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Factors associated with Type I and Type II endometrial cancer

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Abstract

Objective—We investigated risk factors for Type II ($n = 176$) vs. Type I ($n = 1,576$) endometrial cancer (EC) in cases treated at Magee-Womens Hospital between 1996 and 2008.

Methods—Clinical data were available from the University of Pittsburgh Medical Center (UPMC) Network Cancer Registry. Logistic regression was used to estimate the adjusted odds of having Type II EC vs. Type I EC. Risk factors of interest in this analysis were age, race, body mass index (BMI), year of diagnosis, parity, menopausal status, and history of additional primary tumors.

Results—Relative to women with Type I EC, women with Type II EC were more likely to be older at diagnosis (OR: 1.03 per 1 year increase in age, 95% CI 1.01–1.05), of non-white race (OR: 2.95, 95% CI 1.66–5.27), have a history of additional primary tumors (OR: 1.56, 95% CI 1.05–2.32), and less likely to be obese (OR: 0.45, 95% CI 0.29–0.70).

Conclusion—In this large retrospective cohort of patients with EC, the striking difference in risk factors associated with Type II vs. Type I tumors suggests that these subtypes represent different disease entities that require different treatment modalities. Currently, Type II cases have a significantly worse prognosis compared to Type I. Further characterization of risk factors associated with developing Type II tumors is needed to prevent this aggressive malignancy.

Keywords

Endometrial cancer; Epidemiology; Type I; Type II

Introduction

Endometrial cancer (EC) is a common malignancy in the United States and around the world. The incidence of EC exceeds the incidence of cervical, ovarian, vaginal, and vulvar cancers combined [1]. Despite being a common cancer, the mortality rates from this disease (4.1 deaths per 100,000 women) are relatively low, which is mainly attributed to early detection. Between 75 and 80% of cases are diagnosed with tumors confined to the uterus (stage 1), which are effectively treated with hysterectomy [2]. Since the 1960s, EC-related mortality has declined significantly, although recent data suggest that the number of EC deaths may be on the rise [3–6].

Prior to the 1980s, EC was broadly characterized as a single disease. However, observations by Lauchlan, Hendrickson et al. [7–9] and Bokhman led to the description of two distinct types based on histologic and molecular characteristics. Type I EC, commonly referred to as the endometrioid type, comprises 80–90% of all sporadic endometrial cancers [10]. Histologically, these tumors can be adenocarcinoma with or without squamous differentiation and often are well differentiated [11]. Furthermore, epidemiological evidence suggests that the multistep carcinogenic process of Type I endometrial tumors begins with simple endometrial hyperplasia, progresses to complex atypia hyperplasia, and then develops into the precursor lesion, endometrial intraepithelial neoplasia (EIN) [12–14]. Type II EC, or nonendometrioid tumors, encompasses the remaining 10–20% of sporadic endometrial tumors [10]. The two histologies of this subtype are uterine papillary serous carcinoma (UPSC) and clear-cell carcinoma. Both cancers appear to progress from an atrophic endometrium to the precursor lesion, endometrial glandular dysplasia (EmGD) [15–17].

In addition to differences in histology, the etiology and survival related to these two subtypes are vastly different. Type I tumors are the prototypical estrogen-dependent tumors; risk factors that increase women's exposure to circulating levels of estrogen are associated with increased risk of Type I EC. Similarly, factors that decrease progesterone are associated with increased risk of Type I EC. Traditionally cited risk factors for Type I EC are obesity, estrogen replacement therapy (ERT), nulliparity, and medical conditions that result in high estrogen levels, such as estrogen-secreting ovarian tumors and polycystic ovarian syndrome. In addition, Type I tumors are more common than Type II tumors in pre- and perimenopausal women [10].

