Ten-Year Comparison Study of Type 1 and 2 Endometrial Cancers: Risk Factors and Outcomes

Jacqueline Feinberg^a Benjamin Albright^b Jonathan Black^a Lingeng Lu^a
Rachel Passarelli^a Stefan Gysler^a Margaret Whicker^a Gary Altwerger^a
Gulden Menderes^a Pei Hui^a Alessandro D. Santin^a Masoud Azodi^a
Dan-Arin Silasi^a Elena S. Ratner^a Babak Litkouhi^a Peter E. Schwartz^a

^aYale University School of Medicine, New Haven, CT, USA; ^bHospital of the University of Pennsylvania, Philadelphia, PA, USA

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Abstract

Aims: To compare baseline risk factors for type 1 vs. 2 endometrial cancers and analyze these risk factors for association with overall survival and time to recurrence. **Methods:** Retrospective review of 816 consecutive endometrial cancer cases was conducted with diagnosis from January 2005 to December 2010 and clinical course until 2016. Risk factors, treatment, recurrence, and death were compared using 2 sample *t* tests, χ^2 test and Cox Regression models. **Results:** There were 550 cases of type 1 and 266 cases of type 2 cancer. Patients with type 2 disease were older ($p < 0.001$), less obese ($p = 0.03$), non-white ($p < 0.001$), and menopausal ($p = 0.02$). There was no difference in use of oral contraceptives, hormone replacement therapy (HRT), smoking, or major cardiovascular disease. Cox Regression models showed that type 2 disease ($p < 0.001$) and advanced stage ($p = 0.001$) were associated with recurrence. **Conclusions:** Consistent with previous literature, our analysis found that type 2 cancer is more common in non-white, older, and less obese pa-

tients and associated with higher mortality and recurrence. However, inconsistent with previous literature, we found no association between type 2 cancer and diabetes mellitus or use of HRT. These factors should be considered when approaching patients with endometrial cancer.

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Introduction

Endometrial cancer is the most common gynecologic malignancy in both the United States and in other developed countries. It accounts for 6% of malignancies in women worldwide. In the United States in 2017, it is estimated that 61,380 women will be diagnosed with endometrial cancer and 10,920 women will die from the disease [1]. Different histologic subtypes have been used to help describe differences in prognosis of this disease.

Since its inception by Bokhman [2], the classification of type 1 and 2 endometrial cancer has been used to describe risk factors and disease prognosis. Multiple studies have sought to describe the clinical features of these disease types [3–5]. Type 1 endometrial cancer accounts for

65–70% of all cases and includes tumors with International Federation of Gynecologists and Obstetricians (FIGO) grade 1 and 2 endometrioid histology. It is associated with the retention of estrogen receptor and progesterone receptor status and unopposed estrogen exposure. It is often preceded by endometrial intraepithelial neoplasia, is associated with younger age of onset than type 2 cancers, and with deletions in k-Ras, PTEN, or mismatch repair mechanisms [6–8].

Type 2 endometrial cancer includes FIGO grade 3 endometrioid, serous, or clear cell histology. It is associated with black race, absence of unopposed estrogen or loss of estrogen receptor/progesterone receptor status, presentation at later stages, reduced E-cadherin expression, aneuploidy, and mutations or overexpression of HER2/Neu and p53 [9–13]. Type 2 endometrial cancer is typically more aggressive than type 1 cancer and has a poorer prognosis.

Previous studies have separately looked at specific risk factors for type 1 vs. 2 endometrial cancers, but few have followed these cases longitudinally for clinical course and disease outcomes [4, 5, 14]. In this study, we compare baseline risk factors for all endometrial cancer and then analyze these risk factors for association with overall survival and time to recurrence for type 1 and 2 endometrial cancers.

Methods

Study Design

A retrospective cohort study was performed using consecutive patients with the pathologic diagnosis of an endometrial cancer from January 1, 2005, to December 31, 2010, in the Yale New Haven Health system (including Yale New Haven Hospital and Bridgeport Hospital). Diagnosis of pathologic subtype of endometrial cancer was by trained gynecologic pathologists, and cases were reviewed at a multidisciplinary tumor board. Cases were followed for outcomes until June 1, 2016.

