

# Chapter 1

## Epidemiology of Endometrial Carcinoma: Etiologic Importance of Hormonal and Metabolic Influences

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**Abstract** Endometrial carcinoma is the most common gynecologic cancer in developed nations, and the annual incidence is projected to increase, secondary to the high prevalence of obesity, a strong endometrial carcinoma risk factor. Although endometrial carcinomas are etiologically, biologically, and clinically diverse, hormonal and metabolic mechanisms are particularly strongly implicated in the pathogenesis of endometrioid carcinoma, the numerically predominant subtype. The centrality of hormonal and metabolic disturbances in the pathogenesis of endometrial carcinoma, combined with its slow development from well-characterized precursors in most cases, offers a substantial opportunity to reduce endometrial carcinoma mortality through early detection, lifestyle modification, and chemoprevention. In this chapter, we review the epidemiology of endometrial carcinoma, emphasizing theories that link risk factors for these tumors to hormonal and metabolic mechanisms. Future translational research opportunities related to prevention are discussed.

**Keywords** Endometrial carcinoma • Incidence trend • Risk factors • Estrogen • Progesterone • Hormones • Insulin • Inflammation • Adipokines

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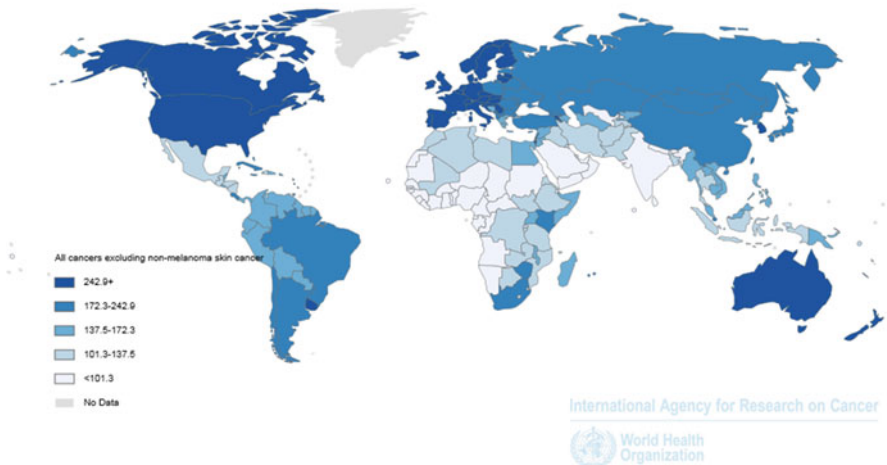
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## Descriptive Epidemiology

Endometrial carcinomas develop from the inner lining of the uterine corpus and account for the substantial majority of tumors affecting the organ [1]. Accordingly, descriptive epidemiological data for uterine cancer, which is frequently the best available category in cancer registries, are often used as a surrogate for endometrial carcinoma rates, as presented below.

Worldwide, there are an estimated 319,500 incident uterine cancers reportedly annually, which account for over 76,000 deaths each year [2]. Incidence rates vary widely; age-standardized incidence rates are higher in North America and most of Europe than in other parts of the world (Fig. 1.1). Within the United States, uterine cancer incidence rates peaked around 1975 in relation to increased use of exogenous unopposed estrogens [3, 4] (Fig. 1.2). After recognition that the use of unopposed estrogens is carcinogenic in the endometrium, the use of these products declined, and age-adjusted endometrial carcinoma incidence rates fell in parallel and then leveled from 1988 to 2006. Subsequently, from 2006 to 2011, incidence rates increased by 2.3 % per year.

In 2015, uterine cancer is estimated to be the fourth most common cancer diagnosed among American women, only exceeded by the incidence of cancers of the breast, lung and bronchus, and colon and rectum [5]. It is estimated that there will be approximately 54,870 new cases of uterine cancer in the United States in 2015 [5]. Studies have projected that uterine cancer incidence rates will continue to rise over the next 15 years [6, 7]. Given increases in the US total population and the rising proportion of older women, these projections suggest an important increase in the uterine cancer burden.



**Fig. 1.1** International incidence for uterine cancer (per 100,000 woman years) age standardized to the world population, 2012 (Source: GLOBOCAN 2012 (IARC))

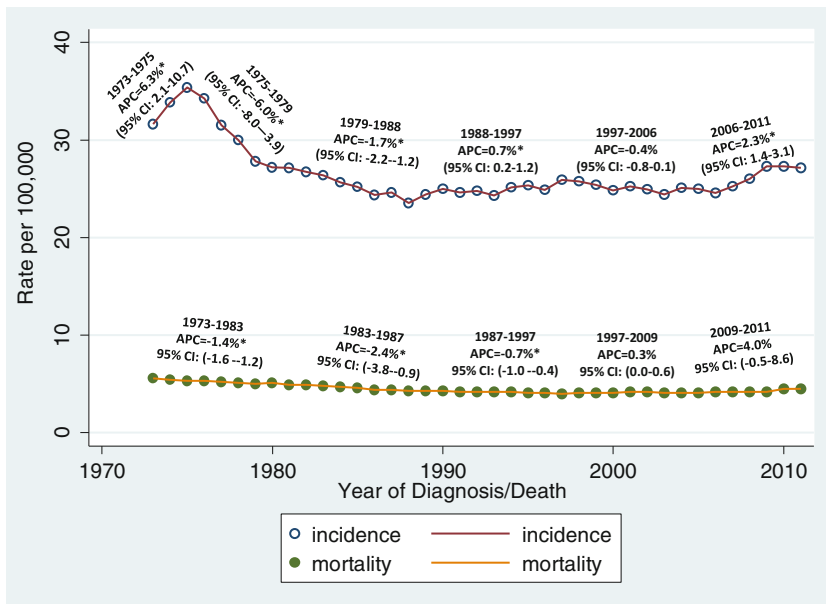


Fig. 1.2 Trends in uterine cancer incidence and mortality rates in the United States 1973–2011

Uterine cancer is most commonly diagnosed after menopause, with the peak incidence occurring between ages of 60 and 70 years. Reported uterine cancer incidence rates among White women have consistently been higher than among non-White women in the United States, but this interpretation is limited by failure to correct for hysterectomy prevalence in registry data (see below) [1]. Between 1999 and 2008, reported incidence rates were relatively stable among White women (average annual percent change=0.1%), but increased among Black women (1.8%), Asian–Pacific Islanders (1.9%), and Hispanics (1.2%) [8]. Registry data also show that age-adjusted incidence rate trends differ by histologic tumor subtype (*discussed below*), with increased incidence of lower-grade endometrioid carcinomas during 1999 through 2006 compared with other subtypes, which remained relatively stable during the same period [9].

Uterine cancer accounts for about 2% of cancer deaths among women in high-income nations [2]. Age-standardized uterine cancer mortality rates are highest in parts of the Caribbean (3.3 per 100,000), Central and Eastern Europe (3.4), Melanesia (3.8), and Micronesia/Polynesia (2.5) and lower in the United States (2.2) [2]. Uterine cancer mortality rates among American women have decreased over the past few decades and have been relatively stable from 1997 to 2009, with a slight rise after 2009 [10] (Fig. 1.2). It is estimated that there will be approximately 10,170 deaths related to uterine cancer in the United States in 2015 [5]. Although Black women experience a lower reported incidence of endometrial carcinoma, they are more than twice as likely to die from the disease as White women [8]. Registry data demonstrate increasing mortality rates in Asian–Pacific Islanders (average annual percent change=1.9%) and non-Hispanics (0.3%) and steady rates in Whites (0.1%), Blacks (0.5%), and Hispanics (0.0%) from 1999 to 2008 [8].

Reported incidence and mortality rates are not corrected for hysterectomy prevalence and, therefore, underestimate rates among women who are at risk but have not undergone a hysterectomy [11, 12]. Hysterectomy prevalence may vary by race and likely other factors; thus, incidence rate ratios that are not corrected for hysterectomy prevalence may be misleading. Further, imperfect distinction of endocervical from endometrial adenocarcinoma, especially prior to routine use of diagnostic immunohistochemical markers, represents another source of error, particularly in older datasets.

Trend analysis based on hysterectomy-corrected data from 1992 to 2008 showed that the endometrial carcinoma incidence rate significantly declined 0.8% per year among White women compared to an increase rate of 3.1% per year among Black women, such that the incidence rates for Black women surpassed those among White women from 2004 to 2008 [12]. Hysterectomy-corrected incidence rates increased for all major histopathologic subtypes among Black women, but declined or showed statistically nonsignificant increases among White women. Another analysis reported that hysterectomy correction had the largest effect on incidence in the southern states in the United States, where hysterectomy prevalence was highest irrespective of race [11].

Most endometrial carcinomas present clinically with abnormal uterine bleeding and vaginal discharge, leading to diagnosis at an early stage [13]. Based on recent SEER 18 data (2004–2011), the estimated overall 5-year survival rate for uterine cancer is 81.5% [14] (Table 1.1). However, prognosis is less favorable among women with non-endometrioid carcinomas and tumors that are higher grade and higher stage (Table 1.1). The current standard management of endometrial carcinoma is total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy [13]. Women with advanced pathologic stage may receive adjuvant therapy, including radiation, vaginal brachytherapy, and chemotherapy [15].

