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14. ABSTRACT
Background Indirect markers of hormone exposures during pregnancy have inconsistently been associated with subsequent risk of breast cancer in the mother. We wanted to examine associations between weights of placental and birth weight and mothers' breast cancer risk. Design A population-based cohort study using data from the Swedish National Registers. We included women who delivered single births between 1982 and 1989 in Sweden (n=314,019). Results In all, 2,216 women developed breast cancer during the follow-up through 2001. Compared to women with placentas weighing less than 500 grams in two consecutive pregnancies, the risk of breast cancer was increased among women whose placentas weighed 500-699 grams in first pregnancy and at least 700 grams in second pregnancy (or vice versa) (adjusted hazard ratio 1.82; 95% confidence interval [CI] 1.07-3.08), and among women whose placentas weighed at least 700 grams in both pregnancies (adjusted hazard ratio 2.05; 95% CI 1.15-3.64). Conclusion These results further support the hypothesis that pregnancy hormones are important modifiers of subsequent maternal breast cancer risk.

15. SUBJECT TERMS
Birth weight, breast cancer, placenta, pregnancy, risk

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INTRODUCTION

There is little question about the importance of hormonal factors in the development of breast cancer [1-4]. During pregnancy, estrogen concentrations are at least ten times higher than during other periods of life. Since estrogens are important for breast carcinogenesis, exposures during pregnancy have been suggested to influence mothers' breast cancer risks [5]. Pregnancy hormones are primarily produced in the placenta [6]. The linkage of the nationwide Swedish research registries provides an opportunity to use prospectively collected data to further investigate the possible associations between indirect markers of hormonal exposures during pregnancy, such as placental weight, offspring's birth weight, pregnancy complications, and subsequent maternal risk of developing breast cancer.

BODY

Task 1. Ethical approval

Permission to perform the study was applied for, granted by the Research Ethics Committee at Karolinska Institutet.

Task 2. Data retrieval

Specified data orders were sent to the National Board of Health and Welfare and Statistics Sweden. These Swedish authorities gave approval to send data from research registers to the research group. The National Board of Health and Welfare used the unique national registration number to perform individual record linkage between the registers (the Medical Birth Register, the Cancer Register, the Cause of Death Register, and the Register of Population and Population Changes). Initial quality control was performed at the National Board of Health and Welfare. Data were transferred to the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.

Task 3. Defining the cohort.

The study base was defined by all primiparous women included in the Swedish Medical Birth Register who delivered single births 1982-89 (n=315,339), of whom 99.6% (n=314,019) had complete information about date of birth and gestational age. Through record linkage to the

Cancer Register, the Cause of Death Register and the Register of the Population and Population Changes, women were followed until Dec 31, 2001, the occurrence of breast cancer, death or emigration, whichever came first.

Information about breast cancer diagnosis was derived from the Swedish National Cancer Register (ICD-7 code 170). Cases were defined as the first breast cancer diagnosed after the first birth through the year 2001. In the cohort of 314,019 women, 2,216 developed breast cancer during the time of follow-up, of whom 2,100 (95%) were diagnosed before age 50.

The following factors were included as possible risk factors for breast cancer: placental weight, birth weight, gestational age, infant's sex, women's age at first birth, co-habiting with infant's father or not, maternal smoking, women's country of birth, height, body mass index, pregnancy-induced hypertensive diseases, and vaginal bleeding in late pregnancy. We also included information about parity number (through 2001), to be used as a time-dependent co-variate.

Task 4. Analysis

Data cleaning

Frequency tables of all exposure variables were performed. Implausible values were considered missing and exposure variables were categorized.

Analyses

The Cox proportional hazard model was used to estimate associations between exposures and breast cancer risk. We studied the associations between exposures at first or second birth and mother's risk of breast cancer. First, we used bivariate analysis to study the associations between the independent variables in breast cancer risk. In this analysis, the independent variables were categorized, and for each category we calculated person-years of follow-up and breast cancer incidence rates stratified by maternal age at first or second birth, respectively. Thereafter, we used Cox proportional hazard model to estimate the relative risk of developing breast cancer in a multivariate analysis. The hazard ratio was used as a measure of relative risk, using 95% confidence intervals.

Task 5. Results

The results have been derived from the publication that this work resulted in [7] The crude incidence rate of breast cancer increased with placental weight (Table 1). Women who delivered an infant with a high birth weight (>4,500 grams) had higher incidence rates of breast cancer than women with lower birth weight infants. Gestational age at first birth did not appear to influence the crude incidence rate of breast cancer among mothers.

Table 1. Pregnancy and Infant Characteristics (Primiparous Women in Sweden, 1982-1989) in Relation to Unadjusted Incidence Rates of Breast Cancer (N=314 019)*

Characteristics	Cohort, No. (%)	Breast Cancer, No. (Incidence Rate)†
Placental weight, g		
≤499	48 512 (20.4)	297 (3.99)
500-599	79 569 (33.5)	526 (4.31)
600-699	64 984 (27.4)	469 (4.70)
≥700	44 433 (18.7)	361 (5.30)
Missing	76 521	563 (4.79)
Birth weight, g		
≤2499	14 369 (4.6)	103 (4.69)
2500-3499	155 758 (49.9)	1045 (4.38)
3500-4499	136 508 (43.7)	1001 (4.78)
≥4500	5761 (1.8)	52 (5.88)
Missing	1623	15 (5.37)
Gestational age, wk		
≤36	16 204 (5.2)	115 (4.63)
37-39	98 399 (31.3)	674 (4.46)
40-41	154 587 (49.2)	1073 (4.53)
≥42	44 829 (14.3)	354 (5.14)
Infant sex		
Boy	161 474 (51.4)	1152 (4.65)
Girl	152 514 (48.6)	1064 (4.55)
Missing	31	0

