Birth size and survival in breast cancer patients from the Uppsala Birth Cohort Study

Running title: Birth size and survival in breast cancer patients

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Abstract

Purpose. Previous studies suggest that larger birth size is associated with a higher breast cancer incidence, but studies on birth measures and mortality in breast cancer cases are scarce. This study investigates survival of women after breast cancer diagnosis (N=437) in the Uppsala Birth Cohort born in 1915-1929. **Methods.** Cox regression was used to analyse mortality from any cause after a breast cancer diagnosis. Birth measures including gestational age (GA), birth weight (BW), BW for GA, birth length (BL) and ponderal index (PI) were converted to standard deviation (SD) scores and all analyses were adjusted for age and calendar time at diagnosis. Analyses were performed with and without adjustment for other birth measures, reproductive history and adult socio-economic position (SEP). **Results.** In fully adjusted analyses, one SD increase in GA was associated with 17% (95% CI 6%-26%) lower mortality and one SD increase in BW was associated with 29% (7%-56%) higher mortality. PI showed a weaker trend in the same direction: HR=1.16 (95% CI 1.03-1.30). **Conclusions**. Our results bring in new evidence that both high GA and low BW predict a better survival in breast cancer cases. Further studies need to investigate mediation of these associations.

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Keywords: breast cancer, birth size, mortality, case fatality, survival

Introduction

Previous studies suggest that larger birth size is associated with a higher breast cancer *incidence* [1]. In addition to the perinatal and developmental determinants of breast cancer, there are a number of well established risk factors for breast cancer which occur later in life. Many of these relate to a woman's reproductive history [2]. Earlier age of menarche and later age of menopause are both associated with higher rates of breast cancer, as is nulliparity. Conversely, the earlier a woman gives birth to her first child, the more children she has and the longer she breast feeds, the lower her risk of developing the disease. Greater adult height and weight at postmenopausal ages are also linked to increased breast cancer incidence [3]. There is no evidence that smoking affects breast cancer incidence, but alcohol is a moderate risk factor [4].

Birth weight (BW) has been extensively studied in relation to mortality. A recent meta-analysis estimated 6% (95% CI: 3%-8%) lower all-cause mortality per one kg higher BW [5]. On the contrary, one kg higher BW was associated with 13% (7%-19%) and 4% (-2% to 10%) higher cancer mortality in men and women, respectively. However, this study did not examine mortality by the type of cancer. Other birth size measures and gestational age (GA) have been less studied in relation to mortality in general and breast cancer mortality in particular.

Socio-economic factors are linked to both breast cancer incidence and survival. Women from more affluent social classes tend to have higher breast cancer incidence but lower mortality from the disease [6]. Weight in adulthood has also been found to have a bearing on breast cancer survival. In a study of over 1,200 breast cancer cases in the UK, heavier women diagnosed with breast cancer had higher all cause mortality rates than lighter women [7]. Shorter time since last child birth and last oral contraceptive use were also associated with increased mortality in the same study. However, the conclusions cannot be generalised widely as three quarters of the women included in the study were premenopausal at diagnosis whereas in general 80% of breast cancer cases are diagnosed in women over 50 years of age [8].

Earlier research into the relationship between birth measures and breast cancer has primarily evaluated incidence [1]. We identified only two published, inconclusive studies on birth measures and mortality in breast cancer cases [9, 10]. The aim of the current analysis is to extend and improve on previous research into the early life determinants of breast cancer in a cohort of Swedish women born in 1915-1929 [11, 12] by investigating long-term survival of women diagnosed as having breast cancer in relation to their birth size extracted from detailed obstetric records. We will also examine shorter-term survival by estimating 5-year breast cancer case fatality in the same population. In addition, possible confounding (or mediating) effects of reproductive history and a range of socio-economic factors measured at birth and later in life are explored.

Material and methods

Study sample

The study sample comprised women from the Uppsala Birth Cohort Study (UBCoS), born between 1915 and 1929 at the Uppsala Academic Hospital in Sweden. The analyses were restricted to women who, according to the Swedish Cancer Registry, were diagnosed with breast cancer since the Registry started in 1958. The primary outcome was chosen to be all cause mortality in the breast cancer cases. A supplementary analysis was conducted specifically on breast cancer mortality in the same women.