**Table 1.1** Five-year survival proportions of uterine cancer by histology and stage in the United States 2004–2011

	All stages (%)	Localized (%)	Regional (%)	Distant (%)
All uterine cancer cases	81.5	95.2	68.2	25.0
Endometrioid	91.5	97.6	79.9	43.4
Mucinous	91.8	98.7	79.2	9.6
Adenocarcinoma	81.1	95.9	63.9	14.7
Clear cell	60.2	86.8	58.3	23.2
Serous	48.4	82.1	47.6	17.0

Actuarial method. Ederer II method used for cumulative expected

Source: Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence—SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (1973–2011 varying)—Linked To County Attributes—Total U.S., 1969–2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014 (updated 5/7/2014), based on the November 2013 submission

## Classification

Classification of endometrial carcinomas based on etiologic factors, histopathologic type, or molecular markers demonstrates substantial, although imperfect consistency. Future development of taxonomies that integrate patient and tumor characteristics may ultimately result in more homogeneous biological categories.

Bokhman's seminal paper in 1983 describing two main types of endometrial carcinomas, based mainly on clinical presentation, laid the framework for developing refined taxonomies that integrate patient and tumor features [16]. As originally described [16], type I carcinomas comprised about 80 % of cancers and were associated with signs and symptoms linked to endocrine and metabolic disturbances. Type I tumors overlap considerably with cancers histopathologically classified as endometrioid, and particularly those that are low or intermediate tumor grade, superficially invasive into the myometrium, and low stage. Type II carcinomas affect women with less overt evidence of hormonal or metabolic dysfunction and, pathologically, tend to be high grade, deeply invasive into the myometrium, and higher stage at detection. Serous carcinomas are perhaps the best histopathologic correlate of type II carcinomas. The dichotomous division of endometrial carcinomas into two (but potentially more histopathologic subtypes) has been modified over time and expanded using modern molecular biology techniques.

The Tumor Cancer Genome Atlas (TCGA) provides a molecular taxonomy of endometrial carcinoma based on integrated multi-platform genomic profiling [17]. Molecular stratification of 248 tumors according to somatic copy-number status, somatic mutation status, and microsatellite instability (MSI) status led to the description of four main molecular subgroups: (1) ultramutated/polymerase E (*POLE* (*polymerase (DNA directed), epsilon, catalytic subunit*)) mutant, (2) hypermutated/microsatellite unstable, (3) copy-number low/microsatellite stable, and (4) copy-number high/serous-like. The first three subgroups are composed largely of endometrioid carcinomas, which approximate Bokhman's type I tumors. In contrast, 94 % of serous carcinomas, 24 % of high-grade endometrioid carcinomas, and 62 % of carcinomas of mixed histologic type are included in the copy-number high/serous-like subgroup. Somatic mutations that are frequent among tumors in subgroups 1–3 correspond to those associated with endometrioid carcinoma overall: *PTEN* (*phosphatase and tensin homolog* (and other members of *PI(3)kinase/AKT* pathway)), *FGFR2* (*fibroblast growth factor receptor*), *ARID1A* (*AT-rich interactive domain 1A (SWI-like)*), *CTNNB1* (*catenin (cadherin-associated protein), beta 1, 88 kDa*), and *KRAS* (*Kirsten rat sarcoma viral oncogene homolog*). Subgroup 2 is associated with high rates of MSI, mostly reflecting DNA promoter methylation silencing of *MLH1* (*mutL homolog 1*). Mutations found in subgroups 1–3 are much rarer among copy-number high/serous-like tumors, which in contrast, are associated with *TP53* (*tumor protein P53*) mutations in 90 % of cases and frequent copy-number alterations, neither of which are prominent features of subgroups 1–3.

Overall, the genomic profile of copy-number high/serous-like endometrial tumors show similarities with basal breast cancers and serous "ovarian" (which

likely includes many fallopian tube primaries) carcinomas, which are also clinically aggressive and less strongly linked to hormonal etiology as compared with other tumor subtypes occurring in their respective sites of origin. Among *TP53*-mutant endometrioid carcinomas (i.e., high grade) in the copy-number high/serous-like subgroup, 50% had concurrent *PTEN* mutations as compared with only 2.6% of serous carcinomas in this subgroup, suggesting that the pathogenesis of carcinomas in the copy-number high/serous-like group may itself be diverse.

It is unclear whether *TP53* mutations represent an early event in the pathogenesis of a subset of endometrioid carcinomas (possibly implying a distinctive etiology) or a late event occurring in established endometrioid carcinomas (reflecting clonal evolution). These possibilities may underscore inconsistencies in etiological associations. For example, in some analyses, risk factor associations for grade 3 endometrioid carcinomas are more similar to non-endometrioid carcinomas than to grade 1 or 2 endometrioid carcinomas [18]. This could reflect the development of a subset of grade 3 endometrioid carcinomas via a “subgroup 4” nonhormonal pathway. In addition, given that distinguishing serous carcinomas from high-grade endometrioid carcinomas [19] is often difficult, misclassification of endometrioid carcinomas that developed via hormonal mechanisms as serous carcinomas could blur etiological distinctions between these subtypes. In fact, some tumors that initially develop as hormonally driven low-grade endometrioid carcinomas may progress to mixed tumors in which the serous component overgrows and obscures the endometrioid areas. This hypothetical scenario could result in serous carcinomas that ostensibly are associated with hormonal risk factors.

TCGA RNA sequencing data suggests that there are three endometrial carcinoma transcriptome clusters: “hormonal,” “mitotic,” and “immunoreactive” [17]. Within the hormonal transcriptome cluster, the levels of *ESR1* (*estrogen receptor 1*) and *PGR* (*progesterone receptor*) mRNA expression, and the levels of estrogen receptor (ER) and progesterone receptor (PR) protein expression, are significantly higher than in either the mitotic or immunoreactive tumor clusters. Moreover, increased levels of progesterone receptor (PR) expression are also characteristic of tumors in the copy-number low/microsatellite stable molecular subgroup, similar to the hormonal transcriptome cluster. Given that excess exposure to estrogen relative to progesterone is proposed as an important mechanism in endometrial carcinogenesis, the identification of tumors with high PR expression may identify tumors that demonstrate distinct associations with hormonal exposures and relative susceptibility to endocrine chemopreventive and treatment strategies.

A subsequent analysis of the TCGA transcriptome and reverse-phase protein array data focused exclusively on endometrioid carcinomas and described four, rather than three, expression clusters [20]. In this classification, one of the four clusters (cluster I) exhibited high expression of *ESR* and *PGR*, was statistically significantly enriched for microsatellite unstable tumors, and was composed almost exclusively of *PTEN*-mutated tumors [20]. Notably, a second cluster (cluster II) was associated with younger obese patients, high rates of *CTNNB1* mutations, and lower survival than patients in cluster I. Since both clusters I and II are associated with obesity, their underlying molecular heterogeneity has been suggested as a possible explanation for some of the clinical heterogeneity that is seen among patients with endometrioid endometrial carcinoma [20].

Considering gene expression data together with copy-number data and pathway interaction data, TCGA has also described five so-called “PARADIGM” tumor clusters, one of which (PARADIGM cluster 5) is enriched with cases from the hormonal expression cluster and shows high levels of MYC (*v-myc* avian myelocytomatosis viral oncogene homolog), FOXA1 (forkhead box A1), and HIF1 (hypoxia-inducible factor 1), alpha subunit (basic helix-loop-helix transcription factor) signaling [17]. This observation is consistent with the biochemical observations that the *c-myc* proto-oncogene is transcriptionally regulated by estrogen [21], the FOXA1 transcription factor can modulate the estrogenic response in breast cancer cells by facilitating binding of ER to target sites on chromatin [22], and *HIF1A* mRNA and protein levels increase in the rat uterus upon estradiol stimulation [23]. Furthermore, the association between ostensibly “hormonally driven” endometrial carcinomas and elevated MYC, FOXA1, and HIF1 signaling noted by TCGA is largely consistent with the findings of other studies of endometrioid carcinomas. For instance, a positive correlation ( $r=0.37$ ,  $p=0.038$ ) has been noted between ER $\alpha$  and c-myc protein expression by immunohistochemical staining in a series of predominantly endometrioid endometrial carcinomas [24]. Likewise, a positive association between ER levels and FOXA1 levels has been noted in primary endometrial carcinomas [25, 26], and a trend toward such an association has been suggested in another study [27]. Moreover, low FOXA1 expression in primary endometrial carcinomas shows a significant association with non-endometrioid histology ( $P=0.002$ ), high tumor grade ( $P=0.003$ ), PR loss ( $P=0.02$ ), ER $\alpha$  loss ( $p=0.003$ ), and reduced disease-specific survival ( $p=0.004$ ) [26]. Finally, a trend toward an association between HIF-1 $\alpha$ , HIF-2 $\alpha$ , and ER expression has been reported in endometrial carcinomas, but these associations were only of borderline statistical significance ( $P=0.06$ ) [28].

## Imbalances in Estrogen and Progesterone as the Main Driver of Endometrial Carcinogenesis

Imbalances in sex steroid hormones—excess stimulation of endometrial epithelium by estrogen relative to progesterone—are often conceptualized as a leading paradigm to account for the etiology of endometrial carcinomas (i.e., mainly type I) [29]. Estrogen, when insufficiently opposed by progesterone, has proliferative effects on the endometrium, which may result in a higher probability of random mutations in oncogenes and tumor suppressor genes. Endometrial cells that acquire multiple mutations without appropriate repair mechanisms may gain a growth advantage and develop into clones of cancer cells [30].

