Cancer Causes Control (2017) 28:819–828
DOI 10.1007/s10552-017-0908-9

ORIGINAL PAPER

Association of endometrial hyperplasia and cancer with a history of gestational diabetes

Paige D. Wartko[1] · Tiffany L. Beck[1,2] · Susan D. Reed[1,2] · Beth A. Mueller[1] · Stephen E. Hawes[1]

Received: 16 September 2016 / Accepted: 25 May 2017 / Published online: 2 June 2017
© Springer International Publishing Switzerland 2017

Abstract
Purpose Excess circulating insulin may contribute to endometrial cancer (EC) development; studies suggest increased risk of EC associated with type 2 diabetes. We investigated whether gestational diabetes is associated with increased risk of EC and its precursor, endometrial hyperplasia (EH).
Methods We conducted a population-based, case–control study of women in Washington State. Cases were women with a hospital discharge record indicating the presence of EH/EC who could be linked to a prior delivery hospitalization or birth record from 1987 to 2013 ($n = 593$). Controls were randomly selected from remaining deliveries, frequency matched 10:1 on delivery year and maternal age at delivery ($n = 5{,}743$). Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).
Results After adjustment for race/ethnicity, maternal age at delivery, and delivery year, EH/EC was associated with a history of gestational diabetes (OR 1.73, 95% CI 1.27–2.35). This association was present for both EH and EC (OR 1.61, 95% CI 1.00–2.60 and OR 1.80, 95% CI 1.22–2.65, respectively). After adjustment for prepregnancy body mass index, the OR for EH/EC was attenuated and became statistically non-significant (OR 1.22, 95% CI 0.87–1.72), except in women <50 years old at the time of case ascertainment (OR 1.49, 95% CI 1.00–2.20). Associations were slightly stronger for EC than EH.
Conclusions We observed an association between EH/EC and a history of gestational diabetes specific to younger women. Future studies focusing on the relationships between gestational diabetes, obesity, and EC, including age at diagnosis, are warranted.

Keywords Case–control study · Endometrial cancer · Endometrial hyperplasia · Gestational diabetes mellitus · Pregnancy · Body mass index

Introduction

Endometrial cancer (EC), the most common gynecologic malignancy in the US, has an incidence of 25 cases per 100,000 woman-years [1]. Endometrial hyperplasia (EH) is a neoplastic proliferation of cells that results in EC precursor lesions. The main biological mechanism leading to development of EH/EC is thought to be prolonged excessive estrogen exposure, which stimulates growth of the endometrium [2]. Factors that increase risk of EC include high body mass index (BMI), anovulation, nulliparity, and use of exogenous estrogens unopposed by progestin, whereas tobacco use decreases risk [3–6]. Incidence is typically greater in non-Hispanic whites than other racial/ethnic groups [7]. Some studies reported a positive association between type 1 diabetes mellitus (T1DM) and/or type 2 diabetes mellitus (T2DM) and EC after accounting for BMI [8–15], although others found no association

This work was presented as a poster at the 28th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research in Denver, Colorado, June 16, 2015.

✉ Paige D. Wartko
pwartko@uw.edu

[1] Department of Epidemiology, University of Washington School of Public Health, 1959 NE Pacific Street, Health Sciences Building, F-262, Box 357660, Seattle, WA 98195-7236, USA

[2] Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA, USA

[16–20]. Additional studies suggest the association between T1DM/T2DM and EC is specific to obese women [21–23]. A proposed mechanism is the hyperinsulinemia pathway, in which excess circulating insulin stimulates the overgrowth of cells in the endometrium, leading to EH/EC [24, 25].

GDM is a disease of relative insulin resistance in pregnancy and a recognized risk factor for development of T2DM later in life [26, 27]. GDM affects 6% of pregnancies in the US [28], with increasing prevalence in recent years, following the rise in obesity [29]. Risk factors for GDM include obesity, advanced maternal age, and American Indian/Alaska Native, Asian, Pacific Islander, or Hispanic race/ethnicity [29, 30].

We sought to estimate the association between GDM and EH/EC by comparing the history of GDM in all women identified with EH/EC in Washington State population-based records and a randomly selected control group of parous women. We hypothesized an increased risk of EH/EC among women with GDM.

Methods

Data collection

We conducted a population-based, case-control study of the association between EH/EC and a history of GDM among parous women. This analysis was considered exempt from formal Institutional Review Board review because the data were de-identified.

Potential cases were all parous women with a diagnostic code for EH/EC from an inpatient hospitalization at a non-federal hospital in Washington State from 1987 to 2013. We restricted to women with complex hyperplasia without atypia (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM, 621.32), endometrial hyperplasia with atypia (either simple or complex, 621.33), endometrial hyperplasia, unspecified (621.30), endometrial intraepithelial neoplasia (621.35), or endometrial cancer (182.0). The relatively mild findings of benign endometrial hyperplasia (ICD-9-CM 621.34) or simple hyperplasia without atypia (621.31) were not included, as most of these women are managed medically and have a low rate of progression to EC [31]. Cases were restricted to women whose hospitalization record could be linked to a prior live birth or fetal death record, not including those occurring at federal hospitals, from 1987 to 2013. Fetal death is defined as death of the fetus at ≥20 weeks gestation [32]. If a case had multiple deliveries over the study period, we selected their most recent delivery. Exclusion criteria for all subjects included pregestational diabetes (T1DM or T2DM), missing GDM information, and delivery prior to 29 weeks gestation, as standard screening for GDM occurs between 24 and 28 weeks (Fig. 1). Additionally, for subjects missing gestational age we restricted to those with birth weight ≥2,000 g, as infants of this size are very rarely <29 weeks gestation. These measures were ascertained from the birth/fetal death record. Cases were excluded if the EH/EC diagnosis was recorded at the time of delivery. Ninety-seven percent of cases were linked to both a birth/fetal death record and a hospital discharge record at the time of delivery, while the remaining 3% were linked only to a birth/fetal death record.

