Published in final edited form as:
J Dev Orig Health Dis. 2013 February ; 4(1): 35–41. doi:10.1017/S2040174412000645.

Perinatal characteristics and breast cancer risk in daughters: a Scandinavian population-based study

R. Troisi[1,*], **T. Grotmol**[2], **J. Jacobsen**[3], **S. Tretli**[2], **H. Toft-Sørensen**[3], **M. Gissler**[4,5], **R. Kaaja**[6], **N. Potischman**[7], **A. Ekbom**[8], **R. N. Hoover**[1], and **O. Stephansson**[8,9]

[1]Divisions of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA [2]Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway [3]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark [4]Department of Information, THL National Institute for Health and Welfare, Helsinki, Finland [5]Nordic School of Public Health, Gothenburg, Sweden [6]Turku University, Turku, Finland [7]Divisions of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA [8]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden [9]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Abstract

The *in utero* origins of breast cancer are an increasing focus of research. However, the long time period between exposure and disease diagnosis, and the lack of standardized perinatal data collection makes this research challenging. We assessed perinatal factors, as proxies for *in utero* exposures, and breast cancer risk using pooled, population-based birth and cancer registry data. Birth registries provided information on perinatal exposures. Cases were females born in Norway, Sweden or Denmark who were subsequently diagnosed with primary, invasive breast cancer (n = 1419). Ten controls for each case were selected from the birth registries matched on country and birth year (n = 14,190). Relative risks (RRs) and 95% confidence intervals (CIs) were estimated using unconditional regression models. Breast cancer risk rose 7% (95% CI 2–13%) with every 500 g (roughly 1 S.D.) increase in birth weight and 7% for every 1 s.d. increase in birth length (95% CI 1–14%). The association with birth length was attenuated after adjustment for birth weight, while the increase in risk with birth weight remained with adjustment for birth length. Ponderal index and small- and large-for-gestational-age status were not better predictors of risk than either weight or length alone. Risk was not associated with maternal education or age, gestational duration, delivery type or birth order, or with several pregnancy complications, including preeclampsia. These data confirm the positive association between birth weight and breast cancer risk. Other pregnancy characteristics, including complications such as preeclampsia, do not appear to be involved in later breast carcinogenesis in young women.

Keywords

birth weight; breast cancer; early life; *in utero*; preeclampsia; prenatal

[*]Address for correspondence: Dr R. Troisi, Dartmouth Hitchcock Medical Center, One Medical Center Drive, 7927 Rubin Building, Room 854, Lebanon, NH 03756, USA. (troisir@mail.nih.gov) .

Introduction

Recent studies of breast cancer have evaluated the hypothesis that prenatal exposures influence subsequent breast cancer development. This area of research is especially challenging as it is rare to have both biological measures in pregnancy and information on cancer diagnosis. Therefore, studies have used proxies for *in utero* exposure (such as birth weight) in epidemiologic studies and when empirical associations have been observed, biological mechanisms have been pursued, for example, whether variation in reproductive hormones and growth factors associated with the factor could explain the findings.

An example of this approach is the epidemiological observation of an, ~60% reduction in breast cancer risk among women born of preeclamptic pregnancies observed in a Swedish population-based study,[1] which is widely cited as evidence of a profound effect of prenatal exposures on breast carcinogenesis. Significant effort has been invested in determining the pathogenic mechanisms underlying this association, including detailed study of steroid hormones and growth factors associated with preeclampsia,[2] and follow-up of daughters born of preeclamptic pregnancies to assess later growth and development.[3] Other maternal, pregnancy and neonatal characteristics have been evaluated in relation to breast cancer risk in previous studies, including maternal age, duration of gestation and birth weight.[4] Assessing the association of rare conditions in pregnancy such as preeclampsia and other placental and pregnancy complications requires very large data sets with decades of observation. Whereas rare complications will not explain the vast majority of cancer cases, they may provide insight into currently unrecognized biological mechanisms that explain other established breast cancer risk factors, for example age at first live birth. We undertook a pooled analysis of linked population-based data from the three Scandinavian countries to assess the risk of breast cancer according to maternal, prenatal and neonatal factors in young women.