This overarching framework is supported by several lines of compelling evidence. First, in healthy premenopausal women, endometrial cell division rates are highest during the proliferative phase of the menstrual cycle, when estradiol levels are high and progesterone levels are low [31]. However, it is postulated that among premenopausal women, physiological levels of estrogen drive maximal proliferation, suggesting that progesterone deficiency, DNA repair defects, or other factors may



figure importantly in the early pathogenesis of endometrial carcinomas [32]. During the secretory phase of the menstrual cycle, a surge in progesterone levels is followed by a plateau of endometrial cell division, secretory differentiation, and then apoptosis prior to menstrual shedding.

In addition, three prospective studies [33–35], which included between 124 and 250 postmenopausal endometrial carcinoma cases, reported positive associations between higher circulating estradiol levels and endometrial carcinoma risk. The relative risk (RR) comparing the highest vs. lowest category of estradiol ranged from 2.1 (95 % confidence interval (CI)=1.2–3.6) [34] to 4.1 (95 % CI=1.8–9.7) [33]. Further, studies that assess endometrial carcinoma risk in relation to circulating levels of sex hormone-binding globulin (SHBG), a protein that binds to estrogen, thereby lowering its bioavailable fraction, report low levels of SHBG which are related to higher endometrial carcinoma risk [33, 34].

Finally, epidemiologic studies (*reviewed in next section*) have shown that factors related to greater lifetime exposure to sex steroid hormones, and more specifically estrogens, including younger age at menarche, older age at menopause, postmenopausal use of unopposed estrogen, and high postmenopausal body mass index (BMI), are associated with increased risk of developing endometrial carcinoma. Conversely, factors related to lower lifetime exposure to estrogen relative to progesterone, such as parity, postmenopausal use of estrogen plus progestin, and combined oral contraceptive (COC) use are related to lower endometrial carcinoma risk.

## **Estrogen and Progesterone Receptors in Endometrial Tumor Tissues**

Evaluating ER and PR expression and function in endometrial tissues is complex. Given that the functionalis (superficial) endometrium is shed cyclically, it is supposed that the deeper basalis, which is not shed with menses, may be the site where stem/progenitor cells reside; accordingly, expression of ER and PR in the basalis may be important in understanding carcinogenesis, but this compartment is only accessible for study in hysterectomy samples, precluding longitudinal study. However, and perhaps paradoxically, the basalis is generally viewed as less hormonally responsive than the functionalis. Further, expression of ER and PR varies across the menstrual cycle and reproductive life, suggesting both temporal and spatial heterogeneity. There are two major forms of each hormonal receptor (ER $\alpha$ , ER $\beta$ ; PRA, PRB), which may have different functions, and ER $\beta$  has multiple splice variants with potentially distinctive actions. Immunohistochemistry has important utility in investigations of hormone receptors in endometrial research because of the intermixing of multiple cell types in normal tissue and the variation in cellular composition over the menstrual cycle and the life course. Accordingly, molecular profiling of tissues without dissection may be difficult to interpret because of cellular admixtures. However, the sensitivity and specificity of reagent antibodies for various hormone markers,



particularly ER $\beta$  in older studies, have been questioned [36]. Finally, important physiological differences between mice and women raise questions about the relevance of hormonal studies in mice and their relevance to women.

Estrogen exerts its cellular effects via its interaction with the ER $\alpha$ , ER $\beta$ , or GPER (G protein-coupled estrogen receptor 1) receptors. Studies of ER $\alpha$ , ER $\beta$ , and ER $\alpha$ / $\beta$  knockout mice have pointed to ER $\alpha$  as the primary mediator of the proliferative response to estrogen in the endometrium and as a transcriptional activator of the progesterone receptor gene in endometrial stromal cells [37]. ER $\beta$  can mediate an antiproliferative response by antagonizing the effects of ER $\alpha$  in the endometrium [38], but the role of ER $\beta$  in endometrial carcinogenesis is unclear and may differ from effects at other organ sites [39], whereas ER $\alpha$  dysregulation in endometrial carcinoma has been studied extensively.

PR is expressed in both the epithelial and stromal cells of the endometrium, and stromal PR acts in a paracrine manner to inhibit proliferation of the glandular epithelial cells [40]. PRA and PRB constitute the two major isoforms of the progesterone receptor, with PRA being the predominant isoform in endometrial stromal cells [41]. Progesterone can mediate distinct biochemical and cellular responses via its interaction with PRA or PRB (reviewed in [42]).

In endometrial tumor tissues and preoperative curettage specimens, both ER and PR protein expression status are closely correlated with tumor histology, grade, depth of myometrial invasion, and clinical outcome [43–53]. Positivity for ER, ER $\alpha$ , PR, PRA, and PRB expression is observed more often in low-grade than high-grade tumors [43, 46–49, 54] and in endometrioid than non-endometrioid carcinomas [44, 48], which is consistent with unopposed estrogen being a strong epidemiological risk factor for the endometrioid subtype. Loss of ER and PR expression is significantly associated with deep myometrial invasion [43, 44, 46]. In both endometrioid and non-endometrioid subtypes, metastatic tumors demonstrate loss of PR expression more often than primary tumors [48]. Within the endometrioid subtype, loss of ER and PR expression correlates with increasing tumor grade and stage [48, 50].

A considerable body of work supports ER, PR, or joint ER/PR protein expression status, as independent prognostic indicators of clinical outcome for endometrial carcinoma [45, 47, 48, 55–58]. Concurrent ER/PR loss is an independent predictor of tumor recurrence [47], lymph node metastasis [56], and reduced disease-specific survival [56]. In early stage disease, losses of ER and ER $\alpha$  protein expression are, respectively, independent predictors of recurrence and death from disease [47, 50]. PR expression status of endometrial carcinomas has been found to be an independent prognostic indicator in several studies (reviewed in [59]). Moreover, loss of PRA expression in early stage disease has been reported to be an independent prognostic factor for relapse [50].

Loss of PR expression in endometrial tumor tissues may also be accompanied by an underlying change in the ratio of PRA and PRB expression [53, 60]. Loss of PRA or PRB expression has been noted in 51–75% of endometrioid endometrial cancers [53, 61], with some studies noting PRB loss more often than PRA loss [53, 60], and others finding the converse [51, 61]. The fraction of endometrioid carcinomas positive

for PRA and PRB expressions declines with increasing tumor grade [61]. Although the expression of PRA and PRB is lower in endometrioid carcinomas than in endometrial hyperplasia (specifically complex atypical hyperplasia (CAH)), data conflict as to whether the balance between PRA and PRB expression is related to functional dysregulation in these early lesions [51, 53]. In one study, a univariate analysis reported that a PRA:PRB ratio of <1 was associated with shorter disease-free survival and disease-specific death [50].

Although ER and PR status are not routinely used in clinical decision-making for endometrial carcinoma, recent reviews have suggested they might be incorporated into clinical practice as biomarkers for risk stratification [62, 63].

### ***Estrogen and Progesterone Tissue Levels***

Bernstein et al. [64] noted that endometrial tumor tissues exhibit higher concentrations of estradiol compared with normal endometrial tissue. Among 78 adenocarcinomas, estrogen levels were higher in low-grade tumors versus high-grade tumors, and in more-invasive tumors versus less-invasive tumors, although these associations did not achieve statistical significance.

Dysregulated expression, in endometrial tumor tissues, of genes and proteins modulating estrogen biosynthesis and metabolism has been the topic of a number of investigations, although findings are not entirely consistent (reviewed in [65]). Estrogen biosynthesis in peripheral tissues, including the endometrium, is driven by the aromatase and sulfatase pathways. The conversion of estrone sulfate to estrone is catalyzed by STS (steroid sulfatase (microsomal), isozyme S) and antagonized by SULT1E1 (sulfotransferase family 1E, estrogen-preferring, member 1) and SULT1E2 (sulfotransferase family 1E, estrogen-preferring, member 1). Compared to normal endometrium, the ratio of *STS:SULT1E1* mRNA and protein expression is increased in endometrial tumor tissues (reviewed in [65]). STS also promotes the conversion of DHEA-sulfate to DHEA, an effect that is antagonized by the actions of SULT2A1 (sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1) and SULT2B1 (sulfotransferase family, cytosolic, 2B, member 1). *SULT2B1* expression is increased in tumor versus adjacent normal endometrium, and moderate levels of the SULT2B1 are detectable in endometrial tumors by immunohistochemistry [65, 66].

*CYP19A1* (cytochrome P450, family 19, subfamily A, polypeptide 1) mRNA levels are low in endometrial tumor tissue and are similar to that of adjacent normal tissue [65, 67]. In contrast *CYP19A1* (aromatase) protein expression, as assessed immunohistochemically, varies widely, possibly related to methodological differences between studies [50, 65, 68–70].