Controls were randomly selected (control:case ratio of 10:1) from all other women with delivery records from 1987 to 2013, frequency matched by year of delivery and maternal age at delivery in 5-year categories (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, ≥45). If a control mother had more than one delivery over the study period, the most recent delivery was used for consistency with case selection. Additionally, controls who delivered at a federal hospital were excluded to match methods for case selection, which inherently excluded subjects with deliveries at federal hospitals (Fig. 1). Controls with a procedure code for hysterectomy at the time of delivery (ICD-9-CM 68.0, 68.3x–68.9x) were also excluded, as they were not at risk for EH/EC after this procedure. Ninety-one percent of controls had a birth/fetal death record linked to a hospital discharge record at delivery; 9% only had birth/fetal death record information.

We initially identified 657 cases and 6,570 controls. After exclusions (Fig. 1), analyses included 593 cases (253 EH and 340 EC) and 5,743 controls.

Measures

Subjects were defined as exposed to GDM if the GDM checkbox on the birth record was marked or an ICD-9-CM diagnostic code for GDM (648.8x) was listed in the hospital discharge record. For the 3% of cases and 9% of controls who were not linked to a hospital discharge record at the time of delivery, the birth record alone determined GDM status. Although we did not have data on GDM testing procedures, the American College of Obstetricians and Gynecologists recommended a 2-part screening procedure for GDM during the study period, consisting of a 1-h, 50 g, screening oral glucose challenge test, which, if abnormal (>140 mg/dL serum blood glucose), was followed by a fasting, 3-h, 100 g, diagnostic oral glucose tolerance test. Abnormal findings at two or more time points from the second test (fasting: ≥95 mg/dL serum blood glucose, 1-h: ≥180 mg/dL, 2-h: ≥155 mg/dL, 3-h: ≥140 mg/dL) resulted in a GDM diagnosis [33]. We included women who initiated prenatal care after

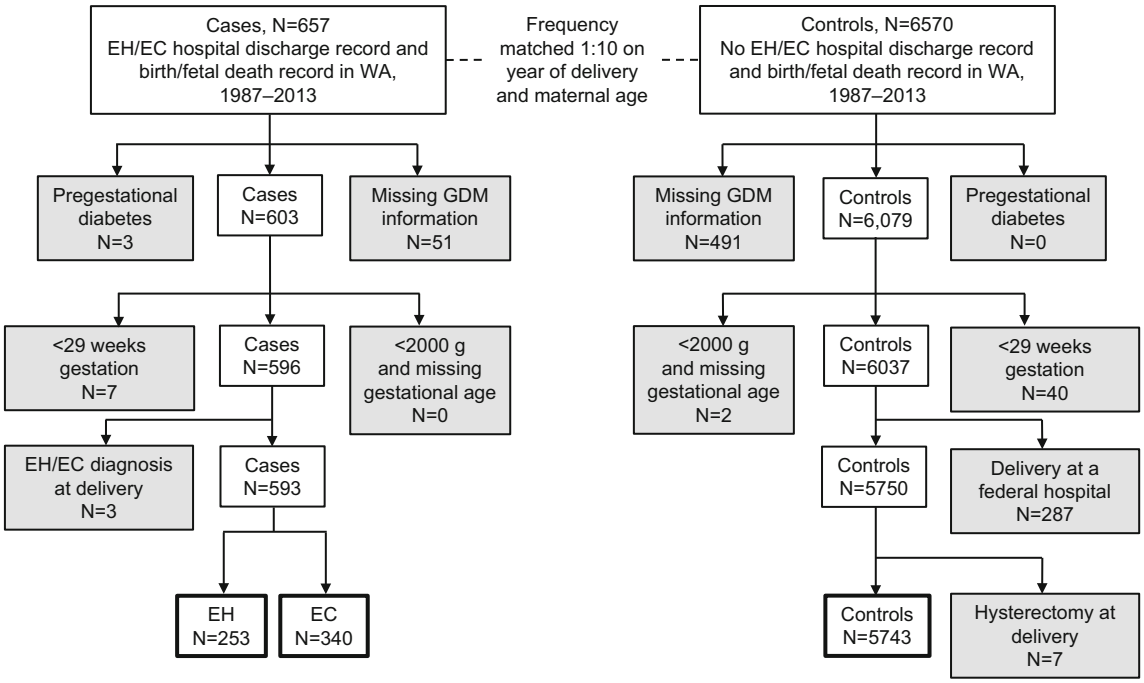

Fig. 1 Case and control selection and exclusion process. *EH* endometrial hyperplasia: ICD-9-CM 621.30, 621.32, 621.33, 621.35, *EC* endometrial cancer: ICD-9-CM 182.0, *WA* Washington State, *GDM* gestational diabetes mellitus

28 weeks, even though they missed the standard GDM screening window, because they had the opportunity for GDM diagnosis during a later prenatal visit or on presentation to the hospital in labor. Gestational age at delivery was calculated from last menstrual period. Where discrepancies of two or more weeks existed between gestational age calculated from last menstrual period and gestational age estimated by a clinician, comparisons were made with birth weight of the infant to assess whether the calculated or estimated value for gestational weeks was most plausible. For women who did not have information on last menstrual period but had a clinical estimate of gestational age, the latter was used.

