Early-life risk factors for breast cancer – prospective follow-up in the Northern Finland Birth Cohort 1966

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Abstract

Background: While some risk factors for breast cancer have been confirmed, less is known about the role of early biological and social risk factors for breast cancer in adult life.

Methods: In a prospective follow-up in the Northern Finland Birth Cohort 1966 consisting of 5308 women, 120 breast cancers were reported via national registers by the end of 2018. Early risk factors were examined with univariate and multivariate analyses using Cox regression analysis. The main results are reported with hazard ratios (HR) and their 95 % confidence intervals (CI).

Results: In the multivariate-adjusted models, women whose mothers lived in urban areas (HR 1.68; 95 % CI, 1.13–2.51) during pregnancy, were low-educated (HR 2.40; 95 % CI, 1.30–4.45) and had been diagnosed with breast cancer (HR 1.97; 95 % CI, 1.09–3.58), had a higher risk for breast cancer in adult life. Lower BMI at the age of 14 associated nonsignificantly with the risk of breast cancer (Mann-Whitney U test, $P = 0.087$). No association between birth size and breast cancer risk in adult life was found.

Conclusions: Early-life residence and socioeconomical conditions may have an impact on developing breast cancer in women in adult life. All breast cancer cases of this study were relatively young and most of them are assumed to be premenopausal.

Impact: This study is one of a few prospective birth cohort studies to examine early-life socioeconomic factors and breast cancer risk in adult life. This study is limited due to small number of cases.

Introduction

Age, genetic and reproductive factors have a significant role in predicting breast cancer risk. The number of menstrual cycles during a woman's lifetime (age of menarche, age of first pregnancy, parity and onset of natural menopause) is strongly connected to higher risk of both premenopausal and postmenopausal breast cancer (1, 2). Of the early factors, some studies have shown a positive connection between birth length (3-7) and birth weight (3, 6, 7) and risk of breast cancer. The connection between birth weight and risk of breast cancer has been found particularly among premenopausal women (8, 9) but this has not been observed in all studies (5, 10). Overweight before puberty and adolescence is associated with lower risk of premenopausal breast cancer (11-13). Along with antenatal period, the time-period between menarche and the first delivery of a child may have a strong impact on developing breast cancer. Physical activity during early-life, especially between menarche and the first pregnancy, has been considered as a protective factor for breast cancer (14, 15). Several epidemiological studies have stated that smoking during youth and before the first delivery of a child is strongly connected with increased risk of breast cancer (16-18). Alcohol consumption, especially before the first birth, has been associated with higher breast cancer risk (19, 20). According to previous studies, the association between maternal smoking and breast cancer in offspring is inconsistent (21, 22).

Higher education level has been associated with higher incidence of breast cancer which may be explained by reproductive factors such as giving birth fewer times and more frequent use of hormone therapy and alcohol (23, 24). Only a few studies have addressed the impact of individuals' early-life socioeconomic backgrounds, for example via parental education and occupation characteristics, on breast cancer risk in offspring in adult life (25, 26). Although multiple risk factors for breast cancer have been determined, the role of antenatal period and birth in breast cancer in adult life is less studied. Our aim was to investigate possible socioeconomic and biological early-life risk factors for breast cancer in a unique prospective 52-year-long birth cohort study.

Materials and Methods

Study design and population

The Northern Finland Birth Cohort 1966 (NFBC1966) is a population-based epidemiologic study of people who were expected to give birth in the northernmost provinces of Finland

during 1966. A total of 12 527 children were born in the northernmost provinces during 1966 and NFBC1966 represented 96.3 % of all births in the area. Initially, the purpose of this birth cohort study was to research risk factors leading to preterm birth and intrauterine growth retardation. (27). Acquisition of the data was initiated during pregnancies by midwives in local antenatal clinics in 1965. The questionnaire was filled in from the 24th to 28th gestational week or if not possible then, later during the pregnancy or after delivery (10.1 % of mothers). At the age of 14, the information of health, lifestyle habits, socioeconomic status and situation of parents was collected using postal questionnaires (coverage 93.6 % of the target population). The postal questionnaire was first sent to the children and then if they did not respond to their parents. If neither of them responded, the same questionnaire was sent to the regional school offices and to the school health nurses.

