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EPIDEMIOLOGY

Placental weight and mortality in premenopausal breast cancer by tumor characteristics

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Abstract Placental weight may be regarded as an indirect marker of hormone exposures during pregnancy. There is epidemiological evidence that breast cancer mortality in premenopausal women increases with placental weight in the most recent pregnancy. We investigated if this association differs by tumor characteristics, including expression of estrogen and progesterone receptors. In a Swedish population-based cohort, we followed 1,067 women with premenopausal breast cancer diagnosed from 1992 to 2006. Using Cox regression models, we estimated hazard ratios for the association between placental weight and risk of premenopausal breast cancer mortality. In stratified analyses, we estimated mortality risks in subjects with different tumor stages, estrogen receptor (ER) or progesterone receptor (PR) status. Compared with women with placental weight less than 600 g, women with a placental weight between 600 and 699 g were at a 50 % increased risk of mortality, however, not significant change in risk was observed for women with placental weight ≥700 g. Mortality risks associated with higher placental weight were more pronounced among ER^- and PR^- breast cancer tumors, where both a placental weight 600–699 g and ≥700 g were associated with a more than doubled mortality risks compared with tumors among women with placental weight less than 600 g. Moreover, stratified analyses for joint receptor status revealed that a consistent increased mortality risk by placental weight was only apparent in women with ER^-/PR^- breast cancer. The increased mortality risk in premenopausal breast cancer associated with higher placental weight was most pronounced among ER^- and PR^- tumors.

Keywords Breast cancer · Premenopausal · Placental weight · Estrogen receptor · Progesterone receptor

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Introduction

Reproductive factors are well-known risk factors for breast cancer, but less is known regarding their effect on breast cancer prognosis. Some pregnancy related factors—such as parity [7, 20, 39], age at first childbirth [1, 30, 50], and time between last childbirth and diagnosis of breast cancer [7,

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39] may be used as indicators for different levels of exposure to pregnancy hormones. Breast cancers, which are diagnosed shortly after childbirth have poor prognosis [7, 24, 29, 36, 39, 43, 45, 48], but the impact of other reproductive factors on survival remain uncertain [1, 7, 29, 30, 36, 45, 50].

Prognostic factors for breast cancer survival include tumor characteristics—stage and histopathology—and biological characteristics, such as expression of estrogen receptor (ER) and progesterone receptor (PR) status [3, 5, 8, 11, 14, 19, 39, 46, 49, 53]. Breast cancer with higher tumor stages [11, 39, 46, 49], ER-negative [39], PR-negative [46] or histopathologic type Ductal [11, 19] breast cancer have poorer survival.

During pregnancy, there is a dramatic increase in levels of estrogens and other hormones primarily produced by the placenta [25]. There is a positive association between placental weight and estrogen levels during pregnancy [18, 25, 37]. In a well-designed prospective study, Mucci et al. [37] showed that there is a statistically significant positive association between placental weight and pregnancy estriol, progesterone, and prolactin levels in maternal serum samples. Thus, placental weight can be considered to be an indirect marker of exposure to hormone levels during pregnancy. During pregnancy and during the years following pregnancy, there is a transient increase in breast cancer risk [31]. These "pregnancy-associated breast cancers" have a larger frequency of ER^- and PR^- tumors, and also a poorer prognosis [17, 38, 43, 47]. In a recent study [32], we found evidence of a positive association between increasing placental weight in the most recent pregnancy and risk of breast cancer mortality. However, due to lack of information, we were unable to investigate whether the influence of placental weight on breast cancer mortality differed by tumor characteristics.

In a Swedish population-based study of more than 1,000 women with premenopausal breast cancer, we had prospectively recorded information on birth characteristics (including placental weight) and tumor characteristics (including stage and hormone receptor status). We hypothesized that the previously observed positive association between placental weight in the most recent pregnancy and risk of breast cancer mortality vary among breast cancers with different tumor characteristics.

Materials and methods

Data sources

The cohort was based on information from two Swedish Regional Quality Registers on Breast Cancer, which was linked to information from population-based registers, held by the Swedish National Board of Health and Welfare and Statistics Sweden. Individual record linkage across these registers was possible through the unique personal identity number, assigned to each Swedish resident [33].