We assessed select variables in EH/EC cases at the time of ascertainment, including age, time since delivery, T2DM, and obesity. T2DM at this time was defined as an ICD-9-CM diagnostic code of diabetes mellitus (250.xx, excluding codes of 250.x1 or 250.x3, which indicate Type I diabetes). Obesity at the time of EH/EC ascertainment was defined as an ICD-9-CM diagnostic code for obesity, unspecified (278.00), morbid obesity (278.01), or obesity hypoventilation syndrome (278.03).

Data analysis

We calculated odds ratios (ORs) with 95% confidence intervals (CIs) using unconditional multivariable logistic regression, adjusting for the frequency matching variables (delivery year and maternal age at delivery) based on an a priori hypothesis of confounding. Variables assessed as potential data-driven confounders included parity (0, 1, 2, ≥3 births prior to the index birth), maternal race/ethnicity (Asian/Pacific Islander, non-Hispanic white, and other), smoking during pregnancy (yes or no), prepregnancy BMI (continuous, in kg/m^2), and multiple gestation (singleton or multiples), as well as education (<12, 12, ≥13 years) and health insurance (private, Medicaid/Medicare, other) as proxies for socioeconomic status. Confounding was defined as a substantial change from the crude OR of approximately 10% or greater in the presence of an association between the potential confounder and the exposure, as well as the outcome. This approach has been found to be sensitive in identifying confounding factors in epidemiologic studies [34–37]. Using these criteria, race/ethnicity and prepregnancy BMI were identified as additional confounders. We also separately evaluated the potentially different associations of EH and EC with GDM.

We conducted an exploratory analysis of effect measure modification by BMI (categorized as normal or underweight: <25.0 kg/m^2; overweight: ≥25.0 to <30.0 kg/m^2; or obese: ≥30.0 kg/m^2) through consideration of a Wald test of the interaction terms and comparison of stratum-specific ORs. Additionally, we conducted an exploratory analysis stratifying by age at EH/EC ascertainment (categorized as <50 years old or ≥50 years old), as cases occurring at a younger age are more likely to have a strong genetic predisposition to cancer [38]. This analysis assessed the association of different types of EH/EC with GDM,

not effect measure modification by a third factor, so we did not conduct a test of interaction.

We used multiple imputation by chained equations to generate values for missing data in covariates, a method described by Azur, et al. [39]. Certain variables were not added to the Washington State birth record until 1992 (prepregnancy weight, maternal education) and 2003 (prepregnancy BMI), and incomplete reporting was prevalent even in years when the variables were included in the birth record (Table 1). Missing values were imputed for prepregnancy BMI, prepregnancy weight, pregnancy weight gain, maternal education, and median income (by census tract) using linear models, smoking during pregnancy using a logistic model, maternal race/ethnicity, small for gestational age (<10th percentile birth weight for gestational age), and insurance status using nominal logistic models, and parity using an ordinal logistic model. These variables were used in addition to GDM, EH/EC, year of delivery, maternal age at delivery, and multiple gestation, which had complete data after exclusions, to estimate values via multiple imputation. We assumed data were missing at random, after conditioning on the variables included in the models [40]. We completed 20 imputations to account for the between-imputation aspect of variability [41].

All analyses were conducted in Stata (version 13.0; StataCorp, College Station, TX). Missing data were imputed using the MI IMPUTE function, and final regression coefficients and confidence intervals were computed from logistic regression models using the imputed datasets with the MI ESTIMATE function.

Results

Characteristics of cases and controls at the time of delivery were similar with respect to maternal age at delivery, insurance status, education, parity, and gestational age (Table 1). Cases were more likely than controls to be non-Hispanic white, to not have smoked during pregnancy, and to be obese. Cases were more likely to have a history of GDM than controls (8.8 and 5.6%, respectively; Table 3).

The median age of cases at the time of EH/EC ascertainment was 47, with a median of 14 years between delivery and ascertainment (interquartile range: 10–18 years; Table 2). At the time of EH/EC ascertainment, 10.8% percent of cases had an ICD-9-CM diagnostic code for T2DM. Among EH/EC cases with a history of GDM, 40.4% had an ICD-9-CM diagnostic code for T2DM by the time of EH/EC ascertainment, and of those without GDM, 8.0% had a code. At the time of EH/EC ascertainment, 23.1% of cases had an ICD-9-CM diagnostic code for obesity. Among EH/EC cases with a history of GDM, 25.0% had an ICD-9-CM diagnostic code for obesity at the time of EH/EC ascertainment, and of those without a history of GDM, 22.9% had a code.

We observed an association between EH/EC and a history of GDM in our analysis adjusting for race/ethnicity, maternal age at delivery, and year of delivery using the imputed datasets (OR 1.73, 95% CI 1.27–2.35; Table 3). However, after additional adjustment for prepregnancy BMI, the association between EH/EC and a history of GDM was attenuated and the confidence interval included one (OR 1.22, 95% CI 0.87–1.72). We observed slightly stronger associations for EC than EH.