Expression of *HSD3B1* (hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1) and *HSD3B2* (hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2), the products of which promote the conversion

of DHEA to androstenedione, appears similar in endometrial tumors versus adjacent normal endometrium [71]. *AKR1C3* (aldo-keto reductase family 1, member C3) promotes the conversion of androstenedione to testosterone, whereas *HSD17B2* (hydroxysteroid (17-beta) dehydrogenase 2) converts testosterone to androstenedione. Whereas *AKR1C3* (aldo-keto reductase family 1, member C3) expression appears similar between adjacent tumor and normal tissues by real-time PCR [71–73], microarray data generated within TCGA indicate increased expression of *AKR1C3* in 6% of high-grade endometrial tumors [17, 74].

*HSD17B1* (hydroxysteroid (17-beta) dehydrogenase 1), *HSD17B7* (hydroxysteroid (17-beta) dehydrogenase 7), and *HSD17B12* (hydroxysteroid (17-beta) dehydrogenase 12) catalyze the conversion of estrone to estradiol. Their expression appears to be unchanged in endometrial carcinomas compared with normal endometrium, and most endometrial carcinomas show weak immunohistochemical staining for these three proteins [65, 73, 75, 76]. The reverse reaction (conversion of estradiol to estrone) is catalyzed by *HSD17B2* (hydroxysteroid (17-beta) dehydrogenase 2) as well as *HSD17B4* (hydroxysteroid (17-beta) dehydrogenase 4) and *HSD17B8* (hydroxysteroid (17-beta) dehydrogenase 8). Several studies have noted increased expression of *HSD17B2* in endometrial tumors, and the *HSD17B2* protein is detectable in endometrial carcinomas by IHC [65, 71, 76, 77]. *HSD17B4* and *HSD17B8* expressions do not appear to differ between endometrial tumor and normal tissues, and tumors show moderate immunohistochemical staining [65, 73].

The expression of genes that regulate estrogen metabolism has also been evaluated in endometrial tumor tissues (reviewed in [65]). As compared with normal adjacent endometrium, endometrial tumors have been observed to have decreased *CYP1B1* (*cytochrome P450, family 1, subfamily B, polypeptide 1*) expression; increased or unchanged *CYP1A7* expression; decreased *CYP3A7* (*cytochrome P450, family 3, subfamily A, polypeptide 7*) expression; unchanged *CYP3A5* (*cytochrome P450, family 3, subfamily A, polypeptide 5*) expression; increased or unchanged *COMT* (*catechol-O-methyltransferase*) expression; increased *UGT2B7* (*UDP glucuronosyltransferase 2 family, polypeptide B7*), *UGT2B15* (*UDP glucuronosyltransferase 2 family, polypeptide B15*), *UGT1A1* (*UDP glucuronosyltransferase 1 family, polypeptide A1*), and *UGT1A3* (*UDP glucuronosyltransferase 1 family, polypeptide A3*) expressions; and increased or unchanged expression of *GSTP1* (*glutathione S-transferase Pi 1*) expression [65, 66, 76, 78, 79].

The expression of genes associated with local progesterone biosynthesis and metabolism has recently been compared between endometrial carcinoma tissues and adjacent normal endometrial tissue [71]. The local biosynthesis of progesterone from cholesterol is dependent on the activities of *STAR* (steroidogenic acute regulatory protein), *CYP11A1* (*cytochrome P450, family 11, subfamily A, polypeptide 1*), *HSD3B1* (hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1), and *HSD3B2* (hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2). *STAR* and *CYP11A1* expressions are decreased in endometrial tumor tissues, whereas *HSD3B1* and *HSD3B2* expressions appear to be unchanged [71]. Progesterone is metabolized by the concerted actions of

AKR1C1 (aldo-keto reductase family 1, member C1), AKR1C2 (aldo-keto reductase family 1, member C2), AKR1C3 (aldo-keto reductase family 1, member C3), SRD5A1 (steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)), and SRD5A2 (steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)), and metabolism can be antagonized by the activity of HSD17B2 (hydroxysteroid (17-beta) dehydrogenase 2). *HSD17B2* expression and *SRD5A2* expression are increased in endometrial tumor tissues, whereas *SRD5A2* expression is unchanged [71]. Data on *AKR1C1–3* gene expression in endometrial tumors is variable. Whereas several studies found no change in *AKR1C1*, *AKR1C2*, and *AKR1C3* expressions between adjacent tumor and normal tissues using real-time PCR [71–73, 77], microarray data generated within TCGA indicate increased expression of *AKR1C1*, *AKR1C2*, and *AKR1C3* in 4–6% of high-grade tumors [17, 74], and immunohistochemical analysis of *AKR1C3* indicates both increased and decreased expression in endometrial carcinoma compared with endometrial hyperplasia [80, 81]. These variable findings might reflect differences in study design or inter-patient variability as suggested by Rižner and Penning [74].

### ***ESR1 and PGR Mutations in Endometrial Carcinoma***

*ESR1*, which encodes ER $\alpha$ , is somatically mutated in about 4% of endometrial carcinomas, and the mutations described thus far localize to the ligand-binding domain or to the DNA-binding domain of ER $\alpha$  [17, 82]. Within the ligand-binding domain, codons 547 and 548 are recurrently mutated in endometrial carcinomas and encode constitutively active, gain-of-function mutants (*ESR1*<sup>Y537S/C/N</sup> and *ESR1*<sup>D538G</sup>) [82, 83]. Because *ESR1*-mutated breast tumors are associated with prior treatment with antiestrogens and aromatase inhibitors, it has been speculated that *ESR1*-mutated endometrial carcinomas may be associated with tamoxifen treatment for concurrent breast cancer [82], although this hypothesis remains to be tested. The frequency of *ESR1* gene amplification in endometrial carcinomas exhibits considerable inter-study variability, with amplification noted in 1–23% of tumors [17, 84, 85], likely reflecting differences in methodological approaches used to assess copy number and possibly population differences [86]. In the TCGA cohort, 6.7% of 240 endometrial carcinomas have somatically mutated or deleted *PGR* [17, 87].

In summary, available data do not provide an entirely clear picture of hormone metabolism at the endometrial tissue level. However, the strong links between hormonal risk factors, exogenous hormone use, and serum hormone levels with endometrial cancer risk underscore the importance of systemic hormone imbalances in endometrial cancer etiology.

## Mouse Models

### *Contributions of Estrogen and Progesterone to Endometrial Tumorigenesis in PTEN Knockout Mouse Models*

*PTEN* tumor suppressor gene abnormalities are frequently identified in endometrioid carcinomas and its precursors [88–91], and focal loss of immunohistochemical expression in normal-appearing endometrial glands has been found in 20–40% of benign endometrium ([92] and unpublished). Moreover, women with Cowden syndrome, which is related to germline *PTEN* mutations, are at increased risk of developing endometrial carcinoma, providing further support for the importance of *PTEN* perturbations in endometrial tumorigenesis [93, 94]. However, *PTEN* mutations alone are insufficient to initiate endometrial carcinoma since approximately 20–40% of women have normal-appearing endometria that demonstrate small foci of *PTEN*-null glands, whereas the lifetime risk of endometrial carcinoma is approximately ten times lower [92]. Additional events that are believed to cooperate with *PTEN* loss to promote endometrial carcinoma include perturbations in other genes, as well as hormonal influences [92, 95]. In regard to the latter point, because unopposed estrogen is a well-established risk factor for endometrioid endometrial carcinoma, there has been great interest in understanding the interplay between steroid hormones and *Pten* loss in the development of endometrial carcinoma, using mouse models.

Studies in oophorectomized *Pten*+/- mice, and in *Pten*+/-/*ER*α-/- mice, have shown that the development of CAH and endometrial adenocarcinoma is independent of estrogen, although estrogen appears to potentiate the outgrowth of invasive carcinoma [96–98]. Similar findings have been made in a mouse model (*Pten*<sup>loxP/loxP</sup>) with conditional deletion of *Pten* in the uterus, in which development of CAH and endometrial carcinoma is also independent of estrogen [99, 100]. Mechanistically, the development of hyperplasia in the absence of estrogen may be explained by the fact that loss of *Pten* function leads to Akt-dependent phosphorylation on ERα-Ser167, resulting in ligand-independent activation of ERα [98]. These observations may be relevant to human endometrial carcinomas since the estrogen independence of CAH in mouse models provides a rationale for the fact that, clinically, some patients present with hyperplasia in the absence of discernible clinical signs of hyperestrogenism [96].

The effect of progesterone on endometrial tumorigenesis in *Pten* mouse models has also been investigated. In oophorectomized *Pten*+/- mice, pretreatment with medroxyprogesterone acetate is insufficient to prevent the development of hyperplasia and adenocarcinoma [97]. Likewise, in oophorectomized mice (*PR*<sup>cre/+</sup> *Pten*<sup>fl/fl</sup>) with conditional deletion of *Pten* in the uterus, progestin pretreatment is unable to prevent endometrial tumor progression, and tumors arising in this context have increased PR expression in the stroma [99]. Furthermore, progesterone alone is insufficient to cause endometrial tumor regression in an endometrial regeneration model in which *Pten*-ablated epithelial cells are admixed with *Pten*-wild type stromal cells [101]. However, in this same regeneration model, co-treatment with progesterone and estrogen results

in endometrial tumor regression, and this effect is dependent on intact PR expression in the stromal cells [101]. Moreover, when mutant KRAS (G12D) is introduced into the *Pten*-ablated epithelial cells in the regeneration model, the outgrowing tumors exhibit reduced stromal PR levels, similar to observations in *Pten*<sup>d/d</sup>*Kras*<sup>G12D</sup> uteri [102] and are refractory to progesterone and estrogen co-treatment, an effect that is reversed by the overexpression of exogenous PR in the stromal cells [101].

