interaction, body fat has been associated with increased risk of endometrial cancer (98). A recent study found that measures of adiposity, such as BMI and body fat percentage, are strongly related to circulating androgens and estrogens, with BMI being the strongest predictor (99). These findings suggest that the metabolism of adipose tissue may play a role in the development of endometrial cancer (99).

**Risk Prediction Models**

Two risk prediction models, one developed in U.S.-based cohorts (104) and the other in a European cohort (105), demonstrated moderate discriminatory ability for established endometrial cancer risk factors (respective discrimination assessed by the area under the curve of 0.68 and 0.77). In the latter model, the addition of prediagnostic serum biomarkers only modestly (1.7%) increased discrimination (106).

**Future Trends**

Projection models indicate that endometrial cancer incidence will continue to rise, mainly as a consequence of rising obesity prevalence (7, 107). Changes in the distribution of other endometrial cancer risk factors also contribute to the projected growth in incidence, including increases in diabetes and metabolic syndrome (108, 109), declines in use of combination hormone therapy (5), and decreases in childbearing and smoking (110, 111). Moreover, hysterectomy for benign conditions has declined in recent decades, particularly among whites, contributing to more at-risk women (18, 112). In the next decade, mortality rates are also projected to increase (113).

**Prevention**

Primary prevention efforts focused on weight loss or use of medications are attractive prevention strategies. For high-risk patients, bariatric surgery is associated with a 44% reduced risk of developing endometrial cancer (114). Among Lynch syndrome patients, there is some evidence that oral contraceptive use may reduce risk (115).

**Screening**

Endometrial cancer screening is not recommended for women in the general population (116). Studies evaluating the use of endometrial biopsy and/or transvaginal ultrasound have generally shown low detection specificity (117). Nonetheless, the American Cancer Society recommends annual screening for Lynch syndrome patients with endometrial biopsy beginning at age 35 years. Development of early detection blood-based biomarkers is being explored (118).

**Future Directions**

Although considered an indolent tumor, the rapid increase in both endometrial cancer incidence and mortality warrants additional etiologic and prevention research. Although progress has been made in identifying risk factors for the most common endometrial cancer subtype, this has not translated into effective primary prevention strategies. Future efforts should be directed at reducing the prevalence of modifiable risk factors (e.g., obesity). Additional research is needed to identify risk factors for aggressive endometrial cancer subtypes, particularly among black women.

To favorably affect survival, research on screening modalities to identify endometrial cancer at early stages is needed. Currently, screening in the general population is not recommended, but efforts to identify high-risk women could be beneficial.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A.S. Felix, L.A. Brinton
Development of methodology: A.S. Felix, L.A. Brinton
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.S. Felix, L.A. Brinton
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.S. Felix, L.A. Brinton
Writing, review, and/or revision of the manuscript: A.S. Felix, L.A. Brinton
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.S. Felix, L.A. Brinton
Study supervision: A.S. Felix, L.A. Brinton

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References


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