Changing Trends in the Epidemiology of Endometrial Cancer

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1.1 Introduction

Uterine corpus cancer (UCC), alternatively referred to as endometrial cancer, is responsible for approximately 5% of the global cancer incidence and 2% of the global cancer mortality among women per year [1]. In 2012, UCC was the 6th most common cancer in women worldwide with an estimated 319,600 cases and was the 14th leading cause of cancer mortality, responsible for an estimated 76,200 deaths [1]. The incidence of UCC is highest in North America and Eastern Europe, and

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incidence rates coincide with several lifestyle factors common to higher-income countries, such as increased obesity, increased lifespan, later age of first childbirth, and fewer childbirths compared to lower-income countries [1]. The American Cancer Society (ACS) estimated that 167,900 new cases and 34,700 deaths would occur in more developed countries in 2012, compared to 151,700 new cases and <65,000 deaths in less developed countries [2]. Furthermore, women in more developed countries experience both a significantly higher lifetime risk of developing UCC (1.8% vs. 0.6%) and a higher cumulative mortality risk from it (0.3% vs. 0.2%) compared to those living in less developed countries [3].

Within the United States (U.S.), UCC is the fourth most common cancer diagnosed in females, accounting for 7% of all female malignancies, and the seventh most deadly, responsible for 5% of all cancer deaths in females [3, 4]. Fifty-three thousand nine hundred and eleven new cases of UCC were reported in 2015 (27 per 100,000) along with 10,733 UCC-related deaths (5 per 100,000) in 2016 [3]. The ACS estimated that 63,230 new cases of UCC would be diagnosed in the United States in 2018, resulting in 11,350 deaths [3, 4]. The incidence rate of UCC increased by 0.7% per year in 2015, while the death rate increased by 1.1% in 2016, with larger increases seen in ethnic minorities than in whites [3]. Overall, the incidence of UCC was higher among blacks and whites (27 per 100,000) than among other racial/ethnic groups (19–23 per 100,000); however, UCC-related deaths were highest among blacks (9 per 100,000) compared to all other racial/ethnic groups (4–5 per 100,000) [3]. The mean age at diagnosis for all types of UCC is 62 years, with 61% of cases diagnosed in women aged 55–74 years [5]. Among all women, 67% of UCC cases are diagnosed at an early stage due to postmenopausal bleeding, with 21% showing regional and 9% showing distant spread [3]. This distribution holds across all racial/ethnic groups except among blacks, where only 55% of UCC cases are localized at the time of diagnosis [3]. Of all cases of UCC, 68% are endometrioid carcinomas, while 24% are other carcinomas, 5% are carcinosarcomas, and 3% are sarcomas; in blacks, however, endometrioid carcinomas comprise only 47% of UCC cases, while 33% are other carcinomas, 12% are carcinosarcomas, and 7% are sarcomas [3].

UCC is typically treated with a combination of surgery, radiation, hormones, and/or chemotherapy, depending on the clinical picture [4]. The 5-year relative survival rate for all stages of UCC from 2007 to 2013 was 81%, and those with locally confined disease had a 5-year overall survival (OS) of 95%, compared to 69% in those with regionally confined disease and 16% in those with distant metastases [4]. The 5-year relative survival rate in all patients with UCC fell from 87% in 1975–1977 to 82% in 1987–1989, but has since remained relatively constant at 83% [4]. The median age at death due to UCC is 70 years, and nearly one-third of women who die from UCC are between the ages of 65 and 74 years [5]. UCC death rates vary among different races/ethnicities and were notably higher among blacks (9 per 100,000) in 2016 than among either whites (5 per 100,000) or those of other races/ethnicities (4 per 100,000) [3]. Between 1999 and 2016, UCC-related deaths increased approximately 21%, 1.1% per year on average, with larger increases seen among Asians/Pacific Islanders (A/PIs) (52%), Hispanics (33%), and blacks (29%) than occurred

in either whites (18%) or American Indians/Alaska Natives (AI/ANs, no significant increase) [3].

1.2 Type I and II Carcinomas

1.2.1 Pathophysiologic and Molecular Distinctions

Despite its varied clinical and histopathologic features, UCC was historically regarded as a single entity until Lauchlan, Hendrickson et al. differentiated uterine papillary serous carcinoma (UPSC) from endometrioid carcinoma, describing it as histologically similar to serous epithelial ovarian carcinoma [6, 7]. Bokhman was the first to classify UCC into two types, each demonstrating distinctive histologic, epidemiologic, and clinical features, which can be broadly characterized as estrogen-dependent and estrogen-independent [8, 9]. Type I carcinomas, referred to as "endometrioid," comprise 80–90% of all sporadic cases of UCC, are histologically adenocarcinomas, and are often well-differentiated [10]. Type II carcinomas, also referred to as "non-endometrioid," comprise the remaining 10–20% of UCC cases, and are made up of UPSC, clear cell carcinomas (CCC), as well as mucinous, squamous, transitional cell, mesonephric, and undifferentiated carcinomas [10]. Grade 3 (G3) endometrioid carcinomas are sometimes considered Type II carcinomas as well [11].

Type I carcinomas are broadly considered to be estrogen-dependent, with risk factors that coincide with chronic exposure to excess estrogen. These include obesity, estrogen-based hormone replacement therapy (HRT), nulliparity, as well as any medical condition resulting in elevated levels of estrogen, such as estrogen-secreting tumors or polycystic ovarian syndrome (PCOS) [10]. Associated comorbidities typically include hyperlipidemia, hypertension, and diabetes mellitus (DM) [8, 12]. Type II carcinomas, by contrast, are not thought to operate through a primarily estrogen-dependent pathway, and typically occur in older multiparous women of normal weight [8, 9]. One RCS (n = 396) found that 22% of UCC cases diagnosed in women >75 years were UPSC compared to only 3% in women <45 years [13]. The picture is not as simple as estrogen dependence versus estrogen independence, however, as a large prospective cohort study (PCS, n = 1,036,909) found that overweight and obese women were 1.26- and 1.94-times more likely, respectively, to develop Type II carcinomas than women of normal weight [14]. Furthermore, another PCS (n = 97,786) found that a body mass index (BMI) >30 kg/m^2 was significantly associated with Type II carcinomas [11]. It should be noted, however, that both studies grouped G3 endometrioid tumors with UPSC and CCC, which may explain the correlation, as other studies that did not group G3 tumors in this fashion showed an inverse relationship between BMI and Type II carcinomas [10]. At this point, it is safe to conclude that while increased BMI may be associated with both Type I and II carcinomas, it is more strongly associated with Type I carcinomas [10].

Advances in translational science have borne out the division of UCC into Type I and Type II carcinomas by demonstrating that variations seen histologically and

clinically correspond to differences in gene expression. In particular, *KRAS* and *PTEN* mutations are common in Type I carcinomas, as is epigenetic silencing of *MLH1*, resulting in microsatellite instability (MSI); these alterations occur with higher frequency in patients with hereditary nonpolyposis colorectal cancer (HNPCC) [15, 16]. Genomic abnormalities in chromosomes 1, 8, and 10 occur in both atypical hyperplasia and Type I carcinomas, and within 40% of histologically normal premenopausal endometrium there exist isolated glands that fail to express *PTEN*, either due to a mutation or a deletion; these glands persist between menstrual cycles, and with progression assume the appearance of atypical hyperplasia [15]. Other mutations that have been identified in Type I carcinomas include *PIK3CA*, *PIK3R1*, *FGFR2*, *ARID1A* (*BAF250a*), and *CTNNB1* (β-catenin) [16].

In contrast to Type I carcinomas, which are usually diploid, Type II carcinomas are typically aneuploid, and have their own characteristic profile of gene alterations [16]. For example, *TP53* (p53) mutations occur early and often in the development of UPSC, as do alterations of *PPP2R1A*, *PIK3CA*, and *PTEN* [15, 16]. Overexpression of human epidermal growth factor receptor 2 (HER-2/*neu*, also known as *cerbB2* or HER2) in UPSC has been demonstrated in smaller studies, and HER-2/*neu* overexpression has been associated with advanced-stage disease, worse progression-free survival (PFS), and worse OS, making it a possible marker of worse overall prognosis in UPSC [17–21]. Dysregulation or overexpression of aldolase C, desmoplakin, integrin-linked kinase (*ILK*), protein kinase C (*PKC*), *CLK,* p16, cyclin E, and *BAF250a* have also been reported in Type II carcinomas [15]. The genetic profile of CCC resembles that of UPSC; however, distinguishing specific mutations between histologic subtypes of Type II carcinomas is challenging due to their rarity and heterogeneity, and this represents a topic for further investigation [16].

1.2.2 Type II-Specific Epidemiologic Factors

Type II carcinomas have their own idiosyncratic epidemiologic features, which are discussed here in more detail. The remainder of this chapter, by contrast, focuses on the epidemiologic features of Type I carcinomas, since these are by far more prevalent. In particular, Type II carcinomas are more common in blacks, which may contribute to racial disparities in UCC survival [8–10]. An analysis of racial differences in four Gynecologic Oncology Group (GOG) chemotherapy trials found the incidence of UPSC to be 39% in blacks compared to only 16% in whites, with worse survival in blacks despite all groups receiving similar surgical and chemotherapeutic treatment [22]. However, disparities in survival were noted regardless of histologic subtype, suggesting that additional factors contribute to reduced survival in this cohort [22].

Overall, Type II carcinomas carry a significantly worse prognosis than Type I carcinomas, with 47% of UCC deaths occurring in Type II carcinomas despite these representing only 11% of diagnosed cases [10]. Furthermore, OS for Type I carcinomas is 83% compared to only 46–53% for UPSC and 42–63% for CCC [23–26]. The stage-adjusted OS is also significantly worse for Type II than for Type I

carcinomas, with Stage I UPSC having an OS of 50–80% compared to 80–90% in Stage I Type I carcinomas [25, 27–29]. There is conflicting data comparing survival between Stage I UPSC and Stage 1 G3 Type I carcinomas [9]. An analysis of the International Federation of Gynecology and Obstetrics (FIGO) data in 2001 (n = 473) found an equivalent OS between Stage I UPSC and Stage I G3 Type I carcinomas (72% vs. 76%); however, an analysis of the Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 2001 (n = 3789) found a significant difference in 5-year disease-specific survival (DSS) between Stage I UPSC and Stage I G3 Type I carcinomas in both the early-stage (74% vs. 86%) and late-stage cohorts (33% vs. 54%) [27, 29].