The epidemiology and biology of Type II tumors are not well characterized, although a few studies report that Type II cases are more likely to be older, of normal weight, multiparous, and African American compared to Type I cases [18–25]. The tumorigenesis of Type II EC is not thought to operate through the estrogen pathway, as normal-weight and parous women

have decreased estrogen exposure compared to obese and nulliparous women. Low incidence of Type II tumors makes this subtype difficult to study.

While the incidence of Type II tumors is low compared to Type I, excess mortality is associated with Type II EC. In an analysis of Surveillance, Epidemiology and End Results (SEER) data, Hamilton et al. [20] reported that while 11% of ECs were Type II, 47% of deaths in the SEER cohort occurred in this subtype. Furthermore, stage-adjusted 5-year overall survival rates for Type II tumors are significantly worse compared to Type I tumors [25]. Understanding the etiology of this rare, under-investigated, and deadly malignancy is important for the primary prevention of these cancers, early detection, and monitoring for relapse. Therefore, the primary goal of the present study is to compare the characteristics of Type I and Type II EC cases treated at Magee-Womens Hospital between 1996 and 2008.

Materials and methods

Data collection

All data for this study were retrieved from the University of Pittsburgh Medical Center (UPMC) Registry Information Services (RIS), a division within the UPMC Network Cancer Registry [26]. The UPMC Network Cancer Registry collects demographic, medical history, diagnostic findings, primary cancer identification, stage, grade, treatment and outcomes information on patients from all UPMC-managed facilities. Certified cancer registrars abstract data from both the paper and electronic medical records into the Cancer Registry database, which is then queried by an RIS research specialist. This study includes cases with an International Classification of Diseases for Oncology (ICD-O 3rd Edition) primary site code between C54.0 and C54.9 and C55.9 who were treated at Magee-Womens Hospital between 1996 and 2008. The coding scheme of this data system has varied over time, and current standardized coding protocols were first used in 1996 [27]. Specific data elements include age at diagnosis, year of diagnosis, height, weight, race, history of additional primary cancer, number of live births (parity), menopausal status, age at menopause, and tumor histology.

Case ascertainment

ECs treated between 1996 and 2008 were identified by the RIS research specialist. Histology subtype (Type I and Type II) was assigned by a trained gynecologic pathologist (MC) based on expertise and previously published literature [9,28]. Type I EC histologies included adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation (ICD-O-3 morphology codes: 8140, 8380, 8382, 8480, 8482, 8560, and 8570). Type II EC histologies included clear-cell carcinomas and papillary serous carcinomas (ICD-O-3 morphology codes: 8310, 8441, and 8460). Slides for nine patients with papillary adenocarcinoma (ICD-O-3 code: 8260) were reviewed by the pathologist and confirmed to be papillary serous carcinoma.

Statistical analysis

Unconditional logistic regression was used to estimate the crude and adjusted odds ratios (ORs) of having Type II versus Type I EC. The factors of interest in this study were categorized as shown in Table 1: race was classified as white or non-white due to the low number of African American, Asian, and other races. Year of diagnosis was coded as 12 indicator variables. BMI was calculated from weight and height as $(\text{weight in pounds} \times 703)/(\text{height in inches})^2$ [29]. BMI was analyzed both as a continuous variable (kg/m^2) and a categorical variable (i.e., underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), and obese ($>30 \text{ kg/m}^2$)) using definitions from the Centers for Disease Control and Prevention [29]. We also incorporated an unknown category when height or weight was missing ($n = 142$, 8.1%). The categorical BMI variable was used in the univariate and multivariable models.

Parity was categorized as no live births, 1 live birth, 2 live births, 3 or more live births, and unknown. History of additional primary cancers and postmenopausal status were coded as no, yes, or unknown. Age at diagnosis and age at menopause were treated as continuous variables.

