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EPIDEMIOLOGY

Birth size in the most recent pregnancy and maternal mortality in premenopausal breast cancer by tumor characteristics

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Abstract The main aim of this study was to investigate possible associations between measures of offspring size at birth in the most recent pregnancy before premenopausal breast cancer diagnosis and the risks of maternal breast cancer mortality, taking tumor characteristics into account. We also aimed to investigate if these associations are modified by age at childbirth, time since childbirth, parity, and age at diagnosis. We followed 6,019 women from their date of premenopausal breast cancer (diagnosed from 1992 to 2008) until emigration, death or December 31st, 2009, whichever occurred first. We used Cox proportional hazard regression models, adjusted for parity, age at diagnosis, and education level, to estimate associations between women pregnancy, cancer characteristics and offspring birth characteristics, and mothers' mortality risk. In stratified analyses, mortality risks were estimated by tumor stage, ER or PR status. There was no association between offspring birth weight (HR = 1.00, 95 % CI 0.99–1.01, when used as a continuous variable), birth weight for gestational age or ponderal index, and premenopausal breast cancer mortality. Similarly, in analyses stratified by tumor stage, receptor status, and time difference between last pregnancy and date of diagnosis, we found no associations between birth size and breast cancer mortality. Our findings suggest that the hypothesis that "premenopausal breast cancer mortality is associated with offspring birth characteristics in the most recent pregnancy before the diagnosis" may not be valid. In addition, these associations are not modified by tumor characteristics.

Keywords Breast cancer · Premenopausal · Birth size · Estrogen receptor · Progesterone receptor

Introduction

Estrogens are well-established risk factors for breast cancer [25, 30] and may also influence breast cancer prognosis. Mortality rates are higher among women diagnosed with breast cancer up to 10 years following delivery, and the

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prognosis is especially poor in women with breast cancer diagnosed during or shortly after pregnancy [2, 4, 12, 15, 21, 23, 31, 32]. Although underlying mechanisms remain unknown, hormonal factors may play a role.

During pregnancy, there is a large increase in hormone production, which is primarily produced by the placenta. Estrogen levels increase with placental weight, which may serve as an indirect marker of pregnancy hormone exposures. In a Swedish study, Larfors et al. [16] showed that increasing placental weight in the most recent pregnancy before breast cancer diagnosis was associated with reduced breast cancer survival. We recently reported that the association between high placental weight and premenopausal breast cancer mortality was modified by tumor characteristics: the risk was most pronounced among estrogen receptor (ER) negative and progesterone receptor (PR) negative tumors [8].

A positive association between birth weight and level of pregnancy hormones, particularly estrogens, has also been documented [10, 13, 22, 28]. Kaijser et al. [13] found that maternal serum estriol levels increased with offspring birth weight, birth weight for gestational age (a proxy for fetal growth), and ponderal index, i.e., the ratio of birth weight and birth length [100 * birth weight (in grams) divided by birth length (in centimetres^3)]. Thus, offspring birth weight, birth weight for gestational age, and ponderal index can also be considered as indirect markers of exposure to hormone levels during pregnancy [13].

A Finnish study, including 3,706 women with reproductive history of which 190 women were later diagnosed with breast cancer, found a statistically significant positive association between ponderal index and risk of breast cancer mortality [27]. However, there was no association between offspring birth weight and breast cancer mortality [26, 27]. To the best of our knowledge, no study to date has examined the association between offspring birth characteristics and breast cancer mortality, taking tumor characteristics into account.

In this large population-based cohort study, we investigated possible associations between measures of offspring size at birth in the most recent pregnancy before premenopausal breast cancer diagnosis and the risks of maternal breast cancer mortality, taking tumor characteristics into account. We also investigated if these associations are modified by age at childbirth, time since childbirth, parity, and age at diagnosis.