Methods

National registries

The Nordic countries maintain nationwide health registries based on mandatory reporting on standardized forms from doctors, midwifes and hospital departments. Additional registries contain data on deaths and immigration. The unique personal identification number (PIN) assigned to each citizen at birth allows linkage among registries. Data for the current analysis were obtained by pooling the linked population-based medical birth registries and cancer registries in Norway, Sweden and Denmark. Ethics approvals were obtained from review boards in Norway and Sweden, and from the U.S. National Cancer Institute. The study was approved by the Danish Data Protection Agency (record no. 2008-41-27679).

The cancer registry in each country records information on all new cancer cases, including reported date of diagnosis and tumor site. The Norwegian Cancer Registry was established in 1951, the Swedish Registry in 1957 and the Danish Registry in 1943. Overall completeness and accuracy of the registries is very high.[5-7]

Each country's medical birth registry contains information on the mother and child for the prenatal period for all pregnancies resulting in a live birth or still birth. Each registry has nearly 100% complete information. The Medical Birth Registry of Norway, established in 1967, requires that midwives and physicians use a standardized reporting form.[8] The Swedish Medical Birth Registry, established in 1973, collects medical record information from prenatal care visits and from delivery rooms.[9,10] The Danish Medical Birth Registry has collected data on all deliveries since 1973, based on midwives' reports.[11] In the current

study, information from national hospital inpatient registries, when available, was used to supplement birth registry data.

Case and control selection

Cases were female singletons at birth who had a subsequent diagnosis of invasive breast cancer (ICD 174) in Norway (1979–2009) Sweden (1989–2009) or Denmark (1999–2010). A total of 1419 breast cancer cases were identified: 866 in Norway, 423 in Sweden and 130 in Denmark. The median diagnosis year was 2007.

For each case, 10 women without breast cancer were selected from the national birth registries matched on birth country, birth year and vital status at the time of the case's diagnosis. This yielded a total of 14,190 controls: 8660 from Norway, 4230 from Sweden and 1300 from Denmark.

Exposure variables

Ponderal index (PI) scores were calculated by dividing birth weight by the cubed value of birth length (kg/m^3). Swedish growth curves based on ultrasound growth estimations during pregnancy were used to calculate small-for-gestational-age (SGA) and large-for-gestational-age (LGA) values for newborns.[12] Birth order was dichotomized as first- or later-born based on all pregnancies from the same mother. Information was available on highest attained maternal education (in Sweden only), multiple gestations, delivery type and maternal pregnancy complications including, severe hyperemesis, preeclampsia, retained placenta, anemia and bleeding. In Denmark, pregnancies complicated by preeclampsia were identified from the Danish National Registry of Patients. Subjects with missing data were excluded only in individual analyses assessing the given missing variable, because there was no reason to believe that missing data for some variables were related to future breast cancer risk.

Statistical analysis

Logistic regression models were used to compute relative risk estimates (RRs) and 95% confidence intervals (CIs). Because conditional models and unconditional models that included the matching factors (i.e. birth country and birth year) provided similar results, only results from the unconditional models are presented. Birth country was omitted from the models because it did not affect results. Initially, separate models were used to evaluate each variable. In subsequent models, variables were added to assess the independence of observed associations.

Results

The age distribution of cases and controls by country is presented in Table 1. The median age at breast cancer diagnosis was 32 years (mean 32.3, s.d. 5.0 years). Maternal education level and length of gestation were not associated with breast cancer risk in daughters. Risk rose with increasing birth size (Table 2). Breast cancer risk increased 7% with every 500 g (roughly 1 s.d.) increase in birth weight. The positive association between birth weight remained (RR 1.09, 95% CI 1.03–1.15) after adjustment for gestational length as a continuous variable. Being born SGA was associated with lower risk and being born LGA was associated with elevated risk, but neither estimate was statistically significant. Birth length also was associated with an increase in breast cancer risk (7% for every 1 s.d. increase), even after adjustment for gestational length (RR 1.07, 95% CI 1.00–1.15). Ponderal index, a measure of weight for a given height (i.e. adiposity) was not a better predictor of risk than either birth weight or length alone. Simultaneously including birth weight and length, and gestational length as continuous variables in the regression model,

yielded an RR of 1.09 (95% CI 0.1.00–1.18) for birth weight, 1.00 (95% CI 0.91–1.10) for birth length and 1.00 (95% CI 0.96–1.03) for gestational length.

