Birth Weight-Breast Cancer Revisited: Is the Association Confounded by Familial Factors?

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Abstract

Purpose: The study aimed to investigate whether the association between birth weight and the risk of breast cancer can be confounded by familial factors, such as shared environment and common genes.

Materials and Methods: Eligible were all female like-sexed twins of the Swedish Twin Registry, born during the period 1926–1958 and alive in 1973. Data were obtained from birth records, and the final study population with reliable birth weight data was made up of 11,923 twins. Hazard ratios (HR) for breast cancer according to birth weight were estimated through Cox regression, using robust SE to account for the dependence within twin pairs. Paired analysis was done to account for potential confounding by familial factors.

Results: In the cohort analysis, a birth weight $\geq 3,000$ g was associated with an increased risk of breast cancer diagnosed at or before 50 years (adjusted HR, 1.57; 95% confidence interval (95% CI), 1.03-2.42) but not with breast cancer with a later onset (adjusted HR, 0.80; 95% CI, 0.57-1.21). From $\geq 2,500$ g, a 500-g increase in birth weight conferred a HR of 1.62 (95% CI, 1.16-2.27) for breast cancer diagnosed at or before 50 years. This risk remained in analysis within twin pairs (HR, 1.57; 95% CI, 1.00-2.48).

Conclusion: In the present study, findings indicate that the association between birth weight and breast cancer risk, seen only in women diagnosed early ($\leq 50$ years), is not confounded by familial factors. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2447–52)

Introduction

Birth weight is positively associated with an increased risk of breast cancer (1–4). Although the association is reported to be most pronounced in breast cancers diagnosed before the age of 50 (1, 2, 5), a recent large reanalysis of individual participant data found no evidence that the associations between birth size and the risk of breast cancer were influenced by age at diagnosis (4).

As originally proposed by Trichopoulos in 1990, breast cancer may originate from prenatal hormone exposure (6). Birth weight can, especially when adjusted for gestational age, be considered an indicator for fetal growth and as such, may be used as a proxy for fetal exposure to growth stimulating factors such as insulin-like growth factors (IGF; refs. 7, 8) and estrogens (9, 10), which may be involved in breast carcinogenesis (11, 12). Like breast cancer, however, fetal growth is largely also determined by genetic and other factors (13, 14), which may confound the association between birth weight and breast cancer. Twins provide unique possibilities to study the influence of shared environment and common genes with respect to the association between birth weight and breast cancer risk; all twins share intrauterine and early environment, with dizygotic twins sharing on average half of their segregating genes and monozygotic twins sharing all of their genes.

Materials and Methods

The Swedish Twin Registry is a population-based registry of twins born in Sweden since 1886 (16). In 1973, all like-sexed twins born during the period 1926-1958 were sent a paper-based questionnaire that included questions regarding the degree of similarity, lifestyle factors, and anthropometric measures, and the response rate was 81% (16). The birth records of twins born from 1926 to 1958 have been retrieved and computerized, with data that include anthropometric measures at birth (birth weight, birth length, and head circumference) and information on last menstrual period, maternal age, parity, and the occupational status of both parents (17). The standard birth length measurement method at the time was by using measuring tape, with the baby lying on its back with stretched legs and the crown of the head against a vertical headboard.

For this study all like-sexed female twins with known zygosity, born during the period 1926–1958, were considered. Of 16,604 female twins who were alive and without previous breast cancer diagnosis at the start of follow-up in 1973, information from birth records was obtained from 13,147 twins (79.2%). Further restrictions due to

References

missing birth weight data \( n = 39 \) and the requirement of correct birth identification of each twin within a twin pair \( n = 1,185 \), resulted in a final study population of 11,923 twins (5,859 intact twin pairs). Gestational age was estimated from the first day of the last menstrual period (self-reported by the mother) and the twin’s birth date. Socioeconomic status at birth was derived from the highest self-reported occupation of the parents and was classified according to recommendations by Statistics Sweden (18).