*Breast cancer diagnosed after first birth but before January 1, 2002.
†Unadjusted incidence rates per 10 000 person-years

Source: Cnattingius et al. JAMA 2005;294:2474-80

Table 2 (below) displays age stratified and multivariate adjusted hazard ratios of breast cancer in relation to placental weight at first birth. The risk of breast cancer generally increased with placental weight. Compared to women with a placental weight of less than 500 grams, women with a placental weight of at least 900 grams faced a 56% increase in risk of breast cancer. In age-adjusted analysis, mothers of infants with a birth weight of at least 4,500 grams had a 30% increased risk of breast cancer compared with mothers to infants with a birth weight between 2,500 and 3,499 grams (Table 2). However, after adjusting for placental weight and other factors, this risk increase disappeared. Compared with women with only one birth, women with at least three births were at reduced risk of breast cancer. Other factors, including gestational age, infant's sex, maternal characteristics, and pregnancy complications, did not influence breast cancer.

Table 2. Placental Weight and Birth Weight in First Birth and Hazard Ratios of Breast Cancer

	Hazard Ratio (95% CI) by Placental Weight, g				*P* for Trend
	<499	500-599	600-699	≥700	
Only age-adjusted*	1.00	1.11 (0.97-1.28)	1.22 (1.05-1.41)	1.34 (1.15-1.56)	<.001
Fully adjusted†	1.00	1.07 (0.90-1.27)	1.17 (0.97-1.41)	1.38 (1.13-1.69)	.001
	Birth Weight, g				
	≤2499	2500-3499	3500-4499	≥4500	
Only age-adjusted	0.98 (0.80-1.20)	1.00	1.11 (1.02-1.21)	1.30 (0.99-1.72)	.008
Fully adjusted†	0.89 (0.63-1.27)	1.00	1.00 (0.87-1.15)	1.08 (0.74-1.57)	.71

Abbreviation: CI, confidence interval.
*Hazard ratios are age-adjusted by stratification for maternal age at first birth.
†Hazard ratios are stratified for maternal age at first birth and adjusted for gestational age, infant sex, age at first birth, height, body mass index, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, diabetes mellitus, and vaginal bleeding in late pregnancy. Parity is included in the analysis as a time-dependent covariate. Placental weight is adjusted for birth weight and birth weight is adjusted for placental weight (in grams).

Source: Cnattingius et al. JAMA 2005;294:2474-80

We then restricted our study population to 121,714 women who had their first and second consecutive single birth during the study period. Of these women, 881 developed breast cancer during the time of follow-up. Compared with women whose placenas had a weight of less than 500 grams in both pregnancies, women whose placentas weighed between 500 and 699 grams in the first pregnancy and at least 700 grams in the second pregnancy (or vice versa) faced an 82% increased in risk of breast cancer, and the corresponding risk among women whose placentas weighed at least 700 grams in both pregnancies was more than doubled (Table 3).

Table 3. Placental Weight and Birth Weight in First and Second Births and Hazard Raios of Breast Cancer.

Characteristics by First/Second Pregnancy	% of Women	Breast Cancer, No. (Incidence Rate)	Hazard Ratio (95% CI)	
			Only Age-Adjusted*	Fully Adjusted†
Placental weight, g				
≤499/≤499	4.1	26 (3.72)	1.00	1.00
≤499/500-699	13.5	103 (4.52)	1.22 (0.79-1.87)	1.44 (0.85-2.43)
≤499/≥700	1.9	16 (5.05)	1.34 (0.72-2.49)	1.27 (0.58-2.78)
500-699/500-699	27.2	208 (4.52)	1.24 (0.82-1.86)	1.34 (0.81-2.24)
500-699/≥700	16.1	167 (6.14)	1.67 (1.11-2.53)	1.82 (1.07-3.08)
≥700/≥700	6.2	69 (6.57)	1.75 (1.11-2.74)	2.05 (1.15-3.64)
Missing	31.0	292 (5.57)		
Birth weight, g				
<2499/<2499	0.5	7 (7.72)	1.46 (0.70-3.09)	1.66 (0.46-5.99)
<2499/2500-3999	4.9	34 (4.13)	0.84 (0.60-1.19)	0.96 (0.55-1.70)
≤2499/≥4000	0.3	3 (5.72)	1.13 (0.36-3.50)	Indeterminate‡
2500-3999/2500-3999	67.0	551 (4.86)	1.00	1.00
2500-3999/≥4000	19.7	196 (5.91)	1.21 (1.02-1.42)	1.07 (0.84-1.38)
≥4000/≥4000	6.8	79 (6.91)	1.42 (1.12-1.79)	1.10 (0.76-1.59)
Missing	0.8	11 (7.47)		

Abbreviation: CI, confidence interval.
*Hazard ratios are age-adjusted by stratification for maternal age at second birth.
†Hazard ratios are age-adjusted by stratification for age at second birth and adjusted for gestational age in first and second births, infant sex in second birth, age at first birth, and other maternal characteristics, and pregnancy complications at second birth (height, body mass index, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, and vaginal bleeding in late pregnancy). Parity is included in the analysis as a time-dependent covariate. Placental weight is adjusted for birth weight and vice versa.
‡No case had complete information on covariates.

Source: Cnattingius et al. JAMA 2005;294:2474-80

KEY RESEARCH ACCOMPLISHMENTS:

- Construction of a data base of 314,019 women with prospectively collected data on pregnancy characteristics and breast cancer.
- Complete follow-up of the study base through 2001.
- Performance of bivariate and multivariate analysis, indicating that placental weight influences mother's risk of breast cancer.
- Finishing of work with poster work and oral presentation to be presented at the Department of Defense Breast Cancer Research Program Meeting, in Philadelphia, June 2005.
- Finishing of manuscript, and submission for publication.