The analysis reported here is based on information from archives and routine registers linked at Statistics Sweden through unique personal identification numbers as a part of the Uppsala Birth Cohort Multigenerational Study [13]: 1) the original UBCoS obstetric records (date of birth, gestational age (GA), birth weight (BW), birth length (BL), birth order, mother's marital status and family social class); 2) the Swedish national censuses for 1960 and 1970 (education, occupational social class of household's main earner, personal earned gross income); 3) the Swedish Cancer Registry (date of diagnosis and characteristics of first cancer and first breast cancer); 4) the Cause of Death Register (date and cause of death); 5) the Swedish Multigenerational Register (date of birth of first biological child, number of children and date of migration) and 6) data on emigrations kept by Statistics Sweden.

Exclusions

A total of 6,781 live female births were registered at the Uppsala Academic Hospital between 1915 and 1929. As twins and triplets tend to be both smaller and lighter at birth, multiple births (N=228) were excluded from the data, leaving 6,553 singletons. 179 of these (2.7%) were lost from the follow-up before personal numbers were assigned and we thus could not trace them in the routine registers. Another 693 females (10.6%) died or emigrated before the follow-up in routine registers started in 1950s, leaving 5,681 women (87% of all singletons) to be traced and followed through the Swedish routine registers up to end 2010. The records of 476 women who had been diagnosed between 1958 and 2010 as having breast cancer were retained. Breast cancer cases who either lacked data on birth measures (N=13) or died on the day of diagnosis (N=2) or migrated before diagnosis (N=1) were excluded since they would not contribute to the main analysis or follow-up time. A total of 460 records remained to be analysed, of which 437 had complete data on socio-economic variables in adulthood.

Follow-up time scale

The start of follow up for each woman was defined as the date on which she was first diagnosed as having breast cancer from 1958 onwards. The end of follow up is defined as 31 December 2010, the last date for which data from the Swedish Cancer Registry and the Cause of Death Register were available. Individuals exited from the study on their date of emigration, date of death or on 31 December 2010, whichever occurred first.

Variable transformations

Prior to excluding the records of the women who had not been diagnosed with breast cancer, a new variable was created to contain a standardised measure of foetal growth. This was calculated as a standard deviation (SD) of BW for each completed gestational week based on the 6,553 live female singleton births, as in Kramer *et al.* (2001) [14]. This measure (BW for GA) was created in order to provide an alternative method of adjusting for GA (in addition to the conventional adjustment in the statistical model). Ponderal index (PI) was calculated from BW and BL ($PI = BW / BL^3$, expressed in kg/m^3). The key predictors of survival from breast cancer investigated were GA, BW, BW for GA, BL and PI. All of them were transformed into SD scores (z-scores) prior to the analysis. For a descriptive purpose, continuous variables were categorised.

Selection of confounding factors

The factors *initially* considered as potential confounders (or mediators) were socio-demographic birth characteristics including maternal age, maternal marital status and family social class; reproductive history of the women themselves, including number of children and age at first child; and adult socio-economic factors such as marital status, educational level, occupational social class and personal income. Preliminary analysis indicated that socio-demographic birth characteristics did not confound associations between birth size and mortality, and they were excluded from further analyses. Marital status and number of children were not found to be important confounders either, but number of children was included in the models based on literature [2].

Statistical analyses

Numbers and proportions of women and their deaths and crude mortality rates were calculated by each category of the birth measures. Cox regression was then performed on a follow-up time scale to calculate hazard ratios (HR) and their 95% confidence intervals (CIs) for death from any cause after a breast cancer diagnosis until the end of 2010. Adjustments were sequentially done in four steps: 1) All analyses were adjusted for age and calendar time at diagnosis; 2) analyses of birth size (BW, BL, PI) were additionally adjusted for length of gestation (GA), and 3) analyses were further adjusted for other birth size variables as appropriate (i.e. GA for both BW and BL; BW and (BW for GA) for BL; and BL for BW), and finally 4) all analyses were further adjusted for other potential confounding (or mediating) variables: age at first child, number of children, adult occupational social class in 1960, educational level at 1970 and personal income at 1970.