### ***Obesity and Endometrial Carcinoma in Animal Models***

The obese Zucker (*fa/fa*) rat serves as an animal model for metabolic syndrome [103]. In terms of their response to estrogen exposure, the endometrium of oophorectomized Zucker rats treated with 17 $\beta$ -estradiol exhibits increased expression of proliferative markers (cyclin A and c-myc), decreased expression of antiproliferative markers (p27Kip1 and sFRP4), and increased Erk1/Erk2 activation, as compared with the endometrium of lean controls [104].

### **Risk Factors for Endometrial Carcinoma**

The epidemiologic evidence implicates factors that increase a woman's exposure to circulating estrogen, relative to progesterone, as the main etiologic drivers of endometrial carcinoma risk (Table 1.2). In this section, we describe relationships between risk factors that are established in the etiology of endometrioid endometrial carcinomas, the most common histologic subtype, with a focus on factors hypothesized to act via hormonal mechanisms. Conceptually, exposures mediated by hormones might act through one or more mechanisms: (1) greater cumulative exposure to estrogens over a lifetime; (2) exposure to supraphysiologic estrogen levels, given the phase of a woman's life course (e.g., postmenopausal levels are physiologically low); and (3) progesterone deficiency (Fig. 1.3).

### ***Non-contraceptive Postmenopausal Hormone Use***

Endometrial carcinoma has long been recognized as a hormonally responsive tumor [3]. As mentioned in an earlier section, the introduction of unopposed estrogen therapy for amelioration of menopausal symptoms was followed by a dramatic increase in the incidence of endometrial carcinoma in the United States [105, 106]. Based on 29 epidemiologic studies, Grady and colleagues [107] reported an RR of 2.3 [95% CI=2.1–2.5] associated with ever use of unopposed estrogen therapy compared with never use. The increased risk became apparent after 1–5 years of use [RR (95% CI)=2.8 (2.3–3.5)], with an increasing trend associated with longer duration of use

**Table 1.2** Summary of etiologic risk factors, magnitude of effect on endometrial cancer risk, and trends in the prevalence of the risk factor

Risk factor [references]	Magnitude of association	Trend in prevalence of risk factor <sup>a</sup>
Non-contraceptive estrogen-alone use [107]	Estrogen use is associated with a 2.3 times higher EC risk compared with nonuse	↓
Non-contraceptive estrogen plus progestin use [131]	Estrogen plus progestin use is associated with a 22% lower EC risk compared with nonuse	↓
Tamoxifen use [168]	Tamoxifen use is associated with a 2.7 times higher EC risk compared with nonuse	↓
Sequential oral contraceptive use [171, 173]	Sequential oral contraceptive use is associated with a 4.6–7.3 times higher EC risk compared with nonuse	↓
Combination oral contraceptive use [174]	Combination oral contraceptive use is associated with a 50% lower EC risk compared with nonuse	Stable
Intrauterine device use [176]	Inert IUD use is associated with a 17% lower EC risk compared with nonuse	↑
Tubal ligation [185]	No association with EC risk	Stable
Excess adiposity [188]	5 kg/m <sup>2</sup> increase in BMI associated with 1.6 times higher EC risk	↑
Physical activity [204]	Physical activity is associated with a 20–30% lower EC risk compared with inactivity	↑
Diabetes [211]	Diabetes is associated with a 2.1 times higher EC risk compared with nondiabetics	↑
Metabolic syndrome [220]	Metabolic syndrome is associated with a 1.4 times higher EC risk compared with women without this disease	↑
Early age at menarche [233]	Early age at menarche is associated with a 1.4 times higher EC risk compared with later age at menarche	↑
Late age at natural menopause [233]	Late age at natural menopause is associated with a 2.2 times higher EC risk compared with early age at natural menopause	↑
Parity [154, 260]	Parity is associated with 20–50% lower EC risk compared with nulliparity	↓
Breastfeeding [133, 233, 240, 251, 260, 264–267]	Insufficient evidence	↑
Infertility [268]	Infertility is associated with a 1.2 times higher EC risk compared with fertile women	↓
Polycystic ovary syndrome [271]	PCOS is associated with a 2.8 times higher EC risk compared with women without this disease	Unknown
Cigarette smoking [272]	Current smoking is associated with a 26–37% lower EC risk compared with never smoking	Stable
Family history [279]	Family history is associated with a 1.8 times higher EC risk compared with no family history	Unknown

<sup>a</sup>Information available from United States Surveillance programs, including National Health and Nutrition Examination Survey (NHANES), Behavioral Risk Factor Surveillance System (BRFSS), and National Survey of Family Growth (NSFG)



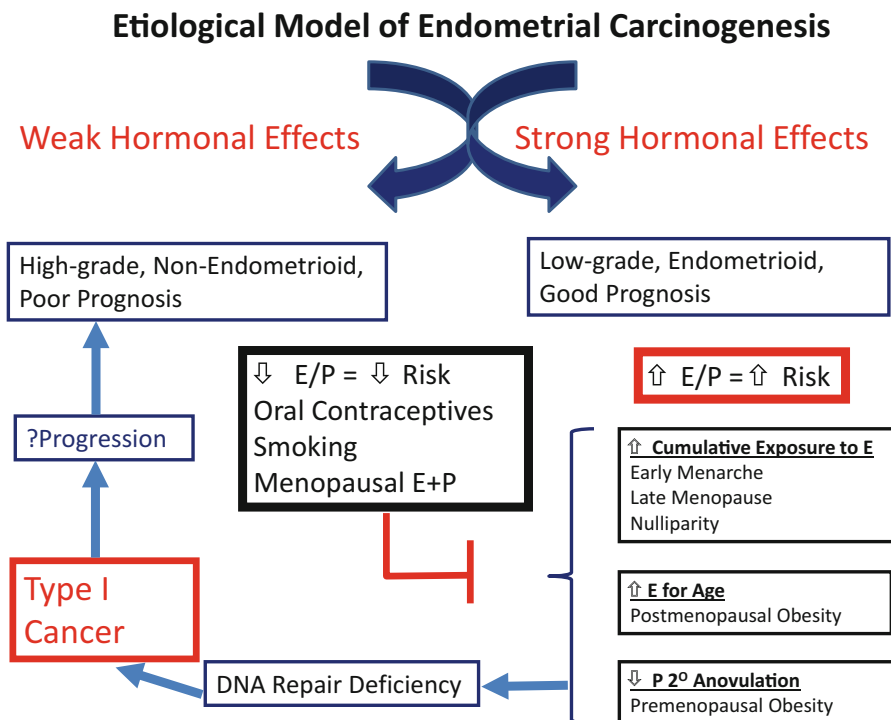


Fig. 1.3 Etiological model of endometrial carcinogenesis

[RR (95% CI), 5–10 years, 5.9 (4.7–7.5);  $\geq 10$  years, 9.5 (7.4–12.3)]. Cessation of unopposed estrogen use has been associated with reduction in endometrial carcinoma risk [108–118]; however, only three studies have demonstrated a reduction in risk equivalent to that of nonusers following 2 years of cessation [109, 111, 114]. Other studies indicate that some elevation in endometrial carcinoma risk remains following 3–5 years of cessation of unopposed estrogen [115, 119–121], while some have shown a slightly elevated risk after 10 years of cessation [112, 122–124].

The type of unopposed estrogen therapy has been evaluated in epidemiologic studies with some inconsistency. Conjugated estrogens, the type most commonly prescribed in the United States [125], were linked with higher endometrial carcinoma risk compared with synthetic estrogens in a previous meta-analysis (RR 2.5 vs. 1.3) [107], while other studies have noted similar magnitudes of risk [113, 118, 121, 126–128]. Most studies observed elevated endometrial carcinoma risk at all commonly prescribed doses compared with never use [111, 117, 118, 121, 126, 127, 129, 130]. One study suggested highest endometrial carcinoma risk with the highest dose of conjugated estrogen [121].

Following the recognition that unopposed estrogen use increases endometrial carcinoma risk, progestin (synthetic progesterone) was introduced to counteract endometrial proliferation among women with an intact uterus. Estrogen plus progestin

therapy has varied in the duration that progestin is delivered. Short-duration formulations, also termed sequential or cyclic, provide a progestin component for less than 15 days per month. A meta-analysis reported increased endometrial carcinoma risk associated with progestin prescribed for fewer than 10 days per month [odds ratio (OR)=1.76 95 % CI=1.51–2.05], whereas progestin given for more than 10 days per month was unrelated to endometrial carcinoma risk (OR=1.07, 95 % CI=0.92–1.24, based on eight studies) [131]. Long-duration formulations, also termed continuous, provide daily progestin and have been linked with lower endometrial carcinoma risk in a meta-analysis of 14 studies (OR=0.78, 95 % CI=0.72–0.86) [131].

