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Award Number: DAMD17-00-1-0447

TITLE: Early Life and Risk of Breast Cancer

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REPORT DATE: August 2004

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2004	Final (1 Jul 00-31 Jul 04)

4. TITLE AND SUBTITLE
Early Life and Risk of Breast Cancer

5. FUNDING NUMBERS
DAMD17-00-1-0447

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The objective was to study the influence of birth weight and of growth during childhood and adolescence on risk of breast cancer. We used a unique material of school charts with information on 161,000 girls born 1930-1975. Information on birth weight, yearly measurements of weight and height during school years and age of menarche was computerized and linked to the Central Registration System (CRS) using an algorithm that matched on birth date and name. This resulted in the identification of CRS-numbers for 141,481 girls (88%). Using the CRS number, information on incident pre- and post-menopausal breast cancer was obtained from the Danish Cancer Registry. During 3,333,359 years of follow-up 3,340 cases of breast cancer were diagnosed. High birth weight, early age at peak growth, greater height, and low BMI at 14 years of age were independent risk factors for breast cancer. Height at age 8 years and the increment in height during puberty (age 8 to 14 years) were also associated with breast cancer. The attributable risk of birth weight, height at age 14 years, BMI at age 14 years, and age at peak growth were 7 percent, 15 percent, 15 percent, and 9 percent, respectively. In conclusion, high birth weight and growth during childhood and adolescence influence breast cancer risk.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Epidemiology, Etiology, Risk Factors, Weight, Growth	132
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

Prefix

This grant was in principle awarded in the summer of 2000. However, we were not allowed to start the project before human subject protection issues had been solved. We on our part had difficulties understanding what exactly was required in terms of documentation but this was finally solved during the fall of 2000. We did not receive an official response and wrote a letter on December 4, 2000 to learn of the status of approval. By e-mail response dated December 15, 2000, we were told that the acting chair approved our study and that we would be hearing soon from the contracting office. Final approval to initiate the study was given on March 6, 2001.

While waiting for permission to start the study on *Early life events and risk of breast cancer* we worked on two other studies that grew out of our first US Army grant (DAMD17-96-1-6321). These have in the meantime been finished and resulted in the following reports:

Study 15: Kroman N, Wohlfahrt J, Mouridsen HT, Melbye M. Influence of tumor location on breast cancer prognosis. Int J Cancer 2003; 105:542-545

Study 16: Kroman N, Holtveg H, Wohlfahrt J, Jensen MB, Mouridsen HT, Toft MB, Melbye M. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast cancinoma. Cancer 2004; 100:688-693

Reports on study 15 and 16 are enclosed as appendix A and B.

Background and aims of the project (DAMD17-00-1-0447)

The aim of the new project was to study the importance of early life events for the risk of breast cancer. Specifically we wanted to study the influence of birth weight and growth during childhood and adolescence on risk of breast cancer in a cohort of more than 150,000 girls on whom information on birth weight and between 6 and 8 subsequent measurements of weight and length during school years was available on their school charts. These measurements had been recorded prior to and independently of the outcome (breast cancer) and as such they were free from recall bias.

It has been quite an undertaking to establish this database, perform the necessary linkages, data cleaning and finally the analysis of a very complicated dataset. For logistical reasons we decided to divide the analytical work in two, an initial phase in which we first addressed objective number one in our proposal (is there an association between birth weight and risk of breast cancer?). In the meantime we computerized subsequent information from the school health records which enabled us to address the remaining objectives regarding the potential influence of growth during childhood and adolescence and age of menarche on risk of pre- and postmenopausal breast cancer..

Study 1. In 1990, Trichopolous hypothesized that breast cancers may originate in utero [1]. The idea is based on the assumption that endogenous oestrogens are important in the aetiology of breast cancer, and that the first exposure of the mammary gland to high concentrations of oestrogens (10-100 times the oestrogen levels achieved later in life) occurs in utero [1]. At this early stage, the mammary gland is largely undifferentiated and may be particularly susceptible to influences that could increase the risk of cancer through accelerated cell growth or by being more prone to exogenous carcinogenic stimuli [1]. Studies have shown that birth weight is associated with oestrogen levels during pregnancy which suggests that birth weight is a useful proxy measure of intrauterine oestrogen measure [2-4].

Studies on the association between birth weight and risk of breast cancer have, however, yielded somewhat conflicting results. Overall, the available literature on birth weight is suggestive of an intrauterine effect on later risk of breast cancer especially for premenopausal breast cancer, but the evidence is in many cases based either on studies with small sample sizes or on data of recalled events that occurred many decades earlier [5-19].

Study 2. Critical periods of early growth, including prenatal growth, may influence the risk of breast cancer. However, most studies have focused on adult measurements, and have shown that tall women have an increased risk of both pre- and postmenopausal breast cancer,[25] whereas obesity is associated with a reduced risk of pre-menopausal breast cancer, and an increased risk of post-menopausal breast cancer.[26] The extent to which these associations in adults reflect growth patterns in early life is unknown. A better understanding of the association between early growth patterns and the risk of breast cancer could improve our understanding of the mechanisms of the disease and prove important for prevention.

BODY

Study 1:

Study population

The study cohort consisted of 161,063 girls born between 1930 and 1975 who attended school in Copenhagen, Denmark. In this period school health records were kept for all pupils. The health records were filled in by nurses or physicians in the school health services on a yearly basis from school start until the child left school. Either or both parents accompanied their child to the first visit, at which they reported the child's birth weight. The complete records are now kept at the Copenhagen City Archives and contain information on e.g. the child's name and date of birth, birth weight and the mothers' name.

The Danish Civil Registration System (CRS) was established on 1 April, 1968 from which date all residents and newborns in Denmark have been given a unique 10-digit person identification number (the CRS-number). The CRS includes information about name, place of birth, and parental identity on all Danish residents and is updated daily with respect to vital and migration status. All other national registries in Denmark, which record individual information, are based on the CRS number, thus serving as a unique key for linkage studies. Information from the CRS have been used to generate a population-based relational database, the Birth Order Study database (BOS), containing information on all men and women born during the period 1 January 1935 to 31 December 1998, who have been assigned a CRS-number [20]. This database contains close to complete information on sibships of children born to these women, parity of women and links between family members. The completeness of the linkage between mother and child in BOS has been estimated to 97,3% for children born before 1968, and complete information for children born hereafter [21].

Information from the school health records has been computerized and linked to the CRS using an algorithm that matched on birth date and name. This resulted in the identification of CRS-numbers for 141,481 girls (88%). The lack of identification of the remaining 12% is partly due to death and emigration before 1 April 1968. Of the 141,468 girls with a CRS-number 106,405 (75%) had information on birth weight.