REPORTABLE OUTCOMES

- Cnattingius S, Torrång A, Ekbom A, Granath F, Petersson G, Lambe M. Placental weight, birth weight and risk of breast cancer after giving birth: a population-based Swedish cohort study. Poster and oral presentation at the Department of Defense Breast Cancer Research Program Meeting, in Philadelphia, June 2005 (poster No. P24-4).

- Cnattingius S, Torrång A, Ekbom A, Granath F, Petersson G, Lambe M. Pregnancy characteristics and maternal risk of breast cancer. JAMA 2005;294:2474-80

CONCLUSIONS:

Our work suggests that placental weight is positively associated with maternal breast cancer risk. These results further support the hypothesis that pregnancy hormone exposures influence mother's breast cancer risk. However, underlying biological mechanisms responsible for these associations remain to be determined. Such mechanisms may not only include pregnancy characteristics, such as placental hormones and breast cell differentiation, but also non-pregnant hormonal and metabolic characteristics associated with placental growth.

PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT

Sven Cnattingius, MD, PhD: Principal Investigator

Mats Lambe, MD, PhD, epidemiologist

Fredrik Granath, PhD, statistician

Gunnar Petersson, BA, programmer

Anna Torrång, B.Sc., statistician

Gunilla Sonnebring, BA, senior administrative assistant

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APPENDICES

The following two Appendices are included:

1. Cnattingius S, Torrång A, Ekbom A, Granath F, Petersson G, Lambe M. Placental weight, birth weight and risk of breast cancer after giving birth: a population-based Swedish cohort study. Poster and oral presentation at the Department of Defense Breast Cancer Research Program Meeting, in Philadelphia, June 2005 (poster No. P24-4).

2. Cnattingius S, Torrång A, Ekbom A, Granath F, Petersson G, Lambe M. Pregnancy characteristics and maternal risk of breast cancer. JAMA 2005;294:2474-80

PLACENTAL WEIGHT, BIRTH WEIGHT AND RISK OF BREAST CANCER AFTER GIVING BIRTH: A POPULATION-BASED SWEDISH COHORT STUDY

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There is little question about the importance of hormonal factors in the development of breast cancer. During pregnancy, serum levels of estrogens, progesterone, human placental lactogene, and placental growth hormones are many times higher than during other periods of life, and levels of insulin-like growth factors (IgFs) are also increased. Since estrogens, IgFs, and probably also other placental hormones are important for breast carcinogenesis, levels of exposure during pregnancy have been suggested to influence the risk of breast cancer in both mothers and offspring. Indirect markers of hormone exposure during pregnancy (i.e., placental weight and birth weight) have inconsistently been associated with subsequent risk of breast cancer in the mother.

We included women included in the Swedish Medical Birth Register, who delivered single births in Sweden 1982-89 (n=314,019). Women were followed-up until December 31, 2001, the occurrence of breast cancer, death or emigration, whichever came first. Proportional hazard models were used to estimate associations between exposures and breast cancer. Hazard ratios (HR) were used to estimate relative risks, using 95% confidence intervals (CI), and final parity number was used as a time-dependent covariate.

In all, 2,216 women developed breast cancer during the follow-up, of which 95% (n=2,100) were younger than 50 years at diagnosis. Compared to women with placentas weighing less than 500 grams at first birth, there was an almost 40% increase in risk of breast cancer among women with placentas weighing at least 700 grams (adjusted HR 1.38; 95% CI 1.13-1.69). Next, we restricted our study population to 121,713 women who had their first and second consecutive single birth during the study period, of whom in all 884 developed breast cancer. Compared to women with placentas weighing less than 500 grams in two consecutive pregnancies, the risk of breast cancer was increased among women whose placentas weighed 500-699 grams in first pregnancy and at least 700 grams in second pregnancy (or vice versa) (adjusted HR 1.82; 95% CI 1.09-3.12), and among women whose placentas weighed at least 700 grams in both pregnancies (adjusted HR 2.10; 95% CI 1.18-3.72). A high birth weight (>4,000 grams) was associated with a significantly increased risk of breast cancer before (adjusted HR 1.42; 95% CI 1.02-1.80), but not after adjusting for placental weight and other covariates (adjusted HR 1.10; 95% CI 0.76-1.59).

Placental weight is positively associated with maternal breast cancer risk. As pregnancy hormones are primarily produced in the placenta, placental weight is probably a better

indirect marker than birth weight of pregnancy hormone exposures. The study lends further support to the hypothesis that pregnancy hormone exposures influence mother's breast cancer risk.

The U.S. Army Medical Research and Materiel Command under DAMD 17-03-01-0741 supported this work.

Pregnancy Characteristics and Maternal Risk of Breast Cancer

Sven Cnattingius, MD, PhD
Anna Torrång, BSc
Anders Ekbom, MD, PhD
Fredrik Granath, PhD
Gunnar Petersson, BSc
Mats Lambe, MD, PhD

Context During pregnancy, serum levels of estrogen, progesterone, and other hormones are markedly higher than during other periods of life. Pregnancy hormones primarily are produced in the placenta, and signs of placental impairment may serve as indirect markers of hormone exposures during pregnancy. During pregnancy, these markers have been inconsistently associated with subsequent risk of breast cancer in the mother.

Objective To examine associations between indirect markers of hormonal exposures, such as placental weight and other pregnancy characteristics, and maternal risk of developing breast cancer.

Design and Setting Population-based cohort study using data from the Swedish Birth Register, the Swedish Cancer Register, the Swedish Cause of Death Register, and the Swedish Register of Population and Population Changes.

