



Original article

Preeclampsia and breast cancer: The influence of birth characteristics



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ABSTRACT

Background: In parous women preeclampsia has been associated with reduced risk of developing breast cancer. Characteristics of births following preeclamptic pregnancies may help understand mechanisms involved in the breast cancer risk reduction inferred by preeclampsia.

Methods: We conducted a register-based cohort study of all Danish women giving birth during 1978–2010 ($n = 778,701$). The association between preeclampsia and breast cancer was evaluated overall and according to birth characteristics by means of incidence rate ratios (IRR) estimated in Poisson regression models.

Results: Compared with women with non-preeclamptic pregnancies only, women with one or more preeclamptic pregnancies were 19% significantly less likely to develop breast cancer (IRR = 0.81 [95% CI 0.72–0.93]). We found some indication of greater risk reduction in women with term births, one or more previous births, and in women giving birth to boys. These findings, however, did not reach statistical significance. Finally, risk reduction was slightly greater following milder forms of preeclampsia.

Conclusion: Our data is compatible with an approximately 20% reduction in risk of developing breast cancer following preeclampsia. Although we find some variability according to birth characteristics, the risk reduction inferred by preeclampsia seems applicable to most preeclamptic pregnancies.

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Introduction

Preeclampsia is a pregnancy related syndrome arising from the placenta, leading to elevated blood pressure and protein excretion in the urine. Preeclampsia may cause milder or more severe damage in organ systems as a result of systemic inflammation and endothelial damage [1]. Preeclampsia is estimated to complicate 3–7% of pregnancies [2], and is one of the leading causes of maternal morbidity and mortality during pregnancy worldwide [3]. The underlying etiology remains poorly understood, but reproductive and maternal characteristics including primiparity, twin pregnancy, ethnicity, age, weight and cigarette smoking have been associated with risk of preeclampsia [4]. Interestingly, a recent meta-analysis reported a 14% reduced risk of breast cancer in women with a history of preeclampsia (HR = 0.86 [95% CI 0.71–1.01]) [5]. Some studies suggest that such risk reduction is conferred to preeclamptic pregnancies with a male fetus only [6]. To further characterize the association between preeclampsia and breast cancer, in the current study we investigated the association

overall and according to birth characteristics using nationwide Danish register-based data.

Material and methods

The investigation is based on person identifiable data obtained from nationwide Danish registers. Register linkage was performed using the unique 10-digit Danish identity number found in all the applied registers. In the Danish Medical Birth Registry (DMBR) [7] we identified all women who gave birth in Denmark during 1 January 1978 through 31 December 2010. Also, from DMBR we obtained information on characteristics of the women's births including live or still birth, birth weight, gestational duration, parity, multiple pregnancy, and offspring sex. We divided birth weight into weight groups (<2500, 2500–3499, 3500–4499, ≥4500), and gestational duration into groups of completed pregnancy weeks (preterm: 22–36, term: 37–41, postterm: 42–44). We classified the 10 percent lightest and heaviest within each completed pregnancy week as born small and large for gestational age, respectively. The middle 80 percent were considered appropriate for gestational age. We excluded births with implausible [8] or missing weight from analyses. Similarly, we excluded multiple pregnancies and births with missing offspring sex. In the Danish

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National Patient Register (DNPR) [9] we identified maternal hospital contacts with preeclampsia occurring during pregnancy. In DNPR hospital contacts are coded according to the International Classification of Diseases [10] 8th revision (ICD-8) during 1978–1993 and 10th revision (ICD-10) during 1994–2010. We used the ICD-8 codes 637.03, 637.04, 637.09, 637.19, 637.99 and 661.3, and the ICD-10 codes O14 and O15 to identify preeclampsia hospital contacts. We subdivided preeclampsia according to severity based on ICD codes (mild: 637.03, 637.99, O14.0, O14.9, severe: all other above pre-eclampsia codes), and onset measured in completed pregnancy weeks (early: 22–33, late 34–44). We obtained date of migration and death for all women from the Danish Civil Registration System (DCRS) [11]. In the Danish Cancer Registry (DCR) [12], we identified women diagnosed with incident breast cancer by the ICD-10 code C50. In DCR all cancer diagnoses occurring since 1943 have been reclassified according to ICD-10.

We evaluated the association between preeclampsia and breast cancer in a cohort design by calculating incidence rate ratios (IRR) with 95% confidence intervals (95% CI), obtained by multiple Poisson regression with the logarithm of person-years at risk as offset. Person-years at risk were calculated from the date of giving birth to the first-coming of end of follow-up, emigration, death, or breast cancer diagnosis. Preeclampsia was included in the model as a time varying exposure denoting whether women had ever had a pregnancy complicated by preeclampsia. Exposed time was counted from time of first preeclampsia diagnosis. All analyses were adjusted for age (5-year age groups), calendar period (5-year calendar periods), parity (1, 2, ≥ 3), and age at most recent birth (5-year age groups) included in the model as time-varying covariates. These covariates were chosen *a priori*. We evaluated the association between preeclampsia and breast cancer overall, according to birth characteristics, and according to preeclampsia characteristics, respectively. We evaluated the influence of birth characteristics by adding interaction terms between preeclampsia and the relevant birth characteristic to the model. The influence of preeclampsia characteristics was evaluated by running separate models for each preeclampsia subtype. All data management and analysis was carried out in SAS version 9.3 [13]. Person-years at risk and events were stratified and aggregated using the %stratify macro [14] and Poisson regression models were evoked using the GENMOD procedure.

