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BRIEF COMMUNICATION

Breast Cancer Risk in Opposite-Sexed Twins: Influence of Birth Weight and Co-Twin Birth Weight

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Most, but not all, studies report a positive association between birth weight, as an indirect marker of prenatal hormone exposure, and offspring breast cancer risk, particularly premenopausal breast cancer. Females from opposite-sexed twin pairs may also be prenatally exposed to androgens from their twin brothers. A Swedish study of opposite-sexed twins with a small sample size found a very strong positive association between female birth weight and breast cancer risk. In this case–control study, nested within a cohort of female opposite-sexed twins, we included 543 breast cancer case subjects diagnosed in the period from 1972 to 2008 and 2715 matched control subjects. Conditional logistic regression estimated the breast cancer risk associated with birth weight and other birth characteristics, including gestational age and co-twin birth weight. All statistical tests were two-sided. There was no association between birth weight (odds ratio = 1.01; 95% confidence interval = 0.70 to 1.46) or twin brother's birth weight and risk of breast cancer, which suggests the previously reported strong positive association may have been a chance finding.

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Birth weight, an indirect measure of estrogen exposure in utero (1–5), is generally (1,6–10), but not always (11–14), positively associated with the offspring's risk of breast cancer, particularly premenopausal breast cancer (4,15–24). Moreover, findings from a twin study suggested that the association is not confounded by familial (shared genetic or environmental) factors (20). A previous Swedish case–control study of opposite-sexed twins found a very strong positive association between female birth weight and subsequent risk of breast cancer (1). Given that the study only included 90 case patients, this could be a chance finding.

It has also been shown that there is an association between levels of circulating androgens and risk of breast cancer (25–27). If female twins in opposite-sexed twin pairs are prenatally exposed to androgens from their twin brothers, this may influence their breast cancer risk.

This case–control study, nested within a cohort of opposite-sexed twins, investigated associations between female and male co-twin birth weight and risk of breast cancer, stratified by age (≤50 or >50 years) at diagnosis. The Swedish Twin Registry includes data on anthropometric measures at birth, date of last menstrual period, maternal age, parity, and the occupational status of parents (28,29). The Swedish Cancer Registry contains individual data on all newly diagnosed malignant tumors in Sweden since 1958 and is more than 98% complete (30). Using the national registration number, a unique personal identifier, it is possible to link information across registries.

From the Swedish Twin Registry, we retrieved data on 13 075 pairs of opposite-sexed twins born during the period from 1926 to 1972, with information on birth characteristics. Within this cohort we performed a nested case–control study, including all breast cancer case subjects diagnosed between 1972 and 2008. Subjects with breast cancer were individually matched by year of birth with five control subjects who were not affected by breast cancer and were alive at the time their matched case subject received a diagnosis of breast cancer (31). In total, there were 543 breast cancer case subjects and 2715 control subjects (Table 1). This provides more than 90% statistical power to detect whether the mean birth weight of the case and control subjects differs by at least 100 grams (alpha = 0.05; standard deviation = 500 grams).

Socioeconomic status was based on the father's profession at the time of birth (unskilled blue-collar worker, skilled blue-collar worker, low-level white-collar worker, intermediate-level white-collar worker, high-level white-collar worker, or self-employed); the mother's profession was used if the father's profession was missing.

Conditional logistic regression estimated odds ratios (ORs) and 95% confidence interval (CIs) for the association between birth weight and risk of breast cancer. We estimated the odds ratios using birth weight as both a continuous variable (risk increase per kilogram increase in birth weight) and a five-category (<2000, 2000–2499, 2500–2999, 3000–3499, and ≥3500 grams) variable.

Starting with the crude model, we consecutively adjusted for potential confounding factors in three different models (Table 2). The number of case/control subjects with missing information for maternal parity and socioeconomic status were 45/225 and 167/897, respectively. We used multiple imputation methods to deal with the missing values (32). The Box–Tidwell test was used to test for nonlinearity of continuous variables.

We also estimated the risk associated with co-twin birth weight and investigated the interaction between female sex and co-twin birth weight. Moreover, the association between difference in birth weight between the brother and sister in the twin pair, as a continuous or categorical variable (500-gram categories), and breast cancer

Table 1. Characteristics, crude odds ratio (OR), and 95% confidence interval (CI) of breast cancer in female twins in opposite-sexed Swedish twin pairs, diagnosed at age 50 years or earlier and after age 50 years*