Participants Women included in the Sweden Birth Register who delivered singletons between 1982 and 1989, with complete information on date of birth and gestational age. Women were followed up until the occurrence of breast cancer, death, or end of follow-up (December 31, 2001). Cox proportional hazards models were used to estimate associations between hormone exposures and risks of breast cancer.

Main Outcome Measure Incidence of invasive breast cancer.

Results Of 314 019 women in the cohort, 2216 (0.7%) developed breast cancer during the follow-up through 2001, of whom 2100 (95%) were diagnosed before age 50 years. Compared with women who had placentas weighing less than 500 g in 2 consecutive pregnancies, the risk of breast cancer was increased among women whose placentas weighed between 500 and 699 g in their first pregnancy and at least 700 g in their second pregnancy (or vice versa) (adjusted hazard ratio, 1.82; 95% confidence interval [CI], 1.07-3.08), and the corresponding risk was doubled among women whose placentas weighed at least 700 g in both pregnancies (adjusted hazard ratio, 2.05; 95% CI, 1.15-3.64). A high birth weight (≥4000 g) in 2 successive births was associated with an increased risk of breast cancer before but not after adjusting for placental weight and other covariates (adjusted hazard ratio, 1.10; 95% CI, 0.76-1.59).

Conclusions Placental weight is positively associated with maternal risk of breast cancer. These results further support the hypothesis that pregnancy hormones are important modifiers of subsequent maternal breast cancer risk.

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HORMONAL FACTORS PLAY A KEY role in the development of breast cancer. Early menarche, late menopause, and long-term use of hormone therapy repeatedly have been shown to be associated with increased risks of breast cancer.[1-4] The short-term and long-term risk-modifying effects of parity also are well documented,[2] but little information is known about the underlying biological mechanisms. Serum levels of estrogens, progesterone, human placental lactogene, and placental growth hormones are many times higher during pregnancy than during other periods of life,[5] and pregnant women also are exposed to elevated levels of insulin-like growth factors.[6] Since several of these hormones have been implicated in breast carcinogenesis,[7,8] it is of interest to explore how different markers of endocrine exposure during pregnancy may be associated with the risk of breast cancer in both mothers and offspring.[9]

Pregnancy hormones primarily are produced in the placenta, and signs of placental impairment may serve as indirect markers of hormone exposures during pregnancy. Cohn et al[10] reported that low placental weight, small placental diameter, maternal floor infarction of the placenta, and elevations in blood pressure between the second and third trimester were associated with relatively strong and independent reductions in maternal risk of breast cancer. Since the included variables generally were presented to maximize apparent effects, an accompanying editorial suggested that "the results should be viewed as hypotheses awaiting testing . . . " and that "studies based on larger number of cases are needed."[11]

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The linkage of the nationwide Swedish research registries provided an opportunity to use data collected prospectively to further investigate the possible associations between indirect markers of hormonal exposures during pregnancy, such as placental weight, offspring's birth weight, pregnancy complications, and subsequent maternal risk of developing breast cancer.

METHODS

Data Sources

The Swedish National Board of Health and Welfare and Statistics Sweden provided access to data from 4 population-based registers. Individual record linkage across these registers was possible through the unique National Registration Number assigned to each Swedish resident.

The Birth Register includes information collected prospectively on more than 99% of all births in Sweden.[12] Information about placental weight was included in the Birth Register between 1982 and 1989. Complications during pregnancy and delivery are classified according to the Swedish version of the *International Classification of Diseases* (*ICDs*): *ICD-8* was used from 1982 to 1986, and *ICD-9* was used from 1987 to 1996. The Cancer Register includes histologically verified cancers, and the completeness has been evaluated to exceed 95%.[13] To facilitate comparisons over time, cancer registration also has been classified according to *ICD-7* for later years. The Cause of Death Register includes information about date and cause of death on all Swedish residents. The completeness has been estimated to exceed 99% (results are available [mainly in Swedish] on the Web: http://www.sos.se/epc/dors/dodsreg.htm). The Register of Population and Population Changes includes information about dates of birth, death, emigration, and immigration of all Swedish residents.

Study Population

The study population was defined as all primiparous women included in the Birth Register who delivered single births between 1982 and 1989 (N=315 339). In the study population, 314 019 women (99.6%) had complete information about date of birth and gestational age, and 121 285 women also had a second consecutive single birth between 1982 and 1989. Through record linkages with the Cancer Register, the Cause of Death Register, and the Register of Population and Population Changes, women were followed up until the occurrence of breast cancer, death, emigration, or end of follow-up (December 31, 2001), whichever came first.

Ascertainment of Exposures and Outcomes

The following information from first and second consecutive single deliveries was collected from the Birth Register: placental weight, birth weight, gestational age (in completed weeks), and sex of infant. The following maternal characteristics were collected: maternal age at delivery, family situation (living with infant's father or not), smoking at registration to antenatal care (nondaily smoking and daily smoking), mother's country of birth (Nordic [ie, Sweden, Denmark, Finland, Iceland, and Norway] or non-Nordic), maternal height and weight (measured at the time of entry to the delivery ward), hypertensive disease during pregnancy (*ICD-8* code 637 and *ICD-9* code 642), diabetes (pregestational and gestational diabetes mellitus [*ICD-8* code 250 and *ICD-9* codes 648A and 648W]), and vaginal bleeding in late pregnancy (*ICD-8* codes 632 and 651 and *ICD-9* code 641). Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Information about the diagnoses of breast cancer was derived from the Cancer Register (*ICD-7* code 170). Cases were defined as the first breast cancer diagnosed after the first birth.

The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden. The research ethics committee did not require the women to provide informed consent.

Statistical Analyses

Crude bivariate associations between the independent variables and breast cancer risk were assessed by unadjusted incidence rates (ie, number of breast cancer cases per 100 000 person-years). Adjusted associations between hormone exposures and breast cancer risk were assessed by weighted Cox proportional hazards models. The time scale used was time since pregnancy, and to control for the effects of both attained age and age at first birth, we chose to condition (weigh) the analysis on age at first birth in 5-year age bands.