Several factors contribute to worse outcomes in patients with Type II compared to those with Type I carcinomas. Type II carcinomas typically present in older patients, with a reported median age at diagnosis of 68 years for UPSC and 64–66 years for CCC, compared to a median age of 63 years for Type I carcinomas [23–26]. Furthermore, only 69% of patients with Type II carcinomas present with early-stage disease (Stage I-II) compared to 86% of patients with Type I carcinomas; notably, 41% of patients with UPSC and 33% of those with CCC present with late-stage disease (Stage III-IV) [24]. Type I carcinomas are typically minimally invasive, whereas Type II carcinomas tend to be deeply invasive, and in contrast to Type I carcinomas, which are more likely to recur locally and are frequently curable with tumor-directed radiotherapy, Type II carcinomas tend to recur distally, limiting the utility of radiotherapy in treatment [9].

Compared to those with Type I carcinomas, patients with Type II carcinomas are more likely to have a history of an additional primary cancer, with breast cancer being the most common, and in fact several retrospective studies have explored the association between breast cancer and UPSC [9, 10]. One retrospective cohort study (RCS, n = 592) noted the development of either a synchronous or subsequent breast cancer in 25% of patients with UPSC compared to only 3.2% of patients with Type I carcinomas, while another RCS (n = 1178) found a significantly higher likelihood of women ≤55 years with a history of breast cancer developing UPSC than Type I carcinoma, independent of Tamoxifen use [30, 31]. A third, smaller RCS (n = 54) found that women with breast cancer who later developed UCC were 2.6-times more likely to have UPSC than a Type I carcinoma, while an analysis of the SEER data from 1988 to 2001 (n = 52,109) found a significantly higher incidence of UPSC in women with a history of breast cancer than in those without it (9.4% vs. 6.3%) [30, 32].

Hypotheses for this phenomenon include similar shared risk profiles, the possibility of radiation therapy administered for one primary cancer inducing the other, both cancers being manifestations of an inherited cancer syndrome, such as HNPCC, or multiple cancers arising from mutations in unidentified cancer-predisposing genes [10]. Tamoxifen use has been proposed as contributing to the apparent association between UPSC and breast cancer; however, the evidence for this is conflicting, and the largest relevant study, a randomized controlled trial (RCT, n = 13,388), found no association between tamoxifen use and UPSC [9, 10]. A potential link between UPSC and hereditary breast–ovarian cancer syndromes is also

controversial, with some case series seeming to show an association between UPSC and *BRCA* mutations and others showing no connection [9, 33]. In the face of conflicting evidence, it has been suggested that mutations in as-yet-undescribed oncogenes may be responsible for observed associations between UPSC and breast cancer [9].

1.3 Age

The lifetime risk of developing UCC is 2.8% (1 in 35), and this risk steadily increases with age, from 0.3% (1 in 342) in women ≤49 years, to 0.6% (1 in 103) in women 60–69 years, to 1.3% in women ≥70 years [4]. The incidence of UCC in "young" women varies depending on the age cutoff used, but is reported to be 14.4% in women <40 years of age, 15% in women <45 years of age, and 12% in women <50 years of age [13, 34–36]. Compared to their older counterparts, younger patients with UCC are more likely to be obese, nulliparous, diabetic, hypertensive, to have polycystic ovaries, and to report a history of ovulatory dysfunction [34, 35]. Tumor grade and depth of myometrial invasion appear to increase with age, although it is uncertain whether this difference is due to progression of disease or simply to a later discovery [13, 24]. An analysis of FIGO data in 2006 ($n = 8807$) found that the mean age of patients with no myometrial invasion was 58.6 years, compared to a mean age of 61.5 years in patients with ≤50% myometrial invasion and 64.9 years in those with >50% myometrial invasion [24]. Younger patients with UCC are also more likely than their older counterparts to present with earlier-stage disease and with more favorable histologic subtypes, although approximately 25% present with Stage II-IV disease and 9% have positive lymph nodes at the time of diagnosis [34, 37]. Notably, this patient population is also more likely to have synchronous ovarian cancer, with a reported rate of 19% [36].

1.4 Race/Ethnicity

1.4.1 Blacks

Studies investigating the relationship between race/ethnicity and UCC risk in the United States have primarily focused on disparities between blacks and whites [38]. Although UCC has a slightly lower incidence among blacks than whites (26.5 vs. 27.0 per 100,000), blacks with UCC experience a significantly higher mortality rate than whites (9.0 vs. 4.6 deaths per 100,000), and survival is substantially lower for blacks at every stage of diagnosis [4, 38, 39]. An analysis of the SEER data from 1992 to 2008 that corrected for patients who had undergone hysterectomy showed an incidence of 136.0 per 100,000 among whites compared to 115.5 per 100,000 among blacks, a 73% and 90% increase, respectively, from the uncorrected totals [40]. The incidence rate increased more in blacks than in whites following this adjustment because blacks undergo hysterectomy more often than whites in the

United States for reasons that remain unclear [41]. From 2005 to 2014 the incidence of UCC increased 1% per year in whites and 2.5% per year in blacks [4]. Notably, the 5-year relative survival rate for UCC remains markedly lower in blacks than in whites (62% vs. 84%), while the death rate increased at a faster pace for blacks than for whites (2.1% vs. 1.5%) between 2006 and 2015 [4].

Overall, blacks are twice as likely to die from UCC as women from any other racial/ethnic group, and multiple factors appear to contribute to this increased mortality, including a higher incidence of aggressive histologic subtypes, idiosyncratic patterns of gene expression, failure to access quality healthcare services, failure to receive standard of care, and an increased incidence of comorbidities [3, 38, 39]. Multiple studies have found that blacks are more likely than whites to be diagnosed with late-stage disease and with more aggressive histologic subtypes [3, 4, 22, 42]. Parsing the impact of histopathologic from socioeconomic factors on UCC outcomes in blacks has been a focus of research for many years; however, relevant studies have yielded inconsistent and conflicting results on nearly every one of these topics.

Increased mortality as a result of more aggressive tumor types and later stage at diagnosis remains an attractive hypothesis to explain racial/ethnic disparities in UCC patients, as multiple studies have shown no significant association between race/ethnicity and outcomes in cohorts who receive similar treatment regimens once results are corrected for stage and histologic subtype [42, 43]. An RCS ($n = 984$) of patients with UCC at all stages found that blacks were much more likely to have Type II carcinomas than whites, including UPSC, carcinosarcoma, and leiomyosarcoma [43]. Blacks had an increased risk of death when all histologic subtypes were included; however, controlling for Type I versus Type II carcinomas revealed no difference in OS between any of the involved races/ethnicities [43]. Another RCS ($n = 766$) of patients with early-stage Type I carcinomas who were matched for stage and adjuvant treatment found that the 5-year recurrence-free survival (RFS) and disease-specific survival (DSS) were significantly lower in blacks than in whites; however, when results were adjusted for other prognostic factors, race/ethnicity was not found to be a significant predictor of outcomes [42]. Findings such as these would seem to indicate a histopathologic reason for racial disparities in UCC patients rather than a socioeconomic one.

Other studies, however, have yielded conflicting results. A retrospective analysis of four GOG trials ($n = 1151$) showed that the median OS in those with late-stage or recurrent UCC was worse among blacks than whites (10.6 vs. 12.2 months) despite the two receiving similar treatment regimens [22]. This disparity persisted even after adjustment for stage, histologic subtype, and grade 1–2 tumors; grade 3 tumors did not show a significant association between race/ethnicity and survival [22]. Racial/ethnic disparities were also seen in tumor responsiveness to therapy, with blacks less likely than whites to experience a complete or partial response to chemotherapy (34.9% vs. 43.2%), a finding that persisted across all four GOG trials [22]. It is uncertain whether these findings run counter to those cited previously, or whether they indicate the presence of specific racial/ethnic disparities in late-stage or recurrent disease that do not exist in early-stage and primary disease. It is

noteworthy, however, that despite representing approximately 30% of the U.S. population, Hispanics and blacks comprise less than 6% of all federally funded clinical trials, a reality which may in part account for the reduced effectiveness of standard treatment regimens in these populations [44].

Molecular differences in tumorigenesis have also been proposed as a potential etiology for racial/ethnic disparities in UCC patients; however, studies have failed to find consistent associations between mutations in single cancer-related genes and OS among racial/ethnic groups [45]. Mutations in the *PTEN* tumor suppressor gene and MSI are associated with favorable clinicopathologic features, *PTEN* mutations have been shown to be more common in whites with advanced disease, and this has been proposed as a reason for an improved prognosis in this cohort [45, 46]. However, in one case–control study (CCS, $n = 39$), *PTEN* mutations were not found to be predictive of improved outcomes after controlling for other clinicopathologic features, and a retrospective analysis ($n = 140$) of tissue samples from patients with late-stage disease showed that although MSI was associated with improved survival, there was no difference in MSI frequency between racial/ethnic cohorts [45, 46].

HER-2/*neu* represents a more promising target gene for elucidating racial/ethnic disparities in UCC, as HER-2/*neu* gene amplification in UPSC has been shown to occur more often in blacks than in whites and to be an important prognostic indicator for poor outcomes [18]. One CCS ($n = 30$) found that patients with UPSC and HER-2/*neu* gene amplification had a significantly shorter survival time from diagnosis to disease-related death compared to controls [18]. Other studies have investigated the role of p53, since its overexpression occurs in approximately 20% of UCC cases and is associated with a worse prognosis [45]. In one CCS ($n = 39$) blacks were seen to have a two- to threefold increased expression of mutant p53 compared to whites at all stages of UCC; however, increased expression of p53 as well as race/ethnicity were only found to be significant prognostic factors in late-stage disease [45]. Furthermore, this study used genome-wide characterization of gene expression in UCC and found it to be indistinguishable between blacks and whites, including the expression of p53, HER-2/*neu*, and *PTEN*, leading the authors to conclude that racial disparities in UCC outcomes cannot be accounted for by tumor-specific gene expression alone [45].

Several authors have documented an increased rate of medical comorbidities in blacks compared to whites, and this represents an attractive avenue for investigation, since conditions like obesity and DM may impact survival both directly by maintaining a more hospitable hormonal environment for tumorigenesis, as well as indirectly by rendering black patients poorer surgical candidates in the setting of a cancer whose primary therapeutic approach is surgical [12, 38]. One RCS ($n = 1144$) found that blacks with both Type I and Type II carcinomas had a higher median BMI than whites, and were twice as likely to have DM [12]. A clear connection between these comorbidities, race/ethnicity, and OS, however, has remained elusive, as DM in this study was associated with a worse OS in patients with Type I carcinomas, but no association was seen in Type II carcinomas, and race/ethnicity was not independently associated with OS in any group [12].