Effect modification of the postmenopausal hormone use—endometrial carcinoma risk relationship by other endometrial carcinoma risk factors—has been observed. With respect to BMI, the factor most consistently evaluated, some studies have shown that increased risk related to unopposed estrogen use is greatest among normal-weight women, perhaps due to a saturation effect of excess circulating estrogens among obese women [111, 112, 120, 132–139]. Even still, the absolute risk of endometrial carcinoma related to unopposed estrogen is highest among obese women [135, 140]. Similarly, endometrial carcinoma risk is greatest among normal-weight women using sequential estrogen plus progestin [134–136, 139, 141]. Conversely, the greatest risk reduction among users of continuous estrogen plus progestin occurs among obese women [134, 135, 138, 139, 142–145].

Among unopposed estrogen users, increased endometrial carcinoma risk irrespective of smoking status has been observed [108, 112, 140, 146–151]. In one study, smokers who were users of estrogen plus progestin had higher endometrial carcinoma risk than nonsmokers; however, risks were not separately evaluated for sequential vs. continuous regimens [141]. Others have not observed this relationship [134, 135, 142]. Parity has been found to modify risk associated with unopposed estrogen in one study [149] but not others [133, 140, 148, 152–154], while women who used oral contraceptives early in life and unopposed estrogens at older ages had a slightly lower endometrial carcinoma risk in one study [148] but not others [155–158]. Neither parity nor oral contraceptive use has been shown to modify relationships between estrogen plus progestin use and endometrial carcinoma risk [135].

### *Selective Estrogen Receptor Modulators*

The use of the selective estrogen receptor modulator tamoxifen, itself a weak estrogen, has been related to increased endometrial carcinoma risk in two randomized breast cancer chemoprevention trials [159, 160]. Subsequent studies have supported this association [161–166], leading the International Agency on Cancer Research (IARC) to classify tamoxifen as a known human carcinogen [167]. Furthermore, a meta-analysis reported a significantly increased risk of endometrial carcinoma with tamoxifen use (RR=2.70, 95 % CI=1.94–3.75) [168]. Tamoxifen has also been linked to increased risk of serous carcinomas and carcinosarcomas in some studies [169, 170], although these tumors are, overall, thought to be less related to sex hormone imbalances.

## ***Contraception Methods***

Early contraceptive formulations delivered potent estrogens for 14–16 days per month, followed by a weaker progestin component delivered for 5–10 days per month. Following several reports showing elevations in the RR of endometrial carcinoma ranging between 4.6 and 7.3 [171–173], these preparations were removed from the market.

The use of combined oral contraceptives (COCs), which contain estrogen and progestin taken daily for 21 days per month, is associated with a 50% lower risk of endometrial carcinoma compared with nonuse [174]. Risk reduction is observed after at least 1 year of use, and increasing duration of COC use is significantly related to progressively greater protection. Furthermore, risk reductions related to COC use have been shown to persist for up to 20 years after discontinuation, suggesting that COCs may be a useful chemopreventive agent providing long-term protection.

Results are mixed regarding the impact of progestin potency on endometrial carcinoma risk. Some suggest that endometrial carcinoma risk is reduced regardless of progestin potency [175], whereas two other studies reported the greatest risk reductions among women using formulations with higher progestin dose [155].

Intrauterine devices (IUDs) have been associated with decreased risk of endometrial carcinoma. In a pooled analysis of four cohort and 14 case–control studies, the use of any type of IUD was related to lower endometrial carcinoma risk (OR=0.81, 95% CI=0.74–0.90) [176], which is in line with two previous meta-analyses [177, 178]. Based on the years of enrollment of studies contributing to the pooled and meta-analyses, risks associated with IUD use likely represent the relationship with inert IUDs. Because the hormone-releasing type of IUD is now the most commonly used IUD in the United States, future epidemiologic studies are needed to investigate a possible association with this type of IUD, which is likely to be more biologically active in the endometrium.

Other contraceptive methods, including injectable contraceptives, implants, and transdermal patches, have been evaluated infrequently in relation to endometrial carcinoma risk [179–182]. As the use of these methods become more prevalent, future studies will be needed to distinguish risks related to exclusive and long-term use of these methods.

Relationships between endometrial carcinoma risk and tubal ligation have been examined in three case–control studies [183–185] and one population-based cohort [186]. Two studies reported a nonsignificantly increased risk of endometrial carcinoma [183, 184], while the other two studies reported moderate, but nonsignificantly, decreased endometrial carcinoma risk [185, 186]. The mechanism is unclear, but potential ovarian devascularization, resulting in reduced total hormone exposure, represents one of several possible explanations.

## ***Excess Adiposity***

Obesity is strongly related to endometrial carcinoma risk [187]. In fact, of all obesity-related cancers occurring among women, higher body mass index (BMI) is most strongly related to endometrial carcinoma risk [188]. Epidemiologic studies demonstrate that obese women have a two- to fivefold elevated risk of endometrial carcinoma compared with normal-weight women [189]. These relationships have been observed in both pre- and postmenopausal women as well as in cohort and case-control studies.

Studies that model BMI continuously report a linear relationship between BMI and endometrial carcinoma risk. For example, in a meta-analysis of 19 cohort studies, Renehan et al. [188] reported the overall RR of endometrial carcinoma to be 1.59 times higher for each 5 kg/m<sup>2</sup> increase in BMI. In the Million Women Study conducted in the United Kingdom, investigators found that increasing BMI was associated with increased incidence of endometrial carcinoma (trend in RR per 10 units, 2.89; 95% CI, 2.62–3.18) [190]. Additionally, a recent retrospective cohort study of overweight and obese women undergoing hysterectomy demonstrated a linear relationship between increasing BMI and endometrial carcinoma risk: each 1 kg/m<sup>2</sup> increase in BMI was associated with an 11% increase in the proportion of patients diagnosed with endometrial carcinoma [191]. Further, each 5 kg increase in adult weight gain was associated with a 39% increase in postmenopausal endometrial carcinoma risk among nonusers of menopausal hormones (95% CI=1.29–1.49) [192]. Among menopausal hormone users, the linear association was observed albeit attenuated (RR=1.09, 95% CI=1.02–1.16). This finding is unsurprising in light of data suggesting that endometrial cells experience their highest mitotic activity when estradiol levels are approximately 50 pg/ml—further increases in estradiol may not result in greater endometrial cell proliferation [193].

Other anthropometric measures, including waist circumference, hip circumference, waist/hip ratio, and waist/height ratio, have been suggested as endometrial carcinoma risk factors [143, 144, 194–200]. Unlike BMI, which is an indicator of total body weight, these measures are thought to better reflect central adiposity. Different adipose compartments may vary in their effects on hormone levels and other factors. Most studies report positive associations between endometrial carcinoma risk with the various body fat distribution measures, which is subsequently attenuated after adjusting for BMI [143, 144, 194, 196, 198].

Evidence for associations between obesity and endometrial carcinoma risk among subgroups of other endometrial carcinoma risk factors was recently synthesized [187]. The categories of overweight and obese were collapsed into an excess body weight category. Although excess body weight was associated with increased endometrial carcinoma risk in most subgroups, some notable differences were observed. Excess body weight was a stronger predictor of risk among nonsmokers (RR=2.69, 95% CI=1.35–2.13) compared with smokers (RR=1.57, 95% CI=1.27–1.93) as well as among diabetics (RR=2.09, 95% CI=1.72–2.54) compared with nondiabetics (RR=1.50, 95% CI=1.25–1.79). Notably, effect estimates

comparing hormone users and nonusers were similar (RR = 1.48 vs. 1.69); however, the type of hormone formulation (pure estrogen versus estrogen plus progestin) was not considered which likely led to similar effect sizes.

Postmenopausal obesity is associated with increased circulating estrogens, attributable to aromatization of androgens in adipose tissue [30, 201]. Obesity is related to lower levels of SHBG, leading to higher bioavailable levels of estrogen and higher insulin levels, which may elevate endometrial carcinoma risk [35, 202]. Other nonhormonal mechanisms for the obesity–endometrial carcinoma association include inflammation and other metabolic pathways (*reviewed in later section*). Among premenopausal women, where estrogen levels are high regardless of BMI, obesity may lead to a greater frequency of anovulatory cycles and relative progesterone deficiency or increased inflammation, which could contribute to increase risk of developing endometrial carcinoma.

### ***Physical Activity***

Four meta-analyses [203–206], which summarized 14 cohort and 12 case–control studies, have reported that moderate physical activity is associated with a 20–30% reduction in endometrial carcinoma risk, regardless of domain (occupational, recreational, household, transport). Adjustment for BMI or other indices of weight attenuates but does not abolish this relationship. One meta-analysis [206] addressed potential dose–response relationships between increasing physical activity and endometrial carcinoma risk and reported that an increase in three metabolic equivalent of task (MET) hours/week was associated with a 2% decreased risk of endometrial carcinoma (RR = 0.98, 95% CI = 0.95–1.00,  $p = 0.02$ ), while an increase of 1 h/week in physical activity was related to a 5% lower risk of endometrial carcinoma (RR = 0.95, 95% CI = 0.93–0.98,  $p < 0.001$ ). Independent of physical activity, sedentary time has been linked with increased endometrial carcinoma risk in a meta-analysis [207]. Endometrial carcinoma risk was significantly higher in women with the highest vs. lowest levels of sedentary behavior (RR = 1.36, 95% CI = 1.15–1.60).