All Swedish citizens are assigned a unique national registration number by which linkages can be made between official records and registers. Reports of death to the Cause of Death Register have been computerized since 1952, and are considered reliable from 1961 onward. Since 1997 the register has been complete, with death certificate coverage of >99% (19). The Cancer Registry holds information on all primary incident cancers in Sweden since 1958 (20). Reporting is mandatory for physicians as well as pathologists and cytologists separately, ensuring all cancers found in autopsy, histologic, and/or cytologic specimens are included and are classified according to the International Classification of Diseases (ICD). Ninety-nine percent of the registered cancers have been morphologically verified (20). In 2006 the registry roughly covered 95% of all cancers reported in the Cause of Death Register, the deficit mainly represented by lung, pancreatic, and prostate cancers in patients >75 y of age. Validation studies restricted to females have found the completeness of the registry to be 99% (21, 22). Incident cases of breast cancer were identified through ICD-9, ICD-10 codes (170, 174, and C50, respectively) during a follow-up period from 1973 to 2006. Censoring occurred at first diagnosis of breast cancer, death, or end of follow-up (December 31, 2006), whichever came first. Because information on date of emigration was not available, individuals with known emigration status in the Twin Registry were excluded from the original cohort (166 of which would otherwise have been included in the final study population).

Cox proportional hazard models were used to estimate hazard ratios (HR) for breast cancer, with age as the underlying time scale. Because the data within each twin pair can be considered correlated we calculated robust SE to account for the dependence within twin pairs (23).

Potential birth cohort effects were adjusted for by fitting stratified Cox regression allowing different baseline hazards for each birth year. All tests of statistical hypotheses were made on the two-sided 5% level of significance. Scaled Schoenfeld residuals (24) for each birth weight category revealed tendencies of nonproportional hazards with age, especially in the higher birth weight category \( \geq 3,000 \) g. The proportional hazards assumption was also tested through an interaction term between birth weight and attained age, and was found to be statistically significant \( P < 0.00001 \). We therefore separately analyzed breast cancer diagnosed at an early or late age \( \pm 50 \) and \( \pm 50 \) y, respectively. To further assess the functional form of the association, Martingale residuals were plotted against birth weight (25). For breast cancer diagnosed at \( \leq 50 \) y there was a positive linear association at birth weights \( \geq 2,500 \) g, and an indication of a weak negative association at birth weights \( < 2,500 \) g. In women diagnosed with breast cancer after 50 y, findings were, if anything, the opposite: weakly negative at \( < 2,500 \) g and no association from \( \geq 2,500 \) g. We consequently assessed the risk of breast cancer for birth weight categories \(< 2,500 \) g and \( \geq 3,000 \) g, respectively, with 2,500-2,999 g as the reference. In multivariable analyses, we used different models to successively control for the effects of gestational age, zygosity, other anthropometric measures at birth (birth length and head circumference), maternal factors (parity and age), socioeconomic status at birth, and height and smoking status in 1973.

In paired analyses the birth weight exposure is replaced by the twin pair mean \( (x_i) \) and the individual deviance from the twin mean \( (x_i-x_j) \) ref. (26). In twins, this latter “within-component” can be considered an approximation of growth that is independent of familial factors (shared by the twins). Thus, if the risk of breast cancer is similar for the deviance from the twin mean birth weight as for the individual birth weight effect in the cohort, we can conclude that the association between birth weight and breast cancer is independent of familial factors. A decrease in the estimated effect would indicate confounding by familial factors, the nature of which could be further elucidated by looking at zygotic groups separately. All twins share early environment; dizygotic twins share on average 50% of their segregating genes, whereas monozygotic twins share approximately 100% of their segregating genes. If the effect of the within component differs according to zygosity, it may give an indication of whether the confounding is more related to shared environment or to common genes. Cox regression for cohort and paired analyses was fitted using PROC PHREG in SAS 9.2.

The paired analysis assumes a linear effect of the exposure. Finding a not strictly linear relationship between birth weight and breast cancer between twins, we could not assume the within-effect to be strictly linear either. If not accounted for in the analyses this could lead to incorrect conclusions about familial confounding. Based on the results from Martingale residual analysis, we therefore carried out paired analysis in twins with birth weights \( \geq 2,500 \) g.