An older analysis of the SEER data from 1992 to 1998 (n = 21,561) found that blacks were significantly less likely to undergo surgery, even after adjustment for stage [47]. Among patients with Stage I UCC, 7.7% of blacks did not undergo surgery compared to only 2.2% of whites, whereas among patients with Stage II disease 20.8% of blacks did not undergo surgery compared to 6.0% of whites; adjusting for the use of surgery in this study reduced racial/ethnic disparities in survival somewhat, but not entirely [47]. The reasons for racial/ethnic disparities in surgical treatment have been shown to be multifactorial and complex, and may include reduced access to care, potentially discriminatory practices by surgeons or other health care organizations, differences in the extent of disease limiting the effectiveness of surgical therapy, and the presence of medical comorbidities making patients poorer surgical candidates [47]. One older CCS (n = 55,533) found that lower income was associated with a lack of treatment in blacks with Stage IV disease [48]. However, more recent studies have shown worse outcomes for blacks compared to whites despite equivalent treatment regimens, while other studies have demonstrated that patients of all races/ethnicities experience worse outcomes when not privately insured [22, 49]. For example, a large RCS (n = 228,511) found that patients of any racial/ethnic identity with advanced disease were less likely to receive standard-of-care postoperative radiotherapy or chemotherapy if they were insured by Medicare than if they had private insurance [49]. Furthermore, those with advanced disease experienced a worse survival if they were either uninsured or insured by Medicare or Medicaid than if they were privately insured [49]. Ultimately, although numerous studies have been conducted on health disparities between blacks and whites in the United States, a better understanding of the etiology of racial/ethnic disparities in UCC outcomes is still needed in order to provide targeted care to those at the highest risk for poor outcomes [39].

1.4.2 Hispanics

Although research into racial/ethnic disparities in UCC incidence and outcomes has historically focused on comparisons between blacks and whites, referred to in this section as non-Hispanic whites (NHWs), recent studies have begun exploring similar issues in more diverse racial/ethnic populations, including Hispanics, A/PIs, and AI/ANs. Hispanics represent the second largest racial/ethnic group in the United States after NHWs, and accounted for approximately 17.8% of the U.S. population in 2016, numbering 57.5 million [50]. The ACS estimates that there will be 6700 new cases of UCC in the Hispanic population in 2018, which will be responsible for 1000 deaths [50]. Hispanics are diagnosed with UCC at a lower rate than NHWs (23.2 vs. 27.0 per 100,000); however, UCC incidence among Hispanics continues to rise at a disproportionate rate compared to NHWs (1.8% vs. 0.5%) [3].

Several studies have shown that Hispanics are more likely to present at a younger age and with later-stage disease than NHWs; however, the existence of treatment and survival differences among Hispanics is more controversial [51]. Further complicating matters is the considerable variation that exists in defining study

populations, as some authors have investigated differences between Hispanics and NHWs, while others have focused on Hispanic Whites (HWs) versus NHWs, and still others have divided Hispanic populations by birthplace or ethnic origin, with resulting uncertainty as to how the findings of these investigations may be compared to one other. The "Hispanic Paradox" is a well-known phenomenon reported in several malignancies, in which Hispanics seemingly experience better outcomes than would be expected based on poor socioeconomic prognostic factors [50, 51]. Several explanations have been proposed for this phenomenon, including statistical limitations, a higher baseline life expectancy in Hispanic populations giving the appearance of an increased DSS, a younger age at presentation conferring a better prognosis, and logistical difficulties with follow-up and death ascertainment, especially in more fatal cancers that often lead to return migration following diagnosis ("salmon bias") [50, 51].

Several epidemiologic studies into racial/ethnic disparities among Hispanics have considered UCC of all types, while others have focused specifically on more aggressive histologic subtypes and higher-grade disease. An analysis of the SEER data from 2000 to 2010 ($n = 69{,}764$) found that Hispanics with UCC of all subtypes and stages presented at a younger age than NHWs, with a mean age of 58.0 years in U.S.-born Hispanics, 59.7 years in foreign-born Hispanics, and 56.5 years in Hispanics of unknown birthplace, compared to a mean age of 63.4 years in NHWs [52]. Hispanics were more likely to present with late-stage disease than NHWs (29.8% vs. 25.7%) and U.S.-born and foreign-born Hispanics were also more likely than NHWs to be diagnosed with a high-risk histology (4.8% and 5.9% vs. 3.9%) [52]. Hispanics of unknown birthplace, most of whom the authors hypothesized were naturalized HWs, had a significantly better OS than NHWs (91.6% vs. 86.5% in NHWs, 79.6% in U.S.-born Hispanics, and 78.4% in foreign-born Hispanics), and most of the survival disparity between Hispanics and NHWs was attributed to cancer characteristics such as stage and nodal status [52].

Investigations focusing on more aggressive subtypes of UCC have found that although Hispanics are more likely to be diagnosed with these varieties, they do not experience any difference in survival compared to NHWs [44, 53]. One large RCS ($n = 43{,}950$) found that like blacks, Hispanics with Type II and high-grade endometrioid carcinomas were more likely than NHWs to present with late-stage disease [53]. Hispanics in this study experienced improved all-cause survival compared to NHWs after controlling for treatment, comorbidities, and sociodemographic and histopathologic variables; however, a similar RCS ($n = 10{,}647$) found no difference in DSS between Hispanics and NHWs [44, 53]. Other authors have reported considerable heterogeneity in the incidence of G3 endometrioid carcinoma, carcinosarcoma, UPSC, and CCC among Hispanic subgroups, but have not found clear survival differences between these groups [54]. One RCS ($n = 26{,}416$) found that compared to NHWs, the overall incidence of Type II carcinomas was higher in blacks, Cubans, and Central and South Americans, but not in Mexicans or Puerto Ricans. Another large RCS ($n = 205{,}369$) found no difference in UCC-related mortality between different Hispanic subgroups [54, 55].

Other authors have focused on differences between HWs and NHWs, finding that although UCC incidence is lower among HWs than NHWs, UCC mortality is higher than would be expected among HWs based on its incidence [56, 57]. An analysis of the SEER data from 1988 to 2009 (n = 14,434) found that like other Hispanics, HWs are more likely to present at a younger age and with late-stage disease than NHWs; however, no difference in either OS or DSS was found after controlling for age, stage, histology, and treatment received [57]. No differences in clinicopathologic characteristics were seen between immigrant and native HWs; however, immigrant HWs had a better OS and DSS than native HWs [57]. A PCS (n = 3286) found that HWs were more likely to be diagnosed at a younger age and with late-stage disease than NHWs, but also found that HWs were more likely to have DM and hypertension, to live in rural low-income areas, and to have less education than NHWs [56]. Notably, this study found that controlling for either comorbidities or education completely eliminated the disparities seen in both DSS and OS for HWs compared to NHWs [56].

1.4.3 Asians/Pacific Islanders

Asian-Americans comprised 6.3% of the U.S. population in 2014, numbering approximately 20 million, and these along with Native Hawaiians and Pacific Islanders (collectively abbreviated A/PI), whose population is approximately 1.5 million, represent the most rapidly growing racial/ethnic group in the United States today [58]. The ACS estimates that there will be 2380 cases of UCC within the A/PI population in 2016, which will be responsible for 350 deaths [58]. A/PIs are diagnosed with UCC at a much lower rate than whites (19.2 vs. 27.0 per 100,000); however, an analysis of the SEER data from 1998 to 2009 (n = 105,083) found that they are more likely than whites to present at a younger age (57.7 vs. 64.3 years), with late-stage disease, and with either UPSC or CCC [3, 59].

Studies have yielded conflicting results on the impact of A/PI race/ethnicity on survival. One RCS (n = 1811) found that A/PIs were more likely to present with higher-grade tumors and less favorable histologic subtypes than whites, A/PIs had a significantly worse OS compared to whites, and A/PI race/ethnicity was found to be a poor prognostic factor on multivariate analysis [60]. Another RCS (n = 10,647), however, found no significant difference in DSS between A/PIs or Hispanics with high-grade endometrioid or Type II UCC compared to whites, and an analysis of the SEER data from 1988 to 2009 (n = 105,083) found that A/PIs had a significantly improved DSS and OS compared to whites, even after controlling for stage, histology, and treatment [44, 59]. A/PI immigrants were diagnosed at a younger age than their native counterparts (57.0 vs. 60.5 years) and were slightly more likely to have UPSC or CCC, although no more likely to present with late-stage disease [59]. A/PI immigrants had a significantly better DSS and OS than A/PI natives, but no differences were seen among A/PI subgroups (Chinese, Japanese, Filipino, Asian Indian/Pakistani) [59].

1.4.4 American Indians/Alaska Natives

There are approximately 5.2 million people in the United States who identify as American Indian and Alaska Native (AI/AN), accounting for 1.7% of the U.S. population [61]. AI/ANs are diagnosed with UCC at a lower rate than whites (23.1 vs. 27.0 per 100,000), and an analysis of the SEER data from 1988 to 2009 (n = 105,083) found a trend that did not quite reach significance for the diagnosis of AI/ANs at a younger age than whites (56.5 vs. 64.3 years) [3, 59]. AI/ANs were no more likely than whites to present with either late-stage disease or with UPSC or CCC, and they had no significant difference in DSS, but did experience a worse OS compared to whites after controlling for stage, histology, and treatment [59]. More investigation is needed to clarify epidemiologic trends in this population.

1.4.5 Global Trends

Cancer is a leading cause of female morbidity and mortality worldwide in both high-income countries (HIC) and in low- and middle-income countries (LMIC) because although women comprise approximately 49.5% of the global population, they represent a more significant proportion of the aging population due to differences in life expectancy and causes of mortality [1]. The cancer burden among women is expected to increase worldwide in conjunction with increasing life expectancy, an effect that is likely to be especially pronounced in LMIC due to changes in risk factors associated with economic development, which include increased rates of smoking, obesity, and physical inactivity, later age at first childbirth, and fewer childbirths [1].

UCC accounts for approximately 5% of the global cancer incidence and 2% of global cancer deaths among women [1]. It is the sixth most common cancer among females worldwide with an estimated 319,600 new cases in 2012 [1]. It is furthermore the fourth most common cancer in HIC with 167,900 estimated new cases in 2012 and an age-standardized ratio (ASR) of 14.7 new cases per 100,000 per year, and the seventh most common cancer in LMIC with 151,700 estimated new cases in 2012 and an ASR of 5.5 new cases per 100,000 per year [1, 2]. Excess body weight is estimated to account for approximately 34% of UCC cases worldwide, and incidence rates in the United States, Central and Eastern Europe, and in several other European countries (e.g., Norway, the United Kingdom, and Spain) have increased concomitantly with increases in average body weight since the year 2000 [1]. A trend toward later parity and decreased parity in rapidly developing countries has also led to increased UCC incidence in these regions [1].

