Research Article

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Placental Weight and Breast Cancer Risk in Young Women: A Registry-Based Cohort Study from Norway

Signe Opdahl[1], Mirjam D.K. Alsaker[1,2], Pål R. Romundstad[1], Anne Eskild[3,4], and Lars J. Vatten[1]

Abstract

Background: Pregnancy has a short-term risk-increasing effect on breast cancer that may be attributed to growth-promoting effects of pregnancy hormones on prevalent but undetected tumors. Results of two previous studies suggested that placental weight may be positively associated with breast cancer risk.

Methods: In a cohort of 338,051 women followed from 1999 to 2008, on the basis of data linkage between the Medical Birth Registry of Norway and the Cancer Registry of Norway, we assessed whether placental weight in a woman's most recent pregnancy was related to breast cancer risk during the first years following pregnancy.

Results: During follow-up (median, 6.0 years; interquartile range, 3.0–8.3 years), 648 women were diagnosed with breast cancer at a mean age of 38.4 years (standard deviation, 5.3 years). Placental weight in the most recent pregnancy was not associated with breast cancer risk: the hazard ratio per 100-gram increase in placental weight was 1.03 [95% confidence interval, 0.96–1.10]. There was a similar lack of association related to mean placental weight across pregnancies and to placental weight associated with the first birth.

Conclusion: We could not confirm previous reports that women who develop large placentas are at increased risk of breast cancer.

Impact: The epidemiologic support for an association of placental weight with breast cancer risk remains inconclusive. More research is needed to identify factors that influence breast cancer risk in young women.
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Introduction

Pregnancy has a dual effect on breast cancer risk indicated by a short-term risk increase followed by a lifelong risk reduction (1, 2). The short-term increase in risk lasts for 5 to 10 years (1, 2) and has been attributed to the promoting effects that pregnancy hormones such as estrogens, progesterone, prolactin, and insulin-like growth factor-I may have on initiated breast cancer cells or prevalent but undetected tumors (3). This hypothesis is supported by indications that women with a family history of breast cancer, who may be more likely to develop breast cancer at a young age, seem more susceptible to the short-term adverse effects of pregnancy than other women (4). Some investigators have found that the increased risk after a pregnancy may be more pronounced among uniparous women (1, 3), whereas others have found a similar risk increase also among women with more than one birth (2).

Breast cancers diagnosed within the first 5 to 10 years following a pregnancy constitute a small proportion of all breast cancer cases (5). Still, the personal and public health impact is considerable as these tumors affect young mothers and typically have a poorer prognosis than breast cancer in older women (5). A deeper understanding of factors that influence the risk of breast cancer in young women is needed as it may provide clues to improve prevention and treatment.

Whether hormone levels during pregnancy are related to subsequent breast cancer risk remains unclear (6–8). During pregnancy, the placenta is the main source or regulator of many of the potentially implicated hormones (9). Although placental weight may be a crude indicator of maternal hormone levels in pregnancy (10–13), 2 studies have previously reported strong associations of placental weight with later breast cancer risk (14, 15). However, more research is needed to clarify whether women who develop large placentas in their pregnancies are at increased risk of breast cancer.

On the basis of the hypothesis that pregnancy hormones may promote the growth of prevalent but undetected tumors, it seems to be most relevant to study the most recent pregnancy before breast cancer diagnosis. Using data from a prospective and nationwide registry-based cohort of Norwegian women, we have investigated

Authors' Affiliations: [1]Department of Public Health and General Practice, Norwegian University of Science and Technology; [2]Department of Oncology, St. Olav's Hospital, Trondheim; [3]Department of Obstetrics and Gynecology, Akershus University Hospital and the Faculty of Medicine, University of Oslo; and [4]Divisions of Epidemiology and Mental Health, Norwegian Institute of Public Health, Oslo, Norway

Corresponding Author: Signe Opdahl, Department of Public Health and Community Medicine, Faculty of Medicine, NTNU, Post box 8905, MTFS, Trondheim N-7491, Norway. Phone: 47-7359-8806; Fax: 47-7359-7577; E-mail: signe.opdahl@ntnu.no

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whether a high placental weight in a woman's most recent pregnancy is associated with increased breast cancer risk during the first years after the pregnancy.