To investigate short-term survival after breast cancer diagnosis, we also performed an analysis of breast cancer case fatality up to 5 years of follow-up. Women who died within 5 years of diagnosis were defined as cases and women who were followed up for at least 5 years without censoring as controls (total N=446). Logistic regression with the same steps of adjustments was performed in this sub-set.

We also analysed all-cause mortality in singleton women from age 35 years onwards in the same cohort in relation to birth size (N=5,599), to examine if our findings reflect a more general association between birth size and mortality rather than a specific association with breast cancer. This was done using Cox regression on the age time scale, but with follow-up being restricted to age 35 years onwards – equivalent to the earliest age at breast cancer diagnosis in this cohort - to ensure comparability with the sub-group of diagnosed cases, and also to exclude known effects of birth measures on infant mortality [15].

To further investigate if associations between birth size and survival in breast cancer cases differ by occupational social class in 1960 or age at diagnosis (pre- vs. post-menopausal using age 50 years as a cut-off), analyses with interaction terms and stratified analyses were performed. Another additional analysis was performed using breast cancer death (N=171) as an outcome instead of death from all causes (N=311). Finally, the main analyses were repeated in the group of women with no other previously diagnosed cancers (N=431) to make sure that other types of cancer that were diagnosed prior to breast cancer in 29 of the 460 breast cancer cases did not affect the estimates.

Investigation of model assumptions

The linearity of the association between continuous variables and mortality was investigated using Martingale residual plots, and by formally testing the statistical significance of a quadratic term in the model. Proportionality of hazards assumption was investigated graphically using Nelson-Aalen plots, and by using a statistical test based on Schoenfield residuals.

The study was approved by the Regional Ethics Committee in Stockholm.

Results

The study population comprised 460 women from the UBCoS who were diagnosed with breast cancer between 1958 and 2010 (the first diagnosis was 15 May 1958 and the last 14 November 2008), and were followed up until the end of 2010. The median age at the time of breast cancer diagnosis was 67 years; only 15% of the women were less than 50 years old at diagnosis (Table 1). A total of 311 of the women (68%) died before the end of follow up. The median follow-up time of women who died and of women who were censored (i.e. emigrated during follow-up or were alive at the end of follow-up) was 8.0 years and 16.7 years, respectively. Breast cancer was classified as the cause in 171 of these deaths (55%).

The numbers and proportions of women and their deaths are given in Table 1 by categorised birth measures and confounding (or mediating) variables. The deaths are given 1) up to 5 years of follow-up (for women who were not censored before) and 2) up to the end of follow-up for all women. There was a downward trend in the proportion of deaths by increasing GA, whereas for BW the trend was upward. For BL and PI no clear trend was observed. Women diagnosed before their 50th birthday or in their 70's or later had a higher proportion of deaths within 5 years of diagnosis than women diagnosed in their 50's or 60's. The corresponding figures for a long-term survival are harder to interpret for women diagnosed in their 70's or later due to censoring at the end of the study. The proportion of deaths up to 5 years of follow-up was highest in women diagnosed in 2000 or later, but this may largely be explained by the higher age of these women. In the long-term follow-up, there was a decreasing trend of deaths over calendar time possibly due to earlier diagnosis and improved treatment, although the figure for 2000-2010 is not comparable to other calendar periods due to high proportion of censored observations. The proportion of deaths was higher in women who had their first child after age 30 and in women with no children but the number of children among the mothers did not show a trend. No clear trends were seen between socio-economic characteristics and proportion of deaths at 5 years or long-term, which may partly be due to low numbers in some of the categories.

The overall crude mortality rate was 51 (95% CI 45-57) per 1,000 person-years. Crude mortality rates by categories of birth measures are not reported here due to a strong confounding by age at diagnosis and calendar year. As expected, there were positive trends between age and calendar time at diagnosis and mortality rate, although a lower proportion of women diagnosed in an old age or within the last decade of follow-up had died by the end of 2010.

The results of the Cox regression analyses for all cause mortality and birth measures are given in Table 2. GA was the only birth characteristic to be statistically significantly ($p<0.05$) associated with survival in the model adjusted only for age and calendar time at diagnosis. Mortality was 14% (95% CI 5%-23%) lower for each SD increase in GA, and the linear association persisted after adjustments for BW, BL and other confounding/mediating variables. On the contrary, higher BW (adjusted for GA in two different ways) was linearly associated with 10% higher mortality for each SD increase in BW and this association strengthened to 22% after adjustment for birth length and further to about 29% after adjustment of other confounding/mediating variables. There was no evidence for a relationship between BL and mortality, but higher PI was associated with 16% (95% CI 3%-30%) higher mortality in the fully adjusted model.