The associations of our outcomes with GDM were similar across BMI categories, although the confidence intervals were wide, likely due to small numbers (Table 4). The Wald test for interaction was statistically non-significant. The association of EH/EC with GDM was greater among women <50 years old at the time of EH/EC ascertainment (OR 2.14, 95% CI 1.49–3.08) than in women ≥50 years old (OR 1.10, 95% CI 0.62–1.95), and this association in younger women was statistically significant even after adjustment for BMI (OR 1.49, 95% CI 1.00–2.20). We lacked sufficient numbers to assess associations by BMI or age of cases separately for EH and EC.

Discussion

We observed that women with EH/EC were more likely to have a history of GDM than women without EH/EC, with stronger associations observed in younger women than older women and for EC than EH. However, these positive associations between EH/EC and GDM were attenuated and became statistically non-significant after adjustment for prepregnancy BMI, except in younger cases. Results were similar when stratified by BMI category. To our knowledge, there are currently no other studies of the association between GDM and EC; our results before stratification by age at case ascertainment were consistent with a previous study of T2DM and EC, which found that any evidence of an association was primarily due to confounding by BMI [16]. Three meta-analyses found positive associations between T2DM and EC [42–44], but BMI was handled inconsistently: some of the studies in the meta-analyses did not account for it, others controlled for it, some considered it an effect measure modifier, assessing associations stratified by obesity status, and some only controlled for prepregnancy weight. Our observation of a stronger association with GDM in younger EH/EC cases was consistent with a previous study of T2DM in EC cases [45], but potentially inconsistent with a study suggesting a stronger association with T2DM in older EH cases [46].

Table 1 Characteristics of women at time of delivery with or without endometrial hyperplasia or cancer

Characteristics	EH/EC cases *n* (%)	Controls *n* (%)
Maternal age at delivery (years)		
<25	51 (8.6)	439 (7.6)
25–34	330 (55.7)	3,137 (54.6)
35–39	145 (24.5)	1,533 (26.7)
≥40	67 (11.3)	634 (11.0)
Maternal race/ethnicity		
White, non-Hispanic	499 (86.3)	4,568 (81.7)
Black, non-Hispanic	6 (1.0)	163 (2.9)
American Indian/Alaska Native	7 (1.2)	86 (1.5)
Asian	32 (5.5)	399 (7.1)
Native Hawaiian/other Pacific Islander	6 (1.0)	13 (0.2)
Hispanic	27 (4.7)	360 (6.4)
Maternal education (years)		
<12	37 (11.2)	337 (10.5)
12	84 (25.4)	839 (26.2)
≥13	210 (63.4)	2,031 (63.3)
Insurance status[a]		
Private	452 (78.5)	3,925 (74.5)
Medicaid/Medicare	102 (17.7)	1,093 (20.7)
Self-pay	10 (1.7)	164 (3.1)
Other	12 (2.1)	90 (1.7)
Parity[b]		
0	129 (22.1)	1,270 (22.5)
1	218 (37.3)	2,141 (37.9)
2	124 (21.2)	1,221 (21.6)
≥3	114 (19.5)	1,017 (18.0)
Multiple gestation		
Singleton	573 (96.6)	5,602 (97.5)
Twins or triplets	20 (3.4)	141 (2.5)
Gestational age (weeks)		
29–36	54 (9.3)	488 (8.7)
37–40	401 (69.0)	3,877 (69.0)
≥41	126 (21.7)	1,255 (22.3)
Smoking during pregnancy		
Yes	64 (11.2)	830 (15.0)
No	510 (88.9)	4,695 (85.0)
Prepregnancy weight		
<150	100 (35.7)	1,611 (58.2)
150–199	103 (36.8)	872 (31.5)
≥200	77 (27.5)	286 (10.3)
Body mass index (median, standard deviation)		
Normal weight/underweight	13 (28.9)	247 (48.6)
Overweight	10 (22.2)	129 (25.4)
Obese	22 (48.9)	132 (26.0)

Numbers may not add to total due to missing data. Percent missing data: maternal race/ethnicity (2.7%), maternal education (44.2%, added to the birth record in 1992), insurance (7.7%), parity (1.6%), gestational age (2.1%), smoking (3.7%), prepregnancy weight (51.9%), body mass index (91.3%, added to the birth record in 2003)

EH, endometrial hyperplasia: ICD-9-CM 621.30, 621.32, 621.33, 621.35; *EC*, endometrial cancer: ICD-9-CM 182.0

[a] Medicaid/Medicare includes charity payer; private includes Indian Health Service

[b] Parity: number of live births prior to the index birth

Table 2 Characteristics of cases at the time of EH/EC ascertainment

Characteristics	EH/EC $n = 593$ n (%)	EH $n = 253$ n (%)	EC $n = 340$ n (%)
Age at case ascertainment (years)			
Median (interquartile range)	47 (41–51)	46 (40–50)	48 (43–52)
<50 years old	384 (64.8)	178 (70.4)	206 (60.6)
≥50 years old	209 (35.2)	75 (29.6)	134 (39.4)
Years between delivery and case ascertainment			
Median (interquartile range)	14 (10–18)	14 (10–18)	14 (9–19)
T2DM	64 (10.8)	24 (9.5)	40 (11.8)
Among women with a history of GDM	21 (40.4)	10 (50.0)	11 (34.4)
Among women without a history of GDM	43 (8.0)	14 (6.0)	29 (9.4)
Obesity	137 (23.1)	53 (21.0)	84 (24.7)
Among women with a history of GDM	13 (25.0)	4 (20.0)	9 (28.1)
Among women without a history of GDM	124 (22.9)	49 (21.0)	75 (24.4)