Materials and Methods

Study population

Data were obtained from the Medical Birth Registry of Norway and the Cancer Registry of Norway. In the Medical Birth Registry, information on all births since 1967 is collected through a standardized form completed by midwives and doctors. Since 1999, information on placental weight has also been included, and therefore, the study population is restricted to women registered with births since 1999. Thus, a total of 348,671 women met the following inclusion criteria: information on date of birth available for all births, singleton births only, and at least one birth between January 1, 1999, and December 31, 2008. We excluded 87 women who were diagnosed with breast cancer before the start of follow-up and 10,533 women (3.0%) with missing information on placental weight and/or length of pregnancy in all their pregnancies. The remaining 338,051 women were followed from the date of their first registered birth after January 1, 1999, until the date of breast cancer diagnosis, death, emigration, or December 31, 2008, whichever came first. Among these 338,051 women, 216,223 gave their first birth after 1998.

Study factors

Placental weight has been registered since 1999. The placenta is weighed according to standardized routines. Immediately after delivery and independent of delivery mode, the placenta is placed in a bowl with membranes and umbilical cord attached. The bowl is weighed within one hour after delivery. The weight of the bowl is subtracted, and the placental weight is reported in grams.

From the Medical Birth Registry, we also obtained information on the following factors: age at first birth, number of previous pregnancies, prepregnancy diabetes mellitus (type I, type II, or unspecified), gestational diabetes (blood glucose levels after glucose tolerance test $\geq$ 7.8 mmol/L), hypertension (blood pressure $\geq$ 140/90 mm Hg after 20 weeks of gestation, measured repeatedly), preeclampsia (hypertension with proteinuria of at least 1+ on a semiquantitative dipstick after 20 weeks of gestation, measured repeatedly), offspring's birth weight in grams, length in centimeters, and duration of pregnancy in completed weeks (based on ultrasound examination in 95.9% of the pregnancies and on the first day of the last menstrual period in 4.1%). The diagnoses of diabetes mellitus and hypertensive disorders were registered by the use of separate check boxes in the standardized form.

Follow-up

The unique identification number of Norwegian citizens was used to link information from the Medical Birth Registry to information on cancer occurrence from the Cancer Registry of Norway, which also includes information on vital status and emigration, as recorded by the Population Registry at Statistics Norway. Invasive breast cancer was registered according to the International Classification of Diseases, 7th edition (ICD-7, code 170). Among women in this study, all breast cancer diagnoses were verified through histologic (99.4%) or cytologic (0.6%) examination. Reporting of new diagnoses of cancer to the Cancer Registry is mandatory by law, and follow-up for breast cancer is considered practically complete (16).

The study was approved by the regional committee for medical research ethics.

Statistical analyses

The association of placental weight with breast cancer incidence was evaluated using Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CI). Placental weight was categorized as <500, 500–599, 600–699, 700–799, and $\geq$800 grams, and the lowest category (<500 g) was used as the reference in the statistical analyses.

We studied the association of placental weight in the most recent pregnancy with breast cancer risk, treating placental weight as a time-dependent variable. Thus, women contributed person-time to one or more categories of placental weight, depending on the placental weight in the most recent pregnancy. To investigate whether the association could be modified by the number of previous pregnancies, we conducted analyses stratified by parity (uniparous, biparous, and triparous). In these analyses, follow-up of women with a given parity (1, 2, or 3) were censored whenever a subsequent birth occurred.

To account for the possibility of measurement error in placental weight, we also investigated whether mean placental weight among a woman's pregnancies was associated with breast cancer risk. After each delivery, mean placental weight was calculated and included as a time-dependent variable.

To facilitate comparison with previous studies (15), we also investigated whether placental weight in a woman's first pregnancy was associated with breast cancer risk. This analysis was restricted to the 216,223 women who had given their first birth after 1998, and differed from the previously described analysis among uniparous women, as there was no censoring at subsequent births.

Analyses of trend were conducted by scoring each category of placental weight with the median value of placental weight within that category. The categories of placental weight were then treated as a continuous variable, and HRs with 95% CI per 100-gram increase in placental weight were estimated.

For all analyses, attained age was used as the time scale. We adjusted for maternal birth year (before 1965, 1965–1969, 1970–1974, 1975–1979, and 1980 or later), age

