

Birthweight as a risk factor for breast cancer

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Summary

Background The mammary gland is largely undifferentiated before birth and may be particularly susceptible to intrauterine influences that could increase the risk of cancer through acceleration of cell proliferation or other pregnancy-related processes. Studies of migrant populations, animal data, and limited epidemiological evidence suggest that breast cancer may originate in utero. In a nested case-control study we assessed whether birthweight and other perinatal factors are associated with risk of breast cancer.

Methods This case-control study was nested within the cohorts of the two Nurses' Health Studies. We used self-administered questionnaires to obtain information from the mothers of 582 nurses with invasive breast cancer and the mothers of 1569 nurses who did not have breast cancer (controls). Information on risk factors for breast cancer during adulthood were obtained from the nurses; multiple logistic regression analysis adjusted for these risk factors.

Findings Birthweight was a significant predictor of breast-cancer risk. With women who weighed 4000 g or more at birth as the reference category, the adjusted odds ratios for breast cancer were 0.86 (95% CI 0.59–1.25) for birthweights of 3500–3999 g, 0.68 (0.48–0.97) for birthweights of 3000–3499 g, 0.66 (0.45–0.98) for birthweights of 2500–2999 g, and 0.55 (0.33–0.93) for birthweights below 2500 g (p for trend 0.004). Prematurity was not significantly associated with risk of breast cancer.

Interpretation Birthweight is significantly associated with breast-cancer risk, which suggests that intrauterine factors or processes affect the risk of breast cancer in the offspring. High concentrations of pregnancy oestrogens may have an important role in breast carcinogenesis, but other pregnancy hormones or intrauterine factors may also be involved.

Lancet 1996; **348**: 1542–46

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Introduction

Before birth the mammary gland is in a partly undifferentiated state and, therefore, may be susceptible to intrauterine influences that could increase the risk of cancer.^{1–3} Terminal end buds—undifferentiated structures in the mammary gland—are found only in young animals; of all the structures of the mammary gland they have the longest S-phase during DNA synthesis in the cell cycle and, thus, may be particularly susceptible to mutation.⁴ Chemically induced rat mammary tumours arise from pre-existing oncogenic *ras* gene mutations, which occur during early organ development.⁵

The hypothesis has been raised that human breast cancer may originate in utero.^{6–9} The observation that the rate of breast cancer in Japanese migrants becomes similar to that of white Americans only after two or more generations accords with the hypothesis of early-life modulation of breast-cancer risk. By contrast, Japanese migrants' risk of colorectal cancer becomes similar to that of the host population within a few decades of migration, which indicates an important role of lifestyle factors in disease aetiology.^{10,11} Ziegler and colleagues' study¹² found that an increase in the risk of breast cancer became apparent in first-generation Asian migrants to the USA, but that the difference in risk between Asian and white American women disappeared only after several generations in the USA.

An intrauterine origin of breast cancer could be linked to oestrogens and other hormones produced during pregnancy or to other pregnancy-related processes. The importance of oestrogens in the aetiology and natural history of breast cancer points to high concentrations of pregnancy oestrogens as possible causes,^{6,7,9} but other factors associated with pregnancy could also be important.^{8,13} Fetal growth is positively associated with concentrations of oestrogens at the extremes of the corresponding distributions, although evidence for an association throughout the usual range of fetal growth is not clear.^{14–17} Le Marchand and colleagues¹⁸ found no association between birthweight and breast-cancer risk, but their study had small numbers of cases.¹⁸ In a study in Sweden,⁷ breast-cancer risk tended to increase with birthweight, birth length, and placental weight, but no association was statistically significant. Sanderson et al¹⁹ reported a positive association between birthweight and risk of breast cancer in premenopausal women in the USA, but not in postmenopausal women; they interpreted their findings as compatible with the hypothesis that links pregnancy oestrogens to risk of breast cancer.

With two large prospective cohort investigations as our study base, we undertook a nested case-control study to assess the association between birthweight and risk of breast cancer, after adjustment for established risk factors for the disease in adult life.