The Quality Registers on Breast Cancer is based on information collected in the six geographically defined Health Care Regions in Sweden. From 1992 onwards, information is collected on diagnostic procedures and treatment, tumor characteristics, including stage at diagnosis (tumor size, lymph node involvement, and existence of distant metastases) and biological characteristics [grade and hormone (estrogen or progesterone) receptor status] in all six regions. With regard to capture of incident breast cancer cases, the Regional Quality Registers are validated against the national Swedish Cancer Register and have a completeness exceeding 95 % [6]. For information on tumor characteristics, the completeness is highest in the Quality Registers covering the Stockholm-Gotland Region and the Uppsala-Örebro Region in Central Sweden.

The Medical Birth Register includes prospectively collected information during pregnancy, delivery, and the neonatal period on virtually all births in Sweden since 1973 [13]. Gestational age is based on early second trimester ultrasound when available; otherwise information about the time of last menstrual period is used. Placental weight was recorded between 1982 and 1989.

The Education, Migration, and Causes of Death Registers provided information about education, and dates of emigration and death, respectively. The Cause of Death Register contains information on all deaths on Swedish residents since 1960. Information is based on death certificates and contains main and contributory causes of death coded according to International Classification of Diseases, 7th–10th versions [6].

Study population

Between 1992 and 2006, there were 40,948 women diagnosed with breast cancer and registered in the Quality Registers covering the Stockholm-Gotland Region and the Uppsala Örebro Region in Central Sweden. At the time of breast cancer diagnosis, women were asked whether they were premenopausal or postmenopausal. Of in total 8,508 women with premenopausal breast cancer, 7,399 were excluded because they were nulliparous or data on placental weight at their last pregnancy before breast cancer diagnosis were not recorded (placental weight was only recorded in births between 1982 and 1989), We excluded eight subjects due to missing information on gestational age and 34 subjects with implausible placental weights. Although breast cancer was recorded as premenopausal or postmenopausal, we preferred to also exclude 24 subjects with recorded premenopausal breast cancer whose age at

diagnosis was more than 55 years. In total, the study cohort included 1,067 women with premenopausal breast cancer and information about placental weight in their last pregnancy before breast cancer diagnosis. We followed the study subjects from the date of breast cancer diagnosis until emigration, death or until December 31st, 2008, whichever occurred first.

Statistical analysis

We used Cox regression models to estimate hazard ratios (HR) with 95 % confidence intervals (CI) as a measure of the association between placental weight and risk of premenopausal breast cancer mortality. Follow-up time was the underlying time scale. Placental weight was considered both as a continuous and a categorized variable (<600, 600–699, and ≥700 g). The cut offs were chosen to ensure that enough number of subjects and events were present in each category. The models were adjusted for gestational age (≤36, 37–38, 39–41, and ≥42 weeks), parity (1, 2, 3, and ≥4), age at diagnosis of breast cancer (<30, 30–34, 35–39, 40–44, 45–49, and 50–54 years), and education level (less than high school, high school, and more than high school).

To check for interaction effects, we added interaction terms of placental weight (categorical variable) and stage of tumor, ER or PR status (categorical variables) and histology of tumor into the full models. We performed stratified analyses to estimate the risks of breast cancer mortality in subjects with different tumor stages (stage 0–1, stage 2, or stage 3–4), ER status (ER^+, ER^-) and PR status (PR^+, PR^-), and histology of tumors (Ductal, Lobular, Other). We also performed the stratified analyses for joint receptor status (ER^+PR^+, ER^+PR^-, ER^-PR^+, ER^-PR^-).

The assumption of proportionality was verified for all of the analyses by including time-by covariate interaction in the model and testing the statistical significance. All analyses were performed using the SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows characteristics of the cohort and crude (unadjusted) mortality risks. Compared with women with placental weight less than 600 g, women with placental weight 600–699 g in the most recent pregnancy had ~50 % higher mortality risk after diagnosis of premenopausal breast cancer. In contrast, no increased mortality risk could be detected for women with a placental weight of 700 g or more. Low age at diagnosis of breast cancer and short time difference (<10 years) between last childbirth and diagnosis of breast cancer were associated with

Table 1 Characteristic of 1067 parous women with premenopausal breast cancer diagnosed 1992–2006, and crude hazard ratios (HR) for mortality