Table 1. Characteristics of the study participants

	All women in the study (N = 338,051)	Primiparous women (216,223)[a]
Mean age at study entry, y (SD)	29.2 (5.2)	27.7 (4.9)
Median time in study, y (interquartile range)	6.0 (3.0–8.3)	4.8 (2.2–7.3)
Age at first birth, y		
<20	27,817 (8.2)	11,509 (5.3)
20–24	104,313 (30.9)	54,492 (25.2)
25–29	124,833 (36.9)	83,231 (38.5)
30–34	62,696 (18.5)	50,330 (23.3)
≥35	18,392 (5.4)	16,663 (7.7)
Total number of pregnancies		
1	106,975 (31.6)	106,975 (49.5)
2	140,768 (41.6)	89,287 (41.3)
3	68,792 (20.3)	18,264 (8.4)
≥4	21,516 (6.3)	1,699 (7.9)
Number of pregnancies during the observation period[b]		
1	193,682 (57.3)	106,975 (49.5)
2	119,118 (35.2)	89,287 (41.3)
3	22,882 (6.8)	18,264 (8.4)
≥4	2,369 (0.7)	1,699 (7.9)
Preeclampsia or pregnancy-induced hypertension		
Yes	32,065[c] (9.5)	16,991[d] (7.9)
No	305,986 (90.5)	199,234 (92.1)
Diabetes mellitus		
Yes	7,369[c] (2.2)	3,229[d] (1.5)
No	330,682 (97.8)	212,996 (98.5)

[a]Women who gave their first birth after 1998.
[b]From January 1, 1999, to December 31, 2008. For primiparous women, this corresponds to the total number of pregnancies.
[c]Women who were registered with these conditions during any of their pregnancies.
[d]Women who were registered with these conditions during their first pregnancy.

at first birth (<20, 20–24, 25–29, 30–34, and ≥35 years), duration of pregnancy (<37, 37, 38, 39, 40, 41, and ≥42 weeks), number of pregnancies, hypertensive disease in pregnancy (including preeclampsia), and diabetes mellitus (pre pregnancy or gestational). In the analyses of placental weight in the most recent pregnancy and in the analyses of mean placental weight, the number of pregnancies, duration of pregnancy, hypertensive disease in pregnancy, and diabetes mellitus were treated as time-dependent variables. The number of pregnancies was categorized as 1, 2, 3, and ≥4. Hypertensive disease in pregnancy and diabetes mellitus were treated as cumulative variables and categorized as ever/never. In the analysis of placental weight in the first pregnancy, only the number of subsequent pregnancies was treated as a time-dependent variable (1, 2, and ≥3).

Birth weight and birth length were considered as consequences of placental function and therefore as potential colliders (17). Therefore, these variables were not included as covariates in the final analyses. Nonetheless, the causal relation between these measures and placental weight is unknown, and we therefore conducted a separate analysis to investigate whether adjustment for birth weight (<2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, 4,000–4,499, and ≥4,500 grams) and length (<47, 47–48, 49–50, 51–52, 53, and ≥54 cm) could influence the association of placental weight with breast cancer risk. In a separate analysis, we also assessed whether a further categorization of placental weights above 800 grams (800–899, 900–999, and ≥1,000 grams) would influence the association with breast cancer risk.

Proportionality between hazards was checked by comparing log minus log plots of survival and by conducting tests based on Schoenfeld residuals.

Table 2. Characteristics of the 501,460 pregnancies included in the analyses

	No. of births (%)	No. of cases	Rate[a]
Duration of pregnancy, weeks			
<37	28,247 (5.6)	40	38
37	24,017 (4.8)	29	33
38	62,558 (12.5)	83	35
39	113,791 (22.7)	149	35
40	140,067 (27.9)	163	31
41	94,305 (18.8)	135	38
≥42	38,475 (7.7)	49	33
Birth weight,[b] g			
<2,500	18,526 (3.7)	21	31
2,500–2,999	47,942 (9.6)	66	39
3,000–3,499	149,396 (29.8)	159	29
3,500–3,999	178,993 (35.7)	240	35
4,000–4,499	84,158 (16.8)	128	38
≥4500	21,854 (4.4)	33	35
Birth length,[c] cm			
<47	25,498 (5.3)	34	37
47–48	64,316 (13.3)	72	31
49–50	166,931 (34.6)	225	36
51–52	156,958 (32.5)	191	32
53	39,590 (8.2)	58	37
≥54	29,815 (6.2)	48	39

[a]Incidence per 100,000 person-years.
[b]Number of pregnancies with information on birth weight is 500,869.
[c]Number of pregnancies with information on birth length is 483,108.