The following factors were included in the models: placental weight, birth weight, gestational age, infant sex, family situation, smoking habits, mother's country of birth, height, BMI, pregnancy-induced hypertensive diseases, vaginal bleeding in late pregnancy, diabetes mellitus, and parity. Because out of the total population only 10 women with diabetes mellitus later developed breast cancer, diabetes mellitus was not included as a covariate in the analysis of successive births and in the stratified analyses. Parity was adjusted for by introducing subsequent births as time-dependent covariates, splitting the risk time according to parities 1, 2, and 3 or more. Gestational age was estimated in completed weeks and categorized as 36 or less, 37, 38, 39, 40, 41, and 42 or more weeks. Other variables were categorized according to TABLE 1.

The hazard ratio was used as a measure of relative risk, using 95% confidence intervals (CIs). To test for trend, the categories for placental weight and birth weight were equidistantly scored and entered as continuous variables into the designated Cox proportional hazards models.

Different models were used to analyze the associations between placental weight, birth weight, and risk of breast cancer. First, placental weight and birth weight were used as continuous variables, and estimated risk of breast cancer related to a 100-g increase in placental weight and a 500-g increase in birth weight. The possibility of using quartiles to categorize placental weight

Table 1. Pregnancy and Infant Characteristics (Primiparous Women in Sweden, 1982-1989) in Relation to Unadjusted Incidence Rates of Breast Cancer (N=314 019)*

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*Breast cancer diagnosed after first birth but before January 1, 2002.
†Unadjusted incidence rates per 10 000 person-years

(≤500 g, 501-580 g, 581-660 g, and ≥661 g) and birth weight (≤3110 g, 3111-3440 g, 3441-3765 g, and ≥3766 g) then was investigated. Thus, the difference in placental weight between the highest and lowest quartiles may be as small as 161 g, and the corresponding difference for birth weight may be as small as 656 g. A problem also arose with imprecise measurements of placental weights because weights primarily were recorded to the nearest 50- or 100-g category. Categorizing placental weight and birth weight into quartiles therefore may not be optimal, since it provides a narrow range of exposures and a risk of misclassifying placental weight. To provide a wider range of exposures and to reduce the risk of misclassification of placental weight, the risk of breast cancer related to placental weight and birth weight in first birth was analyzed using the following categories of placental weight: 499 g and less, 500 to 599 g, 600 to 699 g, and 700 g and more; and birth weight: 2499 g and less, 2500 to 3499 g, 3500 to 4499 g, and 4500 g and more.

A secondary analysis included the risk of breast cancer as it related to placental weight and birth weight in the first as well as the second birth. Again, similar weighted Cox hazards regression models were applied as above, with the difference that they were conditioned by mother's age at second birth and adjusted for mother's age at first birth. To reduce the number of combinations, 3 categories of placental weight (≤499 g, 500-699 g, and ≥700 g) and birth weight (≤2499 g, 2500-3999 g, and ≥4000 g) were used in these analyses.

Whether the effect of placental weight on breast cancer risk was modified by maternal age at first birth and time of follow-up also was investigated. To maximize power, only data from first birth in the entire cohort in the interaction analyses were used and maternal age at first birth by median age among cases (≤30 years and ≥31 years) was dichotomized. Time of follow-up was dichotomized using median time from date of first delivery to date of breast cancer diagnosis (median time of follow-up was 11 years and 7 months). In the interaction analyses, 4 categories of placental weight were used (≤499 g, 500-599 g, 600-699 g, and ≥700 g). Statistical analyses were performed using the SAS program package (SAS Institute Inc, Cary, NC). An outcome with $P<.05$ was considered statistically significant.

RESULTS

In the cohort of 314 019 women who delivered their first singleton birth between 1982 and 1989, 2216 (0.7%) developed breast cancer during the time of follow-up, of whom 2100 (95%) were diagnosed before age 50 years.

Table 1 and TABLE 2 show the distribution of pregnancy and maternal characteristics at first birth in relation to unadjusted incidence rates of breast cancer per 10 000 person-years for the entire cohort. The incidence rate of breast cancer consistently increased with placental weight (3.99 for ≤499 g and 5.30 for ≥700 g) (Table 1). Women who delivered an infant with a high birth weight (≥4500 g) had a higher incidence rate of breast cancer than women who delivered infants with a lower birth weight. Rates of breast cancer were increased among women with a post-term birth (≥42 weeks) compared with women with shorter gestation times. A strong positive association between maternal age at first birth and incidence rate of breast cancer was observed; that is, the older the mother the higher the incidence rate of breast cancer (Table 2). Since maternal age at first birth was relatively evenly distributed over time, this association primarily was mediated by age at first birth reflects age at follow-up. However, the well-documented effect of age at first birth per se on risk of breast cancer[2] also most likely contributed to the obtained association. The incidence rate of breast cancer also increased with maternal height. Women with a high BMI (≥29.0) had lower incidence rates of breast cancer than those women who had lower BMIs, and smokers during pregnancy appeared to have lower incidence rates of breast cancer than nonsmokers.

In the adjusted analyses, placental weight and birth weight as continuous variables were analyzed first. The adjusted hazard ratio of breast cancer related to 100-g increase in placental weight was 1.07 (95% CI, 1.02-1.13; P=.01) in the fully adjusted model. When birth weight was excluded as a covariate, this risk increased (adjusted hazard ratio, 1.09; 95% CI, 1.05-1.14; P<.001). Birth weight was not significantly associated with breast cancer in the fully adjusted model, and the adjusted hazard ratio of breast cancer that related to a 500-g increase in birth weight was 1.05 (95% CI, 0.97-1.14; P=.21). However, when the analysis was repeated after excluding placental weight, the risk of breast cancer related to a 500-g increase in birth weight amounted to an adjusted hazard ratio of 1.11 (95% CI, 1.04-1.18; P<.001).