	All subjects			Aged ≤50 y		Aged >50 y	
Characteristic	Case subjects (n = 543) No. (%)	Control subjects (n = 2715) No. (%)	OR (95% CI)	Case/Control subjects, No.	OR (95% CI)	Case/Control subjects, No.	OR (95% CI)
Birth characteristics							
Birth weight, g							
<2000	43 (7.9)	210 (7.7)	0.98 (0.69 to 1.40)	17/77	1.11 (0.62 to 1.98)	26/133	0.88 (0.56 to 1.40)
2000–2499	156 (28.7)	770 (28.4)	0.97 (0.78 to 1.22)	59/262	1.06 (0.72 to 1.55)	97/508	0.88 (0.66 to 1.17)
2500–2999	212 (39.0)	1017 (37.5)	Referent	74/372	Referent	138/645	Referent
3000–3499	104 (19.2)	604 (22.3)	0.83 (0.64 to 1.07)	40/222	0.81 (0.53 to 1.25)	64/382	0.78 (0.56 to 1.08)
≥3500	28 (5.2)	114 (4.2)	1.18 (0.76 to 1.83)	13/42	1.56 (0.80 to 3.05)	15/72	0.97 (0.54 to 1.75)
Continuous, kg	543	2715	0.96 (0.80 to 1.16)	203/975	0.95 (0.70 to 1.31)	340/1740	0.97 (0.77 to 1.24)
Birth length, cm							
≤46	176 (32.4)	774 (28.5)	1.16 (0.90 to 1.50)	74/285	1.34 (0.88 to 2.04)	102/489	1.07 (0.77 to 1.49)
47–48	154 (28.4)	857 (31.6)	0.92 (0.71 to 1.20)	57/306	1.03 (0.67 to 1.59)	97/551	0.92 (0.66 to 1.27)
49	86 (15.8)	446 (16.4)	0.98 (0.73 to 1.33)	25/158	0.86 (0.50 to 1.48)	61/288	1.09 (0.75 to 1.58)
≥50	122 (22.5)	623 (23.0)	Referent	45/223	Referent	77/400	Referent
Continuous, cm	543	2715	0.99 (0.95 to 1.02)	203/975	0.98 (0.93 to 1.04)	340/1740	0.99 (0.94 to 1.03)
Missing	5 (0.9)	15 (0.6)	—	2/3	—	3/12	—
Head circumference, cm							
≤32	192 (35.4)	981 (36.1)	1.01 (0.76 to 1.35)	81/386	1.31 (0.79 to 2.15)	111/595	0.88 (0.61 to 1.26)
33	126 (23.2)	632 (23.3)	1.03 (0.75 to 1.40)	44/211	1.30 (0.76 to 2.24)	82/421	0.93 (0.63 to 1.36)
34	120 (22.1)	606 (22.3)	1.03 (0.75 to 1.40)	42/206	1.26 (0.73 to 2.18)	78/400	0.94 (0.64 to 1.38)
≥35	79 (14.6)	408 (15.0)	Referent	26/153	Referent	53/255	Referent
Continuous, cm	543	2715	0.99 (0.93 to 1.04)	203/975	0.95 (0.86 to 1.04)	340/1740	1.01 (0.94 to 1.09)
Missing	26 (4.8)	88 (3.2)	—	10/19	—	16/69	—
Gestational age, wk							
<33	14 (2.6)	62 (2.3)	1.11 (0.61 to 2.02)	7/20	1.37 (0.53 to 3.57)	7/42	0.87 (0.38 to 1.98)
33–36	123 (22.7)	599 (22.1)	1.01 (0.80 to 1.28)	38/208	0.84 (0.56 to 1.26)	85/391	1.18 (0.88 to 1.58)
37–38	262 (48.3)	1290 (47.5)	Referent	107/464	Referent	155/826	Referent
≥39	144 (26.5)	764 (28.1)	0.93 (0.75 to 1.16)	51/283	0.80 (0.55 to 1.15)	93/481	1.04 (0.79 to 1.38)
Continuous, wk	543	2715	0.98 (0.95 to 1.02)	203/975	0.98 (0.93 to 1.05)	340/1740	0.98 (0.94 to 1.03)
Twin characteristics							
Co-twin birth weight, g							
<2000	42 (7.7)	162 (6.0)	1.25 (0.86 to 1.81)	18/61	1.31 (0.73 to 2.34)	24/101	1.23 (0.76 to 2.00)
2000–2499	122 (22.5)	592 (21.8)	0.99 (0.78 to 1.26)	42/229	0.75 (0.50 to 1.14)	80/363	1.12 (0.82 to 1.51)
2500–2999	210 (38.7)	1006 (37.1)	Referent	82/347	Referent	128/659	Referent
3000–3499	129 (23.8)	747 (27.5)	0.83 (0.65 to 1.05)	44/267	0.71 (0.47 to 1.06)	85/480	0.88 (0.66 to 1.19)
≥3500	39 (7.2)	207 (7.6)	0.91 (0.63 to 1.30)	16/70	0.96 (0.52 to 1.75)	23/137	0.86 (0.54 to 1.39)
Continuous, kg	543	2715	0.82 (0.68 to 0.98)	203/975	0.80 (0.59 to 1.09)	340/1740	0.81 (0.65 to 1.03)
Missing	1 (0.2)	1 (0.0)	—	1/1	—	0/0	—
Maternal characteristics							
Maternal age, y							
<25	93 (17.1)	453 (16.7)	Referent	34/160	Referent	59/293	Referent
25–29	170 (31.3)	765 (28.2)	1. 09 (0.82 to 1.44)	69/307	1. 03 (0.65 to 1.62)	101/458	1.08 (0.76 to 1.54)
30–34	144 (26.5)	807 (29.7)	0. 87 (0.65 to 1.15)	53/269	0. 90 (0.56 to 1.44)	91/538	0. 84 (0.59 to 1.19)
≥35	135 (24.9)	690 (25.4)	0. 96 (0.72 to 1.28)	47/239	0. 85 (0.52 to 1.39)	88/451	0. 97 (0.67 to 1.38)
Continuous, y	543	2715	0.99 (0.98 to 1.01)	203/975	0.98 (0.95 to 1.01)	340/1740	1.00 (0.98 to 1.02)
Missing	1 (0.2)	0 (0.0)	—	0/0	—	1/0	—
Maternal parity							
Unipara	232 (42.7)	1086 (40.0)	1.29 (0.93 to 1.37)	75/358	0.98 (0.69 to 1.40)	157/728	1.19 (0.94 to 1.51)
Multipara	266 (49.0)	1404 (51.7)	Referent	83/392	Referent	183/1012	Referent
Missing	45 (8.3)	225 (8.3)	—	45/225	—	0/0	—
Hypertensive disease during pregnancy							
Yes	28 (5.2)	140 (5.2)	1.00 (0.66 to 1.52)	15/70	1.00 (0.55 to 1.81)	13/70	0.96 (0.53 to 1.74)
No	515 (94.8)	2575 (94.8)	Referent	188/905	Referent	327/1670	Referent