Physical activity is likely to mediate endometrial carcinoma risk, in part, by enabling weight control and reducing adipose stores, the major site of postmenopausal estrogen synthesis. Further, physical activity is associated with higher SHBG levels, leading to less bioavailable estrogen. Importantly, physical activity in the absence of weight loss has been linked with lower levels of estrogen and improved insulin sensitivity, although the effects are larger with greater loss of body fat [208, 209]. Given that physical activity has been linked with lower endometrial carcinoma risk independent of BMI [206], other biological pathways, including inflammation, immune function, and cell signaling pathways [205], might be affected by physical activity.

## ***Diabetes***

Three meta-analyses have demonstrated increased endometrial carcinoma risk associated with diabetes [210–212]. Importantly, a question of BMI independence remains, given that some studies did not adjust for BMI, which is related to increased risk of both endometrial carcinoma and diabetes. Of the studies included in the syntheses, two cohort studies [213, 214] and one case–control study [215] observed BMI-independent effects of diabetes on endometrial carcinoma risk, which ranged from 1.43 to 1.94. Furthermore, some studies suggest that risk associated with diabetes is strongest in the category of overweight or obese women compared with normal-weight women [116, 213, 215, 216]. For example, one study reported that the RR associated with diabetes among non-obese women was 1.75 (95 % CI=0.93–3.30), whereas in obese women, the RR was 6.39 (95 % CI=3.38–12.06), although the interaction of diabetes and BMI was not significant [213]. Two case–control studies [217, 218] and one cohort study [219] have evaluated risk of endometrial carcinoma in relation to metformin, an antidiabetic medication, all of which were null.

Diabetes has been hypothesized to affect endometrial carcinoma risk through several mechanisms that increase endometrial proliferation, including increasing mediators of endometrial proliferation [estrogen and insulin-like growth factors (IGFs)], or by decreasing levels of the corresponding binding proteins (SHBG and IGFBP), which increases the bioavailability of these factors (*reviewed in later section*).

## ***Metabolic Syndrome***

Metabolic syndrome, which represents a constellation of factors, including obesity, hypertension, insulin resistance, and dyslipidemia, has been linked with increased endometrial carcinoma risk [216, 220–225]. In the largest study to evaluate this relationship (16,323 endometrial carcinoma cases and 100,751 controls), a 40 % increased risk of endometrial carcinoma was observed (OR = 1.39, 95 % CI = 1.32–1.47) [220]. Given the strong relationships between high BMI and endometrial carcinoma risk, efforts to evaluate the relative importance of the other metabolic syndrome components suggest that while BMI is the strongest risk predictor, hypertension and high triglycerides retain statistical significance in mutually adjusted models, albeit with smaller magnitudes of effect.

Metabolic syndrome is likely to increase endometrial carcinoma risk by affecting multiple biologic pathways, including estrogen and progesterone levels, inflammatory cytokines, and insulin (*reviewed in other sections*).

## *Ages at Menarche and Menopause*

Younger age at menarche has been linked with increased endometrial carcinoma risk in some [132–134, 147, 226–237] but not all studies [113, 238–242], whereas older age at menopause has consistently been associated with increased endometrial carcinoma risk [132, 133, 147, 226–233, 236, 237, 239, 241]. A potentially more biologically relevant construct is menstruation span or the interval between menarche and menopause. In a population-based case–control study, a dose–response relationship between endometrial carcinoma risk and increasing years of menstruation was observed: compared with less than 30 years of menstruation, 40 or more years of menstruation were associated with an OR of 2.71 (95% CI=1.67–4.40,  $p$ -trend <0.01) [243]. This association may reflect risk related to exposing the endometrium to a greater cumulative number of proliferative cycles, which in turn increases risk of acquiring mutations.

## *Parity and Related Factors*

Parity and gravidity, which refer to the number of live births and pregnancies, respectively, are associated with decreased endometrial carcinoma risk. Most studies report a 20–50% risk reduction for parous vs. nulliparous women [116, 132–134, 147, 148, 154, 171, 226, 227, 229, 231–233, 236, 238–240, 243–260], with further reductions in risk associated with an increasing number of live births among parous women [116, 132–134, 147, 148, 171, 226, 227, 232, 233, 238–240, 244, 247, 249, 253–258]. An analysis that evaluated associations between endometrial carcinoma and hormone-related risk factors by parity status did not identify differences between nulliparous vs. parous women [154].

Relationships between timing of births and endometrial carcinoma risk are less consistent. Some studies have shown older age at first birth is related to lower endometrial carcinoma risk [230, 251, 256, 258], higher endometrial carcinoma risk [240], or no association [133, 171, 231, 239, 243, 244, 249, 250, 255, 260–262]. In a pooled analysis including 8,671 endometrial carcinoma cases and 16,562 controls, the combined OR per 5-year increase in age at last birth was 0.88 (95% CI=0.85–0.91) [263].

Associations between induced or spontaneous abortions and endometrial carcinoma risk are mixed: induced abortion has been linked with increased risk [231, 260], lower risk [226, 249, 256], or no association [133, 229, 233, 251], whereas spontaneous abortions have not been associated with risk in some [133, 226, 227, 229, 231, 240] but reduced risk in one [249].

Effects of breastfeeding, which may further suppress estrogen exposure, on endometrial carcinoma risk are inconclusive. Studies conducted in Western countries, where cumulative breastfeeding duration is relatively low, have been null [133, 233, 260, 264]. Conversely, studies conducted in countries where breastfeeding duration is typically longer have reported decreased endometrial carcinoma risk associated with longer breastfeeding duration [240, 251, 265–267].



Infertility has been linked with endometrial carcinoma risk in a recent pooled analysis including 8153 endometrial carcinoma cases and 11,713 controls [268]. Infertile women (assessed mainly by self-report) had an increased risk compared with those without infertility concerns, even after accounting for nulliparity (OR=1.22; 95% CI=1.13–1.33).

Pregnancy is associated with higher levels of progesterone-relative estrogen, which may account for its protective effect. In addition, endometrial shedding during birth may offer protection via exfoliation of premalignant or initiated cells. The suggestion that older age at last birth, which should be associated with more recent births, is protective has been presented in support of the exfoliation theory [244, 249].

### *Polycystic Ovary Syndrome*

Polycystic ovary syndrome (PCOS) is characterized by a constellation of abnormalities that increase risk of endometrial carcinoma, including, chronic anovulation, obesity, and diabetes [250]. Prolonged anovulation is accompanied by progesterone deficiency, which is thought to be a key factor in endometrial carcinogenesis among premenopausal women [269]. Although an association between PCOS and cancer has been discussed since the 1940s [270], epidemiological evidence supporting the link is limited. A meta-analysis of data from five epidemiological studies reported that women with PCOS were at a significantly increased risk of endometrial carcinoma (OR=2.79, 95% CI=1.31–5.95) [271]. Importantly, various definitions of PCOS are used throughout the literature, which complicate interpretation. Further, efforts to disentangle the effects of PCOS from its component factors, obesity and insulin resistance, are difficult.

### *Cigarette Smoking*

A consistent inverse relationship between cigarette smoking and endometrial carcinoma risk has been observed in the literature; one meta-analysis demonstrated that current smokers have a 26% (95% CI=0.64–0.84) lower risk in cohort studies and a 37% lower risk in case-control studies (95% CI=0.55–0.72) [272]. The inverse association was demonstrated among postmenopausal, but not premenopausal women. A relationship between more cigarettes per day and lower endometrial carcinoma risk confirms a dose-response relationship; however, relationships between longer duration and younger ages at initiation were not statistically significant in prospective studies [272]. The mechanism by which cigarette smoking reduces endometrial carcinoma risk is unknown; however, some hypothesized antiestrogenic mechanisms, including increased production of 2-hydroxyestrone, which is postulated to be anticarcinogenic [273, 274] and higher progesterone levels in endometrial tissues and in the circulation

[275, 276]. Smokers and nonsmokers do not differ with respect to serum estrogen levels [277]; however, urinary excretion of estriol is lower in smokers than in nonsmokers [278].

## ***Family History***

First-degree family history of endometrial carcinoma is associated with a higher risk of developing endometrial carcinoma compared with individuals lacking a family history. A recent meta-analysis, which included 2339 endometrial carcinoma cases and 16,000 controls, reported an 82 % higher risk (95 % CI = 1.65–1.98) [279]. Cumulative risk of endometrial carcinoma, up to age 70 years, was estimated at 3.1 % (95 % CI 2.8–3.4) for women with a first-degree relative with endometrial carcinoma with a population-attributable risk of 3.5 % (95 % CI 2.8–4.2). This analysis did not find evidence of effect modification by age at diagnosis, by menopausal status, or by the affected family member (i.e., sister vs. mother), although individual studies have reported stronger effects among younger women [171, 256, 280].

Family history of cancer can reflect shared environments or inherited genetic conditions. Inherited predisposition to endometrial carcinoma has been estimated at 5 % [280], with Lynch syndrome accounting for the majority of inherited endometrial carcinomas [281]. Lynch syndrome is characterized by deleterious germline mutations in the DNA mismatch repair genes, *MSH2*, *MSH6*, *MLH1*, and *PMS2*, which result in faulty mismatch repair of errors that occur during DNA replication, manifested as microsatellite instability, detection of abnormal lengths of short repetitive DNA sequences [282]. Women with germline mutations in either *MLH1* or *MSH2* have a 40–60 % lifetime risk of developing endometrial carcinoma [283, 284]. Recently, it has also been discovered that specific germline variants in the *POLD1* gene, which encodes a DNA polymerase, also predispose carriers to develop endometrial cancer in the context of polymerase proofreading-associated polyposis [285, 286].