Ascertainment of cases

Information on incident breast cancer cases was obtained from the Danish Cancer Registry and from the Danish Breast Cancer Cooperative Groups Registry. The Danish Cancer Registry was established in 1942 and is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943 [22]. The Danish Breast Cancer Cooperative Groups Registry (DBCG) was established in late 1976 for the purpose of standardizing and evaluating the treatment of breast cancer in Denmark [23]. In addition to information from the Danish Cancer Registry, DBCG contains information on tumour size and histology, oestrogen receptor status, nodal status, and subsequent treatment.

Statistical methods

The association between birth weight and breast cancer risk was estimated in a cohort design using log-linear Poisson regression. Follow-up for breast cancer began 1 April 1968, or the date of birth, which ever came last, and continued until a diagnosis of cancer, death, emigration, or 31 August 2000, which ever came first.

Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60) and calendar period in 5-year intervals [24]. In additional analyses, adjustments were made for age at first birth (nulliparous, 12-19, 20-24, 25-29, 30-34, 35+) and parity (0, 1, 2, 3, 4+).

The relative risk increase per 1000 g increase in birth weight was estimated by treating birth weight categorized in intervals of 100 g as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. The log-linear assumptions underlying the trend estimation of birth weight were checked in two ways. Firstly by a likelihood ratio test comparing the models with birth weight treated as a continuous and a categorical variable, respectively. Secondly by evaluating the effect of including a quadratic term in the trend analysis.

Poisson regression was uses instead of Cox regression because of the computational efficiency in large datasets. Estimation using Cox regression with age as the underlying time variable gave identical estimates of the main trend and the confidence interval.

Women with recorded birth weights greater than or equal to 6000 g or less than or equal to 500 g were excluded from the main analyses due to a high risk of misclassification in these groups. All analyses were carried out using the SAS statistical software release 8.02 (specifically the PROC GENMOD procedure).

TABLE 1. NUMBER OF BREAST CANCER CASES AND PERSON YEARS OF FOLLOW UP BY AGE, CALENDAR PERIOD, BIRTH COHORT AND BIRTH WEIGHT.

COHORT CHARACTERISTICS	cases (%) (Total = 2,334)		PERSON YEARS / 1,000 (%) (TOTAL = 3,256)	
Age				
0 – 29	32	(1.4)	1452.7	(44.6)
30 – 39	343	(14.7)	852.9	(26.2)
40 – 49	1037	(44.4)	629.1	(19.3)
50 – 59	827	(35.4)	297.2	(9.1)
60 +	95	(4.1)	23.6	(0.7)
Calendar Period				
1968* – 1979	145	(6.2)	1167.6	(36.4)
1980 – 1989	624	(26.7)	1022.8	(31.4)
1990 +	1565	(67.1)	1045.1	(32.1)
Birth Cohort				
1930 – 1939	587	(25.2)	313.4	(9.9)
1940 – 1949	1387	(59.4)	606.5	(38.4)
1950 – 1959	325	(13.9)	445.3	(25.5)
1960 +	35	(1.5)	534.9	(26.2)
BIRTH WEIGHT				
501 – 1499 g	5	(0.2)	13.5	(0.4)
1500 – 2499 g	125	(5.4)	191.6	(5.9)
2500 – 2999 g	305	(13.1)	522.6	(16.1)
3000 – 3499 g	846	(36.3)	1207.5	(37.1)
3500 – 3999 g	717	(30.7)	938.5	(28.8)
4000 – 4499 g	248	(10.6)	298.0	(9.2)
4500 – 5999 g	88	(3.8)	83.8	(2.6)

* Follow-up began 1 April 1968

Estimation of the increase in breast cancer risk according to tumour diameter (< 2 cm, 2-5 cm, ≥ 5 cm), nodal status (negative or positive) and oestrogen receptor status (negative or positive) by 1000 g increase in birth weight were performed as a competing risks analysis, i.e. with censoring as above but counting only the selected case-category as cases.

Result

Number of breast cancer cases and person-years of follow up by age, calendar period, birth cohort and birth weight category are shown in table 1. A total of 2,334 cases of primary breast cancer were diagnosed in the cohort during 3,255,549 years of follow-up. Of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older.

In our main analysis we found a significant positive association between birth weight and breast cancer equivalent to a 9% increase in risk per 1000 g increase in birth weight (95% CI 2% to 17%). If all registered birth weights were included in the analysis (i.e. including birth weight registered as being below 501 g or above 5999 g) the increase in risk was 8% per 1000 g (95% CI 1% to 16%). Data and trend is shown on figure 1.

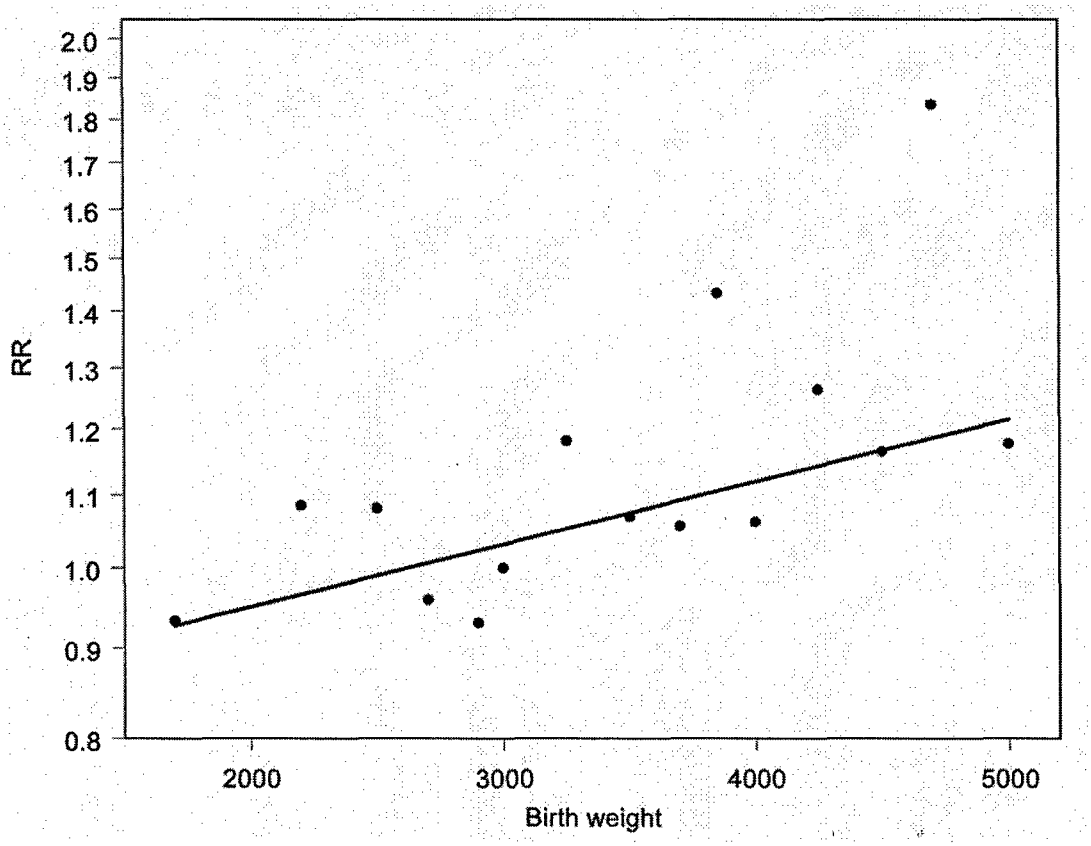

Figure 1. Adjusted relative risk of breast cancer in birth weight intervals of 200 g compared to women with a birth weight between 3000 g to 3199 g. Due to small numbers at the end of the distributions we have grouped the birth weights as: < 2000 g, 2000 – 2399 g, 2400 – 2599 g, 2600 – 2799 g, 2800 – 2999 g, … , 4600 – 4799 g, ≥ 4800 g. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment is made for age and calendar period.