Methods

The case-control study was nested in two prospective cohort investigations—the Nurses' Health Study (NHS I) and the

Nurses' Health Study II (NHS II). The cohorts comprise 121 700 and 116 680 female registered nurses, respectively. The NHS I cohort was established in 1976 and includes women born between 1921 and 1945; the NHS II cohort was founded in 1989 and includes women born between 1946 and 1965. For both cohorts, biennial questionnaires are used to collect information on various exposures and on diagnoses of breast cancer and other disorders. The main associations investigated are between exogenous hormones, diet, and other lifestyle factors and the risks of cancers and cardiovascular diseases among women.²⁰

Up to the 1992 follow-up, 4264 participants in NHS I who had not had breast cancer at baseline were diagnosed with breast cancer. At the time this study was conducted, 245 incident cases of breast cancer were confirmed from the 1991 and 1993 follow-up questionnaires of NHS II. Among these 4509 nurses with breast cancer, we identified 1966 nurses from both cohorts with confirmed invasive or in-situ breast cancer who were alive and had not indicated in previous questionnaires that their mothers had died. For each case we matched two controls who were born in the same year, belonged to the same cohort, and did not have breast cancer (n=3932). We wrote to the selected nurses asking whether their mothers were alive; permission to contact the mother was requested together with the mother's current name and address. Of the 5898 nurses, 5442 (92%) responded to our letters.

Of the nurses who responded, 2488 (46%) provided the names and addresses of their mothers and indicated whether the mother was able to take part in the study. 1809 (33%) mothers had died. Mothers who had Alzheimer's disease, memory loss, or senile dementia, or were otherwise incapable of responding to a questionnaire were excluded from the study. Other reasons for exclusion of mothers were that the nurse was adopted or not brought up by her mother, the mother did not speak English, or the nurse or the mother refused to take part in this study. Overall, 1144 (21%) of mothers, although alive, were excluded from the study for these reasons.

2488 mothers were sent questionnaires; of these, 15 mothers had died in the intervening time and 11 were not able to take part in the study. Of the remaining 2462 mother participants, 2242 (91%) completed and returned the questionnaire; 86 of these mothers had daughters with in-situ breast cancer and were excluded from the analysis. In addition, five nurses were excluded: the diagnosis of breast cancer in one could not be confirmed, and the mothers of four did not report their dates of birth, so we could not be sure that the data reported referred to the daughter participating in the study. Thus, data from 2151 mothers were included in the analyses.

Although the study population consisted of the nurses themselves, the primary exposure information in the study was obtained from their mothers by the self-administered questionnaire which we sent to them. We decided to obtain this information from the mothers because nurses would be mostly aware of their own perinatal characteristics through their mothers who were, thus, the source of the more reliable information. We asked mothers about birthweight, prematurity, smoking during the index pregnancy, and family history of breast cancer, as well as other perinatal and early-life exposures. Mothers were repeatedly reminded to provide information about the daughter who was participating in one of the Nurses' Health Studies. The questionnaires included open-ended questions on birthweight to allow the mothers' answers to be as precise as possible. When the daughter had been born prematurely, we asked how many weeks early the birth had been: less than 2 weeks, 2-4 weeks, or more than 4 weeks.

Birthweight data reported by the nurses in NHS I and NHS II were also available: participants were asked in 1992 and 1991, respectively, about their birthweight. Categories for birthweight were prespecified on the nurses' questionnaires—NHS I: <5 lb, 5 to 5½ lb, more than 5½ lb to 7 lb, more than 7 to 8½ lb, more than 8½ lb to 10 lb, more than 10 lb, not sure; NHS II: <5.5 lb, 5.5-6.9 lb, 7.0-8.4 lb, 8.5-9.9 lb, >10 lb, unknown (1 lb=0.454 kg).

