SHORT COMMUNICATION

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Long-term impact of preeclampsia on maternal endometrial cancer risk

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Background: Endometrial cancer is mainly dependent on oestrogen exposure. Preeclampsia has shown to reduce oestrogen levels hence preeclampsia may affect later endometrial cancer risk.

Methods: We conducted a case–control study of 523 Danish women with endometrial cancer and 52 299 controls during 1978–2010. The association between preeclampsia and later endometrial cancer was evaluated overall and according to preeclampsia onset and type of endometrial cancer in conditional logistic regression models.

Results: We observed no overall association between preeclampsia and endometrial cancer risk (OR = 1.11 (95% CI 0.68–1.81)). This was true for all endometrial cancer subtypes. In an analysis of preeclampsia onset, however, we report a markedly increased risk of endometrial cancer following early-onset preeclampsia (OR = 2.64 (95% CI 1.29–5.38)).

Conclusions: Although we report no obvious association between preeclampsia and endometrial cancer, studying the subset of early-onset preeclampsia may prove fruitful in further understanding the aetiology of endometrial cancer.

Endometrial cancer is the most common gynaecological malignancy affecting postmenopausal women (Purdie, 2003). Endometrial carcinogenesis is thought to be the result of increased proliferation of endometrial cells due to excess oestrogen exposure (Persson, 2000). Preeclampsia is a pregnancy-induced syndrome characterised by elevated blood pressure and protein excretion in the urine (Steegers *et al*, 2010), and has shown to reduce oestrogen and increase androgen and progesterone levels (Nechuta *et al*, 2010). This is thought to underlie the consistent finding of reduced breast cancer risk following preeclampsia (Vatten *et al*, 2002; Innes and Byers, 2004; Nechuta *et al*, 2010; Kim *et al*, 2013; Pacheco *et al*, 2015). Similarly, in the current study we hypothesised that preeclampsia would be associated with reduced risk of later endometrial cancer.

MATERIALS AND METHODS

Study population. We designed the present study as a density sampling case–control study, using data from nationwide Danish registers during the period 1978–2010. From the Danish Medical Birth Registry (Knudsen and Olsen, 1998), we identified all women who gave birth in Denmark during 1 January 1978 to 31 December 2010. We included women with singleton pregnancies ending in a live or still birth (⩾22 weeks of gestation), and women with no record of endometrial cancer prior to pregnancy. We randomly sampled 100 age-matched controls per case who at time of sampling had not received a diagnosis of endometrial cancer. We obtained information on date of migration and death for all cases and controls from the Danish Civil Registration system (Pedersen, 2011).

Preeclampsia. We identified maternal hospital contacts with preeclampsia occurring during any pregnancy from the Danish National Patient Register (Lynge *et al*, 2011). Herein, hospital contacts are coded according to the International Classification of Diseases 8th revision (ICD-8) during 1978–1993 and the 10th revision during 1994–2010. Preeclampsia hospital contacts were identified using the ICD-8 codes 637.03, 637.04, 637.09, 637.19 and 661.3, and the ICD-10 codes O14 and O15. We further subdivided preeclampsia in early-onset preeclampsia (22–33 weeks of gestation) and late-onset preeclampsia (34–44 weeks of gestation) measured in completed pregnancy weeks.

Endometrial cancer. Diagnosis of endometrial cancer was defined according to The International Classification for Oncology 3rd

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Edition (ICD-O-3) and obtained from the Danish Cancer Registry (Gjerstorff, 2011). Women with an incident diagnosis of endometrial cancer were identified using the ICD-O-3 codes C54-C54.9 and C55.9. We further subdivided women with endometrial cancer into cases with hormone-dependent Type-I endometrial cancer (ICD-O-3 codes: 8140, 8380, 8382, 8480, 8482, 8560, 8570) and hormone-independent Type-II endometrial cancer (ICD-O-3 codes: 8310, 8441, 8460). The remaining endometrial cancer types, which are unspecified, rare, and do not share the same histological characteristics as Type-I and Type-II endometrial cancers (ICD-O-3 codes: 80103, 80703, 81433, 82103, 82463, 82603, 83813, 84703, 88003, 88903, 88913, 88963, 89003, 89303, 89313, 89333, 89353, 89503, 89803, 91003, 91053, 99903, 99993), were classified as 'Other'.