**Results**

In the cohort of 11,923 women, 590 developed breast cancer during follow-up. Table 1 presents the distributions of birth, maternal, and adult characteristics, and the risks of breast cancer. The effect of gestational age on breast cancer risk was modest; the suggested negative association for early breast cancer (diagnosed \( \leq 50 \) years) in the highest category of gestational age (42-45 weeks) was based on only three cases. High birth weight (\( \geq 3,000 \) g) was statistically significantly associated with an increased risk of early (\( \leq 50 \) years) but not late (>50 years) breast cancer. Birth length and head circumference were not statistically significantly associated with early breast cancer risk. The risk of early-diagnosed breast cancer increased statistically significantly with height in adulthood (Table 1). Other characteristics, including potential risk factors such as maternal age, parity, and smoking in 1973 were not statistically significantly associated with risk of breast cancer in either age group (Table 1).

In the cohort, high birth weight (\( \geq 3,000 \) g as compared with 2,500-2,999 g) increased the risk of breast cancer diagnosed at or before the age of 50 years [HR, 1.62; 95% confidence interval (95% CI), 1.14-2.30], but not later in life [HR, 0.89; 95% CI, 0.67-1.20; Table 2, Crude]. Adjusting for zygosity, birth length, and head circumference
Table 1. Characteristics and crude hazard ratios of breast cancer in 11,923 like-sexed Swedish twins according to breast cancer diagnosed at 50 y or earlier, and after 50 y

<table>
<thead>
<tr>
<th>Twin characteristics</th>
<th>Zygosity</th>
<th>Birth year</th>
<th>Gestational age, wk</th>
<th>Birth characteristics</th>
<th>Birth weight, g</th>
<th>Birth length, cm</th>
<th>Head circumference, cm</th>
<th>Maternal characteristics</th>
<th>Maternal age, y</th>
<th>Parity</th>
<th>Socioeconomic status at birth</th>
<th>Blue collar worker</th>
<th>Adult characteristics</th>
<th>Height</th>
<th>Smoking</th>
<th>Ever</th>
<th>Never</th>
<th>Ever</th>
<th>Missing</th>
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<tr>
<td></td>
<td>DZ</td>
<td>1926-1936</td>
<td>31-34</td>
<td>&lt;2500</td>
<td>&lt;160</td>
<td>1.01</td>
<td>&lt;32</td>
<td>Unskilled</td>
<td>&lt;20</td>
<td>1.00</td>
<td></td>
<td>Skilled</td>
<td>160-163</td>
<td>1.00</td>
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<td></td>
<td>MZ</td>
<td>1937-1943</td>
<td>35-36</td>
<td>≥2,500</td>
<td>≥160</td>
<td>1.00</td>
<td>≥32</td>
<td>White collar worker</td>
<td>20-24</td>
<td>1.00</td>
<td></td>
<td>Higher skilled</td>
<td>164-167</td>
<td>1.00</td>
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<td>1944-1950</td>
<td>37-41</td>
<td>≥3,000</td>
<td>≥160</td>
<td>1.00</td>
<td>≥34</td>
<td>Self-employed</td>
<td>30-34</td>
<td>1.00</td>
<td></td>
<td>Lower skilled</td>
<td>≥168</td>
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<td>1951-1958</td>
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<td>≥35</td>
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NOTE: HR and 95% CI derived from Cox proportional hazard models. Some percentages do not add up to 100 because of rounding.
Abbreviations: DZ, dizygotic twins; MZ, monozygotic twins.
only slightly attenuated the risks (Table 2, model 2), whereas including gestational age had essentially no effect (Table 2, models 1 and 3). Being born light (<2,500 g) was not statistically significantly associated with breast cancer risk compared with the reference. Additional adjustment for maternal characteristics (parity and age at birth) and adult characteristics (smoking and height) had no influence on the effect of birth weight (data not shown). Further adjustment for socioeconomic status at birth was hampered by a high amount of missing data. However, when we repeated all models including only individuals with complete information on all covariates, socioeconomic status at birth did not alter the association between birth weight and breast cancer risk (data not shown).