* Conditional logistic regression was used to analyze the data using two-sided alpha of 0.05.

Table 2. Risk of breast cancer according to individual birth weight and co-twin birth weight, stratified by age at diagnosis*

Birth weight	Case/control subject, No.	OR (95% CI) Crude	OR (95% CI) Model 1†	OR (95% CI) Model 2‡	OR (95% CI) Model 3§
≤50 years					
Birth weight, g					
<2000	17/77	1.11 (0.62 to 1.98)	1.11 (0.59 to 2.09)	1.09 (0.58 to 2.06)	1.08 (0.57 to 2.04)
2000–2499	59/262	1.06 (0.72 to 1.55)	1.10 (0.74 to 1.63)	1. 09 (0.73 to 1.62)	1.07 (0.72 to 1.60)
2500–2999	74/372	Referent	Referent	Referent	Referent
3000–3499	40/222	0.81 (0.53 to 1.25)	0.84 (0.54 to 1.30)	0.84 (0.54 to 1.30)	0.83 (0.53 to 1.30)
≥3500	13/42	1.56 (0.80 to 3.05)	1.70 (0.85 to 3.40)	1.72 (0.86 to 3.44)	1.75 (0.87 to 3.53)
Continuous, kg	203/975	0.95 (0.70 to 1.31)	0.99 (0.69 to 1.42)	1.02 (0.71 to 1.47)	1.01 (0.70 to 1.46)
Co-twin birth weight, g					
<2000	18/61	1.31 (0.73 to 2.34)	1.26 (0.66 to 2.39)	1.26 (0.66 to 2.39)	1.22 (0.64 to 2.33)
2000–2499	42/229	0.75 (0.50 to 1.14)	0.76 (0.49 to 1.17)	0.76 (0.49 to 1.17)	0.75 (0.48 to 1.16)
2500–2999	82/347	Referent	Referent	Referent	Referent
3000–3499	44/267	0.71 (0.47 to 1.06)	0.71 (0.47 to 1.07)	0.71 (0.47 to 1.07)	0.71 (0.47 to 1.07)
≥3500	16/70	0.96 (0.52 to 1.75)	1.03 (0.55 to 1.94)	1.03 (0.55 to 1.94)	1.02 (0.54 to 1.94)
Continuous, kg	203/975	0.80 (0.59 to 1.09)	0.78 (0.54 to 1.12)	0.79 (0.55 to 1.15)	0.79 (0.54 to 1.14)
>50 years					
Birth weight, g					
<2000	26/133	0.88 (0.56 to 1.40)	0.85 (0.52 to 1.40)	0.84 (0.51 to 1.38)	0. 84 (0.51 to 1.38)
2000–2499	97/508	0.88 (0.66 to 1.17)	0.85 (0.63 to 1.14)	0.85 (0.63 to 1.15)	0. 86 (0.64 to 1.16)
2500–2999	138/645	Referent	Referent	Referent	Referent
3000–3499	64/382	0.78 (0.56 to 1.08)	0.79 (0.57 to 1.09)	0.78 (0.56 to 1.08)	0.77 (0.55 to 1.08)
≥3500	15/72	0.97 (0.54 to 1.75)	0.98 (0.54 to 1.78)	0.98 (0.54 to 1.79)	0.99 (0.54 to 1.80)
Continuous, kg	340/1740	0.97 (0.77 to 1.24)	1.03 (0.79 to 1.35)	1.03 (0.78 to 1.36)	1.03 (0.78 to 1.36)
Co-twin birth weight, g					
<2000	24/101	1.23 (0.76 to 2.00)	1.30 (0.77 to 2.19)	1.29 (0.76 to 2.19)	1.28 (0.76 to 2.18)
2000–2499	80/363	1.12 (0.82 to 1.51)	1.11 (0.81 to 1.52)	1.09 (0.80 to 1.50)	1.09 (0.79 to 1.49)
2500–2999	128/659	Referent	Referent	Referent	Referent
3000–3499	85/480	0.88 (0.66 to 1.19)	0.88 (0.65 to 1.19)	0.87 (0.64 to 1.18)	0.87 (0.64 to 1.18)
≥3500	23/137	0.86 (0.54 to 1.39)	0.86 (0.53 to 1.39)	0.87 (0.54 to 1.42)	0.88 (0.54 to 1.43)
Continuous, kg	340/1740	0.81 (0.65 to 1.03)	0.82 (0.63 to 1.07)	0.82 (0.63 to 1.07)	0.82 (0.63 to 1.07)