UCC is the 14th leading cause of global cancer deaths among women with an estimated 76,200 deaths in 2012 and an ASR of 2.3 deaths per 100,000 per year in HIC, compared to 1.5 deaths per 100,000 per year in LMIC [1]. The highest rates of UCC incidence are seen in North America and Eastern Europe, while the highest mortality rates are seen in Melanesia, Eastern Europe, and the Caribbean [1]. Early diagnosis and treatment of UCC are common in HIC, where the 5-year survival is approximately 80%; in contrast, the 5-year survival remains substantially lower in

LMIC where women have more limited access to health care [1]. For example, the 5-year survival for UCC in Benghazi, Libya is only 17% [1].

1.5 Endogenous Estrogen Exposure

1.5.1 Pathophysiologic Mechanisms of Disease

The sections that follow discuss the epidemiologic risk factors for Type I carcinomas, which comprise roughly 80% of UCC cases; specific epidemiologic risk factors for Type II carcinomas are discussed separately above. Endometrioid adenocarcinoma is hypothesized to develop in the setting of prolonged estrogen exposure that is unopposed by a progestogen [62, 63]. According to this model, excess estrogen stimulates endometrial cell proliferation, thereby increasing the occurrence and subsequent accumulation of cellular mutations [62, 63]. This so-called "unopposed estrogen" hypothesis is primarily supported by epidemiologic data showing a significantly increased risk of UCC in users of estrogen-only oral contraceptive pills (OCPs) and HRT [64, 65]. It is also bolstered by laboratory findings demonstrating that endometrial cells are maximally stimulated in the presence of estrogen during the early follicular phase of the menstrual cycle and minimally stimulated in the presence of progesterone during the luteal phase [66]. The risk of administering unopposed estrogen in OCP and HRT regimens can be eliminated by adding progestogens for ≥10 days per month [67, 68].

Premenopausal women with syndromes of anovulation who also have progesterone deficiency are at increased risk of developing UCC, as are postmenopausal women with elevated circulating estrogen levels, and it has been hypothesized that the risk of endometrial neoplasia correlates in premenopausal women with progesterone deficiency, but in postmenopausal women with estrogen excess [69]. Although androgens do not have a direct stimulatory effect on endometrial cell proliferation, increased levels of circulating androgens are believed to increase UCC risk in postmenopausal women due to aromatization in peripheral tissues (especially adipose tissue) once ovarian production of estrogen ceases [69, 70]. Thus, obesity in postmenopausal women increases circulating levels of estrogen via increased aromatization in peripheral tissues, whereas its effects in premenopausal women are primarily caused by ovulatory cycles and associated progesterone insufficiency [70]. Androstenedione levels also strongly correlate with UCC risk, even when estrone levels are controlled for, leading to the hypothesis that early neoplastic endometrial cells may have the ability to aromatize androstenedione locally, resulting in a survival advantage [70].

1.5.2 Chronic Anovulation

Women with ovulatory dysfunction continue to produce sex hormones, but do not produce them cyclically [71]. Chronic anovulation in this setting results in prolonged exposure to estrogens without concomitant exposure to progesterone,

leading to chronic endometrial proliferation, irregular bleeding, endometrial hyperplasia, and eventually carcinoma [71]. Anovulation may be physiologic at the outset of both menarche and menopause, whereas the causes of pathologic ovulatory dysfunction are many and varied, encompassing primary hypothalamic–pituitary dysfunction, acquired endocrine disorders, and medication side effects [71]. Polycystic ovary syndrome (PCOS) is a common endocrine and multisystem disorder affecting approximately 5–8% of reproductive-aged women [71]. It classically presents with a triad of symptoms that includes hyperandrogenism, menstrual abnormalities, and polycystic ovaries, with commonly associated comorbidities including insulin resistance and the metabolic syndrome [71]. A potential association between PCOS and UCC was first described in the 1950s; however, this risk is still frequently overlooked in clinical practice [71]. One PCS (n = 40,775) found a significantly higher risk of UCC in patients with PCOS than in the comparison cohort, and a recent meta-analysis (n = 72,973) found that PCOS increased the risk of UCC in women of all ages, with this risk even more pronounced in women ≤54 years [71, 72]. Another large PCS (n = 3,493,604) similarly found that PCOS was associated with an increased risk of UCC; however, this increased risk was only present before menopause [73].

1.5.3 Obesity

UCC was the first cancer to be recognized as causally related to obesity, and increasing rates of UCC in Western cultures, which are now approximately 10 times higher than elsewhere, have paralleled increasing rates of obesity [74]. Recent estimates suggest that up to 90% of all UCC cases are to some degree attributable to obesity, and the relative risk (RR) of both developing UCC (RR 7.1) and of dying from it (RR 6.25) is higher for patients with a BMI >40 kg/m^2 than it is for any other obesity-driven cancer [74–76]. UCC arises in the context of prolonged exposure to increased levels of bioavailable estrogen, with obesity contributing to this state in two primary ways: first, adipocytes may directly increase estrogen levels by converting either testosterone, androstenedione, or estrone to estradiol via aromatase; second, insulin resistance, which often accompanies obesity, may lead to decreased levels of sex hormone binding globulin (SHBG), increasing estradiol levels indirectly [74, 77, 78]. Excess levels of estrogen may also lead to chronic progesterone deficiency and chronic inflammation, resulting in continuous endometrial cell proliferation with decreased apoptosis and increased angiogenesis [77, 79]. In contrast to other disorders linked to obesity, the risk of developing UCC is associated with the amount of adipose tissue rather than its distribution [80, 81].

Studies have consistently shown a strong correlation between obesity and UCC risk. One meta-analysis (n = 3,044,538) reported that a 5 kg/m^2 increase in BMI significantly increased UCC risk (RR 1.59), while two large PCSs (n = 495,477, n = 62,573) found a consistent increase in risk as BMI rose above 25 kg/m^2, up to a RR of 4.50 for a BMI >30 kg/m^2 and 6.25 for a BMI ≥40 kg/m^2 [75, 82, 83]. Obesity is particularly associated with an increased risk of UCC in pre- and peri-menopausal

women, who comprise approximately 25% of all cases [74]. Two RCSs (n = 38, n = 188) found that 61% of UCC patients <40 years, 71% of those <45 years, and 56% of those <50 years had a BMI >30 kg/m^2 [36]. Interestingly, UCC risk was also increased in those with a BMI >25 kg/m^2 at 20 years of age and in those whose BMI had increased by 8 kg/m^2 since age 20 (RR 2.38) [83]. Another large PCS (n = 50,376) similarly found associations between weight at a young age, the magnitude of weight gained, and UCC risk, reporting that women with a 1% annual increase in BMI had a 3.2-fold increased UCC risk compared to those who had maintained a stable BMI. This study also found that a 35% increase in BMI conferred significant additional risk of developing UCC (RR 4.12) [84].

Elevated BMI has been shown to increase the risk of both Type I and Type II carcinomas, with the greatest effect seen on Type I disease [10, 85]. One RCS (n = 1411) found that patients with Type I carcinomas were more likely than those with Type II carcinomas to be obese (66% vs. 51%); however, grouping overweight and obese patients together mitigated this difference somewhat (85% vs. 79%) [12]. Several studies have also explored the role of obesity in the stage and tumor grade of UCC at the time of diagnosis. One RCS (n = 396) found that a BMI ≥40 kg/m^2 was associated with endometrioid histology and G1 disease, and other studies have similarly reported obesity-related risk to be higher in less aggressive forms of UCC [37, 86]. Larger and more recent studies that focused solely on endometrioid tumors, however, have found no association between obesity and either stage or tumor grade at the time of diagnosis [87, 88]. Obesity may impact the prognosis of UCC either directly through tumor-associated factors or indirectly via the role of associated comorbidities; however, the magnitude of its impact on survival remains uncertain. One RCS (n = 1411) found that increased BMI was associated with a shorter time to recurrence in Type I carcinomas, but no clear association was seen between BMI and OS for any histopathologic type, tumor grade, or stage [12]. Obese UCC patients have been shown to experience worse outcomes following treatment, and are more likely to die of both their comorbidities and their cancers than their counterparts with a BMI <25 kg/m^2 [74].

The incidence of obesity in the United States is highest among blacks and Hispanics for every age group above 20 years [89]; however, UCC incidence remains highest among whites [85]. One PCS (n = 47,557) found that among blacks, obesity at 18 years of age and amount of weight gained since that time were both associated with an increased risk of UCC [90]. Comorbid Type 2 DM was also associated with increased UCC risk, although positive associations with hypertension and weight distribution were attenuated after controlling for BMI [90]. The interplay between race/ethnicity and obesity on UCC risk remains controversial. One PCS (n = 46,933) of postmenopausal blacks, A/PIs, Hispanics, and whites found the risk of UCC to be similarly increased in women of all races/ethnicities with a BMI >30 kg/m^2 (RR 3.14), and the authors concluded that differences in comorbidities such as obesity did not sufficiently account for differences in UCC risk between these racial/ethnic groups [85]. However, another large PCS (n = 50,376) did find that increases in UCC risk differed across racial/ethnic groups, with only a ≥5% increase in BMI needed to increase UCC risk in Japanese-Americans, compared to a ≥35% increase needed in blacks and whites [84].

1.5.4 Early Menarche and Late Menopause

According to the "unopposed estrogen" theory of endometrial carcinogenesis, any menstrual factors prolonging the duration of estrogen exposure (e.g., early age at menarche, late age at menopause, and nulliparity) are predicted to increase the risk of UCC, while factors shortening or interrupting such exposure (e.g., pregnancy) are predicted to confer a protective effect. Two large prospective cohort studies support these hypotheses: one (n = 24,848) found that UCC occurrence was associated with early age at menarche, late age at menopause, and total length of ovulation span, while another (n = 121,700) found that late age at menarche decreased the risk of UCC, whereas late age at menopause increased it [91, 92].