Compared with women who had a placental weight of less than 500 g, women who had a placental weight of at least 700 g faced a 38% increase in risk of breast cancer (TABLE 3). In age-adjusted analysis, mothers of infants with a birth weight of at least 4500 g had a 30% increased risk of breast cancer compared with mothers of infants with a birth weight between 2500 and 3499 g. However, this increase in risk disappeared in the adjusted analysis (Table 3). When placental weight was excluded from the fully adjusted model, the corresponding risk was 1.22 (95% CI, 0.86-1.73).

Compared with women with only 1 birth from 1983 through 2001, women with at least 3 births were at reduced risk of breast cancer (adjusted hazard ratio, 0.77; 95% CI, 0.64-0.92). Women who were taller had an increased risk of breast cancer (adjusted hazard ratio, 1.33; 95% CI, 1.08-1.63) compared with women with a height from 165 to 169 cm. Compared with women with a BMI from 25.0 to 26.9, women with a BMI of 29.0 or more had a reduced risk of breast cancer (adjusted hazard ratio, 0.85; 95% CI, 0.72-0.99). Women with diabetes mellitus had higher placental weights than women who did not have diabetes mellitus (median weights were 580 g and 610 g, respectively; P<.001, using the Wilcoxon rank sum test). However, diabetes was not associated with breast cancer risk, neither in the age-adjusted nor in the fully adjusted analyses (hazard ratios were 0.77 [95% CI, 0.41-1.43] and 1.07 [95% CI, 0.51-2.25], respectively). Younger women more often were smokers than older women, and smoking during pregnancy was, in the age-adjusted and fully adjusted analyses, not associated with risk of breast cancer. Other factors, including gestational age, infant sex, family situation, mother's country of birth, and pregnancy complications, did not influence breast cancer risk (data not shown).

Next, our study population was restricted to 121 285 women who had

Table 2. Maternal Characteristics (Primiparous Women in Sweden, 1982-1989) in Relation to Unadjusted Inddence Rates of Breast Cancer (N = 314 019)*

Maternal Characteristics	Cohort, No. (%)	Breast Cancer, No. (Incidence Rate)†
Age at first birth, y		
≤19	22 138 (7.0)	31 (0.90)
20-24	119 402 (38.0)	319 (1.73)
25-29	114 544 (36.5)	830 (4.72)
30-34	44 724 (14.2)	632 (9.35)
≥35	13 211 (4.2)	404 (20.4)
Height, cm		
≤159	31 024 (12.4)	177 (3.75)
160-164	67 087 (26.8)	440 (4.28)
165-169	77 270 (30.9)	536 (4.54)
≥170	75 016 (30.0)	602 (5.28)
Missing	63622	461 (4.62)
BMI		
≤24.9	67 671 (28.4)	467 (4.48)
25-26.9	60 432 (25.4)	468 (5.05)
27-28.9	48 338 (20.3)	372 (5.04)
≥29	61 628 (25.9)	366 (3.93)
Missing	75950	543 (4.60)
Smoking		
No	199 642 (70.3)	1445 (4.78)
Yes	84 243 (29.7)	530 (4.09)
Missing	30134	241 (4.83)
Family situation		
Cohabiting	267 926 (91.6)	1878 (4.61)
Not cohabiting	24 432 (8.4)	156 (4.25)
Missing	21 661	182 (4.87)
Country of birth		
Nordic	293 388 (93.7)	2070 (4.58)
Non-Nordic	19 615 (6.3)	134 (4.77)
Missing	1016	12 (8.40)
Pregnancy-induced hypertensive diseases		
No	292 583 (93.2)	2064 (4.58)
Yes	21 436 (6.8)	162 (4.82)
Diabetes mellitus		
No	312 421 (99.5)	2206 (4.60)
Yes	1598 (0.5)	10 (4.25)
Vaginal bleeding in late pregnancy		
No	305 925 (97.4)	2146 (4.57)
Yes	8094 (2.6)	70 (5.67)
Overall	314 019	2216

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.
*Breast cancer diagnosed after first birth but before January 1, 2002.
†Unadjusted incidence rates per 10 000 person-years.

their first and second consecutive single births during the study period, of whom 881 developed breast cancer after the second birth. To increase the power of our estimates, only 3 categories of placental weight (≤499 g, 500 to 699 g, and ≥700 g) and birth weight (<2449 g, 2500 to 3999 g, and ≥4000 g) were used. Compared with women whose placentas had a weight of less than 500 g in both pregnancies, women whose placentas weighed between 500 and 699 g in the first pregnancy and 700 g or more in the second pregnancy (or vice versa) faced an 82% increase in risk of breast cancer (adjusted hazard ratio, 1.82; 95% CI, 1.07-3.08), and the corresponding risk among women whose placentas weighed at least 700 g in both pregnancies was more than doubled (adjusted hazard ratio, 2.05; 95% CI, 1.15-3.64) (TABLE 4). A high birth weight (≥4000 g) in 2 successive births was associated with a significant increase in risk of breast cancer before but not after adjusting for placental weight and other covariates (adjusted hazard ratio, 1.10; 95% CI, 0.76-1.59).