Total	Subject 1,067	Event 180	Crude HR (95 % CI)
Offsprings charactistics (last pregnancy)			
Placental weight (g)			
<600	458	70	Reference
600–699	322	69	1.49 (1.07–2.08)
≥700	287	41	0.90 (0.61–1.32)
Continuous, 50 g	1067	180	1,00 (0.94–1.05)
Mean (SD)	622.27 (123.5)		
Median (range)	610 (220–980)		
Gestational age (weeks)			
≤36	66	10	0.87 (0.43–1.75)
37–38	194	35	Reference
39–41	745	120	0.97 (0.67–1.42)
≥42	62	15	1.35 (0.74–2.47)
Continuous (weeks)	1,067	180	1.09 (0.87–1.37)
Mean (SD)	39.28 (2.0)		
Median (range)	40.00 (23–44)		
The subjects characteristics			
Parity			
1	158	36	Reference
2	559	87	0.73 (0.49–1.07)
3	272	44	0.67 (0.43–1.04)
≥4	78	13	0.58 (0.31–1.10)
Continuous	1,067	180	0.84 (0.70–1.01)
Mean (SD)	2.27 (0.9)		
Median (range)	2.00 (1–7)		
Age at diagnosis (years)			
<30	5	2	1.74 (0.42–7.14)
30–34	14	9	4.07 (2.02–8.20)
35–39	91	34	1.96 (1.29–2.99)
40–44	265	60	1.35 (0.95–1.93)
45–49	458	62	Reference
50–54	234	13	0.54 (0.30–0.99)
Continuous (year)	1,067	180	0.70 (0.61–0.80)
Mean (SD)	45.61 (4.6)		
Median (range)	46.00 (28–54)		
Age at first childbirth (years)			
≤19	51	8	1.47 (0.64–3.40)
20–24	308	47	1.27 (0.74–2.20)
25–29	416	60	1.03 (0.61–1.76)
30–34	208	47	1.37 (0.80–2.37)
≥35	84	18	Reference
Continuous, year	1,067	180	0.97 (0.84–1.12)
Mean (SD)	26.81 (4.8)		
Median (range)	26.00 (15–43)		
Education level			

Table 1 continued

Total	Subject 1,067	Event 180	Crude HR (95 % CI)
Less than high school	127	33	Reference
High school	506	92	0.79 (0.53–1.17)
More than high school	432	55	0.46 (0.30–0.71)
Unknown	2	0	0.00
Time difference between last pregnancy and date of diagnosis, years			
<10	211	82	2.07 (1.52–2.81)
≥10	856	98	Reference
Continuous, year	1067	180	0.92 (0.88–0.95)
Mean (SD)	14.33 (4.8)		
Median (range)	14.30 (2.5–26.8)		
Tumor characteristics			
Stage of tumor			
Stage 0–1	574	51	Reference
Stage 2	304	58	2.02 (1.39–2.95)
Stage 3–4	44	27	9.58 (6.00–15.28)
Unknown	145	44	2.30 (1.53–3.46)
ER status			
Positive	698	79	Reference
Negative	196	54	2.16 (1.00–3.05)
Unknown	173	180	1.76 (1.23–2.53)
PR status			
Positive	674	77	Reference
Negative	219	56	2.13 (1.51–3.00)
Unknown	174	47	1.77 (1.23–2.54)
ER/PR status			
ER^+/PR^+	621	64	Reference
ER^+/PR^-	71	13	1.73 (0.95–3.15)
ER^-/PR^+	48	11	1.79 (0.94–3.40)
ER^-/PR^-	148	43	2.57 (1.74–3.78)
Unknown	179	49	1.95 (1.43–2.83)
Histotype of tumor			
Ductal	718	112	Reference
Lobular	129	21	0.96 (0.61–1.54)
Other	220	47	0.93 (0.66–1.32)

increased risks of premenopausal breast cancer mortality, and mortality risk increased with decreasing educational level. Gestational age, parity, and age at first childbirth did not influence premenopausal breast cancer mortality. As expected, breast cancer mortality increased with stage of breast cancer. Compared with women with ER^+ or PR^+ tumor, women with ER^- or PR^- tumors had higher mortality, respectively,

Adjusting for gestational age, parity, age at diagnosis, and education level did not notably change the overall association between placental weight and breast cancer mortality. In the adjusted analysis, women with a placental weight between 600 and 699 g faced a 50 % increased risk of mortality (HR 1.51; 95 % CI 1.07–2.12) compared with women with a low placental weight (<600 g), However, a placental weight of at least 700 g was not associated with an increased risk of breast cancer mortality (HR 0.88; 95 % CI 0.60–1.30, data not shown in Table).