Materials and methods

The six Swedish Regional Quality Registers capture more than 95 % of the incident breast cancer cases and include data on diagnostic procedures and treatments [3]. In these registries, information on tumor stage and biological characteristics at diagnosis, including grade and hormone (estrogen or progesterone) receptor status, has been collected since 1992. Women who received a diagnosis of premenopausal breast cancer between 1992 and 2008 were identified through two Swedish Regional Quality Registers on Breast Cancer covering the Stockholm-Gotland Region and Central Sweden. These registries included self-reported information about menopausal status.

Women with a recorded pregnancy before diagnosis of premenopausal breast cancer were identified through record linkage to the Swedish Medical Birth Register ($n = 6{,}129$). The Medical Birth Register includes prospectively collected information during pregnancy, delivery, and the neonatal period on virtually all births in Sweden since 1973. Information about vital status and dates of emigration was retrieved from the Swedish Population Register. Highest achieved educational level was obtained from the Education Register. The Cause of Death Register provided information on main and contributing causes of death, coded according to International Classification of Diseases, 7th–10th versions (ICD-7–ICD-10). The unique personal identity number, assigned to each Swedish resident, was used to link individual records across these registries [18].

We excluded 41 women due to missing information on birth weight or gestational age. Women with pregnancies that ended in stillbirth ($n = 18$) and twin pregnancies ($n = 51$) were also excluded. In total, the cohort included 6,019 women with premenopausal breast cancer. As breast cancer was recorded as the main or contributory cause of death for approximately 99 % of the events, death due to all causes was used as the outcome.

The study was approved by the Research Ethics Committee of Karolinska Institutet.

Statistical analysis

We used Cox proportional hazards model to estimate hazard ratios (HR) with 95 % confidence intervals (CI) as a measure of the association between birth characteristics and risk of premenopausal breast cancer mortality. Follow-up was from the date of diagnosis of breast cancer until emigration, death or until December 31st, 2009, whichever occurred first. Follow-up time was the underlying time scale.

Birth weight was considered as a continuous and a categorical variable (<3000, 3000–3499, 3500–3999, 4000–4499, and ≥4500 g). We also estimated associations between birth weight for gestational age and ponderal index and breast cancer mortality. Birth weight for gestational age was estimated using the Swedish reference curve for normal fetal growth and was defined as the ratio of

Table 1 Offspring birth characteristics, hazard ratios (HR), and 95 % confidence interval (CI) for breast cancer mortality. Parous women with premenopausal breast cancer diagnosed 1992–2009 in Sweden

	Subject	Event	Crude HR (95 % CI)	Adjusted HR (95 % CI)[a]
Birth weight (gram)				
<3,000	783	132	1.07 (0.88–1.31)	1.12 (0.90–1.40)
3,000–3,499	1,862	330	1.12 (0.96–1.30)	1.13 (0.97–1.32)
3,500–3,999	2,162	337	Referent	Referent
4,000–4,499	971	181	1.18 (0.99–1.41)	1.16 (0.97–1.40)
≥4,500	241	37	1.04 (0.74–1.45)	1.06 (0.75–1.49)
P for trend			0.42	0.42
Continuous (100 g)	6,019	1,017	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Birth length (cm)				
<49	1,053	181	1.10 (0.92–1.31)	1.14 (0.94–1.38)
49	751	137	1.18 (0.97–1.44)	1.19 (0.98–1.45)
50–51	2,292	365	Referent	Referent
≥52	1,890	334	1.11 (0.95–1.28)	1.10 (0.95–1.28)
Continuous (cm)	5,988	1,017	1.00 (0.98–1.03)	1.00 (0.97–1.02)
Missing	31	0		
Gestational age (weeks)				
≤36	305	42	0.78 (0.57–1.06)	0.74 (0.54–1.01)
37–38	1,070	167	0.95 (0.80–1.12)	0.94 (0.80–1.12)
39–41	4,140	704	Referent	Referent
≥42	504	104	1.15 (0.94–1.42)	1.12 (0.91–1.37)
Continuous (week)	6,019	1,017	1.04 (1.00–1.07)	1.03 (1.00–1.07)
Birth weight for gestational age (%)				
<3	132	33	1.52 (1.07–2.15)	1.55 (1.09–2.21)
3–<10	294	60	1.15 (0.89–1.50)	1.09 (0.84-1.42)
10–90	4,865	801	Referent	Referent
91–97	493	88	1.08 (0.87–1.35)	1.12 (0.90–1.39)
>97	231	35	1.00 (0.71–1.40)	1.05 (0.75–1.48)
Continuous	6,015	1,017	0.97 (0.91–1.02)	0.99 (0.93–1.04)
Missing	4	0		
Ponderal index (%)				
<3	174	36	1.17 (0.84–1.64)	1.25 (0.89–1.77)
3–<10	410	85	1.24 (0.99–1.55)	1.24 (0.99–1.56)
10–90	4,802	799	Referent	Referent
91–97	420	75	1.16 (0.91–1.47)	1.18 (0.93–1.49)
>97	182	22	0.77 (0.51–1.18)	0.78 (0.51–1.19)
Continuous	5,988	1,017	1.01 (0.85–1.20)	1.00 (0.84–1.19)
Missing	31	0		