TABLE 2. INCREASE IN BREAST CANCER RISK PER 1000 G INCREASE IN BIRTH WEIGHT ACCORDING TO AGE. ADJUSTED FOR CALENDAR PERIOD.

Age (years)	cases (Total = 2,334)	$RR_{per\ 1000\ g}$ (95% CI)
0 – 40	375	1.07 (0.90 – 1.28)
40 – 44	453	1.08 (0.92 – 1.26)
45 – 49	584	1.20 (1.04 – 1.38)
50 – 54	502	1.08 (0.92 – 1.25)
55 – 59	325	1.09 (0.91 – 1.31)
60 +	95	0.77 (0.56 – 1.07)
		Test for difference p = 0.30*

* Similar analysis but with binary age groups (< 50 years and ≥ 50 years) revealed no difference in trend according to age, p = 0.29

Table 2 shows the increase in breast cancer risk by 1000 g increase in birth weight stratified by age. The risk increase by birth weight did not vary with age (p=0.30). Analysis of the trend according to year of birth and period likewise showed no variation (data not shown).

To investigate the association with tumour characteristics we used additional data from DBCG on tumour size (<2 cm: N=1132, 2-5 cm: N=680, ≥ 5 cm: N=159, missing: N=363) nodal status (node neg: N=1097, node pos: N=859, missing: N=378) and oestrogen receptor status (ER pos: N=1087, ER neg: N=469, missing: N=778). Estimating the increase in risk of breast cancer according to tumour characteristics by 1000 g increase in birth weight revealed no systematic differences in the trend by tumour characteristics at diagnosis (data not shown).

To further validate the results three additional analyses were performed. Firstly, parity and age at first birth was known for women born in 1935 and later. No confounding effect was found when adjusting for these factors (RR = 9% per 1000 g, 95% CI 2% to 17%). Secondly, some of the identified women had missing information on birth weight. Their breast cancer risk did not vary significantly from women with known birth weight, $RR_{unknown\ vs\ known}$=0.94 (95% CI, 0.86 to 1.03). Thirdly, the estimation was based on the assumption that the association between birth weight and breast cancer can be described by a trend. Goodness-of-fit tests gave no indication that this assumption was inadequate.

Study 2.

Study population

Our study was based on the same cohort as in study 1 of girls born between 1930 and 1975, who underwent regular health examinations in the School Health Service in the Copenhagen municipality. A manual register of the school health records encompasses 161,063 girls. The records include information on annual measurements of weight and height, age at menarche, and birth weight as reported by the parents. Information from these school health records was computerized and linked via name and date of birth to the Danish Civil Registration System (CRS).

The CRS was established 1 April 1968 and all residents and newborns in Denmark have since been given a unique 10-digit person identification number (the CRS number) which is stored along with information on name, place of birth, and parental identity on all Danish residents. The CRS numbers serve as a unique key for linkage with other registries. CRS numbers were identified for 141,393 girls (88 percent) but were missing in the remainder mainly because of emigration, death or changes in surnames before 1968. Information from the CRS was also used to create the variables parity and age at each birth for cohort members.[25,26]

Ascertainment of cases

Information on incident invasive breast cancer cases was obtained from the Danish Cancer Registry (DCR) until the end of 1997 and from the registry of the Danish Breast Cancer Cooperative Group (DBCG) through 2001. The DCR is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943.[27] For women under 70 years of age at diagnosis the completeness of case registration in the clinical DBCG database is >95 percent compared to the DCR.[28]

Statistical methods

Weight and height at ages 8, 10, 12 and 14 years were estimated by linear interpolation of the last measurements before the birthday and first measurement after the birthday. If no measurements after the 14th birthday existed but the levels at ages 8, 10 and 12 were known, the level at age 14 was predicted by best subset regression performed in STATA.[29] BMI was calculated as weight (kg) divided by squared height (m).

Age at peak growth was defined as the age between the two measurements that indicated the maximum growth rate in height . The growth rate between two measurements was estimated as a weighted average of change in height between the two measurements (weight: ½) and the change in both adjacent intervals (weights: ¼ and ¼). With only one adjacent interval the weights were 2/3

and 1/3, respectively. Age at peak growth was estimated in women with 5 or more measurements and where the maximum growth rate was estimated to be 3.5 cm per year or higher.

The association with breast cancer was estimated in a cohort design using log-linear Poisson regression.[30] Follow-up for breast cancer began at age 14 years or on 1 April 1968, whichever came last, and continued until a diagnosis of cancer, death, emigration, or 31 August 2001, whichever came first. Adjustment was made for age (quadratic splines with knots for each 5 years) and calendar period in 5-year intervals.[31] In additional analyses, adjustments were made for age at first birth and parity.

Effect modification by attained age and difference in the effect of change in height and BMI according to age intervals during childhood were evaluated by likelihood ratio tests of heterogeneity. Trends were estimated by treating the categorized variables (assigned the median within category) as continuous variables. The underlying log-linear assumptions were checked by comparing with a categorical model using likelihood ratio tests.

Information on age at menarche had not been computerized originally along with measurements of birth weight, weight and height. We therefore manually retrieved school health records in a nested case-cohort design on all 2,005 women born from 1940 to 1970 who developed breast cancer during follow-up (cases) and a cohort of 5,500 randomly chosen women stratified by birth cohort according to the distribution of cases. Information on age at menarche was retrieved for 3,610 of the women, 950 of whom had breast cancer.

Analyses involving age at menarche were performed using Cox regression with age as the underlying time-variable and with birth cohort as stratum variable. The Cox regression analyses (with robust estimation of variance to avoid overestimation of the precision due to the design-induced over sampling of cases) were performed using the STCOX procedure in STATA v. 8 statistical software.[29] Follow-up was as in the Poisson regression.

The population attributable risks were estimated for each variable in a scenario where each woman was assigned the median in the lowest category (birth weight, height at age 14 years) or highest category (BMI at age 14 years, age at peak growth) (Table 1). The population attributable risks were for each variable estimated based on the risk factor distribution presented in Table 1 and relative risks (estimated from the trend) for each median value of the quintiles.