1.5.5 Estrogen-Secreting Tumors

Ovarian tumors that produce estrogen or its precursor androstenedione may lead to the development of UCC. Sex cord-stromal tumors (SCSTs) are rare neoplasms arising from the ovarian stroma that account for approximately 3–5% of all ovarian malignancies [93]. These are composed primarily of granulosa cell tumors (GCTs), which secrete estradiol, and theca cell tumors/thecomas (TCTs), which secrete androstenedione [94, 95]. Prolonged exposure to tumor-derived estradiol from either tumor type may result in glandular or atypical adenomatous hyperplasia, adenocarcinoma in situ, or invasive carcinoma [95]. Endometrial hyperplasia has been reported in 27% of patients with SCSTs, whereas endometrial adenocarcinoma has been reported in 5–10% of patients with GCTs, and may be its presenting sign [93, 95]. A clinicopathologic review that distinguished 118 GCTs from 82 TCTs found that adenocarcinoma was more prevalent in patients with TCTs (26.8% vs. 12.2%), whereas endometrial hyperplasia was more common in patients with GCTs (55.3% vs. 36.6%) [96]. This same study reported a 66% incidence of hyperplasia or malignancy among all participants, with this combined incidence nearly equal between tumor types [96]. Women who develop SCST-associated endometrial carcinoma usually have well-differentiated, early-stage tumors that carry a good prognosis [95].

1.6 Exogenous Estrogen Exposure

1.6.1 Unopposed Estrogen Therapy

Multiple studies have suggested a causal relationship between the use of "unopposed" estrogen therapy (the administration of estrogen without the addition of a progestogen) and the development of endometrial hyperplasia and subsequent carcinoma [67]. Endometrial hyperplasia is a known precursor to the development of UCC, and thus its presence is often used as an endpoint in prospective trials for patient safety. One RCT (n = 1724) found that 20% of postmenopausal women

taking estrogen alone developed endometrial hyperplasia compared to ≤1% of those also taking a progestogen [97]. It was historically debated whether the use of cyclical unopposed estrogen might be safer than continuous administration, since this regimen was seen as more closely mimicking the natural estrus cycle; however, an RCT ($n = 25$) of postmenopausal women found a 36% rate of endometrial hyperplasia in users of unopposed estrogen with no difference seen between continuous and cyclical administration [97]. Case–control studies have reported a RR of developing UCC as high as 12.0 in ever-users of unopposed estrogen therapy, and up to 15.0 in long-term users, whereas a PCS (n = 23,244) reported a RR of 1.8 following >6 years of use, with cyclical addition of progestogens eliminating this increased risk [98, 99]. Finally, a Cochrane review found that unopposed estrogen therapy at all doses was associated with a significantly increased risk of endometrial hyperplasia following 2–3 years of use compared to placebo, with evidence of both a dose–response and a duration-of-treatment–response relationship, although endometrial hyperplasia was not seen following only 1 year of low-dose estrogen use [67].

It is less certain what impact unopposed estrogen use has on the aggressiveness of cancers that arise as a result of it. One older CCS (n = 363) reported that UCC occurring in users of unopposed estrogen was more likely to present at an earlier stage, with better differentiation, and with less myometrial invasion that UCC arising in nonusers [100]. This study further reported a better 4-year relative survival ratio in unopposed estrogen users than in nonusers (1.05 vs. 0.898), suggesting a better prognosis for UCC arising in this setting [100]. Other studies, however, have found opposite results. A CCS (n = 1217) found that in addition to increasing the risk of early-stage disease, the use of unopposed estrogen for >1 year also increased the risk of late-stage UCC threefold [101]. Additionally, women with ≥1 year of unopposed estrogen use remained at increased risk for at least 10 years following cessation of use [101]. Apparent improvements in survival among estrogen users in some studies may reflect increased access to health care and increased disease surveillance, with a resultant lead time bias [100].

1.6.2 Postmenopausal Hormone Replacement Therapy

Progestogens decrease the proliferation of endometrial glandular cells by down-regulating estrogen receptors, mediating the metabolic inactivation of estradiol, and reducing DNA synthesis [102]. Consequently, several large prospective studies have found that the addition of progestogens to estrogen significantly reduces the risk of developing endometrial hyperplasia and carcinoma compared to the use of estrogen alone [67]. One large RCT (n = 16,608) found that 62.2% of postmenopausal women given unopposed estrogen developed some type of endometrial hyperplasia with 34.4% developing complex hyperplasia or atypia [103]. Overall, these women were more likely than those taking placebo to develop simple (27.7% vs. 0.8%), complex (22.7% vs. 0.8%), or atypical (11.8% vs. 0%) hyperplasia as their most abnormal diagnosis [103]. Those taking continuous estrogen–progestogen therapy did require more frequent endometrial biopsies to assess vaginal

bleeding than those taking placebo (33% vs. 6%); however, they did not experience an increase in the rate of either hyperplasia or UCC [103]. Another large PCS (n = 716,738) found that the RR of UCC was increased with the use of estrogen alone (RR 1.45), but not significantly increased with the addition of a cyclical progestogen (RR 1.05), and in fact decreased with the addition of a continuous progestogen (RR 0.70) [104].

Some studies have reported BMI to be an effect modifier, such that the adverse effects of unopposed estrogen were greatest in nonobese women, while the beneficial effects of combined estrogen–progestogen therapy were greatest in obese women, but other studies have failed to confirm this finding [102, 104–106]. Several studies have attempted to quantify both the optimum monthly duration of progestogen use needed to maximize its protective effect and to determine whether cyclical regimens confer the same protection as continuous administration. One CCS (n = 340) found an increased risk of UCC with <10 days of progestogen use per month compared to ≥10 days (RR 2.4 vs. 1.1) of progestogen use. Similarly, another CCS (n = 1624) found that whereas the addition of a sequential progestogen for <10 days per month only slightly reduced the risk of developing UCC compared to the use of unopposed estrogen (odds ratio [OR] 1.87 vs. 2.17), the addition of a continuous oral sequential progestogen for ≥10 days essentially eliminated this risk (OR 1.07 for both) [68, 107].

Two high-quality prospective studies have yielded conflicting results regarding the benefits of cyclical progestogen use compared to continuous administration. One PCS (n = 224,015) found a significant risk reduction among users of continuous estrogen–progestogen therapy for ≥3 years compared to sequential use for 10–14 days per month (76% vs. 69%), and reported a 276% increased risk when progestogens were only added every 3 months (a so-called "long-cycle regimen") [108]. By contrast, a Cochrane review that examined sequential combined therapy with regimens of 10, 12, and 14 days of a progestogen per monthly cycle, as well as an alternating 3-days-on-3-days-off regimen throughout the cycle, found no increased odds of endometrial hyperplasia or carcinoma at 12, 24, or 36 months with any of these regimens compared to continuous progestogen administration [67]. Several RCTs have assessed the impact of various doses of estrogen and progestogens administered in both continuous and cyclical fashion, with no differences seen in the rates of either endometrial hyperplasia or carcinoma between any of the dosages delivered continuously [67]. The only RCT to find a significant increase in endometrial hyperplasia with cyclical progestogen administration utilized a long-cycle regimen [67].

1.6.3 Tamoxifen, Other SERMs, and Aromatase Inhibitors

Selective estrogen-receptor modifiers (SERMs) are nonsteroidal compounds with dual estrogen-agonist and antagonist activity on estrogen receptors in different tissues [109]. Commonly prescribed SERMs include tamoxifen, which is primarily used in the treatment of ER-positive breast cancer; raloxifene; which is indicated for the treatment of osteoporosis; and toremifene, which is approved for the treatment

of advanced breast cancer [109]. Multiple large RCTs have demonstrated significant increases in the risk of endometrial hyperplasia and carcinoma with tamoxifen use, and this risk has been found to be age-dependent, dose-dependent, duration-of-treatment-dependent, and persisting for extended periods of time following cessation of use [110, 111]. One RCT (n = 1846) found that the frequency of UCC was markedly higher in those given tamoxifen compared to placebo (RR 6.4), although this increase did not reach significance until two years of use, and the greatest increased risk was seen in patients allocated to five years of tamoxifen therapy [112]. Another large RCT (n = 13,388) found that women randomly assigned to receive five years of tamoxifen experienced a significantly elevated risk of UCC (RR 3.28) compared to placebo [113]. Although this risk was not increased in women <49 years, it was significantly increased in those ≥50 years (RR 5.33), with the highest cumulative rate of UCC seen in those with seven years of tamoxifen use compared to placebo (15.64 vs. 4.68 per 1000) [113].

The risk of UCC in young patients (<50) is of particular interest as tamoxifen has shown utility in the prevention of breast cancer in young patients at high risk, notably in those who have developed contralateral breast cancer previously and in those with *BRCA1* or *BRCA2* mutations [114]. One meta-analysis (n = 21,457) found that women who received approximately five years of tamoxifen therapy had an overall increased risk of developing UCC (rate ratio 2.40), with the effects of tamoxifen persisting long after cessation of use [115]. However, the 15-year risk of UCC was strongly correlated with age, with little absolute risk in patients with an entry age of <55 years compared to a much greater risk in those with an entry age of 55–69 years (3.8% vs. 1.1%); the sample size for an entry age ≥70 was too small for a comparison to be made [115]. These results were strengthened by a systematic review of seven RCTs, including data from the NSABP P-1, IBIS-1, and Royal Marsden trials, which found the RR of UCC to be 1.18 in women <50 years given tamoxifen compared to placebo [111].

Several studies have investigated whether UCC arising in the setting of tamoxifen use carries a significantly different prognosis than cases arising sporadically. Early case series reported conflicting results, with more recent case–control and cohort studies doing little to resolve this issue [112, 116]. One CCS (n = 1169) found that tamoxifen use in patients with UCC following breast cancer was associated with a higher-than-expected incidence of late-stage disease (17.4% vs. 5.4%), and tamoxifen users were found to have a worse 3-year DSS than nonusers (76% for use ≥5 years, 85% for use of 2–5 years vs. 94% for nonusers) [117]. Furthermore, long-term tamoxifen users in this study were found to be more likely than nonusers to develop malignant mixed mesodermal tumors (MMMTs) or sarcomas (15.4% vs. 2.9%) and p53-positive tumors (31.4% vs. 18.2%), associations which have been alluded to in numerous case reports [110, 117]. On the other hand, an RCS (n = 73) of patients with a history of breast cancer who subsequently developed UCC found no significant difference in stage, tumor grade, or histologic subtype between those given tamoxifen and those who did not receive it [118]. Numerous studies and case reports have been published on this topic; however, these are of significant heterogeneity and quality, and more investigation is needed [110].

Great uncertainty remains regarding the utility of either oral, transdermal, or intrauterine progestogens in counteracting the proliferative effects of tamoxifen. A Cochrane review of two studies investigating the use of a levonorgestrel-releasing intrauterine device (LNG-IUD) was inconclusive, as neither of the studies under consideration were sufficiently powered to detect the device's ability to prevent either endometrial hyperplasia or carcinoma in tamoxifen users [119]. Likewise, it is unknown whether administering progestogens in any form decreases the risk of UCC in tamoxifen users, and their use for this purpose is not currently recommended [120].