Variable selection for the multivariable logistic regression model was based on the association between each potential factor and the probability of having Type II EC rather than Type I EC using the likelihood ratio test p -value from the univariate logistic regression models. A broad significance level of $p < 0.10$ in the univariate models was used as the criterion for entry into the multivariable model. Pairwise multiplicative interactions between each of the covariates were added to the model one at a time and tested with likelihood ratio tests. Interactions between the covariates were tested using a two-sided alpha of 0.05. The Hosmer and Lemeshow goodness of fit test was performed to assess lack of fit of the final model. This study was approved by the University of Pittsburgh Institutional Review Board.

Results

Between 1996 and 2008, 1,964 patients with EC were diagnosed at Magee-Womens Hospital. Of these, the 1,752 cases with either Type I or Type II EC were included in the present report. Based on the pathology report, Type I tumors accounted for 90% of cases in the study group.

Table 1 compares the frequency of potential risk factors between the tumor types. Approximately 11% of Type II cases were non-white compared to 4% of Type I cases. Year of diagnosis was not significantly different between the two tumor types. A large proportion of all cases were overweight or obese; however, 36% of Type II cases were obese compared to 55% of Type I cases. Forty-five percent of Type II cases had three or more live births compared to 32% of Type I cases. Type II cases were also more likely to have a history of additional primary cancers compared to Type I cases (23.9 vs. 14.2%). Breast cancer ($n = 125$, 47%), ovarian cancer ($n = 32$, 12%), and colorectal cancer ($n = 26$, 10%) were the three most common additional malignancies. Breast and colorectal cancers were more common among the Type II cases, while ovarian cancer was more common among the Type I cases. Menopausal status was also significantly related to tumor type; 86% of Type II cases were postmenopausal compared to 76% of Type I cases. Finally, Type II cases were significantly older than Type I cases (median age: 68 years vs. 60 years).

In the univariate analyses, race, BMI, parity, history of additional primary cancers, menopausal status, and age at diagnosis were significantly associated with type of EC (Table 2). Although year of diagnosis was not significantly associated with tumor type, this variable was retained for adjustment purposes. In the adjusted models, increasing age ($p < 0.001$), non-white race ($p < 0.001$), and history of additional primary cancers ($p = 0.03$) were significantly associated with increased odds of having Type II EC, while obesity was inversely associated with the odds of Type II EC ($p < 0.001$). The Hosmer and Lemeshow goodness of fit test indicated no lack of fit of this model ($\chi^2 = 6.35$, $p = 0.61$). None of the interactions considered were statistically significant.

Discussion

This registry-based study examines the relationship between pretreatment characteristics in Type I and Type II ECs in a large group of patients diagnosed between 1996 and 2008. Factors significantly associated with Type II EC vs. Type I EC were older age, non-white race, lower BMI, and history of additional primary cancers, all of which have been identified in the published literature. Soslow [30], Hamilton [20], and Cirisano [21] have reported that Type II cases are older than their Type I counterparts, although the age differential is most pronounced for uterine papillary serous carcinomas (UPSC) compared to endometrioid tumors.

Furthermore, African Americans make up a disproportionate number of Type II tumors in many case series, with the widest differential being between the UPSC and the endometrioid cases. In the Cirisano study, 34% of UPSC's were African American compared to 15% of cases with endometrioid tumors ($p < 0.0001$); in the Hamilton case series, 15% of cases with UPSC tumors were African American, while 7% of cases with grade 3 endometrioid tumors were African American ($p < 0.0001$) [20,21]. Our study is not directly comparable to the previously mentioned studies, as we grouped all non-white cases together.