Table 3. Placental weight and maternal breast cancer risk among 338,051 Norwegian women

	No. of cases	No. of pregnancies	No. of person-years	Rate[a]	HR[b]	HR (95% CI)[c]
Placental weight in most recent pregnancy, g						
<500	53	43,302	160,214	33	1	1
500–599	116	100,955	378,356	31	0.96	0.97 (0.69–1.35)
600–699	177	141,342	535,038	33	1.01	1.01 (0.74–1.40)
700–799	152	110,723	420,133	36	1.06	1.07 (0.77–1.48)
≥800	150	105,138	401,370	37	1.05	1.07 (0.77–1.49)
Per 100-gram increase	648	501,460	1895,111	34	1.02	1.03 (0.96–1.10)
Mean placental weight, g						
<500	49	41,666	156,119	31	1	1
500–599	117	104,890	390,202	30	1.00	1.01 (0.71–1.42)
600–699	191	150,293	561,395	34	1.10	1.11 (0.80–1.54)
700–799	152	113,317	427,296	36	1.10	1.12 (0.80–1.56)
≥800	139	91,294	360,100	39	1.13	1.16 (0.82–1.63)
Per 100-gram increase	648	501,460	1895,111	34	1.03	1.04 (0.97–1.11)
Placental weight in first pregnancy,[d] g						
<500	28	22,581	111,917	25	1	1
500–599	51	47,927	233,835	22	0.94	0.91 (0.57–1.46)
600–699	74	61,769	299,692	25	1.08	1.04 (0.66–1.64)
700–799	47	45,110	215,311	22	0.92	0.90 (0.55–1.46)
≥800	48	38,836	184,454	26	1.06	1.05 (0.64–1.72)
Per 100-gram increase	248	216,223	1045,210	24	1.01	1.02 (0.91–1.13)

[a]Incidence per 100,000 person-years.
[b]Adjusted for age.
[c]Adjusted for age, parity, age at first birth, length of pregnancy, hypertensive disease in pregnancy, and diabetes mellitus.
[d]Analyses were limited to the 216,223 women who gave their first birth after 1998.

Assumptions were met for all the previously described models.

All analyses were conducted using Stata version 11.1 MP for Windows (Stata Corp.).

Results

A total of 338,051 women without breast cancer at baseline were followed for a total of 1895,111 person years. Median time of follow-up was 6.0 years (interquartile range, 3.0–8.3 years). During follow-up, 648 women were diagnosed with invasive breast cancer. Mean age at diagnosis was 38.4 years (standard deviation, 5.3 years). Among the 338,051 women, 57.3% contributed with one pregnancy, whereas the remaining 42.7% contributed with between 2 and 7 pregnancies. Characteristics of the study participants are shown in Table 1, and characteristics of the included pregnancies are shown in Table 2.

Breast cancer risk among women in different categories of placental weight is presented in Table 3. Placental weight in a woman's most recent pregnancy was not associated with breast cancer risk: the HR per 100-gram increase in placental weight was 1.03 (95% CI, 0.96–1.10). The risk among women with placental weight in the highest category (≥800 grams) in their most recent pregnancy was similar (HR, 1.07; 95% CI, 0.77–1.49) to that of women with placental weight in the reference (<500 grams) category. For mean placental weight, the estimated associations were slightly stronger than that for placental weight in the most recent pregnancy. In women with mean placental weight in the highest compared to the lowest category, the HR was 1.16 (95% CI, 0.82–1.63), and per 100 grams increase in mean placental weight, the HR was 1.04 (95% CI, 0.97–1.11). Among women who gave their first birth after 1998, placental weight in the first pregnancy was not associated with breast cancer risk (HR, 1.02; 95% CI, 0.91–1.13, per 100-gram increase in placental weight).

Table 4 shows associations of placental weight in the most recent pregnancy with risk of breast cancer, stratified by parity. Among uniparous and biparous women, there was no association of placental weight with breast cancer risk (HR per 100-gram increase: 0.98; 95% CI, 0.85–1.13 and 1.02; 95% CI, 0.92–1.12, respectively). Among triparous women, there was a positive but moderate association (HR per 100-gram increase: 1.08; 95% CI, 0.96–1.21). The statistical power in these analyses was limited, with only 11 cases in the reference group, and should therefore be interpreted with caution.