Unlike estrogen and tamoxifen, raloxifene acts as an antagonist on estrogen receptors in the endometrium, and thus its use would not be predicted to increase the risk of developing UCC [114]. Two studies have largely confirmed this hypothesis. One, a CCS (n = 1957), reported a reduced risk of UCC in patients treated with raloxifene compared to those given tamoxifen or placebo (OR 0.50 vs. 1.5 vs. 1.0), and found that endometrial carcinomas arising in raloxifene users were predominantly associated with a favorable stage, tumor grade, and histologic subtype. The second, an RCT (n = 7705), found that although raloxifene led to slight increases in endometrial thickness in some patients compared to placebo, no increased risk of endometrial hyperplasia was seen within the first 3 years of use [114, 121].

Aromatase inhibitors (AIs) are a class of drugs that include exemestane, letrozole, and anastrozole, and which are used in the treatment of breast cancer, endometriosis, for induction of ovulation, and in other estrogen-modulated conditions [122]. Studies have consistently shown a decreased risk of UCC in patients using AIs compared to those using tamoxifen; however, this benefit must be weighed against various other factors, including increased bone loss due to AIs and overall considerations of effectiveness in the treatment and prevention of breast cancer [122]. A large RCS (n = 17,064) of women diagnosed with ER-positive breast cancer found a 48% lower incidence of UCC in patients assigned to AIs compared to those given tamoxifen; no difference in UCC incidence was seen between those using AIs and those given no adjuvant hormonal therapy [123]. One meta-analysis of nine RCTs (n = 31,920) found a 30% decreased 10-year incidence of UCC in those randomized to AIs compared to those given tamoxifen (0.4% vs. 1.2%, rate-ratio 0.33), while another systematic review and meta-analysis (n = 30,023) found that five years of AI use decreased the risk of UCC compared to the same duration of tamoxifen use (OR 0.34) [115, 124].

1.7 Genetic Syndromes

1.7.1 Family History

An estimated 5% of patients diagnosed with UCC at <55 years report a positive family history, and woman with at least one first-degree relative affected by UCC have an increased lifetime risk of developing it themselves compared to the general population (3.1% vs. 1.7%) [125, 126]. No evidence has been found for an increased

risk of Type I carcinoma in women with a first-degree family history of breast, ovarian, or cervical cancer; however, one study reported an increased risk of Type II carcinoma in those with a first-degree family history of breast cancer [126]. Epidemiologic studies have shown an association between UCC and colorectal cancer, likely due to the fact that UCC is the most common extracolonic malignancy arising in Hereditary Nonpolyposis Colorectal Cancer (HNPCC), a syndrome associated with a DNA mismatch repair (MMR) deficiency [125]. Patients occasionally present with UCC alone without colorectal or other cancers, and investigators have recently attempted to define a unique etiology for these so-called "site-specific" cases [125]. Both pedigree and molecular analyses strongly suggest an origin for some cases of UCC that is unrelated to an MMR defect; however, the identity of the specific genes responsible remains elusive [125, 127].

1.7.2 Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant disorder characterized by an increased susceptibility to colorectal, endometrial, and several other cancers [128]. HNPCC is caused by defects in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which result in variably sized nucleotide repeats throughout the genome, a phenomenon known as microsatellite instability (MSI) [128, 129]. High levels of MSI may be caused by either inherited HNPCC-associated genes or they may result from sporadic or non-hereditary MMR gene silencing via DNA methylation, a phenomenon estimated to occur in 15–20% of sporadic UCC cases [129]. A cross-sectional study (n = 58) found that of those with both UCC and a positive first-degree family history of HNPCC, 23% had an MMR gene mutation [128]. Compared to a 3% risk in the general population, the cumulative lifetime risk of developing UCC in those with HNPCC is 40–60%, with a reported risk of 25–42% for *MLH1* carriers, 35–62% for *MSH2* carriers, and 71% for *MSH6* carriers [128–132]. No significant difference in UCC risk has been found between *MLH1* and *MSH2* carriers [131].

Those with HNPCC may have a higher lifetime risk of developing UCC than colorectal cancer, and UCC in many patients represents a sentinel cancer, often diagnosed at an earlier age than colorectal cancer [133]. One cross-sectional study (n = 117) found that 44% of HNPCC patients with metachronous primary cancers were diagnosed with UCC as their first cancer, and 51.5% were diagnosed with a gynecologic cancer (UCC or ovarian cancer) first compared to 48.5% diagnosed with colorectal cancer first [130]. Within this cohort, the median age at the diagnosis was slightly greater for those developing UCC first compared to those developing colorectal cancer first (45 vs. 40 years) [130]. Compared to the general population, women with HNPCC are diagnosed with UCC at a much younger age (48 vs. 63 years), with 57% of cases diagnosed at <50 years and 98% of cases diagnosed at <65 years [128, 129]. The mean age at the diagnosis of UCC is not significantly different for carriers of an *MLH1* or *MSH2* mutation compared to the overall

HNPCC population, although UCC may be diagnosed at an older age in *MSH6* carriers [128]. There is no data to suggest a worse disease-specific prognosis for women with HNPCC-associated UCC compared to those who develop it sporadically [129]. It is uncertain whether cases with elevated levels of MSI (so-called "MSI-high" cases) result in a worse prognosis, as investigations into this issue have reported mixed results [129].

1.7.3 Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder characterized by benign hamartomas and an increased risk for breast, thyroid, endometrial, and other cancers [134]. CS is one of several syndromes associated with *PTEN* mutations, and the presence of UCC was recently added as a major criterion in the revised International Cowden Consortium Diagnostic criteria for CS [135]. Larger case–control studies have reported a 12.5–19% lifetime risk of UCC in CS patients, with a cumulative risk of 1% at age 40, 9% at age 50, and 19% at age 60 [134, 136]. The estimated screening age needed to capture 95% and 100% of UCC cases in this population is 32 and 22 years, respectively [134].

1.7.4 *BRCA1* and *BRCA2* Mutations

Inherited mutations in the *BRCA1* and *BRCA2* genes are widely known to confer a greatly increased risk of breast and ovarian cancer, as well as a smaller, but still significantly increased, risk of several other cancers [31]. Papillary serous carcinoma is the most common histologic subtype of *BRCA* mutation-associated ovarian cancer and UPSC has a known association with breast cancer. Both of these facts have led to speculation that a *BRCA* mutation may increase the risk of developing UCC. Several smaller case reports and retrospective studies have explored these associations with suggestive findings; however, larger retrospective studies have produced conflicting results [33, 137]. One epidemiologic study and two RCSs found no increased incidence of *BRCA* mutations in Ashkenazi Jewish patients with UCC compared to the Ashkenazi Jewish population as a whole, and the authors concluded that UPSC is not a manifestation of any known hereditary breast–ovarian cancer syndrome, that *BRCA* mutations do not predispose to UPSC, and that the observed association between UPSC and breast cancer is likely due to mutations in as-yet-unknown cancer-predisposing genes [9, 31, 33, 138]. Another large RCS (n = 11,847), however, found a significantly elevated risk of UCC in those with a *BRCA1* mutation (RR 2.26) [139]. Two large PCSs have similarly produced conflicting results, with one (n = 857) finding no increased risk of UCC in women who had not previously used tamoxifen, but another (n = 1083) concluding that although the overall risk for UCC was not higher in *BRCA* carriers compared to the general population, the risk for serous/serous-like endometrial carcinoma was increased in those with a *BRCA1* mutation [140, 141]. Further investigation is needed to clarify

this issue, as findings would have relevant clinical implications for both screening and risk-reduction surgery in patients with *BRCA* mutations.

1.8 Fertility-Associated Factors

1.8.1 Nulliparity and Infertility

Parity is protective against UCC, likely due to the effects of progesterone produced to support the pregnancy, and infertile women may be at increased risk for UCC independent of parity, particularly if their infertility is the result of ovulatory dysfunction [142, 143]. PCOS, the most common ovulatory disorder, is accompanied by several risk factors for UCC, such as chronic anovulation, obesity, and hyperinsulinemia, and is discussed in more detail above. A large meta-analysis ($n = 69{,}681$) found an inverse association between parity and UCC risk with a nonlinear dose–response relationship, while an umbrella review of 171 meta-analyses reported a 40% reduction in UCC incidence among parous compared to nulliparous women [143, 144].

Two large studies have shown a reduction in UCC risk with increasing age at last pregnancy; however, the mechanism responsible for this finding remains unclear [143]. A large PCS ($n = 121{,}700$) as well as a pooled analysis of retrospective data ($n = 25{,}233$) found that women who had birthed their last child at age ≥40 years were at a 44–49% decreased risk of developing UCC compared to those who birthed their last child at age ≤29 years [91, 145]. This association was seen in both Type I and Type II carcinomas, and no effect modification was observed from BMI, parity, or exogenous hormone use [145]. The impact of incomplete pregnancy remains unclear. A large PCS ($n = 24{,}848$) found an association between UCC risk and a history of either an induced abortion or a miscarriage late in reproductive life, and the authors hypothesized that the latter scenario may be indicative of progesterone deficiency [92]. A smaller CCS ($n = 1666$), on the other hand, found that both completed and aborted pregnancies were protective against UCC, while another CCS ($n = 702$) concluded that both spontaneous and induced abortions were unrelated to UCC risk [146, 147].

The known protective effect of nulliparity has generated investigations into the impact of infertility treatments on UCC risk, especially since clomiphene citrate, a SERM used for ovulation induction, increases estradiol levels through a mechanism comparable to tamoxifen, which is widely known to increase the risk of UCC [148, 149]. One RCS ($n = 8431$) concluded that ovulation induction with clomiphene citrate increases UCC risk twofold, particularly in larger doses and when given for a longer period of time [148]. Notably, this risk was increased more than threefold in nulligravid women, sixfold in obese women, and more than twelvefold in women who were both nulligravid and obese compared to untreated infertile women [148]. A latency effect was also seen in this study (≥20-years), suggesting that the failure of other studies to find a significant association may be due to shorter follow-up periods [148]. Another large RCS ($n = 20{,}656$) found that UCC

was more common than expected in women with unexplained infertility, irrespective of their *in vitro* fertilization (IVF) status; however, no higher incidence of UCC was seen in women exposed to fertility drugs compared to those unexposed [150]. Currently, the relationship between infertility therapy and UCC risk apart from other accompanying risk factors for infertility (e.g., chronic anovulation and obesity) remains unclear.