In the entire cohort (N=314 019), a significant interaction was observed between mother's age at first birth and placental weight with regard to breast cancer risk (P=.02). Among women aged 30 years or younger at first birth, placental weight was not significantly associated with increased risk of breast cancer (TABLE 5). In contrast, among women aged 30 years or older at first birth, the risk of breast cancer was increased by close to 70% among women who had a placental weight of at least 700 g, compared with women who had a placental weight of less than 500 g (adjusted hazard ratio, 1.67; 95% CI, 1.21-2.30; P<.001). In addition, whether the association between placental weight and breast cancer risk was modified by time of follow-up, using median time from first delivery to breast cancer diagnosis as a cut-off, was tested. No statistically significant interaction was found between placental weight and time of follow-up with regard to breast cancer risk (P=.12).

Table 3. Placental Weight and Birth Weight in First Birth and Hazard Ratios of Breast Cancer

	Hazard Ratio (95% CI) by Placental Weight, g				P for Trend
	<499	500-599	600-699	≥700	
Only age-adjusted*	1.00	1.11 (0.97-1.28)	1.22 (1.05-1.41)	1.34 (1.15-1.56)	<.001
Fully adjusted†	1.00	1.07 (0.90-1.27)	1.17 (0.97-1.41)	1.39 (1.13-1.69)	.001
	Birth Weight, g				
	≤2499	2500-3499	3500-4499	≥4500	
Only age-adjusted	0.98 (0.80-1.20)	1.00	1.11 (1.02-1.21)	1.30 (0.99-1.72)	.008
Fully adjusted†	0.89 (0.63-1.27)	1.00	1.00 (0.87-1.15)	1.09 (0.74-1.57)	.71

Abbreviation: CI, confidence interval.
*Hazard ratios are age-adjusted by stratification for maternal age at first birth.
†Hazard ratios are stratified for maternal age at first birth and adjusted for gestational age, infant sex, age at first birth, height, body mass index, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, diabetes mellitus, and vaginal bleeding in late pregnancy. Parity is included in the analysis as a time-dependent covariate. Placental weight is adjusted for birth weight and birth weight is adjusted for placental weight (in grams).

Table 4. Placental Weight and Birth Weight in First and Second Consecutive Births and Hazard Ratios of Breast Cancer (n = 121 285)

Characteristics by First/Second Pregnancy	% of Women	Breast Cancer, No. (Incidence Rate)	Hazard Ratio (95% CI)	
			Only Age-Adjusted*	Fully Adjusted†
Placental weight, g				
≤499/≤499	4.1	26 (3.72)	1.00	1.00
≤499/500-699	13.5	103 (4.52)	1.22 (0.79-1.87)	1.44 (0.85-2.43)
≤499/≥700	1.9	16 (5.05)	1.34 (0.72-2.49)	1.27 (0.59-2.78)
500-699/500-699	27.2	208 (4.52)	1.24 (0.82-1.86)	1.34 (0.81-2.24)
500-699/≥700	16.1	167 (6.14)	1.67 (1.11-2.53)	1.82 (1.07-3.08)
≥700/≥700	6.2	69 (6.57)	1.75 (1.11-2.74)	2.05 (1.15-3.64)
Missing	31.0	292 (5.57)		
Birth weight, g				
<2499/<2499	0.5	7 (7.72)	1.46 (0.70-3.09)	1.66 (0.46-5.99)
<2499/2500-3999	4.9	34 (4.13)	0.84 (0.60-1.19)	0.96 (0.55-1.70)
≤2499/≥4000	0.3	3 (5.72)	1.13 (0.36-3.50)	Indeterminate‡
2500-3999/2500-3999	67.0	551 (4.86)	1.00	1.00
2500-3999/≥4000	19.7	196 (5.91)	1.21 (1.02-1.42)	1.07 (0.84-1.38)
≥4000/≥4000	6.8	79 (6.91)	1.42 (1.12-1.79)	1.10 (0.76-1.59)
Missing	0.8	11 (7.47)		

Abbreviation: CI, confidence interval.
*Hazard ratios are age-adjusted by stratification for maternal age at second birth.
†Hazard ratios are age-adjusted by stratification for age at second birth and adjusted for gestational age in first and second births, infant sex in second birth, age at first birth, and other maternal characteristics, and pregnancy complications at second birth (height, body mass index, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, and vaginal bleeding in late pregnancy). Parity is included in the analysis as a time-dependent covariate. Placental weight is adjusted for birth weight and vice versa.
‡No case had complete information on covariates.

Table 5. Placental Weight in First Birth and Adjusted Hazard Ratios of Breast Cancer*

Maternal Age at First Birth, y	Hazard Ratio (95% CI) by Placental Weight, g				P Value for Trend
	<499	500-599	600-699	≥700	
≤30	1.00	1.07 (0.86-1.32)	1.15 (0.91-1.45)	1.22 (0.94-1.59)	.11
≥31	1.00	1.08 (0.81-1.43)	1.21 (0.90-1.64)	1.67 (1.21-2.30)	<.001

Abbreviation: CI, confidence interval.
*Analyses stratified by maternal age at first birth. Hazard ratios adjusted for gestational age, birth weight, infant sex, age at first birth, height, body mass index, smoking, family situation, country of birth, pregnancy-induced hypertensive diseases, and vaginal bleeding in late pregnancy. Parity is included in the analysis as a time-dependant covariate.

COMMENT

In the present population-based cohort study, mother's risk of (predominantly premenopausal) breast cancer increased with placental weight.

Compared with women who had a low placental weight (≤499 g) in 2 successive pregnancies, the risk of breast cancer was doubled among mothers whose placentas weighed 700 g or more in both pregnancies. High birth weight was associated with an increase in risk of breast cancer before but not after adjusting for placental weight and other covariates.