Results

In our cohort of 141,393 women the total number of sets of measurements of weight and height was 1,128,505. Overall, 89.0 percent of the girls had 5–12 measurements (median=8). The median age at first measurement was 7.2 years (standard deviation = 1.1 years) and the median age at last

measurement was 14.5 years (standard deviation = 2.0 years). We limited all subsequent analyses to the 117,415 women with complete information on weight and height at ages 8, 10, 12, 14 as well as age at peak growth. In this cohort 3,340 cases of breast cancer were observed during 3,333,359 person-years of follow-up.

As shown in Table 1, the estimated age at peak growth and age at menarche (available in 3,610 women) were inversely associated with the relative risk of breast cancer. Height at age 14 was positively associated with this risk, and BMI at age 14 was inversely associated with the risk of breast cancer. Analysis of birth weight, performed on the 91,601 women for whom it was known, showed a positive association with the relative risk of breast cancer. No confounding effect was found when adjusting for parity and age at first birth.

We investigated whether growth in any specific age interval influenced breast cancer risk by breaking down the association with height at age 14 as associations with height at age 8 and increments in height between age 8 and age 14. We used the age at peak growth to subdivide the age interval between 8 and 14 years age into the categories: "age 8 until peak year", "peak year" and "peak year until age 14". Peak year was defined as the 12-month time period beginning 6 months prior to the calculated exact age at peak growth. Increase in height was significantly associated with the relative risk of breast cancer within all age intervals after adjustment for BMI at age 14, age at peak growth, age and calendar period (Table 2). The relative risk per increase in height was similar in the three age intervals between ages 8 and 14 years (P=0.33, Table 2), whereas the relative risk was significantly higher for changes in height between age 8 and age 14 compared with change in height before age 8 (p = 0.01, Table 2).

We modeled BMI in age intervals as described above with height. BMI adjusted for height at age 14, age at peak growth, age and calendar period was significantly associated with the relative risk of breast cancer within all the age intervals (Table 2). However, the increase in relative risk per increase in BMI was similar in all the age intervals (P=0.77, Table 2), and the increase in relative risk was furthermore similar for changes in BMI between age 8 and age 14 compared with changes in BMI before age 8 (P=0.10, Table 2). No association was found with weight (unadjusted for height) at any age and the risk of breast cancer (data not shown).

Table 1. Adjusted* relative risk (RR) of breast cancer according to birth weight, age at peak growth, age at menarche, height at age 14 and BMI at age 14.

cohort (N=117,415)	cases†	RR (95% CI)
birth weight (median of quintiles)		
2.5 kg	381	1 (ref)
3.0 kg	392	0.98 (0.85–1.13)
3.4 kg	668	1.06 (0.93–1.20)
3.6 kg	150	1.05 (0.87–1.27)
4.0 kg	483	1.17 (1.02–1.33)
trend pr. kg‡	2,074	1.10 (1.01–1.20)
age at peak growth (median of quintiles)		
10.4 year	568	1 (ref)
11.3 year	727	1.04 (0.93–1.16)
12.0 year	703	0.94 (0.84–1.05)
12.8 year	657	0.86 (0.77–0.96)
13.5 year	685	0.84 (0.75–0.93)
trend pr. year‡	3,340	0.97 (0.96–0.98)
age at menarche (median of quintiles)		
11.9 year	193	1 (ref)
12.6 year	201	1.03 (0.85–1.26)
13.2 year	209	1.09 (0.90–1.33)
13.7 year	183	0.94 (0.77–1.15)
14.4 year	164	0.83 (0.67–1.02)
trend pr. year	950	0.96 (0.92–1.00)
height at age 14 (median of quintiles)		
151.1 cm	733	1 (ref)
156.2 cm	678	1.07 (0.96–1.19)
159.8 cm	682	1.18 (1.06–1.31)
162.9 cm	600	1.15 (1.03–1.28)
167.6 cm	647	1.51 (1.36–1.68)
trend pr. 5 cm‡	3,340	1.11 (1.08–1.15)
BMI at age 14 (median of quintiles)		
16.7 kg/m²	644	1 (ref)
18.1 kg/m²	692	0.96 (0.86–1.07)
19.1 kg/m²	736	1.02 (0.92–1.13)
20.3 kg/m²	711	0.99 (0.89–1.10)
22.4 kg/m²	557	0.84 (0.75–0.94)
trend pr. kg/m²‡	3,340	0.97 (0.96–0.98)

* All variables were adjusted for age and calendar period, except for age at menarche, which due to the case-cohort design was adjusted for birth cohort instead of calendar period as described in the methods section

† Birth weight was only known for 91,601 of the 117,415 women, and of these 2,074 developed breast cancer. Information on age at menarche was collected using a case-cohort design in 3610 women, and of these 950 developed breast cancer.

‡ Adjustment for parity and age at first birth did not markedly change the trend estimates.

Table 2. Adjusted relative risk (RR) of breast cancer by change in height and BMI during childhood according to time period.

	time period				
	before age 8 years	between age 8 and age 14	between age 8 and peak year	during peak year*	between peak year and age 14
		$p_{diff}=0.01$‡		$p_{diff}=0.33$‡	
RR per 5 cm change in height†		1.11 (1.07–1.15)	1.17 (1.09–1.25)	1.18 (1.08–1.27)	1.15§ (0.97–1.36) 1.10 (1.00–1.20)
		$p_{diff}=0.10$‡		$p_{diff}=0.77$‡	
RR per kg/m² change in BMI§		0.94 (0.91–0.97)	0.96 (0.93–0.99)	0.95 (0.91–0.99)	0.96 (0.90–1.02) 0.97 (0.93–1.02)

* Peak year is defined as the 12-month time period beginning 6 months prior to the calculated age at peak growth
† Adjusted for age, calendar period as well as age at peak growth and BMI at age 14
‡ Likelihood ratio test of heterogeneity for difference in RR
§ Adjusted for age, calendar period as well as age at peak growth and height at age 14

Table 3. Association between early growth variables and breast cancer, overall and according to age of the women.

	all ages	age < 50 year	age >= 50	test for difference according to age
	RR (95% CI)	RR (95% CI)	RR (95% CI)	
birth weight* trend pr. kg	1.10 (1.01-1.21)	1.14 (1.01-1.28)	1.05 (0.91-1.21)	p=0.39
age at peak growth† trend pr. year	0.94 (0.91-0.97)	0.90 (0.86-0.95)	0.98 (0.93-1.03)	p=0.03
age at menarche‡ trend pr. year	0.99 (0.91-1.07)	0.98 (0.88-1.08)	1.01 (0.87-1.17)	p=0.74
height age 8† trend pr. 5 cm	1.11 (1.07-1.15)	1.11 (1.05-1.17)	1.11 (1.05-1.17)	p=0.62
height increase age 8 to age 14† trend pr. 5 cm	1.17 (1.09-1.25)	1.15 (1.05-1.27)	1.18 (1.07-1.30)	p=0.74
BMI age 14† trend pr. kg/m²	0.95 (0.93-0.97)	0.96 (0.94-0.99)	0.94 (0.92-0.97)	p=0.22

* Adjusted for age at peak growth, height at age 8, height increase age 8 to age 14 and BMI at age 14. Further adjustment for age at menache did not markedly change the estimate.