1.8.2 Breastfeeding

Breastfeeding has long been suspected to impact the risk of developing UCC due to accompanying hormonal changes, since exclusive breastfeeding suppresses ovulation and thereby decreases maternal estrogen levels [151]. Several epidemiologic studies have investigated this association, however with mixed results [152]. A recent meta-analysis (n = 623,570) concluded that each month of breastfeeding decreases UCC risk by 1.2%, even after controlling for both hormone use and BMI, while another meta-analysis (n = 26,222) reported an 11% UCC risk reduction in those who had ever breastfed, even after controlling for parity, BMI, and tumor histology [151, 152]. Longer durations of breastfeeding decreased the risk of developing UCC in a dose–response relationship, although the effect appeared to level off beyond 6–9 months [151].

1.8.3 Contraceptives

More than 300 million women have used OCPs since their introduction in the 1960s, and an estimated 100–150 million women currently use them worldwide [153, 154]. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (n = 596) was foundational for demonstrating the deleterious effects of unopposed estrogen use on the risk of developing UCC, finding that women assigned to estrogen-only OCPs were more likely than those given placebo to develop simple, complex, or atypical hyperplasia compared to those given a combination of estrogen OCPs and depot progesterone injections [155]. As a result, estrogen-only OCPs are no longer considered the standard of care, and either progestogens only or combined estrogen–progestogen formulations (combined OCPs) are used instead.

Multiple large, high-quality studies from diverse geographical regions have demonstrated that combined OCPs confer long-term protection against UCC [102, 106, 154, 156–160]. One CCS (n = 4077) reported a 30% reduction in UCC risk with ever-use of combined OCPs up to an 80% risk reduction following 10 years of use, and a large PCS (n = 46,022) found that combined OCP use reduced the standardized incidence rate of UCC from 29.56 to 19.42 per 100,000 [154]. A large PCS (n = 17,032) found that combined OCP use reduced UCC risk in a dose-dependent manner (RR per month of use: 0.6 for <48 months, 0.4 for 49–96 months, 0.1 for ≥97 months), with the protective effects seen in as few as 3 years of use and with maximal effects occurring after 6–10 years of use [106, 159, 160]. The protection

conferred by combined OCPs has been found to persist for 20–30 years or more following cessation of use, and multiple studies have found no effect modification from age at menarche, parity, BMI, use of menopausal HRT, menopausal status, race/ethnicity, smoking, or alcohol use [102, 106, 154, 156, 159, 160].

Combined OCPs confer a more modest degree of protection in those diagnosed with UCC at a relatively young age. One CCS (n = 775) found a decreased risk of UCC in patients aged <50 years after 1–5 years of combined OCP use compared to never-users, but concluded that >5 years of use did not further decrease this risk [161]. Several studies have considered the impact of various hormone potencies within OCP formulations on UCC risk reduction. An analysis of several CCSs (n = 2991) found that OCPs with high progestogen potency conferred an additional benefit compared to those with low potency for women with a BMI ≥22.1 kg/m^2, but a similar benefit was not seen in those with a lower BMI [157].

Larger studies have primarily investigated the use of estrogen-only and combined estrogen–progestogen OCPs, with data regarding progestogen-only OCPs or depot medroxyprogesterone either nonexistent or of too small a sample size to generate reliable conclusions [158]. As a result, very little is known about the impact of either oral or injectable progestogen-only contraception on UCC risk [158]. Studies regarding intrauterine devices (IUDs), both nonhormonal and hormone-containing, are sparse as well [158]. One recent meta-analysis reported a crude association between nonhormonal IUD use and decreased UCC risk; however, the included studies showed significant heterogeneity, the mechanism of UCC risk reduction from nonhormonal IUDs remains unclear, and further study is needed [162]. Even less data exists regarding levonorgestrel-releasing intrauterine devices (LNG-IUDs). One RCS (n = 2781) found that patients who had previously used an LNG-IUD had a standardized UCC incidence ratio (observed-to-expected ratio) of 0.50, and concluded that such devices may protect against malignant endometrial transformation; however, further investigation is needed [163].

1.8.4 Tubal Ligation

Bilateral tubal ligation (BTL) is a common method of birth control in the United States and is designed to obliterate communication between the uterine and peritoneal cavities [164, 165]. Since exfoliation through the Fallopian tubes represents a potential method of UCC metastasis, it has been questioned whether BTL impacts either the incidence of UCC or its stage at the diagnosis, especially in the case of Type II carcinomas, which spread in a manner similar to ovarian cancer [164, 165]. The largest RCT to explore this issue (n = 76,483) found no effect of BTL on the risk of developing either a Type I or a Type II carcinoma, suggesting that patients undergoing this procedure likely do not have any associated change in their baseline risk for developing UCC [165]. An analysis of the GOG-210 trial (n = 4489) did find an inverse relationship between BTL and both late-stage disease at presentation and peritoneal metastasis; however, BTL was not associated with any survival advantage after adjusting for stage at the diagnosis [164].

1.9 Other Associated Factors

1.9.1 Diet and Phytoestrogens

UCC risk shows considerable geographical variation; for example, Asian women living in Asia have one-tenth the risk of Caucasian women living in Western countries [166]. Such observations have led several authors to investigate the role that diet, exercise, and various other lifestyle factors play in endometrial carcinogenesis [166]. Consumption of whole grains, fresh fruit, and fresh vegetables has been shown to decrease the risk of UCC, and there is evidence that estrogen metabolism can be influenced by dietary fat intake, although this has never been directly investigated in conjunction with the risk of developing UCC [166]. The impact of a vegetarian or high-fiber diet is more inconsistently reported, with a vegetarian diet associated with lower urinary excretion of estradiol and a high fiber diet associated with lower serum E_2 levels in some studies, but not others [166]. A meta-analysis of retrospective data concluded that consumption of meat (particularly red meat) does increase UCC risk, but it found no association with dairy products, and inconsistent evidence for an association with poultry, fish, and eggs [167].

Other authors have considered the impact of diet on UCC risk from the perspective of glycemic index and total carbohydrate content. Dietary glycemic index (GI) is a measure that classifies carbohydrate quality by its effect on 2-hour postprandial blood glucose, whereas glycemic load (GL) is a concept that accounts for both the GI of a given food as well as its total carbohydrate content; in this way, GL represents a measure of both carbohydrate quality (GI) and total quantity [168]. Although long-term consumption of either a high-GL or a high-GI diet may lead to a state of chronic hyperinsulinemia, which has been implicated in the development of UCC, a recent meta-analysis concluded that a high-GL diet was associated with an increased risk of UCC (RR 1.20), particularly among obese women (RR 1.54), whereas a high-GI diet was not [168].

Phytoestrogens (PEs) are nonsteroidal compounds found in a variety of dietary compounds which are structurally similar to endogenous estrogens, but which show both estrogenic and antiestrogenic properties [169]. Although the precise mechanism of these effects is unknown, PEs have been hypothesized to exert antiestrogenic effects in high-estrogen environments and weakly estrogenic effects in low-estrogen environments [166, 170]. PEs are found in isoflavones (e.g., primarily soy products), coumestans (e.g., alfalfa sprouts, beans), lignans (e.g., flaxseed oil, unrefined grain products), flavonoids (e.g., quercetin, kaempferol), stilbenes (e.g., resveratrol), and mycotoxins (e.g., zearalanol) [170]. Two factors have spurred investigations into the role that PEs may play in endometrial carcinogenesis. First, geographical differences in UCC risk and interest in the so-called Asian diet as an explanation for these disparities have prompted investigations into the effects of tofu and other soy products on estrogen metabolism [166]. Second, the potential effect of PEs at the level of the estrogen receptor as well as their impact on estrogen metabolism have generated interest in their use as "natural" alternatives to estrogen-based HRT in postmenopausal women [170, 171]. This use, however, has generated concern that PEs may confer an increased risk of UCC similar to that seen in the use of unopposed estrogen HRT [169–171].

Thus far, investigations into the impact of PEs on UCC risk have yielded inconsistent and contradictory results, with retrospective studies tending to show a decreased risk of UCC with PE use, but prospective studies showing either no association or suggesting a possible increased risk. One CCS (n = 843) found that a higher consumption of tofu and other legumes decreased the risk of UCC by about half for the highest quartile of consumption compared to the lowest, and found similar risk reductions with increased consumption of other sources of PEs such as whole grains, fruits, vegetables, and seaweeds [172]. These effects were, however, limited to nulliparous women and to those without a history of using unopposed estrogen [172]. Another CCS (n = 970) similarly found that consumption of isoflavones and lignans was inversely associated with UCC risk [173]. Among prospective studies, one PCS (n = 46,027) found that total isoflavone intake was associated with a reduced risk of UCC in postmenopausal women; however, no significant association was found with increased consumption of legumes, soy, or tofu [174]. By contrast, an RCT (n = 376) found that long-term treatment (up to 5 years) with PEs in postmenopausal women was associated with an increased occurrence of endometrial hyperplasia, and although no cases of malignancy were detected, suggestion of a plausible mechanism for endometrial carcinogenesis as a result of PE use was concerning [169]. Several factors may explain these contradictory findings: residual confounding may be present due to the large variation in soy and isoflavone intake across racial/ethnic groups; increased PE consumption may be confounded by an overall increased health consciousness in these consumers; and reduction of UCC risk due to some PE-containing products may be mediated by a non-estrogenic mechanism, for example, via an antioxidant or anti-angiogenic mechanism [170, 174].

1.9.2 Ultraviolet Radiation, Calcium, and Vitamin D

Ecological studies have shown an inverse association between ultraviolet (UV) radiation and UCC risk, which has in turn led some authors to explore possible correlations with vitamin D and calcium as well [175]. Consumption of both vitamin D and calcium are highly correlated in the diet, both are metabolically interrelated, both have antiproliferative and pro-differentiation effects *in vitro*, and thus both may work synergistically to reduce cancer risk [176]. A pooled analysis of three CCSs (n = 2134) found no association between dietary vitamin D intake and UCC risk, and a possible inverse association with dietary calcium intake [176]. Ecological studies have important limitations which mitigate their ability to draw causal inferences (e.g., UV exposure may be a proxy for physical activity), and prospective studies are needed to further characterize the relationship between UCC risk and UV radiation, vitamin D intake, and calcium intake [176].