[a] Adjusted for gestational age, parity, and educational level

observed to expected birth weight for gestational age and sex. Birth weight for gestational age was categorized in percentiles (<3, 3–<10, 10–90, 91–97, and >97 %) [19]. As infants within the 10–90 % are considered as being "appropriate for gestational age", this category was used as the reference group [5, 24]. The association was estimated using birth weight for gestational age as a continuous and a categorized variable. We also evaluated the quadratic term for potential non-linear associations between offspring birth characteristics and breast cancer mortality. Ponderal index was categorized in percentile ranges equivalent to the categorization of birth weight for gestational age (<3, 3–<10, 10–90, 91–97, and >97 %). All the models were adjusted for parity (1, 2, 3, and ≥4), gestational age (≤36,

Table 2 Pregnancy factors, tumor characteristics, and hazard ratios (HR) with 95 % confidence interval (CI) for breast cancer mortality. Parous women with premenopausal breast cancer diagnosed 1992–2009 in Sweden

	Subjects	Events	HR (95 % CI)	Adjusted HR (95 % CI)[a]
Pregnancy factors				
Parity				
1	1,250	234	Referent	Referent
2	3,048	504	0.88 (0.75–1.03)	0.88 (0.76–1.03)
3	1,307	201	0.78 (0.65–0.94)	0.82 (0.68–0.99)
≥4	414	78	0.96 (0.74–1.24)	0.99 (0.76–1.28)
Preeclampsia				
Yes	48	7	0.93 (0.44–1.94)	1.01 (0.48–2.12)
No	5,971	1,010	Referent	Referent
Education level				
Below high school	733	174	Referent	Referent
High school	2,695	487	0.83 (0.69–0.98)	0.78 (0.65–0.92)
Above high school	2,584	353	0.61 (0.51–0.73)	0.60 (0.50–0.72)
Missing	7	3		
Age at breast cancer diagnosis (years)				
<30	60	21	3.24 (2.04–5.13)	3.00 (1.89–4.78)
30–34	298	85	2.63 (2.00–3.45)	2.61 (1.98–3.24)
35–39	815	167	1.77 (1.41–2.22)	1.76 (1.40–2.22)
40–44	1,576	290	1.48 (1.21–1.82)	1.49 (1.21–1.82)
45–49	2,129	321	1.19 (0.97–1.45)	1.78 (0.96–1.44)
50–54	1,141	133	Referent	Referent
Continuous (year)	6,019	1,017	0.95 (0.94–0.96)	0.95 (0.94–0.96)
Time between last pregnancy and breast cancer diagnosis (years)				
<5	839	196	1.77 (1.50–2.08)	1.36 (1.09–1.69)
5–9	1,168	228	1.34 (1.15–1.56)	1.22 (1.03–1.46)
≥10	4,012	593	Referent	Referent
Continuous (year)	6,019	1,017	0.88 (0.84–0.93)	0.98 (0.91–1.05)
Tumor characteristics				
Stage of tumor				
Stage 0–1	3,018	288	Referent	Referent
Stage 2	1,852	355	2.15 (1.84–2.52)	2.06 (1.76–2.40)
Stage 3	275	109	5.53 (4.43–6.89)	4.96 (3.97–9.20)
Stage 4	77	49	12.93 (9.54–17.53)	12.22 (8.99–16.60)
Unkown	797	216	2.13 (1.78–2.55)	2.03 (1.70–2.43)
ER status				
Positive	3,821	450	Referent	Referent
Negative	1,246	316	2.15 (1.86–2.48)	1.90 (1.64–2.20)
Unknown	952	251	1.69 (1.45–1.97)	1.43 (1.22–1.68)
PR status				
Positive	3,611	430	Referent	Referent
Negative	1,421	336	2.30 (1.99–2.65)	1.95 (1.68–2.25)
Unknown	987	251	1.67 (1.43–1.96)	1.41 (1.20–1.66)
ER/PR status				
ER+/PR+	3,348	364	Referent	Referent
ER+/PR−	433	82	2.14 (1.68–2.72)	1.79 (1.41–2.29)
ER−/PR+	256	63	1.80 (1.38–2.35)	1.72 (1.32–2.25)
ER−/PR−	986	253	2.59 (2.21–3.04)	2.19 (1.86–2.58)
Unknown	996	255	1.82 (1.55–2.14)	1.53 (1.29–1.80)