Results

During the study period 778,762 women were registered with a total of 1,520,407 births, averaging to 1.95 (range 1–14) births per woman. Women were followed for 12,427,679 person-years at risk during which 9883 events of incident breast cancer were diagnosed. This translates to an overall IR of breast cancer of 79.5 (95% CI 78.0–81.1) per 100,000 person-years at risk. At time of breast cancer diagnosis the mean age of women was 46.0 (range 22.4–70.8) years (data not shown). As shown in Table 1 outlining characteristics of the studied pregnancies, a total of 20,805 (1.4%) pregnancies were complicated by preeclampsia. In our data preeclampsia was more often observed in pregnancies ending in still birth, low birth weight, preterm birth, small size for gestational age, low maternal age, and in primiparity. Also, preeclampsia occurred more often during first part of the study period, and offspring sex did not influence the occurrence of preeclampsia. In total 28,316 preeclampsia hospital contacts were recorded during the 20,805 preeclampsia pregnancies complicated by preeclampsia (data not shown).

Table 2 shows the number of breast cancer events, person-years at risk, crude breast cancer incidence rate and the association between preeclampsia and breast cancer overall and according to birth characteristics. Overall, women with a pregnancy complicated

Table 1

Characteristics of births, Denmark 1978–2010. Number (percentage).

	Pregnancy complicated by preeclampsia		Total (col%)
	Yes (row%)	No (row%)	
Births	20,801 (1.4)	1,495,602 (98.6)	1,520,407 (100)
Birth outcome			
- Live birth	20,725 (1.4)	1,495,227 (98.6)	1,515,952 (99.7)
- Still birth	80 (1.8)	4,375 (98.2)	4,455 (0.3)
Birth weight, grams			
- <2500	3,093 (5.0)	58,890 (95.0)	61,983 (4.1)
- 2500–3499	8,924 (1.3)	673,564 (98.7)	682,488 (44.9)
- 3500–4499	8,041 (1.1)	720,045 (98.9)	728,086 (47.9)
- ≥ 4500	747 (1.6)	47,103 (98.4)	47,850 (3.1)
Term			
- Preterm	2,834 (3.9)	70,519 (96.1)	73,353 (4.8)
- Term	16,700 (1.3)	1,303,737 (98.7)	1,320,437 (86.9)
- Postterm	1,271 (1.0)	125,346 (99.0)	126,617 (8.3)
Size for gestational age			
- Small	3,178 (2.2)	141,268 (97.8)	144,446 (9.5)
- Appropriate	15,458 (1.3)	1,208,952 (98.7)	1,224,410 (80.5)
- Large	2,169 (1.4)	149,382 (98.6)	151,551 (10.0)
Maternal age at birth, years			
- <25	6,456 (1.8)	352,438 (98.2)	358,894 (23.6)
- 25–29	7,821 (1.3)	576,231 (98.7)	584,052 (38.4)
- 30–34	4,505 (1.1)	413,865 (98.9)	418,370 (27.5)
- ≥ 35	2,023 (1.3)	157,068 (98.7)	159,091 (10.5)
Year at birth			
- 1978–1989	7,458 (1.7)	427,832 (98.3)	435,290 (28.6)
- 1990–1999	7,667 (1.4)	531,319 (98.6)	538,986 (35.5)
- 2000–2010	5,680 (1.0)	540,451 (99.0)	546,131 (35.9)
Parity			
- 1	14,125 (1.9)	723,072 (98.1)	737,197 (48.5)
- 2	4,798 (0.9)	545,946 (99.1)	550,744 (36.2)
- ≥ 3	1,882 (0.8)	230,584 (99.2)	232,466 (15.3)
Offspring sex			
- Male	10,822 (1.4)	769,651 (98.6)	780,473 (51.3)
- Female	9,983 (1.4)	729,951 (98.6)	739,934 (48.7)

by preeclampsia were 19% significantly less likely to develop breast cancer (IRR = 0.81 [95% CI 0.72–0.93]) compared with women with non-preeclamptic pregnancies only. No women with a pre-eclamptic pregnancy which ended in a still birth developed breast cancer. Therefore the association was not estimable in this stratum. Despite some fluctuation in IRR between strata the test for interaction came out statistically significant for none of the investigated variables. We found, however, some indication that term birth was associated with greater risk reduction compared with preterm and postterm birth ($p = 0.09$). Term births complicated by preeclampsia were associated with 25% reduced risk of breast cancer (IRR = 0.75 [95% CI 0.65–0.87]). Preterm and postterm births complicated by preeclampsia, however, were not associated with neither reduced nor increased breast cancer risk. Also, association between preeclampsia and breast cancer differed somewhat according to parity ($p = 0.16$) and offspring sex ($p = 0.18$). Reduced risk of breast cancer was found only in women having 2 or more children, and following a pregnancy with a male fetus. Tests for interaction did not come out statistically significant for these variables, however.

In Table 3 breast cancer events, person-years at risk, crude breast cancer incidence and the association between preeclampsia and breast cancer is presented according to severity and onset. The risk of breast cancer was reduced by 28% (IRR 0.72, [95% CI 0.61–0.85]) in women diagnosed with mild preeclampsia, compared with women with non-preeclamptic pregnancies. Women with a diagnosis of severe preeclampsia did not display such risk reduction, however (IRR = 1.01 [95% CI 0.82–1.24]). Testing the contrast between the IRR estimates for mild and severe preeclampsia yielded a significant p -value of 0.01. When we stratified preeclampsia according to the onset of the disease, only women with late onset of preeclampsia had a statistically significant reduced risk of developing breast cancer. Although the risk

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