Table 4. Placental weight in the most recent pregnancy and maternal breast cancer risk, stratified by parity

	No. of cases	No. of pregnancies	No. of person-years	Rate[a]	HR[b]	HR (95% CI)[c]
Placental weight in uniparous women, g						
<500	18	22,581	70,522	26	1	1
500–599	24	47,927	146,279	16	0.72	0.73 (0.39–1.37)
600–699	40	61,769	187,365	21	0.95	0.96 (0.53–1.73)
700–799	29	45,110	135,348	21	0.91	0.93 (0.50–1.73)
≥800	22	38,836	117,096	19	0.76	0.79 (0.41–1.53)
Per 100-gram increase	133	216,223	656,611	20	0.97	0.98 (0.85–1.13)
Placental weight in biparous women, g						
<500	19	13,041	54,367	35	1	1
500–599	53	34,425	145,029	37	1.12	1.06 (0.62–1.81)
600–699	72	51,100	215,104	33	1.02	0.96 (0.57–1.61)
700–799	67	41,811	135,348	39	1.16	1.08 (0.64–1.84)
≥800	65	41,359	170,256	38	1.14	1.08 (0.63–1.83)
Per 100-gram increase	276	181,736	758,729	36	1.03	1.02 (0.92–1.12)
Placental weight in triparous women, g						
<500	11	5,624	26,025	42	1	1
500–599	30	14,128	66,157	45	1.13	1.16 (0.57–2.36)
600–699	47	21,625	101,206	46	1.15	1.19 (0.60–2.34)
700–799	47	18,137	84,712	55	1.35	1.40 (0.70–2.77)
≥800	49	18,944	86,413	57	1.36	1.40 (0.71–2.78)
Per 100-gram increase	184	78,458	364,514	50	1.07	1.08 (0.96–1.21)

[a]Incidence per 100,000 person-years.

[b]Adjusted for age.

[c]Adjusted for age, age at first birth, gestational age, hypertensive disease in pregnancy, and diabetes mellitus.

Crude analysis (adjusted for age only) provided similar results as the fully adjusted analysis, and additional adjustment for birth weight or birth length had no material influence on the results. In a separate analysis, treating placental weights above 800 grams in distinct categories, there was no indication that a particularly high placental weight was associated with increased risk of breast cancer (results not shown).

Discussion

In this prospective study of 338,051 women, placental weight was not associated with breast cancer risk. Associations were similar for placental weight in the most recent pregnancy, for mean placental weight across pregnancies, and for placental weight in the first pregnancy. No clear associations were detected among uniparous, biparous, or triparous women.

We could not confirm the results from previous studies on placental weight and breast cancer risk. In a small study from the United States of both primiparous and multiparous women, it was reported that low placental weight was associated with reduced risk for breast cancer (14). In a large, registry-based study from Sweden, there was a consistent positive association of placental weight in a woman's first pregnancy with later breast cancer risk (15). Compared with those studies, the women in our study were followed up for a shorter period, and the cases were younger at the time of breast cancer diagnosis. However, in the 2 previous studies, there was no evidence that the associations differed by duration of follow-up (14, 15). Therefore, it seems unlikely that the lack of association in our study can be explained by shorter follow-up alone.

In our study, there was no information on the women's body mass index, which could have confounded the association of placental weight with breast cancer risk. A high body mass index is associated with reduced risk of breast cancer among premenopausal women (18), and body mass index is positively associated with placental weight (19). A confounding effect of body mass index could therefore mask a positive association. However, adjustment for preeclampsia or hypertension in pregnancy and diabetes mellitus, both of which are strongly associated with obesity (20), did not influence our estimates. Furthermore, there was no substantial confounding by body mass index in the Swedish study (15). Therefore, our results are not likely to be strongly influenced by the lack of adjustment for body mass index.

Our study encompassed all women who gave birth in Norway during the study period, and information on

incident breast cancer was collected prospectively. Therefore, bias in selection or information recall is unlikely. Misclassification of breast cancer diagnosis is most likely negligible, as reporting of cancer to the Cancer Registry of Norway is mandatory by law, and all breast tumors among women in this study were based on pathology reports. Although attempts are made to standardize measurements of placental weight, some inaccuracy is likely to occur, since placental weight depends on factors such as mode of delivery, removal of blood clots, and time to cord clamping (21). However, misclassification of placental weight is likely to be non-differential with respect to subsequent breast cancer diagnosis, and bias the association towards the null. Using placental weight in the most recent pregnancy and using mean placental weight yielded similar results, but nonetheless, we cannot exclude the possibility that misclassification of placental weight could have masked a possible positive association with breast cancer risk.

It has been reported that the correlation of placental weight is high with maternal pregnancy levels of insulin-like growth factor-I (13) and moderate with maternal levels of sex steroids (10–12). The lack of a clear association of placental weight with breast cancer risk in this study may suggest that differences in placental weight may not reflect differences in pregnancy hormone levels that are relevant for breast cancer risk during the first years following pregnancy.

In conclusion, placental weight was not related to the risk of early breast cancer in this study. More research is needed to clarify whether placental weight is associated with breast cancer risk, and if so, for which age groups it may be of importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts on interest were disclosed.

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