Table 2 continued

	Subjects	Events	HR (95 % CI)	Adjusted HR (95 % CI)[a]
Histological type				
Ductal	4,143	652	Referent	Referent
Lobular	640	103	0.94 (0.76–1.15)	0.95 (0.77–1.17)
Other	820	153	1.00 (0.84–1.19)	0.97 (0.81–1.16)
Unknown	416	109	1.10 (0.90–1.36)	1.09(0.88–1.35)

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

37–38, 39–41, and ≥42 weeks), and education level (less than high school, high school, and above high school).

We estimated the association between birth weight for gestational age and maternal mortality among different subgroups. In stratified analyses, we estimated the risk of mortality in subjects with different tumor stages (stage 0–1, stage 2, stage 3 or stage 4), estrogen receptor status (ER^+, ER^-), progesterone receptor status (PR^+, PR^-), joint receptor status (ER^+PR^+, ER^-PR^+, ER^+PR^-, ER^-PR^-), and histology of tumors (ductal, lobular, other). The models were adjusted for parity, gestational age, education level, and age at cancer diagnosis (<30, 30–34, 35–39, 40–44, 45–49, and 50–54 years).

The assumption of proportionality was verified for all models, by including time-by covariate interaction in the model and testing the statistical significance. As a basis for the linear trend tests across categories of offspring birth characteristics, each subject was assigned the median value of the specific category, and this variable was treated as a continuous variable in modeling. All analyses were performed using the SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows offspring birth characteristics and crude and adjusted maternal mortality risks of breast cancer. We found no statistically significant association between offspring birth weight and maternal mortality of breast cancer, neither when birth weight was used as a continuous (1.00, 95 % CI 0.99–1.01) nor as a categorical variable (*P* for trend 0.42). Compared to women who had an infant with normal birth weight for gestational age (between 10th and 90th percentiles), women with a small for gestational age infant (<3rd percentile) in the most recent pregnancy had an increased mortality risk (HR = 1.55, 95 % CI 1.09–2.21). We found no associations between ponderal index and maternal mortality of premenopausal breast cancer, neither when ponderal index was used as a continuous variable nor when used as a categorical variable (Table 1). In analyses of quadratic term for offspring birth characteristics, we found no statistically significant non-linear associations with the higher-order term of breast cancer mortality, other than a risk associated with birth weight for gestational age (1.04, 95 % CI 1.01–1.07).