Breast cancer risk in daughters did not vary by maternal age or birth order. Risk also was not associated with multiple gestation, delivery type or pregnancies with complications (although the number of cases born of these pregnancies was limited).

Discussion

Studies of perinatal factors and cancer incidence in offspring present several methodological challenges, including the long induction period between exposure and disease diagnosis, the relative rarity of cancer events and general reliance on recalled exposure information. An important strength of our study was the ability to pool information collected in a standardized manner in population-based registries, thereby avoiding the possibility of selection and recall biases.

Several studies have assessed the association between birth weight and breast cancer risk using birth weight as an integrated measure of prenatal nutrition and growth and development. Our finding (7% increase in risk for every 500 g increase in birth weight) is in line with the result of a pooled analysis of individual data from several studies (6% increase in risk for every 500 g increase in birth weight).[13] Birth length also was positively associated with breast cancer risk in this pooled analysis (6% increase in risk per 1 s.d. increase), as it was in our data (7% increase in risk per 1 s.d. increase). When birth weight and length were assessed simultaneously in our study, it appeared that birth weight was the stronger predictor of risk. However, this could stem from greater measurement error affecting birth length, which would decrease the risk estimate toward the null. In contrast, birth length was the stronger predictor of risk in the pooled analysis.[13] PI score, a measure of adiposity, was minimally associated with breast cancer risk in the present study. Our finding of an increase in risk with increasing size appeared to be independent of duration of gestation. One explanation is that exposure to hormones *in utero* could affect breast development and later carcinogenesis. Birth weight is positively associated with maternal circulating concentrations of several hormones and growth factors, such as estrogens, insulin-like growth factor-1 and leptin. However, the association between maternal circulating concentrations and umbilical cord concentrations to which the daughter would be exposed in utero is unclear for some of these analytes.[2] Alternatively, birth size may reflect parental height and thereby correlate with attained height, an established breast cancer risk factor.[14] However, adjustment for maternal height in the pooled analysis only slightly attenuated the association between birth length and breast cancer risk.[13] It is possible that the association of birth size with breast cancer could be mediated through other adolescent and adult risk factors for breast cancer such as age at menarche or mammographic density. Indeed, a study based on Swedish data[15] reported that women with elevated birth weight were at increased risk of developing high mammographic density.

Preeclampsia is a pregnancy complication characterized by hypertension and proteinuria and reflects placental dysfunction. Speculation about the biological underpinnings of an association between preeclampsia and breast cancer include alterations in reproductive hormones known to play a role in breast carcinogenesis, and in growth, angiogenic, inflammatory and immune factors that the daughter is exposed to *in utero*.[2] Ekbom et al.[1] linked a population-based cohort with regional and national cancer registries in Sweden to identify breast cancer cases, and abstracted preeclampsia cases from hospital birth records. Preeclampsia was associated with a nearly 60% risk reduction (OR 0.41, 95% CI 0.22–0.79) after adjustment for maternal age, socioeconomic status and parity, gestational age, 33 weeks, neonatal jaundice, twinning and birth weight. However, the study included only 14