GDM gestational diabetes mellitus, *EH* endometrial hyperplasia: ICD-9-CM 621.30, 621.32, 621.33, 621.35, *EC* endometrial cancer: ICD-9-CM 182.0, *T2DM* type 2 diabetes mellitus: ICD-9-CM 250, excluding codes of 250.x1 or 250.x3, which indicate Type I diabetes; obesity: ICD-9-CM 278.00, 278.01, 278.03

This table presents results from the non-imputed dataset

Our study is strengthened by the population-based design. GDM was ascertained from administrative health records, so it is not affected by recall bias. A previous study in Washington State reported that GDM had a sensitivity of 93.3% and specificity of 99.1% when it was defined as a diagnosis in either the delivery hospitalization or birth record, using the medical record as the "gold standard" [47]. Additionally, we likely captured most EC cases that occurred in Washington State, as cases routinely undergo hysterectomy in inpatient settings, and we utilized diagnostic codes from inpatient hospital discharge records.

Another strength of our study is that we were able to investigate development of T2DM among our cases, observing that 11% of cases also had an ICD-9-CM diagnostic code for T2DM at the time of case ascertainment. We believe the coding of T2DM was relatively sensitive, given that it is well recognized as an important comorbidity, and other studies have observed similar prevalence, with 9–12% of EH/EC cases having T2DM [8, 11, 16, 46]. Because T2DM at the time of EH/EC ascertainment occurred after GDM exposure, failure to adjust for it in our analyses did not lead to bias in our risk estimates. We also do not see T2DM as a true mediator, as GDM is not thought to cause T2DM, but is rather an earlier marker of underlying dysfunction in glucose metabolism [48].

Obesity is known to be the strongest non-genetic risk factor for EH/EC [2]. We were able to investigate obesity at the time of EH/EC ascertainment, observing that twenty-three percent of cases had an ICD-9-CM diagnostic code for obesity at this time. Although we believe the coding of obesity to have high specificity, it may have lower sensitivity, as, until recently, it was less likely to be seen as a true "disease" or billable condition. Previous literature supports the hypothesis that we underestimated prevalence of obesity at the time of case ascertainment, with estimates of obesity in EH/EC cases ranging from 28 to 51% [8, 11, 16, 46]. As with T2DM at the time of case ascertainment, obesity at this time point could not be a confounder, so its exclusion from the models did not lead to biased risk estimates.

However, the lack of complete data on obesity/BMI *prior to pregnancy* is a considerable limitation of our study, as we were unable to fully explore and address potential confounding and/or effect measure modification by this factor. We partially addressed this limitation through our use of multiple imputation to estimate missing data. Although potential non-differential misclassification of the imputed variables could have led to residual confounding by BMI, this method is superior to the most common approach to handling missing data, a complete case analysis. In the commonly used approach, the data are assumed to be "missing completely at random," which means that the distributions of the missing and non-missing values are similar even without adjustment for observed variables [40, 49]. Alternatively, multiple imputation only requires the assumption that the data are "missing at random," meaning there can be systematic differences between the observed and missing values, as long as they are accounted for by observed variables included in the models. Therefore, given a set amount of missing data, the complete case

Table 3 Association between endometrial hyperplasia or cancer and a history of gestational diabetes

	n	Non-imputed dataset		Imputed datasets	
		GDM %	Adjusted[a] OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
Controls	5,743	5.6	1.00 (ref)	1.00 (ref)	1.00 (ref)
EH/EC	593	8.8	**1.62 (1.17–2.23)**	**1.73 (1.27–2.35)**	1.22 (0.87–1.72)
EH	253	7.9	1.49 (0.90–2.45)	**1.61 (1.00–2.60)**	1.10 (0.66–1.82)
EC	340	9.4	**1.70 (1.14–2.55)**	**1.80 (1.22–2.65)**	1.30 (0.85–1.98)

GDM gestational diabetes mellitus, *EH* endometrial hyperplasia: ICD-9-CM 621.30, 621.32, 621.33, 621.35, *EC* endometrial cancer: ICD-9-CM 182.0, *OR* odds ratio, *CI* confidence interval

Statistically significant results are presented in bolded font

[a] Adjusted for race/ethnicity, year of delivery, and maternal age at delivery

[b] Adjusted for race/ethnicity, year of delivery, maternal age at delivery, and body mass index

Table 4 Exploratory analysis of the association between endometrial hyperplasia or cancer and a history of gestational diabetes by age at case ascertainment and prepregnancy body mass index

	Adjusted[b] OR (95% CI)	Adjusted[c] OR (95% CI)
Younger cases (<50 years old at ascertainment)	**2.14 (1.49–3.08)**	**1.49 (1.00–2.20)**
Older cases (≥50 years old at ascertainment)[a]	1.10 (0.62–1.95)	0.83 (0.45–1.52)
Normal and underweight (<25.0 kg/m^2)	1.23 (0.46–3.26)	
Overweight (≥25.0–<30.0 kg/m^2)	1.42 (0.67–3.01)	
Obese (≥30.0 kg/m^2)	1.22 (0.72–2.06)	
p value for interaction[d]	0.95	

OR odds ratio, *CI* confidence interval

Statistically significant results are presented in bolded font

These analyses were conducted using the imputed datasets and are for endometrial hyperplasia (ICD-9-CM 621.30, 621.32, 621.33, 621.35) and cancer (ICD-9-CM 182.0) combined

[a] This analysis was assessing the association of GDM with different types of EH/EC (cases occurring at a younger age are more likely to have a strong genetic predisposition to cancer), not effect measure modification by a third factor like body mass index, so we did not conduct a test of interaction

[b] Adjusted for race/ethnicity, year of delivery, and maternal age at delivery

[c] Adjusted for race/ethnicity, year of delivery, maternal age at delivery, and body mass index

[d] Calculated using a Wald test

approach is more prone to bias due to incorrect assumptions than the multiple imputation approach used in our study.