Reported breast cancer cases were collected from the Care Register for Health Centre (CRHC) administered by the National Institute for Health and Welfare (28) and registers of the Social Insurance Institution of Finland and Finnish Center of Pensions based on the International Classification of Diseases (ICD-10), where invasive breast cancer cases (C50.0 - C50.9) were included in the analysis (29). CRHC is generally known to be suitable for research purposes (30), and, in our study, it was used instead of the Finnish Cancer Registry because CRHC covered all the cases and with CRHC we were able to get a longer follow-up (until the end of 2018), while the cancer data received from Finnish Cancer Registry ended by the end of 2013. Parental cancers were reported by the CRHC and Finnish Center of Pensions. The National Digital and Population Data Services Agency reported the data regarding emigration and cause of deaths by 1 May 2017 and individuals' childbearing history by 1 June 2016 (31). All information from national registers was linked to cohort data using personal identification numbers. The NFBC1966 study has been approved by the Ethical Committee of the Northern Ostrobothnia hospital district.

We restricted the study population to women who have been alive and living in Finland at the age of 25. A detailed exclusion process is presented in Figure 1. As a result, 5308 women were included in the final study. The follow-up time started from 25th birthday and ended at death, emigration, breast cancer diagnosis or the end of the follow-up period on 31 December 2018, depending on whichever came first. Overall, the maximum prospective follow-up time was 28 years.

Risk factor assessments

In this study, we focused on risk factors occurring in an individual's early life. The analysis included variables expressing socioeconomic status (SES) of an individual's parents such as mother's marital status (married, unmarried/divorced/widow), mother's education level (low 0–4 years, intermediate 5–8 years, high 9 years or more) (32), mother's occupation status (caregiver etc., manager or small business owner, worker, farmer or farmer's spouse), father's occupation status (no occupation/worker/farmer or farmer's spouse, manager or small business owner), mother's place of residence (urban, rural), parent's connections to farming (farmer or farmer's spouse, no connection to farming), and ownership of farm animals (yes, no). Mother's mood during pregnancy (normal, depressed), smoking during pregnancy (never-smoked, smoked daily during 12 months before the pregnancy but ended, continued during pregnancy) were also collected.

Maternal malignancies (no malignancies, maternal malignancies other than breast cancer, maternal breast cancer) and paternal malignancies (yes, no) were reported by the national registers described above. Paternal and maternal age at the time of birth (continuous), maternal height (continuous), maternal BMI before pregnancy (continuous) and birth characteristics of an individual were also explored. Instead of birth weight and birth height, we examined birth sizes using standard deviations (SD^c) of national population-based fetal growth standards which consider sex, weight, length, gestational age and plurality of pregnancy (33).

From the questionnaire at adolescence (age of 14) we included the following variables: individual's body mass index (BMI) (continuous), smoking (never-smoked or tried once, smoked twice or more often), drinking (never or once binge drinking, binge drinking twice or more often) and physical activity (once a week, less frequently than once a week), mother's situation (working full-time outside of home, housewife or unemployed/part-time/temporary work/sick leave/pension) and father's situation (working full-time outside of home, unemployed/sick leave/student/pension).

Statistical analysis

All categorical variables were reviewed using crosstabulation analysis with unadjusted relative risk ratios (RRs) and 95 % confidence intervals (CIs). Continuous variables were explored by comparing means and by using the Mann-Whitney U-test after testing normality with visual inspection of histograms, skewness and kurtosis's z-values and the Shapiro-Wilk

test where none of the variables meet the criteria for normal distribution when stratified by status of breast cancer. The adjustment factors used in the multivariate analyses were decided based on previous studies addressed in the Introduction. Multivariate analyses were conducted using a series of Cox's proportional hazard models (with Hazard Ratios (HR), and 95% CIs), where in model 1 we focused on factors occurring during pregnancy and birth and in model 2 we included also risk factors of individuals in later life. Model 1 included early maternal and birth characteristics (maternal malignancies, mother's place of residence and mother's education level, adjusted SD-scores for birth weight and adjusted SD-scores for birth height of an individual). In model 2 we included individuals' characteristics (smoking habits, drinking habits, physical activity, individuals' BMI) at the age of 14 and individuals' parity at the age of 24 (nulliparous, parous) (34). Level of statistical significance was set to $P < 0.05$ and all tests were two-tailed. With the current sample size and assuming proportions 33%/67% in dichotomized variable, the minimum detectable hazard ratio is 1.72 with an 80% power and 5% alpha level. Data modifying and statistical analyses were performed using SPSS Statistics Software version 25.0 (IBM Corporation, Armonk, NY, USA).