In a subsequent step, analyses of placental weight and breast cancer mortality were stratified by tumor characteristics (Table 2). First, analyses were stratified by tumor stage. There was no statistically significant interaction between stage of tumor and placental weight with respect to breast cancer mortality ($p = 0.80$). In the crude analyses, there were no significant associations between placental weight and breast cancer mortality. In the adjusted analysis of premenopausal breast cancer stages 3–4, women with a placental weight between 600 and 699 g and at least 700 g had a four- and a threefold increased mortality risk compared with women with a placental weight of less than 600 g. The reasons for the discrepancy between crude and adjusted risk estimates of placental weight and stage 3–4 breast cancer mortality were primarily effects of adjusting for parity and educational level (data not shown).

There were statistically significant interactions between placental weight and ER and PR with respect to mortality risk ($p < 0.01$ and $p < 0.0001$, respectively). Analyses stratified by ER status showed that the higher mortality risk associated with placental weight among ER^+ tumors was restricted to placental weight 600–699 g (HR 1.87; 95 % CI 1.13-3.11), while among ER^- tumors, both placental weight 600-699 g and ≥700 g were associated with than a doubled mortality risk compared with tumors among women with placental weight less than 600 g. Similarly, an increased mortality risk among PR^+ tumors was (if anything) only observed for women with a placental weight between 600 and 699 g, who had a 60 % increase in mortality, which was of borderline significance. Among women with PR^- tumors, both placental weight 600–699 g and ≥700 g were associated with more than tripled mortality risks compared with women with a placental weight less than 600 g.

In analyses stratified for joint receptor status, a consistent increase in breast cancer mortality with increasing placental weight was found only among women with ER^-/PR^- tumors (Table 3).

Discussion

The results of the present study indicate that the association between increasing placental weight in the most recent pregnancy and premenopausal breast cancer mortality

Table 2 Crude and adjusted hazard ratio (HR) and 95 % confidence interval (CI) for mortality associated with placental weight and tumor characteristics among women with premenopausal breast cancer who had pregnancy during 1982–1989

	Subject	Event	Crude HR(95 % CI)	Adjusted HR(95 % CI)[a]
Tumor characteristics				
Stage 0–1				
Placental weight (g)				
<600	258	18	Reference	Reference
600–699	170	20	1.74 (0.92–3.28)	1.57 (0.82–3.00)
≥700	146	13	1.25 (0.62–2.55)	1.17 (0.57–2.42)
Continuous, 50 g	574	51	0.98 (0.88–1.10)	0.98 (0.87–1.09)
Stage 2				
Placental weight (g)				
<600	117	22	Reference	Reference
600–699	97	27	1.64 (0.93–2.89)	1.70 (0.91–3.17)
≥700	90	9	0.47 (0.22–1.03)	0.47 (0.21–1.07)
Continuous, 50 g	304	58	0.91 (0.82–1.01)	0.88 (0.78–0.98)
Stage 3–4				
Placental weight (g)				
<600	16	9	Reference	Reference
600–699	12	9	1.67 (0.66–4.25)	4.28 (1.23–14.97)
≥700	16	9	1.29 (0.51–3.30)	3.40 (0.96–12.05)
Continuous, 50 g	44	27	1.06 (0.92–1.23)	1.10 (0.94–1.28)
Biological characteristics				
ER^+				
Placental weight (g)				
<600	303	32	Reference	Reference
600–699	217	35	1.63 (1.01–2.64)	1.87 (1.13–3.11)
≥700	178	12	0.58 (0.30–1.12)	0.59 (0.30–1.14)
Continuous, 50 g	698	79	0.97 (0.88–1.06)	0.96 (0.88–1.05)
ER^-				
Placental weight (g)				
<600	81	14	Reference	Reference
600–699	57	20	2.23 (1.12–4.41)	2.51 (1.20–5.25)
≥700	58	20	2.29 (1.16–4.53)	2.41 (1.17–4.99)
Continuous, 50 g	196	54	1.12 (1.01–1.24)	1.11 (0.99–1.23)
PR^+				
Placental weight (g)				
<600	295	33	Reference	Reference
600–699	204	33	1.53 (0.94–2.48)	1.62 (0.99–2.68)
≥700	175	11	0.51 (0.26–1.00)	0.47 (0.24–0.94)
Continuous, 50 g	674	77	0.95 (0.87–1.04)	0.93 (0.85–1.02)
PR^-				
Placental weight (g)				
<600	86	11	Reference	Reference
600–699	72	24	2.92 (1.43–5.96)	3.22 (1.47–7.04)
≥700	61	21	3.03 (1.46–6.29)	3.56 (1.58–8.04)
Continuous, 50 g	219	56	1.17 (1.04–1.30)	1.18 (1.05–1.32)
Histopathology				
Ductal				
Placental weight (g)				
<600	307	39	Reference	Reference