Data Collection

Data were manually extracted from electronic health records. Baseline characteristics, treatment, and clinical course were collected. Dates of death were confirmed with publically available obituary data, or when unavailable but patient death is reported, date of last contact. For patients lost to follow up, the date of last contact was used for the date of censor. Data extraction was performed in parallel by 4 researchers in a standardized fashion using a single data entry form. Institutional Review Board approval was obtained before starting the study.

Statistical Analysis

Baseline characteristics of patients with type 1 and 2 endometrial carcinoma were compared using student's t-test for continu-

ous variables and χ^2 test for dichotomous and categorical variables.

Both time to progression and overall survival were analyzed for hazard ratios (HRs) using Cox regression analysis. For each of the end points, adjusted HRs were also performed to control for risk factors including stage, pathologic characteristics, age, and race. For time to progression analysis, end point was defined as disease recurrence or progression, and patients were suppressed at date of loss to follow-up or death. For overall survival, end point was defined as death by any cause.

Kaplan-Meier plots were constructed to compare time to progression and overall mortality by type 1 vs. 2 endometrial carcinoma. All analyses were performed using Stata 13.1 (Stata Corporation, College Station, TX, USA).

Results

There were 1,022 consecutive cases of uterine cancer diagnosed from January 1, 2005, to December 31, 2010, identified in our tumor registry. Of those cases, 816 were included. Endometrioid-type FIGO grade 1 and 2 cancers were classified as type 1 (550, 67.4%), and endometrioid-type FIGO grade 3 and non-endometrioid were classified as type 2 cancers (266, 32.6%).

Baseline demographic data are available in Table 1. Notably, type 2 tumors were more likely to be diagnosed at an older age (65.6 vs. 62.2, $p < 0.001$), have a lower BMI (32.2 vs. 34.3, $p = 0.03$), have a non-white race (23 vs. 12.7%, $p < 0.001$), be postmenopausal (89.7 vs. 83.6%, $p = 0.02$), and have history of other malignancy (13.5 vs. 8.6%, $p = 0.03$). They had a statistically higher gravidity (2.56 vs. 2.15, $p = 0.005$) and parity (2.13 vs. 1.77, $p = 0.004$). Both types had similar rates of smoking, diabetes, hypertension, use of hormone replacement therapy (HRT), and use of oral contraceptive pills.

Table 2 describes pathologic characteristics of type 1 vs. 2 cancers. Type 2 cancer is diagnosed with a higher nuclear grade ($p < 0.001$), more likely to have lymphovascular space invasion (43.1 vs. 17.8%, $p < 0.001$), lower uterine segment involvement (55.2 vs. 42.4%, $p = 0.001$), have higher depth of myometrial invasion (41.6 vs. 28.8%, $p < 0.001$), and be a higher stage ($p < 0.001$).

Table 3 describes treatment modalities (surgical including which procedures performed, chemotherapy and radiotherapy) utilized for type 1 vs. 2 cancers. Type 2 cancer was more likely to be treated with an open surgical approach (79.4 vs. 64.1%, $p < 0.001$) and include lymph node dissection (93.5 vs. 87%, $p < 0.001$) and omentectomy (61.9 vs. 10%, $p < 0.001$). Regarding chemoradiation, type 2 disease was more likely to have chemotherapy with carboplatin and paclitaxel (51.4 vs. 6.9%, $p < 0.001$)

Table 1. Demographic characteristics of single institution cohort of patients with type 1 and 2 endometrial adenocarcinoma, 2005–2010¹

	Type 1 (n = 550)	Type 2 (n = 266)	p value
Age at diagnosis, years	62.2 (11.8)	65.6 (10.8)	<0.001
Race, %			<0.001
White	87.4	77.1	
Black	5.0	16.2	
Hispanic	3.1	2.6	
Asian	0.9	2.3	
Other	3.7	1.9	
Gravidity	2.15 (1.88)	2.56 (1.83)	0.005
Parity	1.77 (1.61)	2.13 (1.57)	0.004
BMI, kg/m ²	34.3 (9.7)	32.2 (16.0)	0.03
Menopausal, %	83.6	89.7	0.02
Smoker (≥5 pack-years), %	24.4	24.2	0.95
HRT use (>3 months), %	21.5	21.5	1.00
OCP use (>3 months), %	32.4	29.0	0.40
Medical history, %			
Hypertension	58.3	60.3	0.60
Diabetes	26.1	20.6	0.09
Major CV disease ²	5.2	5.4	0.93
Psychiatric disease ³	8.8	8.5	0.87
Other cancer	8.6	13.5	0.03
Prior abdominal surgery	39.1	36.8	0.54

¹ For continuous variables, mean (SD) shown, Student's *t* test for significance; for dichotomous and categorical variables, percent with characteristic shown, Pearson's χ^2 test for significance.