Table 2 shows crude and adjusted hazard ratios for pregnancy factors or tumor characteristics and maternal mortality of premenopausal breast cancer. Risk of premenopausal breast cancer mortality was inversely associated with increasing age at diagnosis, educational level, and time between pregnancy and diagnosis of the cancer. Analysis by tumor characteristics showed that premenopausal breast cancer mortality was positively associated with tumor stage, ER negative, and PR negative tumors. Analysis by joint receptor status revealed that women with ER and PR negative tumors had the highest premenopausal breast cancer mortality (Table 2). Restricting data to women who were born in Nordic countries (i.e., Sweden, Denmark, Finland, Iceland, and Norway) did not change the results (data not shown).

The association between offspring birth weight for gestational age and premenopausal breast cancer mortality stratified by tumor characteristics is shown in Table 3. Stratified analyses revealed that the observed increased mortality risk for the lowest category of birth weight for gestational age was present in those with cancer diagnosed 5–9 years after the pregnancy, in women who were 40 years or younger at the time of diagnosis, in women diagnosed with stage 2 tumors, and in women with ER positive tumors.

Analysis stratified by parity showed that birth weight for gestational age (as a continuous variable) had statistically significant inverse association with mortality of premenopausal breast cancer among uniparous women (HR = 0.87, 95 % CI 0.78–0.98), but not in multiparous women (HR = 1.01, 95 % CI 0.94–1.08). Thus, the increased risk of breast cancer mortality related to birth of a small for gestational age infant before breast cancer diagnosis appeared to be restricted to primiparous women.

Discussion

This population-based cohort study found no association between birth weight, as an indirect marker of perinatal

Table 3 Stratified analyses of offspring birth weight for gestational age (in ‰) and hazard ratio (HR) and 95 % confidence interval (CI) for mother's premenopausal breast cancer mortality

	Subject	Event	Crude HR (95 % CI)	Adjusted HR (95 % CI)[a]
Birth weight for gestational age (%)				
<3	132	33	1.52 (1.07–2.15)	1.55 (1.09–2.21)
3–<10	294	60	1.15 (0.89–1.50)	1.09 (0.84–1.42)
10–90	4,865	801	Referent	Referent
91–97	493	88	1.08 (0.87–1.35)	1.11 (0.90–1.39)
>97	231	35	1.00 (0.71–1.40)	1.05 (0.75–1.48)
Continuous	6,015	1,017	0.97 (0.91–1.02)	0.99 (0.93–1.04)
Quadratic			1.03 (1.00–1.06)	1.04 (1.01–1.07)
Time difference between last pregnancy and date of diagnosis				
<5 years				
<3	14	5	1.49 (0.61–3.64)	1.78 (0.72–4.39)
3–<10	31	8	1.03 (0.51–2.09)	1.21 (0.59–2.49)
10–90	675	155	Referent	Referent
91–97	83	16	0.85 (0.51–1.41)	0.88 (0.52–1.47)
>97	35	12	1.86 (1.03–3.35)	1.95 (1.08–3.53)
Continuous	838	196	1.00 (0.88–1.15)	0.99 (0.86–1.13)
5–9 years				
<3	23	9	2.04 (1.04–3.99)	2.21 (1.11–4.40)
3–<10	48	13	1.53 (0.87–2.70)	1.53 (0.84–2.76)
10–90	942	175	Referent	Referent
91–97	102	24	1.27 (0.83–1.94)	1.25 (0.81–1.91)
>97	52	7	0.78 (0.36–1.65)	0.90 (0.42–1.94)
Continuous	1,167	228	0.94 (0.83–1.06)	0.95 (0.84–1.07)
≥10 years				
<3	95	19	1.41 (0.89–2.23)	1.30 (0.81–2.08)
3–<10	215	39	1.15 (0.83–1.59)	1.06 (0.76–1.48)
10–90	3,248	471	Referent	Referent
91–97	308	48	1.06 (0.79–1.43)	1.08 (0.80–1.45)
>97	144	16	0.80 (0.49–1.31)	0.88 (0.53–1.45)
Continuous	4,010	593	0.94 (0.88–1.02)	0.97 (0.90–1.05)
Age at diagnosis				
≤40 years				
<3	66	20	1.55 (0.99–2.42)	1.72 (1.09–2.72)
3–<10	150	38	1.25 (0.90–1.74)	1.27 (0.90–1.78)
10–90	2,560	493	Referent	Referent
91–97	282	56	1.02 (0.77–1.34)	1.03 (0.78–1.36)
>97	119	23	1.13 (0.75–1.72)	1.19 (0.78–1.81)
Continuous	3,177	630	0.90 (0.91–1.04)	0.97 (0.90–1.04)
>40 years				
<3	66	13	1.51 (0.87–2.63)	1.41 (0.82–2.52)
3–<10	144	22	1.03 (0.67–1.59)	0.95 (0.61–1.46)
10–90	2,305	308	Referent	Referent
91–97	211	32	1.15 (0.80–1.65)	1.21 (0.84–1.74)
>97	112	12	0.83 (0.47–1.48)	0.90 (0.51–1.61)
Continuous	2,838	387	0.94 (0.85–1.03)	0.97 (0.88–1.07)
Tumor stage				
Stage 0–1				
<3	61	6	1.03 (0.46–2.32)	1.11 (0.49–2.54)