Results

A total of 120 female breast cancers were reported based on the national registers after 140209 follow-up years, cumulative incidence being 2.4 %. The median age of onset of breast cancer was 47.8 years (range 28.7–52.1), therefore, most of the breast cancer cases are assumed to be premenopausal. 113 women died and 105 emigrated between ages 25 and 51, and therefore were censored from regression analyses. One woman was diagnosed with another cancer before breast cancer and she was included in the analyses (results were similar also without this case). Among the 120 women with breast cancer 27 (22.5 %) were diagnosed within the 10 years after the last pregnancy and 70 (58,3 %) were diagnosed later. None gave birth after the breast cancer diagnosis and 23 (19.2 %) women were nulliparous.

Unadjusted results are presented in Table 1, 2 and the first column in Table 3. Maternal breast cancer was a statistically significant risk for breast cancer of an individual (RR 2.10; 95 % CI 1.22–3.61). Maternal malignancy other than breast cancer was marginally associated with increased risk in offspring (RR 1.50; 95 % CI 0.98–2.32) but paternal malignancy was not associated with a risk for breast cancer in offspring (RR 0.87; 95 % CI, 0.57–1.34). Women whose mothers lived in urban areas during their pregnancy had a higher risk for breast cancer in adult life compared to mothers who lived in rural areas (RR 1.53; 95 % CI, 1.07–2.19).

Offspring of mothers with a of low-level education had also higher risk for breast cancer, however, after rounding to 2 decimals, the association was not statistically significant (RR 1.67; 95 % CI, 1.00–2.80). Other variables were not statistically significant for risk of breast cancer. None of the continuous variables (data presented in Table 2) were significantly associated with breast cancer risk in adult life. Women diagnosed with breast cancer in adult life were thinner at the age of 14 ($P = 0.087$, Mann-Whitney U test) but statistical significance was not reached.

Mother's residency in urban areas in model 1 (HR 1.77; 95% CI 1.21–2.57) and in model 2 (HR 1.68; 95% CI 1.13–2.51) and mother's low education in model 1 (HR 2.09; 95% CI 1.22–3.55) and in model 2 (HR 2.40; 95% CI 1.30–4.45) were statistically significant after adjustment of maternal factors, birth characteristics or factors in adolescence and early adult life (Table 3). Maternal breast cancer was statistically significant in both models (HR 2.22; 95 % CI 1.28–3.87 and HR 1.97; 95 % CI 1.09–3.58, respectively). Maternal malignancies other than breast cancer did not have an association in either of the two models. None of the confounders included in Model 1 or Model 2 were statistically significant.

Discussion

In the 52-year-long prospective birth cohort study of 5308 women born in the northernmost provinces of Finland in 1966, we found that certain early-life socioeconomic factors, such as maternal place of residence during pregnancy and maternal education level, may have an indirect role in the risk for breast cancer in offspring regardless of history of maternal malignancies and multiple biological factors such as birth characteristics and parity. Consistent with prior evidence (35), history of breast cancer in first-degree family (in our study, maternal) was associated with a twofold increase risk for breast cancer in offspring.

From a socioeconomic perspective, comparing cohort studies from different areas and different periods of time may be problematic and, moreover, SES definitions are difficult to harmonize. In our study, daughters whose mothers were low educated (0–4 years) had higher incidence of breast cancer in adult life, even in multivariate models, but paternal occupation did not have an influence on breast cancer incidence in offspring. The father's education was not available in the current study. Low maternal education has not previously been linked earlier to breast cancer risk. A case-control study reported a significant result for higher paternal education (OR 1.22; 95 % CI 1.03–1.45), but the study included only

postmenopausal breast cancer (36). Two other studies found no association between paternal occupation/employment and breast cancer incidence in offspring (37, 38). Pudrovska et al. reported a significant association between mother's higher education and breast cancer in offspring (HR 1.23; $p < 0.05$) (39), however, in a Scandinavian register-based study of perinatal characteristics in relation to breast cancer risk the effect of maternal education remained insignificant (4). Two studies have found an association between family income and increased breast cancer incidence in offspring (39, 40). Furthermore, in a study based on birth certificates, women with the highest SES at birth had higher risk of breast cancer in adulthood compared to those with the lowest SES (26). In addition, individuals with the highest SES in childhood were more likely to be diagnosed with breast cancer in adult life (HR 1.53; 95 % CI 1.07-2.19) compared to the lowest SES in an ambidirectional study (41). At least two birth cohort studies have researched if early-life socioeconomic status has effect on mammographic breast density, a well-known risk factor for breast cancer, but the results are inconsistent (42, 43).