women with breast cancer who were born of preeclamptic pregnancies. We found no association between maternal preeclampsia and breast cancer in the present study, which included almost twice as many cases. The risk estimate from the Swedish study did not even fall within the CI for the estimate we observed (0.64–1.38). Several other studies with limited numbers of women diagnosed with breast cancer who were born of preeclamptic pregnancies have reported reduced effect estimates, but none were statistically significant.[16-18] The lack of an association with preeclampsia in our data and the positive finding in the Swedish study[1] may be due to a difference in the etiology of preeclampsia in the two studies. The Swedish study's[1] cases were diagnosed from 1874 to 1954, and those in our study were diagnosed from the 1960s to the present. It is possible that overweight and other lifestyle factors may play a larger role in more recently diagnosed preeclampsia than in preeclampsia diagnosed in the past. Also, during the Swedish study period, a substantial proportion of births were delivered at home and those with preeclampsia were referred to the hospital. Thus, the cases in that study likely were enriched with more severe preeclampsia. As well, underascertainment of preeclampsia in our data could have influenced our results, although the prevalence of preeclampsia in the controls in our study, while lower than the prevalence in the United States,[19] may be in line with what would be expected in Scandinavia given the lower prevalence of obesity, a risk factor for preeclampsia, and the primarily Caucasian population, in the latter. In Norway, the rate of preeclampsia was about 2% in 1967–1974 increasing to 3.5% in 1985.[20] A systematic bias is unlikely, as identification of preeclampsia cases should be unrelated to breast cancer risk; random misclassification could have biased our results towards the null.

Study strengths include nearly complete ascertainment of breast cancer in the Scandinavian cancer registries. As well, information on perinatal factors was based on mandatory reporting of birth information. However, despite pooling of all data available from three countries, the number of exposed cases for some factors (primarily pregnancy complications) was low. The main reason was that the registries were established too recently to allow evaluation of breast cancer in women over the age of 40 years. During the next decade, the number of cases recorded in the registries will increase exponentially, improving our ability to evaluate this association. Another concern is that the histology of tumors in the young cases included in our study may differ from that of tumors occurring in older women, among whom cancer incidence is highest. Recent U.S. data suggest that over the last two decades estrogen receptor positive (ER1) cases have increased in younger women (<,40 years), whereas ER1 rates in older women have remained constant.[21] Available data also suggest that the etiology of tumors developing in very young women may have a distinct etiology.[22] Family history of early onset breast cancer is strongly associated with breast cancer risk among very young women,[22] indicating that genetics plays a larger role in development of these tumors. Therefore, we cannot exclude the possibility that perinatal factors are associated with breast cancer in older women.

It should also be noted that we lacked information on established adult risk factors for breast cancer, although it is unlikely that these would be associated with the perinatal factors examined. Studies to date have shown no evidence that adult risk factors confound the association between birth weight and breast cancer.[13,23]

Circulating concentrations of a number of pregnancy hormones, including estrogens, increase as a pregnancy progresses. Levels of other hormones peak earlier in pregnancy and then decline. For this reason, the amount of time spent in utero has been hypothesized to affect the breast through duration of hormone exposure. Alternatively, metabolism of reproductive hormones may be enhanced in pregnancies destined for premature delivery.[24] Like our study, the majority of previous studies have shown no consistent association between gestational age at birth and risk of breast cancer,[25] although two Swedish studies

evaluating the effect of extreme prematurity found increased breast cancer risk in women born at 33 weeks of gestation or earlier.[1,26] However, the later Swedish study included only three breast cancer patients who were born extremely prematurely. In contrast, a Swedish study of female twins found a positive association between gestational age and breast cancer and no increase in risk with preterm birth.[27] A linked registry study conducted in New York state showed a substantially *reduced* breast cancer risk in daughters born before 33 weeks, after adjustment for birth weight and other pregnancy and neonatal characteristics.[17] An earlier study observed no association for preterm births but suggested an increased risk for higher gestational age.[16] These inconsistent results may be explained in part by reasons for preterm birth, which include a mixture of premature rupture of membranes, infection, preeclampsia and other placental complications. Attempts to evaluate these factors in the present study were limited by small numbers.

Our data showed a slight increase in breast cancer risk with increasing maternal age, though the trend was not statistically significant. Modestly increased risks have been observed for daughters born to older mothers in some, but not all studies,[25] and another study[28] also showed a small increase in risk with rising paternal age at the daughter's birth. Birth order generally has not been associated with breast cancer risk.[25] One study[29] did report an inverse association between number of older sisters and risk, though not for number of older brothers, number of younger siblings, sibship, gender ratio or total sibship size. Our data showed no association between breast cancer risk and birth order.