Among the confounding (or mediating) variables in the fully adjusted model, higher age at birth of first child (p=0.03), lower social class (occupational social class in 1960, p=0.05), lower level of education in 1970 (p=0.05), and higher age at diagnosis (p<0.0001) and calendar time at diagnosis (p=0.0013) were associated with poorer survival in women with breast cancer (data not included in the tables). For example, women from manual social class had 34% (95% CI 1%-79%) and women from self-employed social class had 61% (95% CI 11%-234%) higher mortality than women from non-manual social class. Higher personal income had a borderline association with a higher mortality (p=0.07). The association between calendar time and mortality was non-linear, indicating that women diagnosed in the 1980's had the highest mortality. Proportionality of hazards assumption was reasonable in all models ($p \geq 0.01$) and best satisfied in the fully adjusted models ($p \geq 0.50$).

Associations between birth size and 5-year breast cancer case fatality were similar to associations between birth size and longer term mortality in breast cancer cases in terms of effect sizes (Table 2). However, random error in the estimates from the case fatality analyses was much higher due to a shorter follow-up. The estimate for GA was similar (about 15% lower mortality for 1 SD increase in GA) in both analyses, but in the case fatality analyses this effect was not statistically significant.

None of the birth measures was significantly associated with general mortality in singleton women from age 35 years in the same cohort, with or without adjustments for the same confounders as used in the analysis of breast cancer patients (data not shown).

Stratified and interaction analyses (data not shown) indicated that the inverse trend between GA and mortality was somewhat stronger in the combined group of manual, unemployed and self-employed compared to non-manual / supervisor group (HR=0.71 (95% CI 0.59-0.85) vs. HR=0.93 (95% CI 0.81-1.07)) per 1 SD increase in GA adjusted for age and calendar time, interaction p=0.034). Associations between other birth measures and mortality were similar between occupational social classes in 1960.

Associations between birth measures and mortality did not differ between pre- and post-menopausal women (data not shown), however, statistical power to detect interactions was very limited due to the small number of pre-menopausal women (N=69). Results from the analysis where breast cancer death was used as an outcome instead of death from all causes were in the same direction but generally weaker, mostly due to a lower statistical power. The crude death rate and the association estimates from the main analyses remained similar after removing 29 women with other previously diagnosed cancers from the data set.

Discussion

The aim of this analysis was to establish the effect of gestational age and birth size on survival after diagnosis with breast cancer. One SD increase in GA was consistently associated with an estimated 14-17% decrease in mortality, regardless of adjustments for other variables. BL did not show a statistically significant association with mortality in any of the analyses. Higher BW was associated with higher mortality, but only after adjustments for GA and BL. Lower occupational social class, lower educational level, higher age at first child, higher age at diagnosis and calendar time at diagnosis were also associated with higher mortality in breast cancer patients.

Interpretation of the findings and comparison with previous studies

After adjusting for reproductive history and socio-economic characteristics in adulthood, we observed a linear positive relationship between BW and mortality (inverse with survival). Although associations with incidence and mortality are not necessarily expected to align, it is worth noting that findings from earlier research into breast cancer incidence in the UBCoS and other studies are in the same direction [1, 11, 12]. The observed association between BW and survival became stronger after an adjustment for BL, which indicates that the effect may rather relate to adiposity than linear growth. Consistent with this interpretation a similar, albeit slightly weaker, association was also observed for PI in relation to survival.

A previous study in UBCoS indicated decreasing incidence of breast cancer by increasing GA [11], again in the same direction as our finding of improved survival by increasing GA. However, the inverse association between GA and breast cancer incidence was only seen in premenopausal women [11]. In a large pooled analysis, no association between GA and breast cancer incidence was observed [1]. Our analysis with general mortality indicated that our finding of improved survival by increasing GA is specific to breast cancer patients. The estimate was similar regardless of adjustments and the length of follow-up.