Another potential limitation of this study design is that controls were ascertained at the time of delivery, and we did not have follow-up records to confirm continued Washington State residency. However, the incidence rates of EH and EC are low [1, 50], and we would expect few controls to truly be cases who were misclassified because they had no record of an EH/EC diagnosis in our data (due to moving out of Washington State).

A third limitation is that EH cases were not fully ascertained, as studies report only 50–80% of women with atypical EH undergo hysterectomy as primary or secondary treatment, and the more common, less severe complex hyperplasia is often treated pharmacologically or with outpatient procedures [31, 50]. We captured some portion of these women through inpatient hospital records for evaluation of symptoms, such as abnormal uterine bleeding [51].

We did not know whether women had GDM in a previous pregnancy and therefore could not assess whether a history of multiple GDM-affected pregnancies was associated with a greater risk of EH/EC than a single GDM-affected pregnancy. In addition to prepregnancy BMI, we lacked information on other potential confounders, specifically hormonal contraceptive use and physical activity prior to pregnancy.

Due to the limited span between exposure and outcome (26-year maximum), our cases were younger than typical EH/EC cases. Our EC cases had a median age at case ascertainment of 48, as compared with 62 in the US as a whole [52]. Younger age at onset of EC is more often attributed to a genetic cancer predisposition, such as Lynch Syndrome [38], and we had no information about genetic

characteristics. Previous literature reported that 9% of EC cases <50 years old and 4% of EC cases <60 years old, respectively, have Lynch syndrome [38]. Contrary to our hypothesis that a preponderance of Lynch syndrome in younger cases, as compared with older, would lead to an underestimation of risk associated with GDM in the former group [53], we actually observed greater risk in younger women.

It is biologically plausible that GDM may be an earlier marker than T2DM of insulinopathy that leads to EH/EC. Excess circulating insulin may increase endometrial proliferation, and thus EH/EC risk, both directly by attaching to insulin receptors on the endometrial cells [25] and indirectly by lowering sex hormone binding globulin concentrations, thereby raising concentrations of serum estrogen, associated with proliferative endometrium [54]. The circulating level of an insulin-sensitizing hormone, adiponectin, is associated with obesity, T2DM, and endometrial cancer, and may play a role in the association between GDM and EH/EC [55]. Our findings in older women may indicate that the effect of GDM on insulin and adiponectin is too small to increase the risk of EH/EC, or that GDM is associated with increased EH/EC risk, but not strongly enough to detect with the precision of our study. It is possible that altered glucose metabolism has a greater effect on endometrial neoplastic changes in younger, premenopausal women, for whom we found a significant association even after adjustment for BMI, than older, postmenopausal women.

There is evidence that use of insulin may increase risk of endometrial cancer in non-pregnant populations with T1DM [56] through the described pathway of excess circulating insulin stimulating endometrial proliferation. We did not have diabetes treatment information. However, treatment is in the causal pathway between incidence of GDM and EH/EC, so its absence from our models did not bias the findings.

Our study may have important clinical implications for EH/EC prevention if there is truly an association between EH/EC and GDM. Women with a history of GDM who are considering contraceptive options could be recommended to use a progestin-containing intrauterine device, if appropriate given other considerations. These devices have been shown to decrease risk of endometrial cancer in individuals without endometrial proliferation [57] and regress endometrial hyperplasia in those with proliferation [58], in addition to their contraceptive function. In this way, GDM could serve as an early marker of risk that provides an opportunity for EH/EC prevention in some women.

Future research should investigate the relationship between GDM and EH/EC in larger populations with an EH/EC case distribution typical of the general population and complete information on BMI, as well as contraceptive use and physical activity, prior to pregnancy. In addition, assessing the role of multiple GDM-affected pregnancies, GDM treatment, age at EH/EC diagnosis, and obesity and T2DM development after pregnancy may help elucidate mechanisms of the association. Information on insulin resistance during pregnancy may be even more important than a diagnosis of GDM.

In our study of this novel hypothesis, women with EH/EC were more likely to have a history of GDM, but after adjustment for BMI this association was only observed in younger women. As rates of obesity and T2DM increase in the US and abroad, EC rates are also anticipated to increase [59]. There is an urgency to identify additional early and modifiable risk factors for EC if we are to prevent the associated morbidity and mortality [27].

Acknowledgements We would like to thank the Washington State Department of Health for data access, and Mr. Bill O'Brien for data management and programming.

Funding P.D.W. was funded by the following grants: (1) U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, Grant #T76MC00011; (2) National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Reproductive, Perinatal, and Pediatric Epidemiology Training Grant #T32HD052462. The funding sources had no role in this analysis.

Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent We did not obtain informed consent from participants because it is not necessary for a secondary data analysis of de-identified data.