Information on adult-life risk factors for breast cancer was obtained from the large databases already established for each of

	Cases (n=582)	Controls (n=1569)	Age-adjusted odds ratio (95% CI)*
Cohort			
NHS I	461 (79%)	1303 (83%)	NA
NHS II	121 (21%)	266 (17%)	NA
Birth year			
1921-25	16 (3%)	93 (6%)	NA
1926-30	68 (12%)	176 (11%)	NA
1931-35	105 (18%)	307 (20%)	NA
1936-40	121 (21%)	347 (22%)	NA
1941-45	136 (23%)	331 (21%)	NA
1946-50	70 (12%)	169 (11%)	NA
1951-55	40 (7%)	86 (5%)	NA
1956-60	20 (3%)	47 (3%)	NA
1961-63	6 (1%)	13 (1%)	NA
Age at menarche (years)†			
≤11	134 (23%)	371 (24%)	1.0
12	167 (29%)	427 (27%)	1.09 (0.84-1.43)
13	179 (31%)	461 (30%)	1.08 (0.83-1.40)
14	71 (12%)	182 (12%)	1.12 (0.80-1.57)
≥15	27 (5%)	117 (8%)	0.65 (0.41-1.03)
Parity			
0	69 (12%)	174 (11%)	1.00
1	59 (10%)	133 (8%)	1.13 (0.74-1.72)
2	199 (34%)	500 (32%)	1.04 (0.74-1.45)
3	155 (27%)	405 (26%)	1.01 (0.71-1.43)
≥4	100 (17%)	357 (23%)	0.76 (0.52-1.12)
Age at first birth (years)‡			
≤24	290 (57%)	859 (62%)	1.00
25-29	183 (36%)	437 (31%)	1.23 (0.99-1.53)
≥30	40 (8%)	99 (7%)	1.21 (0.81-1.81)
Body-mass index (kg/m²)			
≤21	217 (37%)	437 (28%)	1.00
21.1-23.0	165 (28%)	470 (30%)	0.72 (0.57-0.92)
23.1-25.0	99 (17%)	269 (17%)	0.75 (0.56-1.00)
25.1-29.0	66 (11%)	232 (15%)	0.58 (0.42-0.80)
>29	35 (6%)	156 (10%)	0.44 (0.30-0.67)
Family history of breast cancer†			
First-degree relative	124 (21%)	209 (13%)	1.80 (1.41-2.31)
Second-degree relative	208 (36%)	366 (23%)	1.82 (1.48-2.24)

*Adjusted for age in 5-year categories and NHS cohort (I and II). †Numbers do not always add up to total study population because of missing information on some variables. ‡Denominator for % is parous women.

Table 1: Odds ratios for breast cancer in relation to adult characteristics of nurses with breast cancer and controls

the two continuing cohort studies. These variables had been reported by the nurses themselves and included age from year of birth, age at menarche, parity, age at first birth, menopausal status, height, and weight. Data recorded at baseline in the two cohorts—ie, before diagnosis of breast cancer in the cases—were used in the analysis (1976 for NHS I and 1989 for NHS II). Information on family history of breast cancer was available from the nurses (mother or sisters with breast cancer) and the mothers (mother herself, grandmothers, or aunts with breast cancer); thus, we collated separate variables that differentiated between first-degree and second-degree relatives with breast cancer.

Since cases and controls were matched before the mothers' participation in this study was known, matching was incomplete for many participants. Thus, data were analysed as unmatched, after adjustment for the original matching variables (ie, birth year and study cohort).

Associations between perinatal variables and risk of breast cancer were assessed by multiple logistic regression, with adjustment for year of birth in 5-year intervals. Data on birthweight were grouped in five categories (<2500 g, 2500-2999 g, 3000-3499 g, 3500-3999 g, ≥4000 g). Further multiple logistic regression analysis was used to find out whether crude associations were confounded by adult or other perinatal variables. Other breast-cancer risk factors were included as categorical indicator variables: age at menarche (<12, 12, 13, 14, ≥15 years), parity (0, 1, 2, 3, ≥4), age at first birth (<25, 25-29, ≥30), body-mass index (≤21.0 kg/m², 21.1-23.0 kg/m², 23.1-25 kg/m², 25.1-29.0 kg/m², ≥29.1 kg/m²), first-degree and second-degree family history of breast cancer. Variables were