Our fully adjusted model included potential confounders as well as mediating factors which could be situated on the causal pathway between size at birth and survival. Therefore we also reported analyses unadjusted for these factors. The association between BW and mortality became slightly stronger after adjustment for potential confounding (or mediating) factors. This may be explained by tracking of SEP from childhood to adulthood and the fact that BW is lower in low SEP groups which also have a higher mortality. The adjustment for adult SEP will then strengthen the observed positive association between BW and mortality in breast cancer cases, due to negative confounding. It appears that age at diagnosis, educational level and personal income also introduce negative confounding between BW and mortality, and the full effect of size at birth is concealed if they are not adjusted for. The fully adjusted model is therefore the most informative of the models considered in this study.

The associations observed between gestational age and birth size with survival were linear in this study. Pre-diagnostic weight status in adulthood has been reported to have a non-linear effect on survival in breast cancer patients in some studies, underweight and morbidly obese women having the highest all-cause mortality [16]. If the BW association with mortality was entirely mediated by later body size, one would expect to see a similar non-linear association between BW and survival. However, there might be other pathways of mediation of effects of early growth on survival. Also, the non-linear shape of the association between pre-diagnostic weight status and mortality may not be present or be equally strong in all populations. Pre-diagnostic weight may also be prone to measurement error, especially when self-reported data have been used which is often the case [16]. In this study, we did not have data on pre-diagnostic weight.

We identified only two previous studies that had investigated the association between birth size and survival after a breast cancer diagnosis. An American study that examined associations between perinatal characteristics and survival in breast cancer patients involved a subset of 1,024 cases from a case-control study and thus used potentially unreliable retrospective methods of obtaining information on birth characteristics (including proxy respondents for women who had already died) as well as being subject to selection bias [9]. Furthermore, the original case-control study was restricted to women diagnosed with breast cancer before the age of 45. Differences in associations with survival between pre- and postmenopausal women could therefore not be explored. The study suggested higher all-cause mortality in women diagnosed with breast cancer and born with a high BW (≥4,000g), HR=1.8 (95% CI: 1.0-3.1). Since 92% of these deaths were breast cancer related, the results were similar for cause-specific mortality. The median follow-up time in this study for living cohort members was 12.3 years. Our study in older women (85% over 50 years at diagnosis) shows BW association in the same direction. Another study of 311 breast cancer cases diagnosed in Norway suggested a poorer survival in breast cancer patients with a high BL (≥52 cm), HR=1.9 (1.1-3.4), but did not find clear associations with BW or PI [10]. This study used death from breast cancer as an outcome, and the median follow-up time in the study was 9 years. The results from our study are in contradiction with this study. However, we cannot draw strong conclusions due to the limited statistical power in both studies.

Previous studies in our cohort identified a linear positive association between birth size and breast cancer incidence only in premenopausal women [11, 12]. As only 69 (15%) of the 460 participants in the current study were diagnosed with breast cancer prior to age 50, the lack of evidence for differences between premenopausal and postmenopausal women in terms of survival could be attributed to insufficient statistical power. However, the findings from this study are consistent with results from the American study of exclusively premenopausal women [9] which found that higher BW impaired survival, suggesting that the survival experiences of premenopausal and postmenopausal women may be very similar.

The increased survival prospects in this study of women from households where the main earner was a non-manual or supervisory worker is consistent with previous research which has shown that women from more affluent social classes have improved breast cancer survival. The finding that larger personal income adjusted for social class and education impaired survival is unexpected. This effect was, however, only borderline significant (p=0.07) and we speculate that if it is real, it may reflect number of hours worked and could be a proxy for stress or relate to women who are too busy to engage with health care services rather than an effect of income per se.

Strengths and limitations of the analysis

The main strength of this analysis was the quality of the data. Obstetric measures such as BW and BL were taken from medical records. As they were measured and recorded at the time, they cannot be subject to recall bias. GA, though, was calculated on the basis of the women's last menstrual period and is therefore subject to possible misclassification. Some researchers have suggested that ultrasound scans, which were obviously not yet developed in 1929, are a slightly more accurate measure of GA [17].

Selection bias may affect the external validity of the results because only 60% of people in the Uppsala region gave birth in hospital during the period in which this data were collected. People who lived closer to the hospital are more likely to have given birth there, as were poor women. At the time, hospital delivery was free whilst women wanting a home birth had to pay a midwife to attend [15]. However, the original cohort was representative of the Uppsala region and Sweden in 1915-1929 in terms of infant mortality [18]. Selection bias should not have affected the internal validity of the results as there were few losses to follow up from the UBCoS.