² Includes history of congestive heart failure, myocardial infarction, and stroke.

³ Includes diagnoses of depression, anxiety, bipolar, and schizophrenia.

BMI, body mass index; HRT, hormone replacement therapy; OCP, oral contraceptive pills; CV, cardiovascular.

Table 2. Pathologic characteristics of single institution cohort of patients with type 1 and 2 endometrial adenocarcinoma, 2005–2010¹

	Type 1 (n = 550)	Type 2 (n = 266)	p value
Histologic type, %			<0.001
Endometrioid			
adenocarcinoma	100	35.3	
Serous adenocarcinoma	0	38.0	
Clear cell carcinoma	0	6.0	
Mixed adenocarcinoma	0	20.7	
FIGO grade, %			<0.001
Grade 1	55.6	0	
Grade 2	44.4	0	
Grade 3	0	100	
Nuclear grade, %			<0.001
Grade 1	15.0	0	
Grade 2	76.8	8.0	
Grade 3	8.2	92.0	
Lymphovascular invasion, %	17.8	43.1	<0.001
Lower uterine segment invasion, %	42.4	55.2	0.001
Myometrial invasion depth, %	28.8 (28.1)	41.6 (35.9)	<0.001
Tumor dimension, cm	2.69 (2.36)	3.55 (3.33)	0.001
Stage, %			<0.001
I	77.8	54.8	
II	10.1	8.1	
III	10.6	22.4	
IV	2.0	14.7	

¹ For continuous variables, mean (SD) shown, Student's *t* test for significance; for dichotomous and categorical variables, percent with characteristic shown, Pearson's χ^2 test for significance.

and radiation (86.2 vs. 66%, $p < 0.001$), primarily vaginal brachytherapy, in stage I disease and more likely to receive chemotherapy with carboplatin and paclitaxel in stage II disease (61.9 vs. 11.5%, $p < 0.001$).

Table 4 describes characteristics associated with cancer recurrence, and Table 5 describes characteristics associated with death. Type 2 disease has the highest HR for association with both recurrence (HR 3.44, 95% CI 1.75–6.77, $p < 0.001$) and death (HR 2.99, 95% CI 1.87–4.77, $p < 0.001$). When examined by histologic subtype, serous adenocarcinoma has the highest adjusted HR for time to recurrence (HR 7.48, 95% CI 3.36–16.6, $p < 0.001$), as well as death (HR 3.42, 95% CI 1.89–6.17, $p < 0.001$). In addition to cancer type (type 2) and stage (stages III and IV), myometrial invasion was associated with increased risk of

recurrence and death were (HR 3.52, 95% CI 1.19–10.4, $p = 0.02$ and HR 3.00, 95% CI 1.43–6.28, $p = 0.004$, respectively). Age greater than 65 (HR 1.72, 95% CI 0.75–3.97, $p = 0.20$) was associated with increased risk of recurrence and death. In adjusted models, smoking (HR 1.70, 95% CI 1.05–2.75, $p = 0.03$) was also independently associated with the risk of death, though not with recurrence.

Figure 1 redemonstrate the association between type 2 disease and increase risk for death (HR 4.00, 95% CI 2.97–5.40, $p < 0.001$) and recurrence (HR 4.46, 95% CI 2.95–6.75, $p < 0.001$) using Kaplan–Meier curves. When adjusting for covariates, type 2 remains an independent risk factor for both death (HR 2.99, 95% CI 1.87–4.77, $p < 0.001$) and recurrence (HR 3.44, 95% CI 1.75–6.77, $p < 0.001$).