## ***Genetic Risk of Endometrial Carcinoma***

Candidate gene studies (reviewed [287]) have reported on the association between common single nucleotide polymorphisms in several biological pathways, such as sex steroid hormone [288–295] and obesity [296–298], in relation to endometrial carcinoma risk, although not all studies found significant associations. In addition, agnostic evaluations of the relationship between common genetic variants and endometrial carcinoma risk have been conducted using the genome-wide association study (GWAS) approach [299–301]. These efforts have identified a novel candidate locus, rs4430796, at the *HNF1B* gene region on chromosome 17q12 [299], but subsequent studies did not establish a link with endometrial carcinoma risk that reached genome-wide significance [301, 302]. Further, an exome-wide association study did not find rare variants associated with endometrial carcinoma risk [303].

### ***Other Risk Factors***

Studies evaluating diet, alcohol, nonsteroidal anti-inflammatory drugs, endometriosis, uterine fibroids, pelvic inflammatory disease, and sexually transmitted infections as possible endometrial carcinoma risk factors have yielded uncertain conclusions [304–308]. Meta-analyses of the existing data are appropriate for certain risk factors, whereas additional studies are needed for sparsely investigated risk factors.

### ***Etiologic Heterogeneity***

The risk factor relationships described in this section are most applicable to the prevalent type I tumors. A number of studies have investigated relationships between the established endometrial cancer risk factors and incidence of histologic subtypes [18, 309–312]. Taken together, these studies demonstrate that factors related to endometrial cancer risk overall are also associated with risk of the individual histologic subtypes. However, the magnitude of associations differs. For example, relative to controls, obesity ( $\text{BMI} \geq 40 \text{ kg/m}^2$ ) was associated with higher risk of endometrioid ( $\text{RR}=6.88$ , 95%  $\text{CI}=5.95\text{--}7.96$ ), serous ( $\text{RR}=2.85$ , 95%  $\text{CI}=1.80\text{--}4.52$ ), clear cell ( $\text{RR}=4.36$ , 95%  $\text{CI}=2.16\text{--}8.82$ ), mucinous ( $\text{RR}=3.29$ , 95%  $\text{CI}=1.51\text{--}7.19$ ), and mixed tumors ( $\text{RR}=3.49$ , 95%  $\text{CI}=2.06\text{--}5.90$ ) [312]. The overlap in risk factor associations between histologic subtypes supports the need for molecular classification of endometrial carcinomas to develop improved risk factor profiles for specific tumor subtypes.

## **Non-estrogenic Mechanisms of Endometrial Carcinogenesis**

Elevated endogenous estrogens may not fully account for the endometrial carcinoma association with obesity, the strongest risk factor for endometrial carcinoma. Mounting evidence from epidemiologic studies suggests that metabolic and endocrinologic abnormalities, reflected in elevated androgens, insulin, inflammatory mediators, and adipokines, may also contribute to endometrial carcinoma risk among obese women. Several of these factors, such as insulin resistance, increased levels of leptin, decreased levels of adiponectin, and chronic inflammation, are proposed to be important in obesity-related carcinogenesis (mechanisms reviewed in [29, 313]).

Androgens are hypothesized to play a role in endometrial carcinogenesis through their conversion to estrogen by aromatase in the adipose tissue after menopause [32]. However, it is currently not clear whether androgens also have a direct effect on the etiology of endometrial carcinoma [314–316]. Data from a case-control study ( $n=276$  endometrial carcinoma cases) showed that higher serum levels of androstenedione were associated with a two- to threefold elevated risk of endometrial carcinoma in pre- and postmenopausal women, even after adjusting for levels

of estrogen [317]. In contrast, more recent nested case–control studies ( $n=124$  and 247 endometrial carcinoma cases) reported that elevated levels of androstenedione were not associated with risk [34] or this risk disappeared after adjusting for estrogen [33]. Increased endometrial carcinoma risk was also observed with elevated testosterone levels [33, 34] and with DHEAS in one study [33] but not another [34].

A pronounced metabolic change associated with obesity is the development of insulin resistance, which is linked with higher levels of circulating insulin (also referred to as hyperinsulinemia) [29, 313]. Insulin is a known mitogen, and endometrial tissues express high-affinity insulin receptors, which are consistent with a direct effect of insulin on endometrial cancer cells in culture [318, 319]. Further, cell line studies have shown that insulin, through its regulation of IGFBP1, increases IGF1 activity in the endometrium [320, 321]. Insulin and IGF share extensive amino acid sequence homology and use a common PI3K (phosphoinositide kinase-3)/AKT/mTOR signaling pathway that promotes cell survival and proliferation [322]. Insulin is described to also suppress levels of SHBG, leading to higher levels of bioactive estrogen.

Epidemiologic evidence has consistently supported a positive relationship between overall endometrial carcinoma risk with higher levels of insulin [35, 323–325] and C-peptide (a stable marker of pancreatic insulin secretion) [202, 326, 327]. Fewer studies have reported on free IGF1 levels, with some reporting an inverse association, albeit an inconsistently statistically significant relationship [35, 324, 326, 328–331]. However, epidemiological studies reporting on the possible association with serum levels of different isoforms of IGFBP have been inconclusive [35, 324, 325, 328–332].

Inflammation has also been implicated in endometrial carcinoma etiology. Chronic inflammation can induce cell division, increasing the possibility of replication error and ineffective DNA repair, and directly increase estrogen production [333]. Few epidemiological studies have investigated the association between risk of endometrial carcinoma and inflammatory markers, namely, IL-1 receptor antagonist (IL-1RA) [334], C-reactive protein (CRP; [323, 334, 335]), interleukin (IL)-6 [323, 334, 335], and tumor necrosis factor (TNF)- $\alpha$  [323, 335, 336]. Among these inflammatory markers, an increased level of CRP has been most consistently associated with elevated risk of endometrial carcinoma [323, 334, 335]. The risk association was statistically significant, even after adjusting for BMI alone or adjusting for BMI, estradiol [335], and markers of insulin separately [323, 335], albeit the association was slightly attenuated after the adjustments. These data indicate that inflammation, in addition to elevated estrogen and hyperinsulinemia, may provide the link between obesity and endometrial carcinoma risk.

Adipose tissue is considered an endocrine organ that secretes a large range of proteins. Of interest, an altered level of cytokines, known as adipokines, such as adiponectin and leptin, has been associated with adipose tissue dysfunction [313]. Previous case–control studies have reported that low adiponectin level is associated with endometrial carcinoma, even after controlling for BMI [337–340]. Fewer numbers of case–control studies nested within prospective cohort studies have been evaluated and have reported inconsistent results: two studies reported an inverse association [332, 341],

whereas the other two reported no association [342, 343]. Results from case–controls studies that suggested a positive association between increased leptin levels [337, 338, 344] and elevated endometrial carcinoma risk have been confirmed in two prospective studies using pre-diagnostic levels of adiponectin in serum [341, 342]. Three prospective studies evaluating the leptin to adiponectin ratio observed that a higher ratio was associated with elevated risk of endometrial carcinoma [340–342]. One study that evaluated the association between visfatin in relation to endometrial carcinoma risk did not find an association [341]. Recently, a factor analysis of various pre-diagnostic plasma hormones, binding proteins, and cytokines in 233 endometrial carcinoma cases and 446 matched controls identified three relatively independent and physiologically well-defined pathways that were associated with postmenopausal endometrial carcinoma risk: steroids, insulin resistance/metabolic syndrome, and inflammation [336]. Serum profiling of a panel of metabolic dysfunction analytes in a case–control analysis (15 amino acids and 45 acylcarnites) has also identified candidate serum biomarkers associated with endometrial cancer, but confirmation in prospective data has not been published to date [345].

## Summary and Future Directions

The total number of endometrial carcinoma cases in high-income nations is increasing secondary to growing populations, extended life expectancy, reduced performance of hysterectomy, and increasing obesity. The slow development of most endometrial carcinomas from recognized precursors suggests the potential for early detection or preventive interventions to improve clinical outcomes. However, better methods to identify women at greatest risk of developing endometrial carcinoma would enable more efficient testing of new approaches. Toward that goal, efforts to develop useful models to predict risk of endometrial carcinoma are needed [346]. Given that obesity is a strong risk factor for endometrial carcinoma, but also extremely prevalent, understanding which obese women are at greatest risk may contribute importantly to the success of this effort. Improved etiological understanding of endometrial cancer has enabled the development of targeted prevention trials that include interventions such as levonorgestrel-impregnated intrauterine devices, metformin, and weight loss [347].

Finally, efforts to detect endometrial carcinoma at early stages (and potentially at the precursor stage) using molecular testing of cervical cytology samples or tampons [348–350] have shown preliminary promise and may help bridge identification of high-risk populations, enabling timely interventions and reduction in mortality. Given the expected increases in endometrial cancer incidence, streamlined clinical triage will be important; abnormal vaginal bleeding is among the most frequent gynecologic complaints, and although benign in the vast majority of cases, identifying the subset of women who have early carcinomas or precursors could reduce mortality and lessen treatment-related morbidity.

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