References

1. U.S. Cancer Statistics Working Group (2016) United States Cancer Statistics: 1999–2013 Incidence and Mortality Web-based Report. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, Atlanta. Available at: https://www.cdc.gov/uscs.
2. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD (1997) Risk factors and hormone levels in patients with serous and endometrioid uterine carcinomas. Mod Pathol 10:963–968
3. Inoue M, Okayama A, Fujita M, Enomoto T, Tanizawa O, Ueshima H (1994) A case–control study on risk factors for uterine endometrial cancer in Japan. Jpn J Cancer Res 85:346–350
4. Epplein M, Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS (2008) Risk of complex and atypical endometrial hyperplasia in

relation to anthropometric measures and reproductive history. Am J Epidemiol 168:563–570; discussion 571–566. doi:10.1093/aje/kwn168
5. Grabner M (2012) BMI trends, socioeconomic status, and the choice of dataset. Obes Facts 5:112–126. doi:10.1159/000337018
6. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D (1995) Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 85:304–313. doi:10.1016/0029-7844(94)00383-O
7. Wartko P, Sherman ME, Yang HP, Felix AS, Brinton LA, Trabert B (2013) Recent changes in endometrial cancer trends among menopausal-age U.S. women. Cancer Epidemiol 37:374–377. doi:10.1016/j.canep.2013.03.008
8. Lai GY, Park Y, Hartge P, Hollenbeck AR, Freedman ND (2013) The association between self-reported diabetes and cancer incidence in the NIH-AARP Diet and Health Study. J Clin Endocrinol Metab 98:E497–E502. doi:10.1210/jc.2012-3335
9. Hemminki K, Li X, Sundquist J, Sundquist K (2010) Risk of cancer following hospitalization for type 2 diabetes. Oncologist 15:548–555. doi:10.1634/theoncologist.2009-0300
10. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A (2008) Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 98:1582–1585. doi:10.1038/sj.bjc.6604313
11. Weiss JM, Saltzman BS, Doherty JA, Voigt LF, Chen C, Beresford SA, Hill DA, Weiss NS (2006) Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. Am J Epidemiol 164:56–62. doi:10.1093/aje/kwj152
12. Parazzini F, La Vecchia C, Negri E, Riboldi GL, Surace M, Benzi G, Maina A, Chiaffarino F (1999) Diabetes and endometrial cancer: an Italian case–control study. Int J Cancer 81:539–542
13. Weiderpass E, Gridley G, Persson I, Nyren O, Ekbom A, Adami HO (1997) Risk of endometrial and breast cancer in patients with diabetes mellitus. Int J Cancer 71:360–363
14. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH (1997) Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 89:1360–1365
15. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P (1994) A case–control study of diabetes mellitus and cancer risk. Br J Cancer 70:950–953
16. Luo J, Beresford S, Chen C, Chlebowski R, Garcia L, Kuller L, Regier M, Wactawski-Wende J, Margolis KL (2014) Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer 111:1432–1439. doi:10.1038/bjc.2014.407
17. Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I, Hammar N (2011) Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer. Cancer Causes Control 22:1163–1171. doi:10.1007/s10552-011-9794-8
18. Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, Zauber AG, Olson SH (2009) Risk of endometrial cancer in relation to medical conditions and medication use. Cancer Epidemiol Biomarkers Prev 18:1448–1456. doi:10.1158/1055-9965.EPI-08-0936
19. Anderson KE, Anderson E, Mink PJ, Hong CP, Kushi LH, Sellers TA, Lazovich D, Folsom AR (2001) Diabetes and endometrial cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 10:611–616
20. Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN (1997) Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res 57:5077–5085
21. Friberg E, Mantzoros CS, Wolk A (2007) Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev 16:276–280. doi:10.1158/1055-9965.EPI-06-0751
22. Shoff SM, Newcomb PA (1998) Diabetes, body size, and risk of endometrial cancer. Am J Epidemiol 148:234–240
23. Lucenteforte E, Bosetti C, Talamini R, Montella M, Zucchetto A, Pelucchi C, Franceschi S, Negri E, Levi F, La Vecchia C (2007) Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. Br J Cancer 97:995–998. doi:10.1038/sj.bjc.6603933
24. Bishop EA, Lightfoot S, Thavathiru E, Benbrook DM (2014) Insulin exerts direct effects on carcinogenic transformation of human endometrial organotypic cultures. Cancer Invest 32:63–70. doi:10.3109/07357907.2013.877479
25. Nagamani M, Stuart CA (1998) Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am J Obstet Gynecol 179:6–12
26. Chodick G, Elchalal U, Sella T, Heymann AD, Porath A, Kokia E, Shalev V (2010) The risk of overt diabetes mellitus among women with gestational diabetes: a population-based study. Diabet Med 27:779–785. doi:10.1111/j.1464-5491.2010.02995.x
27. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, Delahanty LM, Montez MG, Ackermann RT, Zhuo X, Knowler WC, Ratner RE, Diabetes Prevention Program Research Group (2015) The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab 100:1646–1653. doi:10.1210/jc.2014-3761
28. Committee on Practice Bulletins-Obstetrics (2013) Practice Bulletin No. 137: gestational diabetes mellitus. Obstet Gynecol 122:406–416. doi:10.1097/01.AOG.0000433006.09219.f1
29. Hunt KJ, Schuller KL (2007) The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin N Am 34:173–199, vii. doi:10.1016/j.ogc.2007.03.002
30. Xiong X, Saunders LD, Wang FL, Demianczuk NN (2001) Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes. Int J Gynaecol Obstet 75:221–228
31. Lacey JV Jr, Chia VM (2009) Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas 63:39–44. doi:10.1016/j.maturitas.2009.02.005
32. Barfield WD, Committee on Fetus and Newborn (2011) Standard terminology for fetal, infant, and perinatal deaths. Pediatrics 128:177–181. doi:10.1542/peds.2011-1037
33. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 26(Suppl 1):S5–S20
34. Maldonado G, Greenland S (1993) Simulation study of confounder-selection strategies. Am J Epidemiol 138:923–936
35. Bliss R, Weinberg J, Webster T, Vieira V (2012) Determining the probability distribution and evaluating sensitivity and false positive rate of a confounder detection method applied to logistic regression. J Biom Biostat 3:142. doi:10.4172/2155-6180.1000142
36. Rothman KJ, Greenland S, Lash LT (2008) Modern epidemiology, 3rd edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia
37. Grayson DA (1987) Confounding confounding. Am J Epidemiol 126:546–553
38. Kwon JS, Scott JL, Gilks CB, Daniels MS, Sun CC, Lu KH (2011) Testing women with endometrial cancer to detect Lynch syndrome. J Clin Oncol 29:2247–2252. doi:10.1200/JCO.2010.32.9979
39. Azur MJ, Stuart EA, Frangakis C, Leaf PJ (2011) Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 20:40–49. doi:10.1002/mpr.329