Our finding of a positive association between placental weight and breast cancer risk may reflect that exposures to elevated levels of pregnancy hormones influence the risk of breast cancer. The role of estrogens in breast carcinogenesis is well established, and serum estrogen levels are at least 10 times higher during pregnancy compared with other times of life.[9] Estradiol is considered more biologically active than estriol.[7,8] However, estriol is the dominating estrogen during pregnancy,[14] and maternal serum levels of estriol have, in contrast to maternal serum levels of estradiol, been positively associated with placental weight.[15]

The association between placental weight and breast cancer risk also may be explained by exposures to other hormones or other maternal factors. For example, maternal serum levels of the anti-estrogenic hormones testosterone and α-fetoprotein also increase during pregnancy[16,17] and are further increased among women with preeclampsia.[18,19] Preeclampsia has been associated with a reduced risk of breast cancer,[10,20-22] and the occurrence of preeclampsia interferes with placental growth and function.[23] If high serum levels of testosterone and α-fetoprotein are associated with low placental weight, the antiestrogenic effects of these hormones may explain the association between low placental weight and low risk of breast cancer. Insulin-like growth factors also are important for breast carcinogenesis,[7,8] and placental weight has been shown to be positively associated with maternal serum levels of insulin-like growth factor 1.[6]

Finally, several maternal factors may influence both placental weight and mother's risk of breast cancer. We controlled for the possible influence of parity, maternal height, body mass index, smoking, and hypertensive diseases during pregnancy, but only maternal height is positively associated with both placental weight and premenopausal risk of breast cancer.[7,24,25] Ethnicity was not an issue, since we primarily included white women and also controlled for mother's country of birth. We did lack information about weight gain during pregnancy, which has been shown to be positively associated with placental weight[24] and overall risk of breast cancer.[26] The influence of fetal factors on placental growth may be limited, because placental growth precedes and influences fetal growth.[27,28]

We found that the association between placental weight at first birth and breast cancer risk may be more pronounced among women aged 30 years or older at first birth. These results support previous findings of a larger short-term increase in the risk of breast cancer after childbirth among women who were older (35 years or older) at their first delivery.[29] The transient increased risk of breast cancer after childbirth has been suggested to reflect a promotional effect of elevated pregnancy hormones on premalignant or preexisting malignant cells, and women in higher childbearing ages are more likely to harbor tumor cells whose malignant transformation have already begun.[7] Results from a Danish study indicate that a possible association between high birth weight and increased risk of breast cancer may be restricted to breast cancer occurring shortly after delivery.[30] We could not demonstrate that time since delivery modified the effect of placental weight, but our study includes primarily women with premenopausal breast cancer. Hence, we cannot exclude that the risk of breast cancer related to placental weight may be modified by time of follow-up.

Birth weight also is positively associated with maternal serum levels of estrogen.[14] We observed that birth weight was positively associated with increased breast cancer risk before but not after adjusting for placental weight. Because the placenta is the major source of most pregnancy hormones, this finding seems reasonable, given the close correlation between placental weight and birth weight.[31]

We could not replicate previous findings that hypertensive diseases during pregnancy have a protective effect on a mother's risk of developing breast cancer.[10,20-22] Information on hypertensive diseases predominantly was based on diagnostic codes using *ICD-8*, and results from a previous validation study suggested that the specificity of the diagnoses "hypertensive diseases during pregnancy" was much lower using *ICD-8* than *ICD-9* codes.[32] Thus, we cannot exclude that the negative results in our study may reflect an imprecise classification of exposures.

The Swedish Birth Register provided a powerful study base, and it enabled us to include information from first births of more than 2000 women who later developed breast cancer. Our data set also permitted adjustments for total parity and other known and possible risk factors for breast cancer. Because the large majority of cases were diagnosed before age 50 years, it is unlikely that confounding by menopausal status occurred. In contrast to previous studies, we were able to include information on placental weight and other maternal exposures from 2 consecutive pregnancies in a large cohort of women. Information about the exposures was collected prospectively, which precludes recall bias.

Growth of the placenta stops earlier than fetal growth,[27] and degenerative changes in placental tissue are common at term.[33] Placental weight includes both vital and degenerative placental tissue and is probably an imprecise measure of the endocrine capacity of placental tissue. Moreover, the amount of blood in the placenta influences placental weight, and routines to clear the placenta from blood after childbirth may differ between hospitals. In the present investigation, information about placental weight was

missing in approximately 24% of all pregnancies, but it is unlikely that systematic differences exist in postpartum routines of placental management between women who later develop and those who do not develop breast cancer. Thus, such shortcomings should, if anything, bias the results toward the null. Notwithstanding these potential limitations, our study was able to demonstrate a substantially increased risk in maternal breast cancer associated with higher placental weight.

We were limited to the available information found in the Swedish registers. Importantly, we had no information on hormone measurements during pregnancy, and we had to rely on indirect hormone markers. We also lacked information on familial history of breast cancer, and both breast cancer and birth weight are at least partly genetically determined.[7,24] Ninety-five percent of the included breast cancer cases were diagnosed before age 50 years, and our conclusions should be restricted to women with premenopausal breast cancer.

Our findings support the hypothesis that exposure to pregnancy hormones during the limited time-window represented by a pregnancy appears to influence mothers' subsequent risk of breast cancer. In addition, placental weight appears to be a better indicator of the hormonal milieu than birth weight or other included birth parameters. Underlying biological mechanisms responsible for the observed associations may not only be limited to a direct growth enhancing effect on breast cells during childbearing, but also may be due to maternal characteristics or genetic factors associated with placental growth.

Author Contributions: Dr Cnattingius had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cnattingius, Ekbom, Granath, Lambe.
Acquisition of data: Cnattingius, Lambe.
Analysis and interpretation of data: Cnattingius, Torrång, Ekbom, Granath, Petersson, Lambe.
Drafting of the manuscript: Cnattingius.
Critical revision of the manuscript for important intellectual content: Torrång, Ekbom, Granath, Petersson, Lambe.
Statistical analysis: Torrång, Granath, Petersson.
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