Some studies, unlike ours, have observed a slight increase in breast cancer risk among women born of a multiple gestation.[25] Our findings were limited by small numbers of twins. Results from twin registries, with larger sample sizes, have been mixed. In a study based on the Danish Twin Registry,[30] twins were at a higher risk of breast cancer compared with the general population. In contrast, the Finnish Twin Registry showed lower breast cancer rates in female twins than in the general population.[31] During the time period we studied, the Scandinavian birth registries lacked information on zygosity, but dizygotic twins would account for most multiple gestations recorded in the birth registries. An examination of the zygosity of twins based on the Swedish Twin Registry, showed some evidence of elevated breast cancer risk for dizygotic but not monozygotic twins compared with both the population[32] and with singleton births.[1] Still, in a study among same-sex twins based on the Swedish Twin Registry, breast cancer risk was found to be higher in monozygotic than dizygotic twins, suggesting that the disease has a genetic component, particularly among younger cases.[33]

Evidence for a positive association between birth size and breast cancer risk is accumulating, and research should continue to focus on understanding the underlying pathogenic mechanism. Our data did not indicate associations with other maternal and perinatal characteristics. Although data from birth registries provide unbiased information to characterize pregnancies, the time period since the registries' establishment is only now becoming long enough to assess cancer risk in older populations. The next decade will provide increasing opportunities to study rare, perinatal exposures with breast cancer risk among women in a greater age range.

References

1. Ekbom A, Hsieh C-C, Lipworth L, Adami H-O, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst. 1997; 89:71–76. [PubMed: 8978409]
2. Troisi R, Potischman N, Hoover RN. Prenatal risk factors for breast cancer: exploring the underlying mechanisms. Cancer Epidemiol Biomarkers Prev. 2007; 16:1700–1712. [PubMed: 17855685]

3. Vatten LJ, Romunstad PR, Holmen TL, et al. Intrauterine exposure to preeclampsia and adolescent blood pressure, body size and age at menarche in female offspring. Obstet Gynecol. 2003; 101:529–533. [PubMed: 12636958]
4. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. Lancet Oncol. 2007; 8:1088–1100. [PubMed: 18054879]
5. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register – a sample survey for year 1998. Acta Oncologica. 2009; 48:27–33. [PubMed: 18767000]
6. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009; 45:1218–1231. [PubMed: 19091545]
7. Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prev. 2002; 11:359–364. [PubMed: 12195162]
8. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstetricia et Gynecologica Scandinavia. 2000; 79:435–439.
9. Socialstyrelsen. Medicinska födelseregistret. 2009 Retrieved September 7, 2009, from http://www.socialstyrelsen.se/Statistik/statistik_amne/graviditet/MFR.htm.
10. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med. 1990; 18:143–148. [PubMed: 2367825]
11. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull. 1998; 45:320–323. [PubMed: 9675544]
12. Maršál K, Persson P-H, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Pædiatr. 1996; 85:843–848.
13. Silva dos Santos Silva I, De Stavola B, McCormack V, Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk ofBreast Cancer. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS Med. 2008; 5:e193. [PubMed: 18828667]
14. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000; 152:514–527. [PubMed: 10997541]
15. Tamimi RM, Eriksson L, Lagiou P, et al. Birth weight and mammographic density among postmenopausal women in Sweden. Int J Cancer. 2010; 126:985–991. [PubMed: 19642103]
16. Sanderson M, Williams MA, Daling JR, et al. Maternal factors and breast cancer risk among young women. Paediatric Perinatal Epidemiol. 1998; 12:397–407.
17. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol. 2000; 152:1121–1128. [PubMed: 11130617]
18. Lahmann PH, Gullberg B, Olsson H, et al. Birth weight is associated with postmenopausal breast cancer risk in Swedish women. Br J Cancer. 2006; 91:1666–1668. [PubMed: 15477861]
19. Tucker MJ, Berg CJ, Callaghan WM, Hsai J. The black-white disparity in pregnancy-related mortality from 5 conditions: differences in prevalence and case-fatality rates. Am J Public Health. 2007; 97:247–251. [PubMed: 17194867]
20. Klungsøyr K, Morken NH, Irgens L, Vollset SE, Skjaerven R. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. Paediatr Perinat Epidemiol. 2012; 26:190–198. [PubMed: 22471678]
21. Anderson WF, Katki HA, Rosenberg PS. Incidence of Breast Cancer in the United States: current and future trends. J Natl Cancer Inst. 2011; 103:1397–1402. [PubMed: 21753181]
22. Althuis MD, Brogan DD, Coates RJ, et al. Breast cancers among very young premenopausal women (United States). Cancer Causes Control. 2003; 14:151–160. [PubMed: 12749720]
23. Oberg S, Cnattingius S, Sandin S, Lichtenstein P, Iliadou A. Birth weight-breast cancer revisited: is the association confounded by familial factors? Cancer Epidemiol Biomarkers Prev. 2009; 18:2447–2452. [PubMed: 19690178]
24. Tapanainen J, Koivisto M, Vihko R, Huhtaniemi I. Enhanced activity of the pituitary-gonadal axis in premature human infants. J Clin Endocrinol Metab. 1981; 52:235–238. [PubMed: 6780586]
25. Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. Cancer Causes Control. 1999; 10:561–573. [PubMed: 10616825]