To date, obesity is the strongest risk factor for the development of EC, with the underlying mechanism being increased estrogen exposure [15]. Consequently, the link between obesity and endometrial cancer is stronger for cases with Type I tumors, the prototypical estrogen-dependent tumor. In the present study, compared to normal-weight cases, obese cases had an OR of 2.22 of having Type I EC rather than Type II EC. Although this finding is consistent with the estrogen hypothesis, two prospective studies have reported that increasing BMI also is a risk factor for the development of Type II EC. In the 1 million Norwegian women study, Bjorge et al. [31] reported that overweight and obese women were 1.26 and 1.94 times more likely, respectively, to develop Type II cancer compared to normal-weight women over a 25-year follow-up. Likewise, McCullough et al. reported that a BMI of 30 kg/m² or greater was significantly associated with developing Type II tumors (RR: 2.87, 95% CI 1.59–5.16). Importantly, both studies combined grade 3 endometrioid tumors with UPSC and clear-cell tumors in their analyses, which may explain the association between obesity and Type II tumors in these studies. Furthermore, both studies compared cancer cases to healthy controls. BMI may have an important role in the development of all ECs; however, the effect appears to be stronger for Type I cancers compared to Type II cancers.

In this study, Type II cases had an OR of 1.56 of having a history of an additional primary cancer compared to Type I cases ($p = 0.03$). The most common additional primary cancer in this cohort was breast cancer. Of the Type II cases with an additional primary, 59.5% had breast cancer, compared to 44.6% for the Type I cases ($p = 0.07$). Several hypotheses for an association between Type II EC and additional cancer primaries exist. First, these cancers may share similar risk factor profiles. Second, radiation treatment for proximate cancers may increase the incidence of radiation-induced ECs or vice versa. Third, the presence of multiple cancers may be a manifestation of inherited cancer syndromes, such as hereditary nonpolyposis colorectal cancer syndrome; however, these genetic disorders are relatively rare in the population. Finally, multiple cancer primaries may be a result of mutations in unidentified cancer-predisposing genes [24].

Potential limitations of this study include patient selection and misclassification biases. Although all cases in this study received their first course of treatment at Magee-Womens Hospital, not all cases were diagnosed at this facility. Forty-five percent of the cases in this study came to Magee-Womens Hospital after being diagnosed elsewhere; these patients could be significantly different from the patients who were diagnosed and treated at Magee-Womens Hospital. The referred cases may be more advanced or suffer from multiple comorbidities that require specialty care at a large academic hospital such as Magee-Womens Hospital. Second, our use of registry data obtained through data abstraction from medical records allows for potential data entry errors. The UPMC Cancer RIS performs rigorous quality control on certain data elements, which enhances their reliability; we focused only on those variables in our analyses. As the UPMC Network Cancer Registry is the official source of cancer statistics for the Pennsylvania Department of Health and maintains a reputation of high quality, misclassification bias is not a major concern.

The major strengths of this study include a large cohort of patients, reliable data, and central pathology review at a single institution. Overall, this study included 1,752 patients with EC,

including 176 Type II cases. Compared to other single-institution studies of EC, our study included a substantial number of Type II cases. In other case series, the number of Type II cases has ranged between 32 and 87, excluding a study which examined patients from the population-based SEER registry [22,30,32,33]. Furthermore, we only included cases that were treated at Magee-Womens Hospital instead of including the entire pool of EC cases available from the UPMC Network Cancer Registry. The fact that all cases were centrally reviewed by gynecologic pathologists at Magee-Womens Hospital increases confidence in the validity of the tumor type definitions.

The etiology of Type II tumors remains elusive. The findings from this study verify previously published reports. In our study, BMI was inversely associated with having Type II EC, which suggests that this carcinogenic pathway is not driven by excess estrogen exposure. Importantly, a large proportion of Type II cases in this study were overweight or obese (27.3 and 36.4%, respectively). Finally, this study adds to the growing body of literature related to an association between multiple primary cancers and Type II EC. Future studies on the etiology of the rare yet aggressive Type II subtype should examine risk factors that are not related to estrogen exposure, in order to identify novel mechanisms of endometrial carcinogenesis.