Statistical methods. We explored the association between preeclampsia and later endometrial cancer by odds ratios (OR) with 95% confidence intervals estimated in conditional logistic regression models. Analyses were carried out using the PHREG procedure in SAS version 9.4 (SAS Institute Inc., 2008).

Further, we conducted subgroup analyses according to subtype of endometrial cancer and onset of preeclampsia. All analyses were adjusted for age at first birth (5-year age groups), parity (1, 2, ⩾3), diabetes (yes *vs* no) and maternal educational attainment (primary education, upper secondary education, vocational education, short cycle higher education, university or higher education).

RESULTS

During the study period, a total of 523 women were diagnosed with endometrial cancer and a total of 52 229 age-matched women without endometrial cancer were sampled as controls. At time of endometrial cancer diagnosis, the mean age of women was 50 (range 24–68) years (data not shown).

Table 1 shows characteristics of the studied cases and controls. Compared with controls, cases were more often primiparous and more often had diabetes. Cases and controls were on average 29 years old when delivering their first child (28.8 years (range: 17–46) and 29.2 years (range-15–52), respectively; data not shown. Cases had given birth to an average of 1.89 children (range 1–7), while the similar figure for women in the control group was 2.03 (range 1–13; data not shown).

Table 2 shows the prevalence of preeclampsia among cases and controls and the association between preeclampsia and later endometrial cancer overall and according to cancer subsets. Having had a pregnancy complicated by preeclampsia was observed in 18 (3.4%) cases and 1515 (2.9%) controls, which corresponds to an adjusted overall OR of 1.11 (95% CI 0.68–1.81). In the cancer subgroup analyses, we found women with preeclampsia to have a 19% increased risk of Type-I endometrial cancer (OR = 1.19, 95% CI: 0.70–2.05). No women with preeclampsia developed Type-II endometrial cancer during the study period, why the association was not estimable, and we observed no association between preeclampsia and other types of endometrial cancer (OR = 1.01, 95% CI 0.32–3.20).

Table 3 shows the prevalence of preeclampsia stratified according to onset of preeclampsia among cases and controls and associated OR (95% CI). Women with early-onset preeclampsia had a markedly increased risk of later endometrial cancer, while women with late-onset preeclampsia tended to have a slightly reduced risk compared with women without preeclampsia (OR = 2.64, 95% CI 1.29–5.38 and OR = 0.73, 95% CI 0.38–1.42, respectively).

Table 1. Characteristics of cases and controls according to age at time of sampling, age at first birth, parity, diabetes and the mother's educational attainment. Numbers (column percentage)

	Cases ($n = 523$)	Controls ($n = 52\,299$)
Age at time of sampling (years)		
<51	272 (52.0)	27 200 (52.0)
⩾51	251 (48.0)	25 099 (48.0)
Age at first birth (years)		
<25	140 (26.8)	11 724 (22.4)
25–29	193 (36.9)	19 420 (37.1)
30–34	114 (21.8)	13 402 (25.6)
⩾35	76 (14.5)	7753 (14.8)
Parity		
1	186 (35.6)	14 429 (27.6)
2	237 (45.3)	25 778 (49.3)
⩾3	100 (19.1)	12 092 (23.1)
Diabetes		
Yes	18 (3.4)	882 (1.7)
No	505 (96.6)	51 417 (98.3)
Education		
University or higher	38 (7.3)	3889 (7.5)
Short cycle higher	139 (26.8)	15 677 (30.3)
Vocational	177 (34.2)	17 465 (33.8)
Upper secondary	20 (3.9)	2159 (4.2)
Primary	144 (27.8)	12 469 (24.1)

DISCUSSION

In summary, we report that preeclampsia did not alter the overall risk of endometrial cancer. This finding is in agreement with a Swedish cohort study reporting no obvious association between preeclampsia and risk of endometrial cancer (Mogren *et al*, 2001). We set out with the anticipation that women with preeclampsia would be at reduced risk of later endometrial cancer analogous to what is observed in breast cancer (Innes and Byers, 2004; Nechuta *et al*, 2010; Kim *et al*, 2013; Pacheco *et al*, 2015). We observed no such risk reduction, not even in analyses confined to women with the oestrogen-sensitive endometrial cancer subtype I.

Evidence suggests that breast cancer is sensitive to a combination of oestrogens and progesterone (Anderson, 2002), whereas endometrial cancer is generally dependent solely on oestrogen exposure (Henderson and Feigelson, 2000), which may explain the differing effects of preeclampsia on breast and endometrial cancer risk. Alternatively, the lack of an overall association may reflect that our exposure is subject to misclassification or due to residual confounding. Moreover, preeclampsia may carry other risks that outweigh the positive consequences of hormonal fluctuations.