Table 3. Surgical staging and adjuvant treatment for single institution cohort of patients with type 1 and 2 endometrial adenocarcinoma, 2005–2010¹

	Type 1 (n = 550)	Type 2 (n = 266)	p value
Surgical approach, n %			<0.001
Open/abdominal	348 (64.1)	208 (79.4)	
Minimally invasive ²	195 (35.9)	54 (20.6)	
Surgical staging procedures, n %			
Pelvic lymph node dissection	470 (87.0)	243 (93.5)	<0.001
Para-aortic lymph node dissection	357 (66.2)	212 (81.5)	<0.001
Omentectomy	54 (10.0)	161 (61.9)	<0.001
Adjuvant/salvage treatment by stage, n %			
Stage I	(n = 425)	(n = 142)	
Radiotherapy ³	275 (66.0)	119 (86.2)	<0.001
Carbo/taxol chemotherapy	28 (6.9)	71 (51.4)	<0.001
Other chemotherapy	18 (4.2)	23 (16.2)	<0.001
Stage II	(n = 55)	(n = 21)	
Radiotherapy ³	49 (90.7)	17 (81.0)	0.24
Carbo/taxol chemotherapy	6 (11.5)	13 (61.9)	<0.001
Other chemotherapy	4 (7.3)	2 (9.5)	0.75
Stage III	(n = 55)	(n = 58)	
Radiotherapy ³	46 (88.5)	49 (87.5)	0.88
Carbo/taxol chemotherapy	48 (92.3)	46 (85.2)	0.25
Other chemotherapy	7 (12.7)	22 (37.9)	0.002
Stage IV	(n = 11)	(n = 38)	
Radiotherapy ³	8 (88.9)	20 (60.6)	0.11
Carbo/taxol chemotherapy	10 (90.9)	30 (85.7)	0.66
Other chemotherapy	6 (54.6)	15 (39.5)	0.37

¹ Note that the denominator for each field varies from the total *n* due to incomplete treatment data for some patients.

² Minimally invasive techniques include laparoscopic, robotic, and vaginal surgery.

³ Radiotherapy consisted primarily of vaginal brachytherapy (566 cases, 96.2%), as well as whole pelvis radiation (17 cases, 2.9%) and primary vaginal brachytherapy with salvage whole pelvis radiation (5 cases, 0.9%).

Discussion

By examining demographics, baseline health characteristics, treatment, and outcomes between patients diagnosed with type 1 and 2 endometrial cancers, we found results that were both consistent and inconsistent with previous literature. Consistent with previous literature, we found that significant risk factors for type 2 disease include lower BMI, non-white race, and older age; BMI is particularly relevant because it is a modifiable risk factor. Additionally, our longitudinal findings showed that type 2 disease is a stronger predictor of disease recurrence and death than type 1 disease, and that type 2 disease, smoking and older age are independently associated with death. However, our findings cast doubt on particular associations previously identified: we did not find diabetes mellitus and use of HRT as risk factors for type 1 vs. 2 disease.

Findings Consistent with Prior Literature

Consistent with previous literature, and similar to findings in other large cohort studies, we found that particular risk factors (BMI, race, and age) influence type 1 vs. 2 disease [3–5]. Of these, obesity is unique as a modifiable risk factor that is increasing in prevalence. In our cohort, BMI is 3 kg/m² higher in the type 1 cancer patients vs. type 2 cancer patients (*p* < 0.001). This correlates with a prospective study of 1 million women in Norway where BMI >30 had a relative risk of 2.70 for type 1 and 2.06 for type 2 endometrial cancer [15]. Importantly, the risk associated with obesity is not isolated to BMI at the time of diagnosis. In fact, childhood obesity in girls as young as 7 has been linked to development of endometrial cancer [16]. Mechanistically, obesity is one of the most correlated risk factors for type 1 endometrial cancer because of the clear relationship with increased estrogen exposure that leads to development of endometrial intraepithelial

Table 4. Cox proportional hazard models for recurrence for single institution cohort of patients with type 1 and 2 endometrial adenocarcinoma, 2005–2010