	Cases (n=550)	Controls (n=1478)	Age-adjusted odds ratio (95% CI)*	Multiple logistic odds ratio (95% CI)†
Birthweight (g)				
≥4000	65 (12%)	136 (9%)	1.00	1.00
3500–3999	141 (26%)	332 (23%)	0.85 (0.59–1.22)	0.86 (0.59–1.25)
3000–3499	209 (38%)	592 (40%)	0.71 (0.50–0.99)	0.68 (0.48–0.97)
2500–2999	105 (19%)	311 (21%)	0.68 (0.47–0.99)	0.66 (0.45–0.98)
<2500	30 (5%)	107 (7%)	0.56 (0.34–0.93)	0.55 (0.33–0.93)
Premature birth	(n=571)	(n=1525)		
Not premature	522 (92%)	1381 (91%)	1.00	1.00
<2 weeks	17 (3%)	55 (4%)	0.76 (0.44–1.32)	0.76 (0.43–1.35)
2–4 weeks	24 (4%)	63 (4%)	0.96 (0.59–1.56)	0.90 (0.54–1.47)
>4 weeks	8 (1%)	26 (2%)	0.81 (0.36–1.80)	1.04 (0.46–2.38)

Numbers for cases and controls do not add up to total study population because of missing values. *Adjusted for age in 5-year categories and NHS cohort (I and II). †Adjusted for age in 5-year categories, cohort, parity, age at first birth, age at menarche, body-mass index, and family history of breast cancer; women with missing values were excluded.

Table 2: Odds ratios for invasive breast cancer in relation to perinatal factors reported by mothers

selected for inclusion in the models on the basis of biological plausibility and evidence of confounding.²¹ Modification of the association between birthweight and subsequent risk of breast cancer by age at diagnosis was also investigated. Cases were divided into three groups by age at diagnosis of breast cancer (<45, 45–50, >50). Since individual matching was incomplete, all controls were used for all strata, except those controls who would have been too old at baseline (1976 for NHS I participants and 1989 for NHS II participants) or too young at the end of the study (1992 for NHS I participants and 1993 for NHS II participants) to become a case at the age of diagnosis of the cases in the respective stratum.

Although information on birthweight and other perinatal characteristics provided by the nurses may not have been as accurate as that reported by their mothers, we used the data on birthweight reported by the daughters to examine the association with breast-cancer risk. Agreement between this alternative and the primary analysis (based on birthweight reported by mothers) would increase confidence in the results.

We used a test for trend based on the logistic model to assess whether birthweight and breast-cancer risk were monotonically associated.²² For this test, birthweight information obtained from the mothers was used as a continuous variable; midpoints of the prespecified birthweight categories of the daughters' reports were used.

Results

Characteristics of the 582 breast-cancer cases and 1569 controls are shown in table 1. The median year of birth of the mothers who took part in this study was 1914 for case mothers and 1913 for control mothers. Of the 582 cases, 393 (67%) were premenopausal at diagnosis, 137 (24%) were postmenopausal, and 52 (9%) were perimenopausal or of uncertain menopausal status. Age at menarche of older than 15 years, parity of four or more children, and age at first birth of younger than 24 years tended to be associated with reduced risk of breast cancer in the study population, as expected. A higher body-mass index (recorded in 1976 for NHS I and 1989 for NHS II) was associated with a lower risk of breast cancer; this inverse association has been previously found in other studies. A family history of breast cancer was associated with an increased risk of breast cancer.

Of the 2151 mothers who took part in the study, 2028 (94%) reported the birthweight of their daughters and 2096 (97%) provided data on duration of gestation. Of the 2151 nurses included in the study, 1887 (88%) had reported their birthweight on the questionnaires.

Low birthweight was associated with significantly reduced risk of breast cancer (table 2): the risk of breast cancer for women who weighed 2500 g or less at birth was less than half that for women who weighed more than 4000 g at birth (age-adjusted odds ratio 0.56 [95% CI

0.34–0.93]). Adjustment for several established risk factors for breast cancer did not appreciably change this association (0.55 [0.33–0.93]). Moreover, there was a significant decreasing trend in the odds ratio with decreasing birthweight ($p=0.008$ for age-adjusted odds ratios, $p=0.004$ for multiple logistic odds ratios). Adjustment for race, smoking status of the mother during the index pregnancy, and menopausal status, height, or smoking history of the nurse at baseline, did not significantly change the association between birthweight and breast-cancer risk. Prematurity was not significantly associated with breast-cancer risk.