† Mutually adjusted. Further adjustment for birth weight and age at menache did not markedly change the estimate.

‡ Adjusted for age at peak growth, height at age 8, height increase age 8 to age 14 and BMI at age 14. Further adjustment for birth weight did not markedly change the estimate.

The correlation coefficients between the five variables in Table 1 as well as height and BMI at age 8 years were all less than 0.4 with three exceptions: height at age 8 and 14 (0.88), BMI at age 8 and age 14 (0.74), and age at menarche and age at peak growth (0.60). The correlation coefficients with birth weight were all less than 0.20.

After further mutual adjustment (Table 3) birth weight, height at age 8, height increase between age 8 and age 14 and BMI at age 14 remained independently associated with breast cancer with trends similar to those presented in Tables 1 and 2. Performing similar analyses in the nested case-cohort, where age at menarche was known, revealed that adjustment for it did not affect these associations.

The effect of age at peak growth was enhanced after adjustment for other growth factors, whereas adjustment for age at menarche did not affect the association between age at peak growth and breast cancer. Age at menarche was not associated with the relative risk of breast cancer after adjustment for the pubertal growth factors (Table 3).

Only age at peak growth had a significantly different association in women younger than 50 years (Table 3).

To evaluate the impact of these variables on the population, we calculated population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases would be diminished by 7 percent. Similar figures for height at age 14 years, BMI at age 14 years, and age at peak growth were 15 percent, 15 percent, and 9 percent, respectively.

KEY RESEARCH ACCOMPLISHMENTS

- **A significant association between birth weight and breast cancer was found equivalent to an increase in risk of 9% per 1000 g increase in birth weight (95% CI 2% to 17%).**
- **The increase was observed for all age groups, representing both pre- and post-menopausal women, and irrespective of tumor characteristics. Adjustment for age at first birth and parity did not influence the results.**
- **Not only high birth weight, but also early age at peak growth, greater height, and low BMI at 14 years of age were independent risk factors for breast cancer. Height at age 8**

years and the increment in height during puberty (age 8 to 14 years) were also associated with breast cancer. No confounding by age at menarche, age at first birth and parity was observed.

- **The attributable risk of birth weight, height at age 14 years, BMI at age 14 years, and age at peak growth were 7 percent, 15 percent, 15 percent, and 9 percent, respectively.**

REPORTABLE OUTCOMES

Publications:

Ahlgren M, Sørensen TIA, Wohlfahrt J, Haflidadóttir A, Holst C and Melbye M. Birth weight and risk of breast cancer in a cohort of 106,405 women. **Int J Cancer 2003; 107: 997-1000.** (Appendix C).

Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA. Growth patterns and the risk of breast cancer in women. **N Engl J Med 2004; 351: 1619-26.** (Appendix D). Editorial regarding this article is enclosed as appendix E.

Databases:

Database on 161,000 women born 1930-75 with information on birth weight and yearly measurements of weight and height during school years. Additional information regarding later reproductive history and cancer outcome.

PhD thesis:

Ahlgren M. Birth weight and growth during school years and risk of cancer. PhD Thesis. University of Copenhagen 2004, Copenhagen. (Appendix F). Opponents were professor Dimitrious Trichopoulos, Harvard University School of Public Health, Boston, USA; professor Leiv Bakketeig, University of Southern Denmark, Denmark, and professor Michael Rørth, Oncology Center, Danish University Hospital Copenhagen, Denmark.

CONCLUSION

Using a unique and very large collection of school health records combined with effective follow-up, we found that high birth weight, early age at peak growth, greater height, low BMI at age 14 years, and high growth rate in childhood —particularly around puberty — were all independent risk factors for breast cancer. Our results are in accord with the positive association between adult height and pre- and post-menopausal risk of breast cancer,[25] and the inverse association between BMI and risk of pre-menopausal breast cancer.[32] However, we also identified specific periods of early growth that are important to the risk of breast cancer.

Birth weight, a proxy for in utero growth and prenatal exposures, has been studied by several authors, and most[33-42] but not all[43-47] have found support for an association with breast cancer. In a previous study of women from the same population but without information on subsequent growth we also found a significant association.[48] In the present study, we show that the association of breast cancer with birth weight is independent of the effect of subsequent growth patterns and timing of puberty on the risk of breast cancer.

Four studies have explored the association between pubertal growth and the risk of breast cancer in cohorts where actual measurements of weight and height were obtained, although on a much more limited scale than in our study.[39,40,49,50] In agreement with these studies we found BMI at ages 8, 10, 12 and 14 years to be inversely associated with the risk of breast cancer. By using height at age 14 years, which serves as a good proxy for adult height,[51] we also confirmed the finding of a direct association between adult height and risk of breast cancer. Our finding of an increment in the relative risk of 11 percent per 5 cm increase in height was very similar to results from a very large study of adults.[26] Our data allowed us to investigate whether the influence of final height was modified by the growth pattern. Height at age 8 and the increment in height around puberty were both associated with breast cancer, but the latter was stronger, suggesting a special impact of pubertal growth. In contrast, analyses of BMI did not reveal any time interval in which changes in BMI were of special importance.

We found a linear trend between decreasing age at peak growth and increasing risk of breast cancer, which was independent of other measures. Adult height is only to some extent linked to ages at peak growth and menarche, and it is possible that different factors control these variables. Age at peak growth most likely reflects the initiation of puberty. In a Norwegian study age at

menarche was found to increase breast cancer risk by 4 percent for each year of decrease in age at menarche.[52] We also found age at menarche was associated with a risk of breast cancer, but not when age at peak growth was included. Thus, previous findings could reflect that age at menarche is a proxy for age at peak growth or that both reflect the importance of age at onset of puberty. Another indication of the importance of puberty was our finding that centimeters accumulated between age 8 and 14 years conferred a higher risk of breast cancer than those accumulated up to age 8 years.

We did not have information on family history of breast cancer, history of benign breast disease, and hormone replacement therapy. Although these influence breast cancer risk they are unlikely to vary by childhood height and weight and as such confound our estimates. Another limitation of our study was the inability to analyze adult weight and BMI. Thus, whereas adolescent height is closely correlated with adult height and hence well elucidated in this study, weight has a weaker correlation. In a large population-based British cohort, height at age 16 years had a correlation of 0.92 with height at age 33 years compared to a correlation with weight of 0.63.[51]

To illustrate the quantitative contributions of the growth factors to the overall risk of breast cancer we also calculated the population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases would be diminished by 7 percent. Similar figures for height at age 14 years, BMI at age 14 years, and age at peak growth were 15 percent, 15 percent, and 9 percent, respectively.