1.9.3 Exercise

Because UCC predominates in affluent, more industrialized nations with higher levels of obesity and more sedentary lifestyles, several authors have investigated

potential associations between exercise, inactivity, a sedentary lifestyle, and UCC risk. A meta-analysis of prospective data found that physical activity was associated with a 30% reduction in UCC risk, while greater sitting time was associated with an increased risk [177]. Another meta-analysis of both prospective and retrospective data similarly found that all intensities of exercise conferred a significant reduction in UCC risk; however, this effect was only seen in obese women [178]. Furthermore, a large PCS ($n = 24,460$) found that inactivity and high energy intake are risk factors for UCC, independent of BMI [179]. Risk declined with recreational activity corresponding to a minimum of four hours per week as well as with increased occupational activity, and women ≥50 years were seen to benefit the most from having an active lifestyle [179].

1.9.4 Diabetes and Hypertension

Diabetes mellitus (DM) strongly correlates with an increased risk of UCC, and although its impact is complicated by obesity, a common comorbidity of Type 2 DM, excess body weight alone cannot fully explain this association [180, 181]. Rather, it is likely that other metabolic characteristics of DM such as hyperinsulinemia and insulin resistance contribute to endometrial carcinogenesis independent of BMI [182, 183]. Insulin receptors have been discovered on each type of endometrial cancer cell *in vitro*, including ER-negative cell lines, and insulin has been subsequently postulated to increase endometrial proliferation by acting as a mitogen and augmenting the effects of insulin-like growth factors [166, 184]. Two large studies, one a meta-analysis ($n = 96,003$) and the other a PCS ($n = 36,761$), each concluded that diabetics were at a two- to threefold increased risk of developing UCC compared to nondiabetics [180, 181]. Although many studies have focused on an association between UCC risk and Type 2 DM, three studies have examined Type I DM and have found a significant positive association in these cases as well [180].

The impact of DM seems to be magnified by several of its common comorbidities. One PCS ($n = 36,773$) demonstrated a sixfold increased risk of UCC among diabetics with concurrent obesity, and a ninefold increased risk in those with both obesity and a low level of physical activity [185]. Furthermore, uncontrolled diabetics have a significantly higher risk of developing UCC than those who are well-controlled [186]. One CCS ($n = 2663$) that examined common comorbidities of insulin resistance that collectively comprise the metabolic syndrome concluded that overweight/obesity, hypertension, DM, and glucose metabolic disturbance were all associated with an increased risk of UCC [186]. Hypertension in particular was associated with a sixfold increased risk, and this risk was nearly doubled when coupled with overweight/obesity [186]. A number of smaller CCSs have similarly established an association between hypertension and UCC, even after controlling for elevated BMI [187]. DM has been shown to impact survival in UCC patients, with one RCS ($n = 1411$) reporting a worse disease-free survival (DFS) and OS in diabetics with Type I carcinomas, but finding no impact on survival in those with either Type II carcinomas or high-grade lesions [12].

1.9.5 Cigarette Smoking

Cigarette smoking is thought to exert an antiestrogenic effect by either producing weight loss, inducing menopause at an earlier age, or via alterations in hormone metabolism [188]. A recent meta-analysis of both prospective and retrospective data found that ever-smoking was associated with a reduced risk of UCC, while a PCS (n = 62,573) concluded that this risk reduction was independent of either BMI or age at menopause [188, 189]. In particular, smoking 20 cigarettes per day was associated with a 16% risk reduction in prospective studies and a 27% risk reduction in case–control studies [188]. This risk reduction was significant in postmenopausal, but not premenopausal women, and was stronger among HRT users than in nonusers [188].

1.9.6 Alcohol

There is inconsistent evidence for an association between alcohol intake and UCC risk. A recent meta-analysis of both prospective and retrospective data found no significant association overall; however, stratified analyses revealed a slightly increased risk with liquor consumption, which was not replicated for beer or wine [190]. One PCS (n = 46,933) found that postmenopausal women who consumed ≥2 drinks per day had a twofold increased risk of UCC compared to both nondrinkers and women who drank <2 drinks per day, with both of the latter groups having essentially no increased risk [85]. However, another PCS (n = 62,573) found no association between alcohol consumption and UCC risk, including no dose-dependent trends or associations with types of beverages [189].

1.9.7 Coffee and Tea

Coffee and tea are the most widely consumed beverages in the world, both containing many antioxidant compounds, and the intake of caffeine-containing beverages has been previously associated with increased levels of SHBG and decreased levels of bioavailable testosterone [191, 192]. These considerations have led several investigators to explore a potential association between caffeine-containing drinks and UCC risk. Meta-analyses of retrospective data have shown some protective effects; however, prospective studies have found weak, if any, associations between caffeine intake and UCC risk [193, 194]. Two large PCSs have been conducted regarding coffee and tea consumption. The first (n = 67,470) found that drinking <4 cups of coffee per day was not associated with a reduced UCC risk; however, consumption of ≥4 cups per day was associated with a 25% risk reduction compared to those who consumed <1 cup per day [195]. Tea consumption was not associated with UCC risk; however, this study was conducted in the United States, where black tea is consumed much more heavily than green tea [195]. The second PCS (n = 560,356) found no significant association between UCC risk and consumption of either coffee or tea [194].

1.9.8 Aspirin

Chronic inflammation resulting from obesity may work either in conjunction with, or in addition to, hormonal imbalances to produce UCC, and some authors have suggested that exposure of the endometrium to chronic inflammation is in fact one of the primary pathogenic implications of a hyperestrogenic state [79]. Chronic inflammation mediates carcinogenesis by stimulating the release of proinflammatory cytokines, enhancing angiogenesis, suppressing the immune system, and generating reactive oxygen species, which damage DNA [196]. An inflammatory state may also directly increase estrogen production and induce rapid cell division, thus increasing the probability of replication errors, ineffective DNA repair, and resulting mutations [79].

This hypothesis as well as previous studies showing a reduced risk of several cancers with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has led to the identification of aspirin and other NSAIDs as potential therapeutic agents for the prevention of either primary or recurrent UCC [196]. One CCS (n = 2138) found that ever-use of aspirin in the previous 5 years was associated with a significantly lower UCC risk (OR 0.78) compared to controls, while the use of ≥2 aspirin per week reduced this risk by almost half (OR 0.54) [197]. Upon meta-analysis, risk reduction from aspirin use was only seen in obese women, and no risk reduction was seen with use of either acetaminophen or any other NSAID [197]. Other studies have demonstrated a potential role for low-dose aspirin in the prevention of recurrent UCC following primary therapy and staging [196]. One RCS (n = 1687) found that low-dose aspirin was associated with improved OS and DSS in UCC patients following primary therapy, with the greatest effects seen in those <60 years, those with a BMI >30 kg/m^2, those with Type I carcinoma, and in those who had received whole pelvic radiotherapy [196]. Additional high-quality, prospective studies are needed, however, before aspirin can be safely recommended as a therapeutic agent in the treatment of UCC.

1.10 Summary

UCC remains a significant source of morbidity and mortality worldwide, and its impact is especially pronounced in Western and more industrialized nations. It also represents a locus of significant health disparities, especially among blacks in the United States, who are more likely than whites to present with aggressive histologic subtypes and late-stage disease, and who experience increased overall mortality and worse disease-related outcomes. Epidemiologic research is increasingly shifting its focus towards the Hispanic population, as this cohort now represents the largest minority racial/ethnic group in the United States. Recent studies reveal that Hispanics are diagnosed at a younger age than whites, and are more likely to present with late-stage disease; however, they do not appear to experience a worse prognosis as a result of these tendencies. Advances in technology have allowed for more precise characterization of UCC subtypes on the genomic level, increasing

knowledge of pathologic mechanisms of tumorigenesis, improving the current understanding of health disparities among racial/ethnic groups, and suggesting potential avenues for the development of novel therapeutic agents.

The increased incidence of UCC in Western and more industrialized nations has led to several avenues of investigation, which may be broadly summarized as those exploring dietary and environmental differences between cultures and those considering differences in common medical comorbidities. With rare exception, traditional advice regarding a healthy diet and lifestyle (e.g., eating a diet high in fruits and vegetables, remaining active and exercising regularly, and maintaining a healthy BMI) appears to be efficacious in reducing UCC risk; however, protective environmental factors remain elusive. The use of estrogen without an accompanying progestogen, either for contraception or hormone replacement, has been shown to greatly increase UCC risk, whereas combined OCPs confer protection that lasts decades following cessation of use. As both hormonal and nonhormonal implantable contraceptive devices become increasingly common within the United States, high-quality studies are needed to confirm their hypothesized protective effects against UCC.

Clinicians should remain vigilant in counseling those at increased risk for UCC, including tamoxifen users, patients with PCOS, and those with hereditary cancer syndromes such as HNPCC, especially since more than half of those affected by this syndrome present with a gynecologic malignancy first. Further investigation is needed into the impact of breast–ovarian cancer syndromes on UCC risk; however, there is currently no clear evidence of an increased risk of UCC in those with a *BRCA* mutation. The proposal of an inflammatory mechanism in UCC tumorigenesis is intriguing, and may portend a future role for aspirin in either the primary or secondary prevention of UCC; however, further studies are needed to confirm the efficacy of aspirin for this use, and to weigh potential adverse effects against possible benefits.

Key Points

- Uterine corpus cancer (UCC) is the 6th most common cancer worldwide and the 14th most deadly, responsible for an estimated 319,600 new cases and 76,200 deaths per year.
- The average age of UCC diagnosis is 62 years, with 61% of cases occurring in women aged 55–74 years.
- Type I carcinomas account for 80–90% of UCC cases and arise in the setting of chronic estrogen exposure, whereas Type II carcinomas are rarer, have a higher median age of occurrence, and are less influenced by estrogen.
- Blacks are more likely than whites to develop Type II carcinomas, and they experience worse outcomes than other racial/ethnic cohorts in the United States at every stage of disease for unclear reasons.
- Hispanics present with UCC at a younger age than non-Hispanic whites and are more likely to present with late-stage disease, but they do not appear to experience worse outcomes as a result.
- Polycystic ovary syndrome significantly increases the risk of developing UCC, especially in younger patients.

- The use of estrogen unopposed by a progestogen greatly increases UCC risk, as does tamoxifen use; neither raloxifene nor commonly used aromatase inhibitors appear to increase this risk.
- Patients with the hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) may have a higher lifetime risk of developing UCC than colorectal cancer, and often present with UCC first.
- Parity, breastfeeding, and the use of combined oral contraceptives (OCPs) all confer protection against UCC; however, the impact of intrauterine devices and progestogen-only OCPs remains unknown.
- Type 2 diabetes mellitus increases UCC risk two- to threefold, and its effects are magnified by obesity, hypertension, physical inactivity, and poor disease control.

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All of the authors have diligently contributed to the conception, development, and preparation of this manuscript, including the literature search, concept organization, and data interpretation. All of the authors have read and approved the final draft for publication.

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