After adjustment for adult-life risk factors for breast cancer, the odds ratio associated with a birthweight of less than 2500 g relative to a birthweight of 4000 g or more was 0.43 (0.22–0.86) for cases diagnosed in 1989 or later, and 0.71 (0.34–1.49) for long-term survivors of breast cancer. However, this difference in the strength of the association was not significant ($p=0.32$).

Stratification of the relation between breast cancer and birthweight by age at diagnosis (table 3) showed that the trend was significant among women who were 45 years or younger at diagnosis (p for trend 0.05) or 45–50 years at diagnosis (p for trend 0.03). Among women who were older than 50 years at diagnosis the trend was not significant (p for trend 0.18).

Age at diagnosis of cases stratified by birthweight (g)	Cases	Controls	Multiple logistic odds ratio (95% CI)*
<45 years			
≥4000	20	103	1.00
3500–3999	56	274	0.89 (0.47–1.69)
3000–3499	75	500	0.61 (0.33–1.12)
2500–2999	39	257	0.62 (0.32–1.20)
<2500	12	89	0.51 (0.21–1.22)
45–50 years			
≥4000	21	123	1.00
3500–3999	42	308	0.79 (0.43–1.44)
3000–3499	78	555	0.81 (0.47–1.42)
2500–2999	30	287	0.56 (0.30–1.06)
<2500	7	100	0.41 (0.16–1.05)
>50 years			
≥4000	24	99	1.00
3500–3999	43	215	0.91 (0.51–1.63)
3000–3499	55	372	0.65 (0.37–1.13)
2500–2999	36	208	0.81 (0.44–1.47)
<2500	11	74	0.73 (0.32–1.63)

Numbers for cases and controls do not add up to the entire study population because of missing values. *Adjusted for age in 5-year categories, NHS cohort (I and II), parity, age at first birth, age at menarche, body-mass index, and family history of breast cancer; women with missing values were excluded.

Table 3: Odds ratios for invasive breast cancer in relation to birthweight reported by mothers and stratified by age at diagnosis in daughters

Birthweight (lb)	Cases (n=499)	Controls (n=1388)*	Odds ratio (95% CI)	
			Age-adjusted odds ratio*	Multiple logistic odds ratio†
>8.4	71	167	1.00	1.00
7.0-8.4	244	645	0.89 (0.65-1.22)	0.88 (0.63-1.22)
5.5-6.9	144	436	0.79 (0.56-1.11)	0.76 (0.54-1.08)
<5.5	40	140	0.68 (0.43-1.07)	0.68 (0.43-1.07)

Numbers for cases and controls do not add up to the total study population because of missing values. The prespecified categories on the questionnaire for nurses were in lb; 1 lb=0.454 kg.

*Adjusted for age in 5-year categories and NHS cohort (I and II). †Adjusted for age in 5-year categories, cohort, parity, age at first birth, age at menarche, body-mass index, and family history of breast cancer; women with missing values were excluded.

Table 4: Odds ratio for invasive breast cancer in relation to birthweight reported by nurses

The Spearman correlation coefficient between birthweight reported by the mothers and that reported by the nurses themselves was 0.77 in the control group. Multivariate odds ratios for breast cancer in relation to birthweight as reported by the nurses themselves are shown in table 4. Although there is still a trend of decreasing breast-cancer risk with decreasing birthweight, the trend is weaker than that based on the more reliable birthweight reports of the mothers (p for trend 0.05 for age-adjusted odds ratios, 0.04 for multivariate odds ratios).