Our studies had sufficient power to detect weak, but relevant associations, and they avoided various risks of bias. Information on birth weight and the measurements of height and weight was recorded during school years, making differential misclassification unlikely. The validity of parents' report of their child's birth weight(s) is very high.[53] We based our cohort on all children attending schools in a well-defined area of Denmark and followed them through our national registries. The Danish social structure further diminished risk of diagnostic bias as free and equal access to health care is provided for all citizens.

The biological background for our findings needs to be elucidated and mechanistic models including modified susceptibility seem warranted. Adult height and the prevalence of obesity have increased and the age at menarche has decreased within the last century,[54,55] showing that changes in some environmental conditions are important, probably operating in interaction with genetic factors. Nutritional status, for example, is related to an increased gain in height in childhood and earlier onset of puberty.[56]

An increased total number of menstrual cycles over a lifetime may explain the association between the early onset of puberty (and thus early age at peak growth) and an increased risk of breast cancer. However, this explanation may be too simple. Even a two-year delay in age at menarche would result in only a limited number of "lost" menstrual cycles compared with the total number of lifetime cycles. The breast epithelium undergoes final differentiation at first pregnancy and it is a generally held belief that differentiated cells are less prone to carcinogenic effects than undifferentiated cells.[57] Whereas some differentiation of breast epithelium occurs before the first pregnancy, breast cells present before menarche are most likely the least differentiated. Since the female breast begins developing well before the start of menstrual cycles[58] it is possible that age at peak growth is really an indicator of the age at which the breast starts growing, and hence an influence on the risk of breast cancer .

Our finding that high BMI protects against breast cancer contrasts with studies showing that overweight in girls is associated with earlier menarche.[59] This suggests that the effect of childhood obesity on breast cancer does not occur via a contribution to the acceleration of puberty as early menarche has an opposite effect of obesity. However, the estrogens produced by adipose tissue may promote differentiation of the breast epithelium.

Overall, our results provide evidence that factors influencing fetal, childhood, and adolescence growth are important independent risk factors for breast cancer in adulthood. Compared with known risk factors such as age at first birth and parity, the association with early growth is of great strength and independent hereof, indicating that the exposures or conditioning processes during this period is of particular importance in relation to adult breast cancer.

REFERENCES

1. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990; 335(8695):939-940.
2. McFadyen IR, Worth HG, Wright DJ, Notta SS. High oestrogen excretion in pregnancy. Br J Obstet Gynaecol 1982; 89(12):994-999.
3. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990; 1(3):247-250.

4. Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000; 11(3):315-319.
5. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152(12):1121-1128.
6. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC. Birthweight as a risk factor for breast cancer. Lancet 1996; 348(9041):1542-1546.
7. Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, Stuver SO. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002; 86(1):89-91.
8. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001; 93(1):60-62.
9. Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, Daling JR. Perinatal factors and risk of breast cancer. Epidemiology 1996; 7(1):34-37.
10. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, Barker DJ. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001; 85(11):1680-1684.
11. Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A, Hulthen L. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001; 84(9):1193-1198.
12. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000; 83(7):964-968.
13. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997; 89(1):71-76.
14. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992; 340(8826):1015-1018.
15. Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998; 12(4):397-407.
16. Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988; 57(4):437-439.

17. Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER, Baron JA, Trichopoulos D, Willett WC. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002; 11(2):207-210.
18. Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002; 86(1):84-88.
19. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: A study among like-sexed twins. Int J Cancer 2001; 91(2):248-251.
20. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997; 89(13):939-947.
21. Westergaard T. Birth Order and Cancer Risk. PhD-thesis, University of Copenhagen 1997; Copenhagen: Department of Epidemiology Research, Danish Epidemiology Science Center:1-82.
22. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997; 44(5):535-539.
23. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988; 27(6A):627-647.
24. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995; 6(4):356-365.
25. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001; 23:313-42.
26. Tretli S. Height and weight in relation to breast cancer morbidity and mortality. A prospective study of 570,000 women in Norway. Int J Cancer 1989; 44:23-30.
27. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997; 44:535-9.
28. Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000; 11:669-74.
29. Stata v. 8.0 Base Reference Manual (4 volumes). Stata Press, 2003.
30. SAS/STAT User's Guide, Version 8, Volumes 1, 2, and 3. SAS Publishing, 2003.

31. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995; 6:356-65.
32. Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev 2001; 10:15-32.
33. Andersson SW, Bengtsson C, Hallberg L et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001; 84:1193-8.
34. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152:1121-8.
35. Michels KB, Trichopoulos D, Robins JM et al. Birthweight as a risk factor for breast cancer. Lancet 1996; 348:1542-6.
36. Sanderson M, Williams MA, Malone KE et al. Perinatal factors and risk of breast cancer. Epidemiology 1996; 7:34-7.
37. Vatten LJ, Maehle BO, Lund Nilsen TI et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002; 86:89-91.
38. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001; 93:60-2.
39. Hilakivi-Clarke L, Forsen T, Eriksson JG et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001; 85:1680-4.
40. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000; 83:964-8.
41. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992; 340:1015-8.
42. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: A study among like-sexed twins. Int J Cancer 2001; 91:248-51.
43. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997; 89:71-6.
44. Sanderson M, Williams MA, Daling JR et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998; 12:397-407.
45. Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988; 57:437-9.

46. 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; 11:207-10.
47. Sanderson M, Shu XO, Jin F et al. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002; 86:84-8.
48. Ahlgren M, Sorensen T, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003; 107:997-1000.
49. Herrinton LJ, Husson G. Relation of childhood height and later risk of breast cancer. Am J Epidemiol 2001; 154:618-23.
50. Le Marchand L, Kolonel LN, Earle ME, Mi MP. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988; 128:137-52.
51. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. Am J Clin Nutr 1997; 66:1094-101.
52. Kvale G, Heuch I. Menstrual factors and breast cancer risk. Cancer 1988; 62:1625-31.
53. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997; 145:58-67.
54. Petersen TA, Rasmussen S, Madsen M. [BMI of Danish school children measured during the periods 1986/1987--1996/1997 compared to Danish measurement in 1971/1972]. Ugeskr Laeger 2002; 164:5006-10.
55. Rasmussen S, Petersen TA, Madsen M. [Body height of 6-15-year-old school children measured in the period 1986/1987 to 1996/1997. Compared with Danish measurements in 1971/1972]. Ugeskr Laeger 2002; 164:5011-5.
56. He Q, Karlberg J. Bmi in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res 2001; 49:244-51.
57. Russo J, Russo IH. Cellular basis of breast cancer susceptibility. Oncol Res 1999; 11:169-78.
58. Howard BA, Gusterson BA. Human breast development. J Mammary Gland Biol Neoplasia 2000; 5:119-37.
59. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974; 185:949-51.