In the cohort analyses, we only identified a statistically significant positive association between birth weights ≥3,000 g and breast cancer diagnosed at 50 years or earlier. Because the association between birth weight and early-onset breast cancer was not linear at <2,500 g, we restricted further analyses to early-onset breast cancer in twins with birth weight ≥2,500 g. Table 3 shows the crude and adjusted effects of a 500-g increase in birth weight in the cohort and within twin pairs. In all intact pairs with birth weights ≥2,500 g, the increased risk for early-onset breast cancer per 500-g increase in birth weight was similar in the cohort (HR, 1.53; 95% CI, 1.21-1.93) and in the within-pair analysis (HR, 1.46; 95% CI, 1.00-2.13; Table 3). Adjusting for factors not shared by twins (such as other anthropometric measures at birth, and smoking and height in 1973) increased both the point estimates and the estimated variations slightly (Table 3, models 1 and 2). Stratified analyses by zygosity further widened the CIs. After full adjustments the estimates were in fact similar in dizygotic twins (HR, 1.58; 95% CI, 0.93-2.69) and monozygotic twins (HR, 1.42; 95% CI, 0.63-3.24; Table 3, model 2). The interaction term between the deviation from the twin mean birth weight and zygosity was not statistically significant in any model (P = 0.46 in the crude, P = 0.34 in model 1, and P = 0.39 in model 2).

Discussion

In this large cohort of Swedish twins, high birth weight conferred an increased risk of breast cancer diagnosed before or at the age of 50 years. We found that this association was independent of familial factors, such as shared early environment and common genes.

Our cohort findings are in agreement with the results from recent reviews and meta-analyses (1-4). We found an increased risk of breast cancer with birth weights ≥3,000 g. This lack of a strictly linear dose-response effect conflicts with some previous reports of a positive linear trend (27-31), although Vatten et al. (2002) and McCormack et al. (2003) used birth weights <3,000 g as reference, preventing interpretation of possible effects of lower birth weights. While there have been reports of J- or U-shaped relationships between birth weight and breast cancer risk (32-35), we found no conclusive evidence of an increased risk of breast cancer with low birth weight, nor did the latest meta-analysis by Park et al. (2008) or the reanalysis by Silva et al. (2008). Although some previous studies have found birth length a stronger predictor than birth weight of breast cancer risk (4, 30), birth length had no effect on risk of breast cancer in this study. Birth length is probably more sensitive to measurement error than is birth weight, and it is possible that imprecise measurement of birth length in this older cohort could explain the lack of effect on breast cancer risk in this study.

Several others have reported that birth weight risks are more pronounced in breast cancers diagnosed at younger ages (27, 31-36), and in this study the effect of birth weight was restricted to breast cancer diagnosed at or before 50 years. This could potentially reflect a greater relative influence of perinatal risk factors at younger ages (32), or cancers being inherently different in their nature. However, in a large reanalysis of individual participant data from 32 studies there was no indication of age modifying the effect of birth weight on breast cancer risk (4). Family history is a strong risk factor for early-onset breast cancer (37, 38). If genes involved in breast carcinogenesis are also connected to the regulation of fetal growth, the association between birth weight and breast cancer could be confounded by genetic factors. There could also be confounding from other factors associated with breast cancer and birth weight, including socioeconomic status, lifestyle, and dietary habits. Previous attempts to control for confounding by adjusting for socioeconomic factors has had limited effect on the association (1). To

Table 2. Birth weight and risk of breast cancer diagnosed at or before 50 y and after 50 y in 11,923 Swedish twins

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Crude</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>≤50 y (n_cases/ntot)</td>
<td>233/11,923</td>
<td>225/11,363</td>
<td>227/11,508</td>
<td>219/10,995</td>
</tr>
<tr>
<td>Birth weight, g</td>
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<tr>
<td>&lt;2,500</td>
<td>1.31 (0.95-1.79)</td>
<td>1.27 (0.89-1.79)</td>
<td>1.41 (0.97-2.05)</td>
<td>1.37 (0.93-2.01)</td>
</tr>
<tr>
<td>≥2,500-2,999</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥3,000</td>
<td>1.62 (1.14-2.30)</td>
<td>1.63 (1.14-2.32)</td>
<td>1.57 (1.03-2.40)</td>
<td>1.58 (1.03-2.42)</td>
</tr>
<tr>
<td>&gt;50 y (n_cases/ntot)</td>
<td>357/10,286</td>
<td>333/9,776</td>
<td>337/9,912</td>
<td>315/9,447</td>
</tr>
<tr>
<td>Birth weight, g</td>
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<tr>
<td>&lt;2,500</td>
<td>1.08 (0.86-1.37)</td>
<td>1.02 (0.79-1.31)</td>
<td>0.98 (0.71-1.34)</td>
<td>0.96 (0.68-1.34)</td>
</tr>
<tr>
<td>≥2,500-2,999</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥3,000</td>
<td>0.89 (0.67-1.20)</td>
<td>0.87 (0.64-1.18)</td>
<td>0.81 (0.58-1.14)</td>
<td>0.80 (0.57-1.12)</td>
</tr>
</tbody>
</table>

NOTE: HR and 95% CI derived from Cox proportional hazard models.

n_cases/ntot, number of cases/total number of twins.