Table 3 continued

	Subject	Event	Crude HR (95 % CI)	Adjusted HR (95 % CI)[a]
3–<10	159	21	1.29 (0.83–2.02)	1.19 (0.75–1.89)
10–90	2,460	225	Referent	Referent
91–97	226	29	1.46 (0.99–2.15)	1.46 (0.99–2.16)
>97	110	7	0.74 (0.35–1.56)	0.89 (0.42–1.89)
Continuous	3,016	288	1.01 (0.90–1.12)	1.01 (0.91–1.13)
Stage 2				
<3	43	17	2.04 (1.25–3.33)	2.19 (1.32–3.62)
3–<10	74	19	1.30 (0.82–2.07)	1.35 (0.84–2.17)
10–90	1,502	282	Referent	Referent
91–97	159	25	0.81 (0.54–1.22)	0.77 (0.51–1.17)
>97	74	12	0.95 (0.53–1.69)	0.96 (0.54–1.71)
Continuous	1,852	355	0.87 (0.79–0.96)	0.87 (0.79–0.96)
Stage 3–4				
<3	11	5	1.05 (0.43–2.56)	1.05 (0.42–2.61)
3–<10	23	11	1.16 (0.62–2.15)	1.10 (0.58–2.11)
10–90	267	120	Referent	Referent
91–97	31	15	1.21 (0.71–2.08)	1.09 (0.63–1.92)
>97	19	7	0.97 (0.45–2.07)	1.00 (0.44–2.28)
Continuous	351	158	1.02 (0.89–1.17)	1.04 (0.90–1.20)
Receptor status				
ER+				
<3	76	16	1.87 (1.13–3.08)	1.86 (1.11–3.12)
3–<10	182	26	1.10 (0.74–1.64)	1.10 (0.74–1.65)
10–90	3,106	353	Referent	Referent
91–97	296	38	1.13 (0.81–1.58)	1.10 (0.78–1.54)
>97	157	17	1.03 (0.64–1.68)	1.11 (0.68–1.81)
Continuous	3,817	450	0.97 (0.89–1.06)	0.97 (0.89–1.06)
ER−				
<3	25	9	1.44 (0.74–2.80)	1.48 (0.75–2.90)
3–<10	65	17	1.02 (0.62–1.66)	1.02 (0.62–1.68)
10–90	996	253	Referent	Referent
91–97	117	30	1.08 (0.74–1.57)	1.13 (0.77–1.65)
>97	43	7	0.62 (0.29–1.31)	0.70 (0.33–1.50)
Continuous	1,246	316	0.94 (0.85–1.05)	0.97 (0.87–1.08)
PR+				
<3	64	12	1.62 (0.91–2.88)	1.67 (0.93–3.01)
3–<10	179	25	1.07 (0.71–1.60)	1.05 (0.70–1.59)
10–90	2,953	343	Referent	Referent
91–97	275	36	1.10 (0.78–1.54)	1.06 (0.75–1.50)
>97	136	14	0.96 (0.56–1.64)	1.05 (0.61–1.80)
Continuous	3,607	430	0.97 (0.89–1.06)	0.98 (0.89–1.07)
PR−				
<3	34	13	1.66 (0.95–2.90)	1.69 (0.96–2.99)
3–<10	66	17	1.05 (0.64–1.71)	1.07 (0.65–1.76)
10–90	1,121	265	Referent	Referent
91–97	136	31	1.03 (0.71–1.50)	1.04 (0.72–1.52)
>97	64	10	0.66 (0.35–1.23)	0.71 (0.37–1.33)
Continuous	1,421	336	0.93 (0.85–1.03)	0.95 (0.86–1.05)