	Time to progression			
	unadjusted HR		adjusted HR ¹	
	95% CI	p value	95% CI	p value
Type/histology				
Type 1 (endometrioid FIGO 1/2)	Ref.		Ref.	
Type 2	4.46 (2.95–6.75)	<0.001	3.44 (1.75–6.77)	<0.001
Endometrioid FIGO ³	4.31 (2.52–7.39)	<0.001	2.01 (0.81–5.00)	0.13
Serous adenocarcinoma	6.37 (3.94–10.3)	<0.001	7.48 (3.36–16.6)	<0.001
Clear cell carcinoma	3.44 (1.06–11.2)	0.04	2.81 (0.73–10.8)	0.13
Mixed adenocarcinoma	1.77 (0.70–4.52)	0.23	2.23 (0.70–7.10)	0.18
Stage				
Stage I	ref.		Ref.	
Stage II	1.86 (0.94–3.72)	0.08	2.02 (0.72–5.67)	0.18
Stage III	3.43 (2.09–5.63)	<0.001	1.87 (0.81–4.34)	0.14
Stage IV	11.0 (6.22–19.52)	<0.001	5.01 (1.95–12.9)	0.001
Pathologic characteristics				
+LVSI	4.70 (3.06–7.22)	<0.001	1.88 (0.89–3.98)	0.10
Myometrial invasion ²	9.58 (5.12–17.9)	<0.001	4.61 (1.54–13.8)	0.006
Largest tumor dimension, cm	1.12 (1.03–1.23)	0.01	0.99 (0.87–1.13)	0.92
Age at diagnosis, years				
≤65	Ref.		Ref.	
≥66	2.45 (1.37–4.40)	0.01	1.39 (0.57–3.38)	0.47
Race				
White	Ref.		Ref.	
Non-white	1.86 (1.16–3.00)	0.01	0.79 (0.34–1.85)	0.59

¹ Adjusted HRs are adjusted for all other variables with estimates included in the given column of the table.

² Continuous decimal, range 0 (no invasion) to 1 (100% invasion).

LVSI, lymphovascular space invasion; FIGO, federation of gynecologists and obstetricians; HRs, hazard ratios.

neoplasia and subsequent development of a low-grade malignancy. Further, while higher BMI is associated with type 1 cancer, it is also important to note that even in the type 2 patients, the average BMI is also obese, at 32 kg/m², suggesting that obesity alone is not enough to predict development of type 1 vs. 2 cancer.

This study's findings with respect to longitudinal outcomes were also consistent with prior studies. First, our hazard model shows that type 2 disease alone is the most influential risk factor for both recurrence and death. Second, results by histologic subtype found that serous adenocarcinoma is most strongly associated with recurrence and death, followed by clear cell and grade 3 endometrioid adenocarcinoma [13, 17–19]. Third, older age and smoking also have independent associations with earlier death, which is consistent with national data [20, 21]. Fourth, our unadjusted HRs, which show significance between hypertension and major cardiovascular disease

with death, illustrate the effect of multiple comorbidities on earlier death in this population. Fifth, our unadjusted HRs show that non-white race is also a risk factor, which is an unfortunate finding consistent with prior studies of disparities in care of these patients [22]. Overall, these findings are consistent with the previously understood course of the disease types given the more aggressive histology of type 2 disease, as well as diagnosis at a later stage.

Findings Inconsistent with Prior Literature

However, for particular risk factors, our data contradict previous studies. Specifically, we find no association between diabetes mellitus and HRT use with type 1 vs. 2 disease. While multiple previous studies have found linkages, more recently that linkage has been increasingly questioned [4, 23–26]. Our findings support the more recent literature on DM and HRT that has been increasingly contradicting earlier studies.

Table 5. Cox proportional hazard models for death for single institution cohort of patients with type 1 and 2 endometrial adenocarcinoma, 2005–2010