40. Bhaskaran K, Smeeth L (2014) What is the difference between missing completely at random and missing at random? Int J Epidemiol 43:1336–1339. doi:10.1093/ije/dyu080
41. Schafer JL (1997) Analysis of incomplete multivariate data. Chapman & Hall, London
42. Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 50:1365–1374. doi:10.1007/s00125-007-0681-5
43. Zhang ZH, Su PY, Hao JH, Sun YH (2013) The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer 23:294–303. doi:10.1097/IGC.0b013e31827b8430
44. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM (2014) Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol 135:163–171. doi:10.1016/j.ygyno.2014.07.095
45. Saltzman BS, Doherty JA, Hill DA, Beresford SA, Voigt LF, Chen C, Weiss NS (2008) Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. Am J Epidemiol 167:607–614. doi:10.1093/aje/kwm333
46. Epplein M, Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS (2008) Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. Am J Epidemiol 168:563–570. doi:10.1093/aje/kwn168
47. Lydon-Rochelle MT, Holt VL, Cardenas V, Nelson JC, Easterling TR, Gardella C, Callaghan WM (2005) The reporting of preexisting maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. Am J Obstet Gynecol 193:125–134. doi:10.1016/j.ajog.2005.02.096
48. Williams MA (2011) In: Louis GMB, Platt RW (eds) Reproductive and perinatal epidemiology. Oxford University Press, New York
49. Graham JW (2009) Missing data analysis: making it work in the real world. Annu Rev Psychol 60:549–576. doi:10.1146/annurev.psych.58.110405.085530
50. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, Voigt LF, Weiss NS (2009) Incidence of endometrial hyperplasia. Am J Obstet Gynecol 200(678):e671–e676. doi:10.1016/j.ajog.2009.02.032
51. Reed SD, Newton KM, Garcia RL, Allison KH, Voigt LF, Jordan CD, Epplein M, Swisher E, Upson K, Ehrlich KJ, Weiss NS (2010) Complex hyperplasia with and without atypia: clinical outcomes and implications of progestin therapy. Obstet Gynecol 116:365–373. doi:10.1097/AOG.0b013e3181e93330
52. SEER Cancer Statistics Factsheets: Endometrial Cancer. National Cancer Institute. http://seer.cancer.gov/statfacts/html/corp.html
53. Koepsell TD, Weiss NS (2003) Epidemiologic methods: studying the occurrence of illness. Oxford University Press, Oxford
54. Maggino T, Pirrone F, Velluti F, Bucciante G (1993) The role of the endocrine factors and obesity in hormone-dependent gynecological neoplasias. Eur J Gynaecol Oncol 14:119–126
55. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, Rinaldi S, Dossus L, Slimani N, Lundin E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Mesrine S, Joulin V, Linseisen J, Rohrmann S, Pischon T, Boeing H, Trichopoulos D, Trichopoulou A, Benetou V, Palli D, Berrino F, Tumino R, Sacerdote C, Mattiello A, Quiros JR, Mendez MA, Sanchez MJ, Larranaga N, Tormo MJ, Ardanaz E, Bueno-de-Mesquita HB, Peeters PH, van Gils CH, Khaw KT, Bingham S, Allen N, Key T, Jenab M, Riboli E (2007) Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab 92:255–263. doi:10.1210/jc.2006-1371
56. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W (2003) Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst 95:1797–1800
57. Soini T, Hurskainen R, Grenman S, Maenpaa J, Paavonen J, Pukkala E (2014) Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol 124:292–299. doi:10.1097/AOG.0000000000000356
58. Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, Higgins R, Zaino R, Mutter GL, Society of Gynecologic Oncology Clinical Practice Committee (2012) Management of endometrial precancers. Obstet Gynecol 120:1160–1175. doi:10.1097/AOG.0b013e31826bb121
59. Eheman C, Henley SJ, Ballard-Barbash R, Jacobs EJ, Schymura MJ, Noone AM, Pan L, Anderson RN, Fulton JE, Kohler BA, Jemal A, Ward E, Plescia M, Ries LA, Edwards BK (2012) Annual report to the nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer 118:2338–2366. doi:10.1002/cncr.27514