Discussion

The early years of life are increasingly thought to be important in the aetiology of breast cancer. In 1969, Cole and MacMahon²³ proposed this hypothesis on the basis of the strong risk associations with age at menarche and age at first pregnancy. The hypothesis that breast cancer may, to a certain extent, originate in utero was based on the assumption that endogenous oestrogens are important factors in the aetiology of breast cancer and that first exposure of the mammary gland to high concentrations of oestrogens occurs in utero.⁶ Oestrogens are mammatropic, as well as being established growth factors, and, as such, they induce cell proliferation.²⁴ Rapid cell division per se may affect risk of breast cancer without genotoxicity by increasing the probability of irreparable DNA damage.²⁵ Moreover, high oestrogen exposure in utero may prime the mammary tissue for excessive responses at puberty or during early adult life.⁸

In this study, increasing birthweight was associated with increasing risk of breast cancer. However, the apparent birthweight effect was appreciable only at the extreme tails of the distribution: between the 10th and 90th centiles of birthweight in the control series the odds ratio varied only from 0.66 to 0.86. Although babies who are born prematurely are more likely to have a lower birthweight than those born at term, prematurity itself was not found to be associated with risk of breast cancer, even in the crude analysis. Weight relative to gestational age may be more important than weight at birth; infants born prematurely would be heavier if born at term.

Studies in Sweden have suggested that birthweight and other indicators of birth size may predict breast-cancer risk.^{7,26} In these studies routinely completed birth records were used; no attempt was made to control for adult-life risk factors for breast cancer. In an American study,¹⁹ there was a positive association between birthweight and risk of breast cancer among women aged 45 years and younger. Our findings strongly suggest that birthweight is an

important risk factor for breast cancer in later life. The difference in birthweight between American and Asian women,²⁷ and the difference in risk of breast cancer between these populations provide ecological support for our findings.

The validity of recalled data is of concern in an investigation of an event that occurred decades earlier. Although some misclassification of exposure is unavoidable, the recall of birthweight is likely to be non-differential in nature and, thus, would have led only to an underestimation of the true association. The accuracy of birthweight information in the NHS II cohort has been assessed.²⁸ In a sample of 538 participants and their mothers, information on birthweight given by the mothers was compared with data on birth certificates obtained from departments of vital statistics in four states of the USA.²⁸ The high correlation observed ($r=0.85$) reflects the accuracy of mothers' recall of remote pregnancy-related events. Others²⁹ have shown accurate maternal recall of birthweight. Pregnancy is an important event in a woman's life, likely to be recalled with especial clarity.

Selection bias is an unlikely explanation of the results of this study. Although more than half of the contacted nurses were not included in the study, the main reasons for exclusion were that their mothers had died (33%) or were unable to respond to a questionnaire because of Alzheimer's disease, senile dementia, or memory loss; neither age at death nor any of these disorders is known to be associated with birthweight of daughters. Confounding by established adult-life risk factors for breast cancer was accounted for by our analyses, and residual confounding away from the null is unlikely given the direction of the changes in the odds ratio estimates from univariate to the multivariate analyses.

Biological plausibility and coherence are as important as internal validity for the interpretation of epidemiological findings. High birthweight has been previously associated with other types of cancer.³⁰⁻³²

In this study, the association between birthweight and risk of breast cancer was stronger in younger than in older women. This finding is biologically plausible because the aetiological heterogeneity of breast cancer may cover prenatal as well as postnatal and adult-life risk factors. Moreover, this finding accords with the results of Sanderson et al.¹⁹ Most of the breast cancers in our study population, however, were in women who were premenopausal at diagnosis, thus inferences for postmenopausal women might not be possible.

The association with breast-cancer risk was stronger for birthweight reported by the mothers than for birthweight reported by the nurses themselves. The discrepancy can be explained by the extent of random misclassification of birthweight information from the two sources—daughters are likely to derive this information from their mothers who, in this instance, can be thought of as the reference standard.

This study provides evidence that intrauterine factors influence breast-cancer risk. Production of several hormones and other biological variables change substantially during pregnancy and are, therefore, likely to interact among themselves and with exogenous factors, such as nutrition. Thus, the intrauterine origin of breast cancer does not necessarily implicate pregnancy oestrogens, although a role for these hormones seems highly likely. Whatever mechanisms underlie the

association between birthweight and breast-cancer risk, the concept of prenatal aetiological components for breast cancer changes the conventional view of the origin and pathogenesis of this malignant disorder and, perhaps, other cancers in adult life.

This study was supported by a grant from the Massachusetts Department of Public Health and by grants CA 55075, CA 40356, and CA 50385 from the National Cancer Institute.

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