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Table 1Patient demographic and epidemiologic characteristics by tumor type ($n = 1,752$)

	Type I EC ($n = 1,576$) n (%)	Type II EC ($n = 176$) n (%)	p -value ^a
Race			
White	1,511 (95.9)	157 (89.2)	<0.001
Non-white	65 (4.1)	19 (10.8)	
Year of diagnosis			
1996	108 (6.9)	15 (8.5)	0.16
1997	83 (5.3)	18 (10.2)	
1998	133 (8.4)	12 (6.8)	
1999	110 (7.0)	8 (4.5)	
2000	125 (7.9)	11 (6.2)	
2001	104 (6.6)	10 (5.7)	
2002	91 (5.8)	16 (9.1)	
2003	115 (7.3)	9 (5.1)	
2004	122 (7.7)	8 (4.5)	
2005	117 (7.4)	16 (9.1)	
2006	151 (9.6)	14 (7.9)	
2007	162 (10.3)	20 (11.4)	
2008	155 (9.8)	19 (10.8)	
Body mass index			
Underweight (<18.5 kg/m ²)	12 (0.8)	7 (4.0)	<0.001
Normal (18.5–24.9 kg/m ²)	238 (15.1)	44 (25.0)	
Overweight (25–<29.9 kg/m ²)	326 (20.7)	48 (27.3)	
Obese (>30 kg/m ²)	871 (55.3)	64 (36.4)	
Unknown	129 (8.2)	13 (7.4)	
Parity (# of live births)			
0	384 (24.4)	31 (17.6)	0.002
1	230 (14.6)	14 (7.9)	
2	413 (26.2)	45 (25.6)	
3+	511 (32.4)	80 (45.4)	
Unknown	38 (2.4)	6 (3.4)	
History of additional primary cancer			
No	1,328 (84.3)	131 (74.4)	0.006
Yes	224 (14.2)	42 (23.9)	
Breast cancer	100 (6.3)	25 (14.2)	
Ovarian cancer	30 (1.9)	2 (1.1)	
Colorectal cancer	20 (1.3)	6 (3.4)	
Other cancers	74 (4.7)	9 (5.1)	
Unknown	24 (1.5)	2 (1.7)	
Menopausal status			

	Type I EC (<i>n</i> = 1,576) <i>n</i> (%)	Type II EC (<i>n</i> = 176) <i>n</i> (%)	<i>p</i> -value ^a
Premenopausal	289 (18.3)	15 (8.5)	0.002
Postmenopausal	1,191 (75.6)	151 (85.8)	
Unknown	96 (6.1)	10 (5.7)	
	Median ± IQR	Median ± IQR	
Age at diagnosis	60.0 ± 17.0	68.0 ± 15.5	<0.001
Age at menopause	50.0 ± 5.0	50.0 ± 4.5	0.90

^a Likelihood ratio *p*-value

Table 2

Multivariable logistic regression model to predict Type II endometrial cancer ($n = 176$) vs. Type I endometrial cancer ($n = 1,576$)

Variable	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ^a	Likelihood ratio p -value ^b
Race			
Non-white	2.81 (1.65, 4.81)	2.95 (1.66, 5.27)	<0.001
Body mass index			
Underweight (<18.5 kg/m ²)	3.16 (1.18, 8.46)	2.59 (0.90, 7.45)	<0.001
Overweight (>25 kg/m ² and <29.9 kg/m ²)	0.80 (0.51, 1.24)	0.82 (0.52, 1.29)	
Obese (>30 kg/m ²)	0.40 (0.26, 0.60)	0.45 (0.29, 0.70)	
Unknown	0.54 (0.28, 1.04)	0.48 (0.23, 0.99)	
History of additional primaries			
Yes	3.16 (1.18, 8.46)	1.56 (1.05, 2.32)	0.09
Unknown	0.80 (0.51, 1.24)	1.30 (0.34, 4.94)	
Age at diagnosis ^c	0.40 (0.26, 0.60)	1.03 (1.01, 1.05)	<0.001

Reference groups: white race, normal weight, no history of additional primaries, nulliparous, and premenopausal

^a Adjusted for year of diagnosis, race, BMI, history of additional primaries, age at diagnosis, parity, and menopausal status

^b From the adjusted model

^c Centered at 62 years