26. Ekbom A, Erlandsson G, Hsieh C, et al. Risk of breast cancer in prematurely born women. J Natl Cancer Inst. 2000; 92:840–841. [PubMed: 10814680]
27. Hübinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer. 2001; 91:248–251. [PubMed: 11146453]
28. Hemminki K, Kyyrönen P. Parental age and risk of sporadic and familial cancer in offspring: implications for germ cell mutagenesis. Epidemiology. 1999; 10:747–751. [PubMed: 10535790]
29. Titus-Ernstoff L, Egan KM, Newcomb PA, et al. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2002; 11:207–210. [PubMed: 11867509]
30. Holm, NV.; Gedda, L. Twin Research 3: Epidemiological and Clinical Studies. Alan R. Liss, Inc.; New York.: 1981. Studies of cancer etiology in the Danish Twin Population. I. Breast cancer; p. 211-216.
31. Kaprio, J.; Teppo, L.; Koskenvuo, A.; Pukkala, E.; Gedda, L. Twin Research 3: Epidemiological and Clinical Studies. Alan R. Liss, Inc.; New York: 1981. Cancer in the adult same-sex twins: a historical cohort study; p. 217-223.
32. Braun MM, Ahlbom A, Floderus B, Brinton L, Hoover RN. Effect of twinship on incidence of cancer of the testis, breast and other sites (Sweden). Cancer Causes Control. 1995; 6:519–524. [PubMed: 8580300]
33. Ahlbom A, Lichtenstein P, Malmström H, et al. Cancer in twins: genetic and nongenetic familial risk factors. J Natl Cancer Inst. 1997; 89:287–293. [PubMed: 9048832]

Table 1

Number of breast cancer cases and controls by country and age group

Age at diagnosis (years)	Norway		Sweden		Denmark	
	Cases	Controls	Cases	Controls	Cases	Controls
<20	7	70	7	70	2	20
20–24	24	240	26	260	14	140
25–29	108	1080	137	1370	56	560
30–34	276	2760	223	2230	58	580
35–39	352	3520	30	300	0	0
40–43	99	990	0	0	0	0
Total	866	8660	423	4230	130	1300

Table 2

Risk estimates for perinatal factors and breast cancer among daughters in pooled data from Norway, Sweden and Denmark