Higher breast cancer incidence for daughters with low-educated mothers could be explained by an accumulation model where lower SES in early life leads to more intense and/or longer-lasting exposures during a lifespan (44). For example, lower SES during early life may have an association with earlier pubertal development, thus indirectly increasing the risk of breast cancer in adulthood (45, 46). However, puberty timing of our study group was not known, and moreover, no association between family SES and menarche was found in a survey and register data of randomly selected subsample of Finns born between 1966 and 1980 (47). Lower childhood SES may lead to poorer health and higher risk of cancer in adult life via quality of maternal nutrition, dietary habits during childhood and low-level physical activity (48), but physical activity was not a significant confounder in our study. On the other hand, parental education level is a decent predictor for children's attainments (39, 49) and the higher-educated have a tendency to conduct reproductive behavior favorable for risk of breast cancer (23, 50)

In our study, daughters of mothers who lived in urban areas during pregnancy were more likely to be diagnosed with breast cancer in adult life compared to those whose mothers lived in rural areas. However, we did not have data on individuals' residency throughout childhood. Some studies have observed that breast cancer incidence is higher in urban areas (51, 52). To our knowledge, only two studies have investigated the relation between residency in early life and subsequent breast cancer incidence (53, 54). A study regarding the

possible connection between fish consumption and adolescence residency and subsequent breast cancer incidence did not reveal a strong connection between residency during adolescence among women who were born in Iceland between 1908–1935, although there was an inverse association between hormone receptor-negative tumors and living in coastal areas from birth to the age of 20 years (HR 0.78; 95% CI, 0.61–0.99), which might be explained by high-frequency fish consumption (53). In a prospective French cohort consisting of 75 889 women (aged 38–66) born in urban areas, a significantly higher risk for breast cancer in adult life was seen compared to women who were born in rural areas (adjusted HR 1.07; 95 % CI 1.01–1.14). In the French study, connection between residency at birth and breast cancer in adult life was stronger than residency in adult life, which could suggest that environmental factors and exposures in early life have an important role in determining a risk profile, regardless of residency in adulthood (54). Our results are consistent with the study conducted by Binachon et al., however, neither of the previous studies were able to prospectively follow individuals from birth.

Our results of lower BMI at the age of 14 and increased breast cancer incidence are consistent with previous studies regarding of premenopausal breast cancer (11-13) although statistical significance was not reached in our material. The phenomenon has been explained by different possible pathways. One theory is an inverse link between weight and density of breast tissue developing during adolescence (55) since convincing evidence shows mammographic density is a high risk factor for breast cancer (56). Secondly, greater adipose tissue in puberty has been shown to have a connection to lower peak height growth, which also could indirectly decrease the incidence of breast cancer (13). Thirdly, childhood BMI is inversely associated with cancer-promoting insulin-like growth factor 1 hormone levels in adulthood (57, 58) and in addition, weight may inversely affect sex-hormone levels such as total estrogen levels before menopause but evidence on the connection between BMI and different sex hormone levels is inconsistent (59). Unlike previous studies, we did not find a connection between maternal and antenatal anthropometric features and breast cancer incidence in adult life. Whether this is due to inclusion of only relatively young women in our study remains unclear. Individuals' birth sizes were moderately smaller than means of national standards, however these references were constructed based on birth register data of infants born in 1996–2008 (33).

Our study has multiple strengths. First, over 50-year-old birth-cohorts are rare, and being a prospective study, the data reported can be assumed to be uninfluenced by later breast cancer

diagnosis. For example, when conducting a questionnaire from the past, individuals who have been diagnosed with cancer or some other disease might report factors affecting risk of the outcome more specifically causing recall bias. Secondly, the amount of reported cancer cases is highly reliable because of national mandatory reporting. Thirdly, the population-based nature of the sample increases the heterogeneity of the study population. In addition, almost none of the previous studies have adjusted antenatal anthropometrics with plurality and gestational age, although some have used the Ponderal Index (kg/m^3) (3, 4, 6).