Table 3 continued

	Subject	Event	Crude HR (95 % CI)	Adjusted HR (95 % CI)[a]
Joint receptor status				
ER+PR+				
<3	61	11	1.73 (0.95–3.16)	1.77 (0.95–3.29)
3–<10	168	23	1.15 (0.75–1.76)	1.16 (0.75–1.78)
10–90	2,728	285	Referent	Referent
91–97	254	31	1.14 (0.79–1.65)	1.10 (0.76–1.60)
>97	133	14	1.07 (0.63–1.83)	1.18 (0.69–2.02)
Continuous	3,344	364	0.98 (0.89–1.08)	0.98 (0.89–1.09)
ER+PR−				
<3	12	5	2.41 (0.97–5.98)	2.61 (0.97–7.05)
3–<10	12	2	0.75 (0.18–3.07)	0.44 (0.06–3.30)
10–90	345	66	Referent	Referent
91–97	40	6	0.86 (0.37–1.98)	0.88 (0.38–2.06)
>97	24	3	0.74 (0.23–2.37)	0.77 (0.24–2.50)
Continuous	433	82	0.93 (0.76–1.12)	0.92 (0.75–1.11)
ER−PR+				
<3	3	1	1.20 (0.17–8.64)	1.25 (0.16–9.95)
3–<10	11	2	0.64 (0.16–2.62)	0.64 (0.15–2.74)
10–90	218	55	Referent	Referent
91–97	21	5	0.89 (0.35–2.22)	0.96 (0.37–2.49)
>97	3	0	0.00	0.00
Continuous	256	63	0.98 (0.76–1.28)	1.00 (0.76–1.31)
ER−PR−				
<3	22	8	1.42 (0.70–2.89)	1.50 (0.72–3.08)
3–<10	54	15	1.08 (0.64–1.83)	1.13 (0.66–1.92)
10–90	774	198	Referent	Referent
91–97	96	25	1.09 (0.72–1.65)	1.15 (0.75–1.75)
>97	40	7	0.63 (0.30–1.34)	0.74 (0.34–1.58)
Continuous	986	253	0.93 (0.83–1.04)	0.96 (0.85–1.07)
Parity				
Uniparous				
<3	47	13	1.61 (0.92–2.83)	1.72 (0.96–3.11)
3–<10	100	27	1.49 (0.99–2.23)	1.42 (0.93–2.16)
10–90	993	174	Referent	Referent
91–97	81	16	1.14 (0.68–1.91)	1.12 (0.67–1.87)
>97	28	4	0.88 (0.33–2.36)	0.87 (0.32–2.36)
Continuous	1,249	234	0.89 (0.79–1.00)	0.87 (0.78–0.98)
Multiparous				
<3	85	20	1.44 (0.92–2.24)	1.51 (0.96–2.37)
3–<10	194	33	0.95 (0.67–1.36)	0.99 (0.70–1.41)
10–90	3,872	627	Referent	Referent
91–97	412	72	1.08 (0.84–1.37)	1.07 (0.84–1.36)
>97	203	31	1.02 (0.71–1.47)	1.09 (0.76–1.57)
Continuous	4,766	783	1.00 (0.94–1.07)	1.01 (0.94–1.08)