	Overall survival			
	unadjusted HR		adjusted HR ¹	
	95% CI	<i>p</i> value	95% CI	<i>p</i> value
Type/histology				
Type 1 (endometrioid FIGO 1/2)	Ref.		Ref.	
Type 2	4.00 (2.97–5.40)	<0.001	2.99 (1.87–4.77)	<0.001
Endometrioid FIGO ³	3.56 (2.44–5.48)	<0.001	2.67 (1.40–5.08)	0.003
Serous adenocarcinoma	4.43 (3.05–6.45)	<0.001	3.42 (1.89–6.17)	<0.001
Clear cell carcinoma	4.58 (2.20–9.51)	<0.001	2.80 (1.09–7.19)	0.03
Mixed adenocarcinoma	3.66 (2.25–5.96)	<0.001	2.92 (1.49–5.74)	0.002
Stage				
Stage I	Ref.		Ref.	
Stage II	1.98 (1.23–3.20)	0.005	1.65 (0.78–3.50)	0.19
Stage III	2.36 (1.59–3.51)	<0.001	1.27 (0.69–2.36)	0.45
Stage IV	10.9 (7.30–16.1)	<0.001	4.12 (2.06–8.21)	<0.001
Pathological characteristics				
+LVSI	2.97 (2.20–4.01)	<0.001	1.17 (0.68–2.02)	0.54
Myometrial invasion ²	8.49 (5.43–13.3)	<0.001	3.14 (1.48–6.67)	0.003
Largest tumor dimension, cm	1.09 (1.03–1.14)	0.003	0.98 (0.88–1.08)	0.62
Age at diagnosis, years				
≤55	Ref.		Ref.	
56–65	2.03 (1.20–3.45)	0.009	1.43 (0.64–3.16)	0.38
66–75	3.04 (1.80–5.14)	<0.001	2.10 (0.94–4.69)	0.07
76–85	7.40 (4.32–12.7)	<0.001	5.42 (2.41–12.2)	<0.001
≥86	11.5 (5.78–23.0)	<0.001	3.99 (1.25–12.8)	0.02
Race				
White	Ref.		Ref.	
Non-white	1.48 (1.03–2.13)	0.04	0.94 (0.51–1.72)	0.84
Comorbidities				
Hypertension	1.71 (1.25–2.36)	0.001	1.53 (0.93–2.54)	0.10
Major CV disease ²	3.71 (2.41–5.71)	<0.001	1.47 (0.74–2.95)	0.28
Smoker (≥5 pack-years)	1.58 (1.15–2.19)	0.005	1.68 (1.02–2.75)	0.04
Other cancer	1.44 (0.94–2.22)	0.10	1.06 (0.55–2.04)	0.87

¹ Adjusted HRs are adjusted for all other variables with estimates included in the given column of the table.

² Continuous decimal, range 0 (no invasion) to 1 (100% invasion).

³ Includes congestive heart failure, myocardial infarction, and stroke.

LVSI, lymphovascular space invasion; CV, cardiovascular; FIGO, federation of gynecologists and obstetricians; HRs, hazard ratios.

Specifically regarding DM, the difference observed may be attributable to multiple factors including differences in populations studied or an increasing prevalence of DM as the population BMI continues to increase. Specifically regarding HRT, previous studies have found substantial evidence showing association between HRT use with any type of endometrial cancer [24]. However, when analysis is performed by histological subtypes, results in prior studies have not consistently found an association with a specific subtype [14, 25, 26]. As in our findings, this may suggest that type 2 cancer is also hormonally respon-

sive, or that grade 3 endometrioid histology confounds findings by type.

Looking Forward

While this study is one of the largest studies in a population from 2 institutions of its kind and provides a robust sample of data, this study is limited by its retrospective and observational design, as well as by demographics of patients specific to its geographical area. To note, while it is also possible that differences in treatments by disease type could skew results, that is not likely here. That is, in

Fig. 1. Kaplan-Meier survival plots, adjusted and unadjusted, for (a) time to progression and (b) overall survival, by type 1 vs. 2 endometrial cancer, cohort presenting 2005–2010.

reviewing surgical and chemoradiation treatment received by patients with type 1 vs. 2 disease, our cohort's treatment was consistent with National Comprehensive Cancer Network guidelines.

As our knowledge and understanding of cancer genetics evolves, not only will we be able to identify additional tumor types [27], but we also will have the opportunity to acquire and analyze specific genetic data associated with each individual case of cancer. We hope to include this information in future data sets in an ef-

fort to better understand endometrial cancer. For now, our improved understanding of the risk factors for type 1 vs. 2 endometrial cancers should be used to counsel patients with new diagnoses of endometrial cancer.

Disclosure Statement

The authors declare no conflicts of interest.

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