*Model 1 adjusted for gestational age (categorized).
†Model 2 adjusted for zygosity, birth length, and head circumference (categorized).
‡Model 3 adjusted for gestational age, zygosity, birth length, and head circumference (categorized).

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Recently, there has been increasing interest in the potential role of epigenetic changes, not least in the field of early origins of adult disease (8, 46). Potential epigenetic effects may, due to differing gene expression, also result in individual differences within monozygotic twin pairs (47). Fetal growth may in part be epigenetically determined, through imprinting (48). Most imprinted genes are also expressed in the placenta, and may through altered placental function regulate the supply line to the fetus (48). The imprinted IGF2 gene has been proposed to control both placental supply and fetal demand for nutrients (8), and loss of imprinting and biallelic expression of the IGF2 allele has been linked to both breast cancer development and growth (49). With respect to our findings, any individual epigenetic change acquired during prenatal life (in response to environmental stimuli) would appear independent of familial factors.

Restrictions of the study sample were made to ensure reliable birth weight information. In the paired analysis the requirement of available birth weight data on both subjects in a pair resulted in loss of power, hampering particularly further stratification by zygosity. We also need to consider the issue of generalizability from twin studies. The fetal hormonal exposure of a twin is, as previously discussed, not well known, nor is the singleton experience. If the fetal hormone exposure is higher in twins than in singletons we would, according to the hormone hypothesis, expect a higher incidence of breast cancer in twins, which has been shown by some (38, 50, 51) and refuted by others (32, 52, 53). Nevertheless, we could show an association between birth weight and breast cancer similar to that extensively reported among singletons, suggesting that fetal growth may have similar health consequences among twins and singletons.

The association between birth weight and breast cancer with an early onset seems to be independent of familial factors, indicating that the prenatal experience is of importance for breast cancer risk in younger ages. In the continued efforts to understand how fetal factors influence breast cancer etiology, our findings support further investigation of prenatal exposures or events, not related to familial factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

References

5. World Cancer Research Fund/American Institute for Cancer

Table 3. Cohort and within hazard ratios of breast cancer diagnosed at or before 50 y, for a 500 g increase in birth weight in twins with birth weight ≥2,500 g

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All (n_cases/n_tot)</td>
<td>1.21 (0.56-2.62)</td>
<td>1.38 (0.64-2.95)</td>
<td>1.42 (0.63-3.24)</td>
</tr>
<tr>
<td>Cohort</td>
<td>1.21 (0.56-2.62)</td>
<td>1.38 (0.64-2.95)</td>
<td>1.42 (0.63-3.24)</td>
</tr>
<tr>
<td>Within</td>
<td>1.53 (1.00-2.34)</td>
<td>1.56 (0.94-2.59)</td>
<td>1.58 (0.93-2.69)</td>
</tr>
<tr>
<td>DZ (n_cases/n_tot)</td>
<td>37/2,458</td>
<td>37/2,394</td>
<td>31/2,067</td>
</tr>
<tr>
<td>Within</td>
<td>1.21 (0.56-2.62)</td>
<td>1.38 (0.64-2.95)</td>
<td>1.42 (0.63-3.24)</td>
</tr>
<tr>
<td>MZ (n_cases/n_tot)</td>
<td>95/4,428</td>
<td>91/4,242</td>
<td>85/3,618</td>
</tr>
<tr>
<td>Within</td>
<td>1.53 (1.00-2.34)</td>
<td>1.56 (0.94-2.59)</td>
<td>1.58 (0.93-2.69)</td>
</tr>
</tbody>
</table>

NOTE: HR and 95% CI derived from Cox proportional hazard models. Effects shown for all twins and for MZ and DZ twins separately.

Model 1 adjusted for birth length and head circumference.

Model 2 adjusted for birth length, head circumference, and smoking and height in 1973.

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