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

hormonal exposure, and maternal premenopausal breast cancer mortality. These null findings also remained in analyses stratified by tumor characteristics, including time between pregnancy and breast cancer diagnosis, tumor stage, and receptor expression status. There was an inverse association between birth weight for gestational age and mortality of premenopausal breast cancer among uniparous women.

We are unaware of any study investigating the association between offspring birth size and maternal breast cancer mortality risk, taking tumor characteristics into account. The results of the present study are not consistent with the findings of our recent study [8] in which we found an increased mortality risk in premenopausal breast cancer associated with higher placental weight in the most recent pregnancy. The reported effect modification by tumor characteristics in our previous study [8]—the risk was most pronounced among estrogen receptor (ER) negative and progesterone receptor (PR) negative tumors—was not present in this study. As the placenta is the main source of pregnancy hormones, placental weight might be a more robust and independent marker of hormone exposures during pregnancy than birth weight [29], which may explain the inconsistency between the two studies. In a study examining the association between reproductive factors and risk of premenopausal breast cancer [6], the effect of birth weight disappeared after adjusting for placental weight. Moreover, placental weight or birth weight could be markers of other exposure(s) which could affect breast cancer mortality. For example, disproportionately large placentas could reflect a chronic process requiring placental overgrowth, such as maternal anemia or malnutrition [17], but whether such factors influence breast cancer mortality remain highly speculative.

Unexpectedly, we found increased maternal mortality risk among women giving birth to small for gestational age offspring. The increased risk was restricted to uniparous women when we considered the association in subcategories of parity. Although the mechanism of these unexpected associations is not clear, it is conceivable that it might be due to comorbidities in the mother—such as autoimmune diseases [7, 20]—or other risk factors such as cigarette smoking [14], which could affect both offspring birth weight and mortality. However, we cannot rule out that these findings are due to chance.

Strengths of this study include the large sample size and population-based design including virtually all women in Central Sweden diagnosed with premenopausal breast cancer during the study period. Moreover, as we used prospectively recorded information about pregnancy characteristics and detailed information on tumor characteristics retrieved from separate data sources, recall bias is not an issue. The Breast Cancer Quality Register provided high quality and virtually complete information on stage and characteristics of tumor at diagnosis, including grade and hormone (estrogen or progesterone) receptor status [9]. The population covered in this study is approximately 4 million living in both urban and rural areas, and is likely to be representative of the whole Swedish population.

This study has some limitations. We used birth weight, birth weight for gestational age, and ponderal index as indirect markers of pregnancy hormonal exposure. These factors could also represent markers of other exposures which might be associated with breast cancer mortality or modify the association under investigation. Another limitation is that we did not always have detailed information on the first pregnancy which is suggested as an important factor to control for [11]. Furthermore, gestational age was estimated based on the first day of last menstruation (LMP), an estimation prone to misclassification due to possible incorrect recall [1, 33].

In conclusion, our findings suggest that the hypothesis that "premenopausal breast cancer mortality is associated with offspring birth characteristics in the most recent pregnancy before the diagnosis" may not be valid. In addition, these associations are not modified by tumor characteristics.

Part of the results is presented in the European Congress of Epidemiology, Aarhus, Denmark, 2013.

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Conflict of interest Jan Adolfsson had advisory role in Ferring Pharmaceuticals, March–August 2014. The other authors declare that they have no conflict of interest.

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

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