APPENDIX A

Int. J. Cancer: **105,** 542–545 (2003)

Publication of the International Union Against Cancer

INFLUENCE OF TUMOR LOCATION ON BREAST CANCER PROGNOSIS

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Our objective was to investigate the influence of primary tumor location on breast cancer prognosis. We used a population-based registry since 1977 that has collected detailed information regarding clinical and histopathological presentation, postoperative therapy and follow-up status on Danish women with breast cancer. Nodal status and relative risk of dying was estimated according to primary tumor localization in the breast. Overall, 35,319 patients with primary breast cancer were included in the study. After adjustment for prognostic factors, the risk of dying increased significantly (up to 21%) with increasing distance of tumor location from the axilla. This trend was seen both among women with and without spread to the axillary lymph nodes. In conclusion, survival is significantly better for women with a tumor in the upper lateral quadrant than tumors located elsewhere in the breast. Our finding of a similar trend according to distance from the axilla among women with positive axillary lymph nodes who all are allocated to systemic therapy suggests that a better lymph node staging procedure alone is unlikely to eliminate these survival differences. Other reasons for the observed differences should be sought to help improve survival for women with breast cancer.

Key words: *breast cancer; prognosis; staging procedures; lymph nodes; tumor location; population-based*

Axillary lymph node status is the single most important prognostic factor in primary breast cancer and the significance of a proper axillary dissection both with regard to staging and local tumor control is well-established.[1] Recent efforts to optimize the existing staging system with the sentinel node lymphadenectomy have put renewed focus on the prognostic importance of nodal status in breast cancer.[2–5]

From anatomical studies it is known that lymphatic drainage from the breast goes not only to the axillary lymph nodes, but also to the internal mammary nodes, the supraclavicular nodes, and to lymph nodes outside these locations.[6,7] Today's emphasis on axillary nodal status raises an important clinical question as to whether some women with breast cancer are misclassified as low-risk patients because axillary dissection does not reveal spread of the disease to the lymphatic system. In 1 study women with medially located tumors were found to be less likely to be classified as having node positive disease compared to other women with breast cancer.[8] Despite this, these women had a reduced chance of survival compared to women with lateral tumors.

We extended this line of investigation on the prognostic effect of tumor location based on a large and very detailed population-based registration of breast cancer patients in Denmark.

PATIENTS AND METHODS

Registries

In 1977, the Danish Breast Cancer Cooperative Group (DBCG) started nationwide prospective studies on treatment of breast cancer.[9] The primary surgical treatment of patients allocated in treatment protocols included total mastectomy plus axillary clearance (90% of the population), or lumpectomy with axillary dissection. Patients were classified as having either low-risk disease or high-risk disease according to histopathological criteria. Low-risk patients were observed without further adjuvant treatment apart from radiotherapy to the residual breast of women who had breast-conserving surgery. High-risk patients were allocated to adjuvant systemic therapy or radiotherapy. No treatment allocation was based on tumor location in the breast. Patients with bilateral breast cancer or inflammatory cancer, distant metastases, with contraindication to the planned postoperative therapy, or patients who were not treated according to the surgical guidelines were not allocated to any of the protocols (miscellaneous group). Guidelines for risk group allocation and treatment have been described in detail elsewhere.[9–12]

Primary clinical and histopathological data and data concerning postoperative therapy and status at follow-up visits are all registered by the DBCG based on specific forms submitted by the participating departments of surgery, pathology and oncology. Location of the tumor was determined based on an indication made by the surgeon on a figure (Fig. 1). When a tumor was located in the borderline between 2 areas, it was assigned to 1 of the 2 areas by randomization according to date of birth.

Survival of patients was established by reference to the Danish Civil Registration System (CRS), established in 1968. Since then, a unique identification number has been assigned to all residents in Denmark. Individual information is kept under the personal identification number in all national registers permitting accurate linkage of information between different registries. The CRS registry keeps updated files on vital status including dates of death and emigration. A detailed description of the information included in this registry is given elsewhere.[13]

Subjects

Permission to perform the study was obtained in advance from the National Scientific Ethics Committee and the Data Protection Board. Information on patients in the DBCG-registry was linked with the CRS-registry to obtain information on vital status. The study was restricted to women less than 70 years at diagnosis, because the DBCG restricted the data collection to this group of women. Women included in the DBCG-program since 1977 and diagnosed with breast cancer before September 1, 1998, were followed from time of diagnosis until date of death, emigration, or October 1, 1998, whichever occurred first.

Statistical analysis

Associations between tumor characteristics and location were evaluated by χ^2 statistics. The association between location and survival was investigated using Cox proportional hazard regression with adjustment for axillary nodal status (0, 1–3, 4–9, ≥10

Grant sponsor: Danish National Research Foundation; Grant sponsor: Department of the US Army; Grant number: DAMD17-96-1-6321.

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Received 17 September 2002; Revised 9 January 2003; Accepted 10 January 2003

DOI 10.1002/ijc.11116

positive nodes), tumor size (≤2 cm, >2 cm and up to 5 cm, >5 cm) histologic grading (I, II–III, non-ductal carcinomas, age at diagnosis (<35 years or in 5-year intervals in patients >35 years), and patients without information on histologic grading), year of diagnosis (1977–81, 1982–88, 1989–98) and protocol allocation (allocated, not treated according to surgical guidelines, not allocated for other reasons). Test for effect modification was carried out as test for interaction between categorized variables. All analyses were carried out with the use of SAS.[14]

RESULTS

By September 1, 1998, 35,319 women with primary breast cancer less than 70 years of age were registered in the DBCG. The cohort represented a total of 237,364 person-years of follow-up. Median follow-up were 5.3 years, and 25% of the patients had a follow-up time of more than 10 years. Distribution of patients according to tumor characteristics and tumor site is given in Table I. Compared to laterally located tumors, tumors located medially tended to be smaller ($p < 0.001$) and has significantly less nodal involvement ($p < 0.001$). Tumors with central location were found to be larger ($p < 0.001$), associated with higher risk of nodal involvement ($p < 0.001$), and with lower chance of having histologic grading I ($p < 0.001$) compared to laterally located tumors. Estrogen-receptor status, which was available on 21.124 of the breast cancers (59.8%), did not vary by tumor location. Similarly, there was no association between age at time of diagnosis and tumor localization in the breast.

To further analyze tumor characteristics according to the position of the primary tumor in one of the four quadrants, women with central tumors, women with bilateral disease, and women without information on tumor location or nodal status were excluded, leaving 27,234 women for further analysis. Nodal status according to tumor site is given in Figure 2, and further details on tumor site, tumor size and nodal status is given in Table II. The chance of being axillary node negative was significantly greater for women with medial tumors compared to lateral tumors in the subgroup with tumors ≤2 cm ($p < 0.001$) and women with tumors being >2 cm and ≤5 cm ($p < 0.001$). The same trend was seen for the group of women with large tumors (>5 cm), but the differences did not reach significance ($p = 0.38$).