Linkage of the UBCoS with Swedish national census information enabled the analysis to be adjusted for reproductive history and a wide range of potential socioeconomic confounders. Nevertheless, this does not rule out the possibility of residual confounding. Subsequent height and weight measurements from infancy would have been useful in assessing potential mediation of the associations via rapid weight gain particularly in babies with low GA. Furthermore, data on alcohol consumption, an established risk factor for breast cancer incidence, were not available. Data on adult height and post-menopausal weight were also not available. Both measures are associated with increased breast cancer incidence [3] and, although they could have been on the causal pathway between birth size and survival, it would nevertheless have been interesting to include them in models in order to estimate the extent to which the effects of BW and BL are mediated through them.

Our results showed robustness in various ways. The effect sizes estimates were not materially different between breast cancer mortality and all cause mortality analyses, or between analyses restricted to a 5-year follow-up and analyses of long-term survival. Also, using different methods of adjusting for GA gave similar results in the analysis of BW.

Conclusions

Our results suggest that both higher GA and lower BW (adjusted for GA and BL) predict an improved survival in breast cancer cases. This study strengthens the current evidence that size at birth is related to breast cancer survival as well as incidence. It also brings in new evidence of the relationship between GA and survival in breast cancer patients that has not been reported before. These associations persisted after adjustments for reproductive history and socio-economic characteristics. Further studies are needed to investigate in more detail how the observed associations are mediated.

List of abbreviations used

BL = Birth length

BW = Birth weight

CI = Confidence interval

GA = Gestational age

HR = Hazard ratio

IQR = Interquartile range

PI = Ponderal index

SEP = Socio-economic position

UBCoS = Uppsala Birth Cohort Study

Conflict of interests

The authors declare that they have no conflict of interest.

Authors' contributions

IK conceived, designed and coordinated the study, and contributed to drafting the manuscript. IdSS participated in the design of the study and helped to draft the manuscript. RJ carried out preliminary statistical analyses and drafted the first version of the manuscript. US performed the statistical analyses included in the paper and drafted the final version of the manuscript. All authors read and approved the final manuscript.

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Table 1. Characteristics of the study population with numbers and proportions of deaths by category.

Variable name, unit	Categories	Total N (%)	Deaths N (%) up to 5 years of follow-up[a]	Deaths N (%) up to the end of follow-up
Gestational age (GA), weeks	≤37	70 (15)	20 (29)	53 (76)
	38-39	143 (31)	38 (28)	100 (70)
	40-41	199 (43)	48 (25)	130 (65)
	≥42	48 (10)	7 (16)	28 (58)
	Mean (SD): 39.8 (2.2)			
Birth weight (BW), g	<3000	83 (18)	22 (27)	51 (61)
	3000-3499	163 (35)	40 (26)	111 (68)
	3500-3999	162 (35)	35 (22)	109 (67)
	≥4000	52 (11)	16 (31)	40 (77)
	Mean (SD): 3417 (511)			
Birth length (BL), cm	≤49.0	111 (24)	32 (30)	73 (66)
	49.5-50.0	90 (20)	20 (22)	60 (67)
	50.5-51.0	107 (23)	24 (23)	68 (64)
	51.5-52.0	60 (13)	14 (24)	43 (72)
	≥52.0	92 (20)	23 (26)	67 (72)
	Mean (SD): 50.6 (2.4)			
Ponderal Index (PI), kg/m^3	≤24.63	114 (25)	27 (25)	80 (70)
	24.64-26.38	119 (26)	26 (23)	74 (62)
	26.39-27.89	116 (25)	37 (32)	82 (71)
	≥27.90	111 (24)	23 (22)	75 (68)
	Mean (SD): 26.3 (2.5)			
Age at diagnosis, years	<50	69 (15)	18 (26)	52 (75)
	50-59	90 (20)	15 (17)	64 (71)
	60-69	111 (24)	24 (22)	77 (69)
	≥70	190 (41)	56 (32)	118 (62)
	Mean (SD): 64.9 (12.5)			
Calendar time at diagnosis	1958-1969	41 (9)	11 (27)	34 (83)
	1970-1979	85 (18)	18 (21)	68 (80)
	1980-1989	108 (23)	25 (23)	76 (70)
	1990-1999	141 (31)	33 (23)	96 (68)
	2000-2010	85 (18)	26 (37)	37 (44)
Age at first child, years	15-24	177 (38)	36 (21)	107 (60)
	25-29	116 (25)	22 (19)	79 (68)
	30+	77 (17)	25 (33)	55 (71)
	Never	90 (20)	30 (35)	70 (78)
Number of children	0	90 (20)	30 (35)	70 (78)
	1	119 (26)	25 (22)	80 (67)
	2	132 (29)	35 (27)	83 (63)
	3	80 (17)	14 (18)	52 (65)
	≥4	39 (8)	9 (25)	26 (67)
	Median (IQR): 2 (1, 3)			
Occupational social class in 1960	Not working	15 (3)	5 (36)	11 (73)
	Manual	131 (29)	35 (28)	89 (68)
	Non-manual / supervisor	253 (56)	53 (22)	165 (65)
	Self-employed	56 (12)	17 (31)	41 (73)
Education in 1970	Elementary (≤10 years)	395 (90)	90 (24)	267 (68)
	Secondary (11-12 years)	9 (2)	2 (22)	5 (56)
	Post-secondary (≥13 years)	36 (8)	6 (18)	22 (61)
Personal income in 1970, Kr	No personal income	108 (24)	32 (30)	73 (68)
	<10,000	98 (22)	18 (19)	61 (62)
	10,000-19,999	103 (23)	16 (16)	65 (63)
	≥20,000	140 (31)	36 (26)	101 (72)
	Median (IQR): 11,540 (800, 22,235)			
Total		**460 (100)**	**113 (25)**	**311 (68)**