Table 2 continued

	Subject	Event	Crude HR(95 % CI)	Adjusted HR(95 % CI)[a]
600–699	222	48	1.73 (1.14–2.65)	1.90 (1.23–2.94)
≥700	189	25	0.95 (0.57–1.56)	0.91 (0.54–1.53)
Continuous, 50 g	718	112	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Lobular				
Placental weight (g)				
<600	53	7	Reference	Reference
600–699	35	9	2.57 (0.95–6.94)	4.46 (1.26–15.84)
≥700	41	5	0.93 (0.29–2.92)	0.73 (0.19–2.77)
Continuous, 50 g	129	21	0.99 (0.84–1.16)	0.93 (0.80–1.09)
Other				
Placental weight (g)				
<600	98	24	Reference	Reference
600–699	65	12	0.80 (0.40–1.61)	0.84 (0.40–1.78)
≥700	57	11	0.81 (0.40–1.65)	0.85 (0.40–1.81)
Continuous, 50 g	220	47	0.96 (0.85–1.09)	0.96 (0.85–1.10)

[a] Adjusted for gestational age, parity, age at diagnosis, and education level

differs by tumor receptor status. A positive association between placental weight and breast cancer mortality was more pronounced among ER^- and PR^- tumors than among ER^+ and PR^+ tumors. These results confirm and extend on our previous findings that placental weight influences the risk of premenopausal breast cancer mortality [32]. However, we did not find a dose–response association between placental weight and overall risk of premenopausal breast cancer mortality.

Analyses in relation to joint receptor status revealed that a consistent increase in breast cancer mortality with increasing placental weight was restricted to patients with ER^-/PR^- tumors. It has been suggested that breast cancer tumors should be categorized based on the status of both ERs and PRs, rather than categorizing ER and PR separately [44]. ER^-/PR^- tumors are more frequent in premenopausal breast cancer, while ER^+/PR^+ tumors occur more frequently in postmenopausal breast cancer [3, 44, 54, 56]. Moreover, ER^- and PR^- tumors have higher stage [3, 44, 54], higher proliferation rate [41, 51, 54] and higher S-phase fraction [41, 55]. The distribution of receptors is more age dependent [2–4, 9, 12, 16, 19, 57] than related to menopausal status. ER^- breast cancer rates increase with age during premenopausal period, and flatten to a constant level after 50 years, while the rate of ER^+ tumors increases with older age, with the greatest risk occurring after 70 years [4, 57]. A significantly higher frequency of ER^-/PR^- tumors has been reported among cases with pregnancy related breast cancers [38, 43]. This pattern suggests that premenopausal hormonal exposures have greater impact on receptor negative tumors than on receptor positive tumors. However, the biological mechanism underlying the observed increased risk of breast cancer mortality among patients with ER^-/PR^- tumors and higher placental weight is not clear.

This study showed that the premenopausal breast cancer mortality in women with ER^- and PR^- tumors is higher compared with women with ER^+ and PR^+ tumors, which is consistent with the results of previous studies [3, 7, 11, 14, 15, 26, 39]. In a large cohort study, Dunnwald et al. [15] found that compared with women with ER^+/PR^+ tumors, women with ER^+/PR^-, ER^-/PR^+, or ER^-/PR^- tumors experienced higher risks of premenopausal breast cancer mortality. This risk increase was largely independent of demographic and clinical tumor characteristics, and the highest risk was observed in patients with ER^-/PR^- tumors. While studying ER^+/PR^- and ER^-/PR^+ tumors could be problematic due to the low frequency of these types of tumors [3, 22, 44, 56], it has been suggested that the presence of estrogen and ERs is necessary for synthesis of PRs. Thus, identifying a tumor with receptor status as ER^-/PR^+ could be a false diagnosis due to laboratory mistake [27]. Receptor positive tumors could also change to receptor negative status over time [23].