Table 2. Preeclampsia and risk of endometrial cancer overall and according to type of endometrial cancer

	Overall ($n = 523$)			Type-I ($n = 393$)			Type-II ($n = 21$)			Type-III ($n = 109$)		
Preeclampsia	Cases, *n* (col%)	Controls, *n* (col%)	OR (95% CI)	Cases, *n* (col%)	Controls, *n* (col%)	OR (95% CI)	Cases, *n* (col%)	Controls, *n* (col%)	OR (95% CI)	Cases, *n* (col%)	Controls, *n* (col%)	OR (95% CI)
Yes	18 (3.4)	1515 (2.9)	1.10 (0.68–1.80)	14 (3.6)	1515 (2.9)	1.19 (0.69–2.04)	0 (0)	1515 (2.9)	NE	4 (3.7)	1515 (2.9)	0.99 (0.31–3.13)
No	505 (96.6)	50 784 (97.1)	1 (ref.)	379 (96.4)	50 784 (97.1)	1 (ref.)	21 (100)	50 784 (97.1)	1 (ref.)	105 (96.3)	50 784 (97.1)	1 (ref.)

Abbreviations: CI = confidence interval; col% = column per cent; NE = not estimable; OR = odds ratio. OR adjusted for age at first birth, parity, diabetes and educational attainment.

Table 3. Preeclampsia and endometrial cancer risk according to onset of preeclampsia

Preeclampsia	Cases, *n* (col%)	Controls, *n* (col%)	OR (95% CI)
Early onset	9 (1.7)	292 (0.6)	2.62 (1.28–5.34)
Late onset	9 (1.7)	1223 (2.3)	0.73 (0.38–1.42)
No	505 (96.6)	50 784 (97.1)	1 (ref.)

Abbreviations: CI = confidence interval; col% = column per cent; OR = odds ratio. OR adjusted for age at first birth, parity, diabetes and educational attainment.

Women with a mild degree of preeclampsia who did not require hospital treatment were misclassified as unexposed in our study. The diagnosis of preeclampsia, however, did not depend on future diagnosis of endometrial cancer. Consequently, this non-differential misclassification of exposure might have led us to underestimate any true association of preeclampsia and subsequent endometrial cancer.

Information on important confounders, including hormone-replacement therapy (HRT) and body mass index (BMI), physical activity and smoking was not available in the health registers. High BMI markedly increases the risk of endometrial cancer (Lindermann *et al*, 2008), as well as preeclampsia (Duckitt and Harrington, 2005). Therefore, we cannot reject the possibility that the increased risk of endometrial cancer observed among women with early-onset preeclampsia is in part due to confounding from BMI. High BMI and diabetes are strongly correlated (Hossain *et al*, 2007) and the association between diabetes and endometrial cancer is largely explained by body weight (Luo *et al*, 2014). Thus, we argue that adjustment for diabetes indirectly and partially also adjusted our results for BMI. HRT increases the risk of endometrial cancer (Beral *et al*, 2005), and is also considered a risk factor for developing cardiovascular disease (Chong and Lip, 2002). Also, independent of HRT, preeclampsia has been associated with an increased risk of cardiovascular disease (Bellamy *et al*, 2007). Therefore, women with preeclampsia will less often have been offered HRT treatment at menopause compared with women without preeclampsia in the present study. Lack of adjustment for HRT has left our estimated association between preeclampsia and later endometrial cancer conservative. Physical activity and smoking protect against preeclampsia (Magnus *et al*, 2008; Sibai *et al*, 1997) and endometrial cancer (Moore *et al*, 2010; Setiawan *et al*, 2013; Terry *et al*, 2002). Residual confounding by these variables may likely underestimate any true association.

Strengths of the current study include the prospective nature of data, a low risk of selection bias and the large study population. By design, we ensured that the exposure predated the outcome and matching controls to cases on exact age with 1-day precision eliminated confounding from age. Also, because controls were randomly selected among all Danish women giving birth, we markedly reduced the risk of selection bias.

In conclusion, we observe an elevated risk of later endometrial cancer following preeclampsia, but only among women with early-onset preeclampsia. We encourage others with additional data on BMI and HRT to pursue the possibility that this is not an incidental finding.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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