Our study has several limitations. The homogeneity in Northern Finland population during the 1960s may have impact on the variance in SES. Due to relative low number of breast cancer cases, we were not able to study rare risk factors. Some of categorical variables had to be combined. Since the biological subtype of breast cancer may have an impact on early-life risk factors, the lack of knowledge of siblings' breast cancer history and the presence of possible breast cancer predisposing mutations such as BRCA1 and BRCA2 makes it difficult to differentiate the strength of possible genetic vulnerability from environmental factors. Furthermore, since the breast cancer cases in our material are relatively young and some of them have been diagnosed couple of years after individual's own pregnancy, there may have an overrepresentation of triple-negative breast cancers, which can be considered as a potential confounder in our study. We adjusted for several early-risk factors, but we were not able to adjust for some factors, such as age at menarche, use of hormonal therapy, and adulthood SES, weight, height, alcohol and tobacco use. Menopausal status was also not known. Answers on the 14-year questionnaire about tobacco and alcohol use may also include bias.

In conclusion, early-life factors such as place of residence and maternal SES may have an indirect role related to the risk of breast cancer of relatively early onset regardless of history of maternal breast cancer or other malignancies. Since these results apply especially to relatively young women, more data aggregated prospectively throughout lifetime is needed.

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Tables

Table 1. Crosstabulations and unadjusted risk ratios (RRs) for each variable.

Variable	Total n = 5308 ^a	No. of breast cancer cases n = 120 (%)	Unadjusted RR (95 % CI)
Mother's marital status			
married	5089	117 (2.3)	ref
unmarried/divorced/widow	199	3 (1.5)	0.66 (0.21–2.06)
Mother's place of residence			
rural	3541	68 (1.9)	ref
urban	1767	52 (2.9)	1.53 (1.07–2.19)
Mother's education			
high (9 years or more)	1795	39 (2.2)	1.01 (0.68–1.50)
intermediate (5–8 years)	2924	63 (2.2)	ref
low (4 years or less)	499	18 (3.6)	1.67 (1.00–2.80)
Mother's occupation			
caregiver etc.	1740	38 (2.2)	ref
manager or small business owner	667	16 (2.4)	1.10 (0.62–1.96)
worker	1579	40 (2.5)	1.16 (0.75–1.80)
farmer or farmer's spouse	1247	25 (2.0)	0.92 (0.56–1.51)
Father's occupation			
manager or small business owner	1237	29 (2.3)	ref
worker, farmer or no occupation	3839	88 (2.3)	0.98 (0.65–1.48)
Is either of parent a farmer?			
yes	1338	25 (1.9)	ref
no	3728	91 (2.4)	1.31 (0.84–2.03)
Ownership of farm animals (cows/pigs/sheep/chickens)			
yes	1518	28 (1.8)	ref
no	3790	92 (2.4)	1.32 (0.87–2.00)
Mother's mood during pregnancy			
normal	4457	101 (2.3)	ref
depressed	725	18 (2.5)	1.10 (0.67–1.80)
Was the pregnancy planned/hoped?			
appropriate time	3290	72 (2.2)	ref
should have happened later	1276	34 (2.7)	1.22 (0.81–1.82)
not at all	606	13 (2.1)	0.98 (0.55–1.76)
Maternal smoking			
never-smoked	4120	94 (2.3)	ref
smoked before pregnancy but stopped	343	6 (1.7)	0.75 (0.33–1.69)
smoked during pregnancy	670	18 (2.7)	1.18 (0.72–1.94)
Maternal malignancies			
breast cancer	368	15 (4.1)	2.10 (1.22–3.61)
other malignance than breast cancer	924	27 (2.9)	1.50 (0.98–2.32)
no malignancies	4016	78 (1.9)	ref
Paternal malignancy			
no	4030	94 (2.3)	ref
yes	1278	26 (2.0)	0.87 (0.57–1.34)
Binge drinking at the age of 14			
never or 1 time	4126	93 (2.3)	ref
twice or more often	839	21 (2.5)	1.11 (0.70–1.77)
Smoking at the age of 14			
never or 1 time	3001	70 (2.3)	ref
twice or more often	1979	44 (2.2)	0.95 (0.66–1.38)
Physical activity at the age of 14			
at least once a week	3416	80 (2.3)	ref
less frequently than once a week	1498	34 (2.3)	0.97 (0.65–1.44)
Mother's situation at the age of 14			
working full-time outside of home	1694	64 (2.4)	ref
housewife	2682	39 (2.3)	0.97 (0.65–1.43)
unemployed, part-time/temporary work, sick leave or pension	511	9 (1.8)	0.74 (0.37–1.47)
Father's situation at the age of 14			
working full-time outside of home	3797	83 (2.2)	ref
unemployed, sick leave, or student or pension	770	22 (2.9)	1.31 (0.82–2.08)

^a Number of missing data varied in variables from 0 to 741 (0–14 %).