Consistent with our results, Lukanova et al. [34] found an increased risk of breast cancer associated with higher concentration of estrogen during first trimester of pregnancy and higher proportion of receptor negative tumors among women diagnosed before age 40. The authors speculate that there is a direct association between concentration of estrogen and ER-negative tumors, which is supported by an animal study, showing that breast cancer tumors require estrogen for their formation and progression in spite of negativity of ER [21]. However, Peck

Table 3 Crude and adjusted Hazard Ratio (HR) and 95 % confidence interval (CI) for mortality associated with placental weight and joint status of estrogen receptor (ER) and progesterone receptor (PR) among women with premenopausal breast cancer who had pregnancy during 1982–1989

	Subject	Event	Crude HR(95 % CI)	Adjusted HR(95 % CI)[a]
ER^+ PR^+				
Placental weight (g)				
<600	268	28	Reference	Reference
600–699	192	27	1.43 (0.84–2.44)	1.60 (0.92–2.80)
≥700	161	9	0.48 (0.23–1.03)	0.44 (0.21–0.95)
Continuous, 50 g	621	64	0.94 (0.85–1.05)	0.92 (0.83–1.03)
ER^+ PR^-				
Placental weight (g)				
<600	30	2	Reference	Reference
600–699	24	8	5.42 (1.15–25.55)	13.25 (1.16–151.29)
≥700	17	3	2.28 (0.38–13.68)	5.43 (0.48–61.48)
Continuous, 50 g	71	13	1.17 (0.91–1.50)	1.20 (0.91–1.56)
ER^- PR^+				
Placental weight (g)				
<600	25	5	Reference	Reference
600–699	9	4	2.32 (0.62–8.68)	9.66 (1.27–73.34)
≥700	14	2	0.73 (0.14–3.75)	0.53 (0.09–3.18)
Continuous, 50 g	48	11	0.96 (0.48–1.89)	0.96 (0.76–1.21)
ER^- PR^-				
Placental weight (g)				
<600	56	9	Reference	Reference
600–699	48	16	2.29 (1.01–5.18)	2.69 (1.12–6.47)
≥700	44	18	3.06 (1.37–6.82)	3.86 (1.56–9.57)
Continuous, 50 g	148	43	1.15 (1.02–1.30)	1.17 (1.03–1.32)

[a] Adjusted for gestational age, parity, age at diagnosis, and education level

et al. [42] did not find a clear association between estrogen levels in third trimester of pregnancy and risk of breast cancer. Moreover, a recent large cohort study did not find any association between placental weight and breast cancer risk [40]. Taken together, the results of these studies indicate that estrogens may be of importance in proliferation of breast cells during early stage of pregnancy.

In this study, we found no association between parity and breast cancer mortality, collaborating findings of some previous studies [1, 29, 30, 45, 50]. However, other studies have reported lower [20, 35] or higher breast cancer mortality [10, 28, 39, 43] associated with increasing parity. These discrepant results could be due to differences in study designs. For example, pre- and postmenopausal breast cancers have different risk profiles with respect to mortality, and most studies do not investigate pre- and postmenopausal breast cancer separately [10, 20, 28, 35, 39, 43]. The observed association between placental weight and lobular premenopausal breast cancer is based on few events and could be chance finding.

Strengths of this study include the population-based design including virtually all women in Central Sweden diagnosed with breast cancer during the study period. In addition, recall bias was not an issue by the use of prospectively recorded information about pregnancy characteristics and detailed information on tumor characteristics retrieved from separate data sources. The source population for Regional Clinical Quality Registers for Breast Cancer in the Uppsala/Örebro and Stockholm/Gotland regions is about 4 million (43 % of the Swedish population) living in both urban and rural areas, and is representative of Swedish population as a whole. The completeness of the information on tumor characteristics is among the highest in the Quality Registers covering these regions.

In contrast to our previous study [32], we did not find a dose–response relationship between placental weight and overall risk of premenopausal breast cancer mortality. In our previous study, stratified analyses revealed that this dose–response relationship was only apparent in pregnancy-associated breast cancer—women diagnosed with breast cancer during pregnancy or up to 2 years after

childbirth [32]. In the present investigation, we were unable to study associations between placental weight and mortality in women with pregnancy-associated breast cancer, since information on placental weight was not collected after 1989 and the Quality Registers of breast cancer started to collect information on tumor characteristics in 1992. Thus, our study design prevented us to study the association between placental weight and mortality in pregnancy-associated breast cancer, i.e., the time window when exposure to pregnancy hormones may be most important for breast cancer survival. Other limitations include small number of events (deaths), which limited our statistical power. For this reason, we had to categorize tumor stage only in three groups instead of the standard classification [52].

In conclusion, our study supports the hypothesis that hormone levels during pregnancy might influence premenopausal breast cancer mortality, and that this association differs by tumor receptor status. The increased mortality risk associated with higher placental weight observed in ER^- and PR^- tumors suggests that premenopausal hormonal exposures might have greater impact on these tumors.

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Ethical standards The study was approved by the research ethics committee of Karolinska Institutet.

Conflict of interest The authors declare that they have no conflict of interest.

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