* Conditional logistic regression was used to analyze the data using two-sided alpha of 0.05. Multiple imputation analysis was used to deal with missing data. CI, confidence interval; OR, odds ratio.

† Model 1 adjusted for gestational age.

‡ Model 2 adjusted for gestational age, maternal age, parity, and hypertensive disease during pregnancy.

§ Model 3 adjusted for the variables in model 2 and socioeconomic status.

risk was estimated. Because the etiology of pre- and postmenopausal breast cancer may differ, analyses were stratified by age at diagnosis, using 50 years as the cutoff for pre- and postmenopausal breast cancer.

All statistical tests were two-sided, and values less than .05 were considered to be statistically significant. All analyses were performed using SAS 9.2 statistical software (SAS Inc, Cary, NC). The study was approved by the research ethics committee at Karolinska Institutet.

We found no associations between birth weight and other independent variables and breast cancer risk (Table 1). Stratified analyses for premenopausal or postmenopausal breast cancer revealed no association.

There were no associations between birth weight (OR = 1.01; 95% CI = 0.70 to 1.46) or co-twin birth weight and risk of premenopausal or postmenopausal breast cancer in any of the crude or adjusted models (Table 2). Also, there were no associations between the difference in female and male birth weight and risks of premenopausal or postmenopausal breast cancer (data not shown). Analysis in which both female birth weight and co-twin birth weight were included in the model as continuous variables revealed no statistically significant association. There was no interaction between female and male birth weight for risk of premenopausal (P = .91) or postmenopausal breast cancer (P = .62).

Our findings are consistent with the results of several previous negative cohort (33–35) and case–control studies (6,11–13,36–39). Many original studies (9,15,16,21,23,40) and three meta-analyses (22,41,42) reported a modestly increased risk of breast cancer associated with high birth weight (9,15,16,21,23,40), particularly for premenopausal breast cancer (15–21,23,40). However, many studies suffer from a limited sample size, and publication bias cannot be ruled out.

An earlier Swedish study of breast cancer in opposite-sexed twins with 90 case–control pairs found a 12-fold higher risk when comparing the heaviest with the lightest twins (1). Because the previously published study and this study used similar information and had similar design, they share study strengths and weaknesses with one notable exception: sample size. Therefore, it is conceivable that the results of the previous study may have been a chance finding.

Recall bias is not a concern because the data were collected at the time of delivery. We controlled for some important confounding factors during early life, such as maternal sociodemographic factors. However, we had no information on exposures between birth and breast cancer diagnosis, such as contraceptives or hormone replacement therapy, which could be a confounding factor (43). Another limitation is that we used birth weight as a proxy for estrogen and other prenatal hormone exposures.

In conclusion, we could not replicate the previously reported strong association between birth weight and breast cancer risk in opposite-sexed twins (1), which may have been a chance finding.

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