Table 2. Characteristics of continuous variables.

Variable	Total N = 5308	Breast cancer (n = 120)		Control group (n = 5188)		Mann-Whitney U	
	Total (N)	Cases (n)	Mean (SD)	Cases (n)	Mean (SD)	Z	P-value (2- tailed)
Maternal age (years)	5307	120	27.8 (6.25)	5187	27.9 (6.65)	- 0.009	0.99
Paternal age (years)	5042	117	30.6 (7.42)	4925	31.1 (7.22)	- 0.77	0.44
Maternal height (m)	5045	112	1.60 (0.060)	4933	1.60 (0.055)	- 0.54	0.59
Maternal pre-pregnancy BMI ^c (kg/m ²)	4868	107	23.0 (3.34)	4761	23.1 (3.24)	- 0.47	0.64
Birthweight (g)	5308	120	3390 (593)	5188	3400 (549)	- 0.56	0.57
SD ^c -correction ^a	5027	117	- 0.47 (1.35)	4910	- 0.38 (1.25)	- 1.13	0.26
Birth length (cm)	5265	120	49.7 (2.16)	5145	49.8 (2.45)	- 0.55	0.59
SD ^c -correction ^b	5027	117	- 0.32 (1.19)	4910	- 0.46 (2.90)	- 1.05	0.30
BMI ^c at the age of 14 (kg/m ²)	4661	110	18.9 (2.02)	4551	19.4 (2.51)	- 1.71	0.087

^a Standard deviations (SD^c) of national population-based fetal growth standards which consider sex, weight, length, gestational age and plurality of pregnancy (33)

^b BMI = body mass index

Table 3. Hazard ratios (HRs) and 95 % confidence intervals (95 % CI) for mother's place of residence during pregnancy, mother's education level and mother's malignancies in relation to breast cancer in offspring.

Person-years		Unadjusted model (BC ^c 120)	Model 1 ^a (BC ^c 117)	Model 2 ^b (BC ^c 106)
Adjustments			1. maternal place of residence 2. maternal education 3. maternal malignancies 4. individual's birth length (SD ^c) 5. individual's birth weight (SD ^c)	1. model 1 2. individual's smoking at the age of 14 3. individual's drinking at the age of 14 4. individual's physical activity at the age of 14 5. individual's BMI ^d at the age of 14 6. individual's parity at the age of 24
Risk factors	n		HR (95 % CI)	HR (95% CI)
mother's place of residence				
rural	93,855	1.00 (reference)	1.00 (reference)	1.00 (reference)
urban	46,354	1.56 (1.09-2.24)	1.77 (1.21-2.57)	1.68 (1.13-2.51)
mother's education level				
low < 4 years	13,224	1.69 (1.00-2.85)	2.09 (1.22-3.55)	2.40 (1.30-4.45)
intermediate 5-8 years	77,838	1.00 (reference)	1.00 (reference)	1.00 (reference)
high ≥ 9 years	46,774	1.04 (0.70-1.55)	0.94 (0.63-1.42)	1.17 (0.76-1.80)
mother's malignancies				
no cancer	106,352	1.00 (reference)	1.00 (reference)	1.00 (reference)
other cancer than BC ^c	24,249	1.53 (0.99-2.37)	1.46 (0.93-2.29)	1.27 (0.78-2.09)
breast cancer	9607	2.17 (1.25-3.76)	2.22 (1.28-3.87)	1.97 (1.09-3.58)

^a Model 1 adjustment: birth weight (SD-score, continuous), birth length (SD-score, continuous)

^b Model 2 adjustment: Model 1 + individual's smoking (never-smoked or tried once, smoked twice or more often) and drinking habits (never or once binge drinking, binge drinking twice or more often) at the age of 14, physical activity at the age of 14 (at least once a week, less frequently than once a week), individual's BMI at the age of 14 (continuous), individual's parity at the age of 24 (nulliparous, parous).

^c BC = breast cancer

^d BMI = body mass index

Figure Legends

Figure 1. Excluding process for individuals based on specific criteria.

Figures

Figure 1