[a]Women censored before 5 years of follow-up were excluded from these figures, remaining N = 446.

Table 2. Association of birth size with long-term mortality and 5-year breast cancer case fatality.

	Unit (SD equivalent)	**Adjusted for age and calendar time**	**Adjusted additionally for GA**	**Adjusted additionally for BW and/or BL[a]**	**Fully adjusted[b]**
Long-term mortality		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Gestational age (GA)	2.2 weeks	0.86 (0.77, 0.95)	N.A.	0.84 (0.75, 0.94)	0.83 (0.74, 0.94)
Birth weight (BW)	511 g	1.03 (0.91, 1.15)	1.10 (0.97, 1.24)	1.22 (1.02, 1.46)	1.29 (1.07, 1.56)
BW for GA	N.A.	1.10 (0.98, 1.24)	N.A.	1.22 (1.05, 1.40)	1.27 (1.09, 1.47)
Birth length (BL)	2.4 cm	0.95 (0.85, 1.06)	1.01 (0.90, 1.13)	0.87 (0.73, 1.04)	0.85 (0.70, 1.02)
Ponderal Index (PI)	2.5 kg/m^3	1.11 (0.99, 1.24)	1.13 (1.01, 1.27)	N.A.	1.16 (1.03, 1.30)
5-year case fatality		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Gestational age (GA)	2.2 weeks	0.83 (0.66, 1.04)	N.A.	0.84 (0.66, 1.07)	0.85 (0.65, 1.12)
Birth weight (BW)	511 g	0.96 (0.77, 1.19)	1.02 (0.81, 1.30)	1.23 (0.85, 1.78)	1.37 (0.91, 2.07)
BW for GA	N.A.	0.99 (0.79, 1.24)	N.A.	1.16 (0.86, 1.55)	1.25 (0.91, 1.73)
Birth length (BL)	2.4 cm	0.87 (0.70, 1.09)	0.92 (0.73, 1.17)	0.79 (0.54, 1.14)	0.79 (0.52, 1.18)
Ponderal Index (PI)	2.5 kg/m^3	1.14 (0.91, 1.43)	1.17 (0.93, 1.46)	N.A.	1.21 (0.94, 1.57)

[a]GA adjusted for BW and BL, BW and (BW for GA) adjusted for BL, and BL adjusted for BW. [b]Additionally adjusted for age at first child, number of children, adult occupational social class in 1960, educational level at 1970 and personal income at 1970.