Characteristics	Cases (*n* = 1419) *n* (%)	Controls (*n* = 14,190) *n* (%)	RR	95% CI
Maternal education (years) *				
<12	269 (70.8)	2663 (69.5)	1.00	–
12+	111 (29.2)	1167 (30.5)	0.94	0.75–1.19
Missing	43	400		
Gestational duration (weeks)				
Per week	1320	13,253	1.01	0.99–1.04
<37	59 (4.5)	635 (4.8)	0.91	0.69–1.20
37–40	807 (61.1)	7926 (59.8)	1.00	–
41+	454 (34.4)	4692 (35.4)	0.95	0.84–1.07
Missing	99	937		
Birth weight (g)				
Per 500 g	1416	14,174	1.07	1.02–1.13
<2500	63 (4.5)	617 (4.6)	0.99	0.76–1.29
2500–3999	1154 (81.5)	11,147 (82.7)	1.00	–
4000+	199 (14.1)	1773 (12.5)	1.14	0.98–1.34
Missing	3	16		
SGA				
No	1238 (95.6)	12,302 (94.9)	1.00	–
Yes	57 (4.4)	656 (5.1)	0.86	0.66–1.14
Missing	124	1232		
LGA				
No	1249 (96.5)	12,604 (97.3)	1.00	–
Yes	46 (3.6)	354 (2.7)	1.31	0.96–1.79
Missing	124	1232		
Birth length (cm)				
Per cm	1414	14,125	1.07	1.01–1.14
<49	241 (17.0)	2679 (19.0)	0.88	0.76–1.03
49–52	979 (69.2)	9623 (68.1)	1.00	–
53+	194 (13.7)	1823 (12.9)	1.05	0.89–1.23
Missing	5	65		
Ponderal index				
Per unit (kg/m^3)	1413	14,120	1.01	0.99–1.02
<25	329 (23.3)	3376 (23.9)	0.99	0.86–1.13
25–29.9	916 (64.8)	9290 (65.8)	1.00	–
30+	168 (11.9)	1454 (10.3)	1.17	0.99–1.39
Missing	6	70		
Maternal age (years)				
Per 5 years	1491	14,910	1.04	0.96–1.09
<25	577 (40.7)	6087 (42.9)	1.00	–

Characteristics	Cases (*n* = 1419) *n* (%)	Controls (*n* = 14,190) *n* (%)	RR	95% CI
25–29	488 (34.4)	4669 (32.9)	1.10	0.97–1.25
30–34	238 (16.8)	2316 (16.3)	1.09	0.93–1.27
35+	116 (8.2)	1118 (7.9)	1.09	0.89–1.35
Missing	0	0		
Birth order				
First born	586 (41.3)	5820 (41.0)	1.00	–
Later born	833 (58.7)	8370 (59.0)	0.99	0.89–1.10
Missing	20	0		
Multiple gestation				
Singleton	1395 (98.3)	13,895 (97.9)	1.00	–
Multiple	24 (1.7)	295 (2.1)	0.81	0.53–1.23
Missing	0	0		
Delivery type				
Vaginal	1352 (95.3)	13,518 (95.3)	1.00	–
Cesarean section	67 (4.7)	672 (4.7)	1.00	0.77–1.29
Missing	0	0		
Maternal bleeding**				
No	1268 (98.4)	12,616 (97.9)	1.00	–
Yes	21 (1.6)	274 (2.1)	0.76	0.49–1.19
Missing	0	0		
Retained placenta				
No	1400 (98.7)	14,013 (98.7)	1.00	–
Yes	19 (1.3)	177 (1.3)	1.07	0.67–1.73
Missing	0	0		
Pregnancy anemia**				
No	1279 (99.2)	12,786 (99.2)	1.00	–
Yes	10 (0.8)	104 (0.8)	0.96	0.50–1.85
Missing	0	0		
Preeclampsia				
No	1390 (98.0)	13,880 (97.8)	1.00	–
Yes	29 (2.0)	309 (2.2)	0.94	0.64–1.38
Missing	0	1		
Hyperemesis**				
No	1277 (99.1)	12,801 (99.3)	1.00	–
Yes	12 (0.9)	89 (0.7)	1.35	0.74–2.48
Missing	0	0		

CI, confidence interval; LGA, large for gestational age; RR, relative risk; SGA, small for gestational age.

*From Sweden only.

**From Sweden and Norway only.