The independent prognostic effect of tumor location was analyzed by performing a multivariate analysis including tumor size, nodal status, histologic grading, age at diagnosis, protocol allocation, year of treatment and tumor site. After adjustment, women with upper lateral tumors did significantly better than other women (Table III). Overall, survival in this group of women was between 15–20% better than among women with a primary tumor site in 1 of the other 3 quadrants. Among women who were classified as having no spread to the lymph nodes in the axilla, similar or worse discrepancies in survival between the upper lateral and 3 other quadrants were observed. Among axillary node positive women, survival remained significantly worse for women with a primary tumor in the lower lateral or medial quadrant compared to the upper lateral quadrant. For this group of node positive women, however, there was no significant difference in survival between those with a primary tumor in the upper medial compared to upper lateral quadrant. The differences in prognosis according to tumor location were not modified by tumor size ($p = 0.77$, data not shown). The results were unchanged when the analysis were restricted to women who could not have had their tumor location allocated according to date of birth due to a location between 2 quadrants.

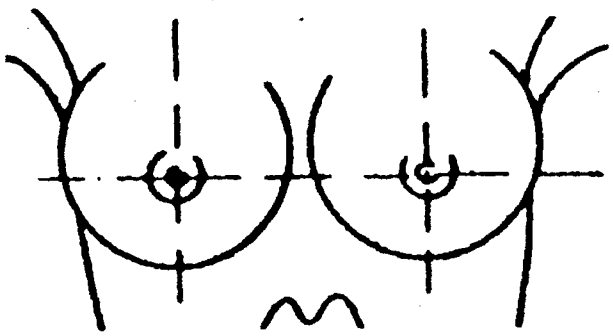

FIGURE 1 – Surgeon's figure for localization of the tumor.

DISCUSSION

Our study shows that the prognosis in breast cancer patients differs significantly according to tumor location. Women with a primary tumor in the upper lateral quadrant had significantly better survival than women with a tumor in 1 of the other 3 quadrants. They were, however, also the group of women most likely to be diagnosed with metastatic spread to the axillary lymph nodes. In contrast, women with tumors in the 2 medial quadrants had the worst prognosis but were also the least likely to be diagnosed with axillary node positive tumors. An explanation for these seemingly contradictory associations is that treatment allocation according to axillary lymph node spread is insufficient. Thus, a proportion of

TABLE I – DISTRIBUTION ACCORDING TO TUMOR CHARACTERISTICS AND LOCATION OF 35,319 BREAST CANCER PATIENTS OPERATED IN DENMARK 1977–1998[1]

	Lateral		Medial		Central	Not indicated
	Upper	Lower	Upper	Lower		
Total	17,659	4,559	5,987	2,212	2,584	2,318
Positive nodes						
0	8,960 (50.7)	2,301 (50.5)	3,704 (61.9)	1,233 (55.7)	868 (33.6)	844 (36.4)
1–3	4,964 (28.1)	1,302 (28.6)	1,351 (22.6)	567 (25.6)	683 (26.4)	507 (21.9)
4–9	2,214 (12.5)	562 (12.3)	488 (8.2)	206 (9.3)	527 (20.4)	240 (10.4)
≥10	785 (4.5)	161 (3.5)	142 (2.4)	67 (3.0)	263 (10.2)	90 (3.9)
No information	736 (4.2)	233 (5.1)	302 (5.0)	139 (6.3)	243 (9.4)	637 (27.5)
Tumor size						
≤ 2 cm	8,717 (49.4)	2,476 (54.3)	3,289 (54.9)	1,256 (56.8)	741 (28.7)	830 (35.8)
> 2 cm, ≤ 5 cm	6,560 (37.2)	1,525 (33.5)	2,028 (33.9)	714 (32.3)	1,009 (39.1)	643 (27.7)
> 5 cm	1,074 (6.1)	189 (4.2)	209 (3.5)	70 (3.2)	515 (19.9)	139 (6.0)
No information	1,308 (7.4)	369 (8.1)	461 (7.7)	172 (7.8)	319 (12.4)	706 (30.5)
Histologic grading						
I	4,521 (25.6)	1,220 (26.8)	1,679 (28.0)	580 (26.2)	517 (20.0)	457 (19.7)
II + III	9,275 (52.5)	2,342 (51.4)	3,118 (52.1)	1,148 (51.9)	1,349 (52.2)	858 (37.0)
ND[1]	3,863 (21.9)	997 (21.9)	1,190 (19.9)	484 (21.9)	718 (27.8)	1,003 (43.3)

[1]Tumor location, *n* (%).–[2]Patients with non ductal carcinomas and patients without available histologic grading.

women with tumors in *e.g.*, the upper medial quadrant and with no spread to axillary nodes most likely had lymphatic dissemination of their disease to lymph nodes outside the axilla, and thus should have been allocated to a more aggressive treatment program than the one given to them. Support for this view is given by our finding that women with upper medial and lateral tumor locations had a more equal survival when restricting the analysis to those with positive axillary nodes whereas survival was 30% worse among women with upper medial compared to upper lateral tumors among those classified as axillary node negative.

The internal mammary lymph nodes have been found the most important destination of lymph drainage outside the axilla.[15] Based on 250 breast lymphoscintigraphies among normal women, Vendrell-Torné *et al.*[7] found that drainage from the lower medial quadrant in 30% of cases occurred exclusively to the internal mammary nodes, 56% drained to both the axilla and internal mammary nodes and 14% drained exclusively to the axilla. It is noteworthy that women in our study with a tumor in the lower medial quadrant of the breast had a more than 20% increased risk of dying compared to women with a tumor close to the axilla. Drainage from the lower lateral quadrant was reported more diverse with only 30% of cases having exclusively drainage to the axilla and 10% exclusively to the internal mammary nodes. Drainage to other areas occurred in 12% of the cases.

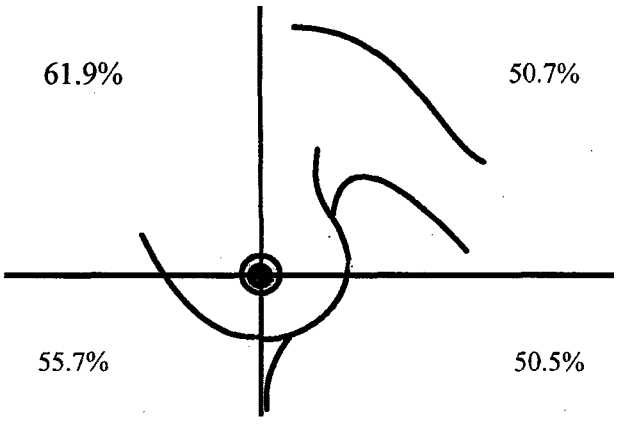

FIGURE 2 – Distribution of negative axillary nodal status according to quadrant location of tumor among 30,417 women (<70 years of age) operated in Denmark 1977–97.

The fact that information on metastatic spread of breast cancer may be missed by restricting lymph node dissection to the area around the axilla has lead to increased use of a sentinel node dissection principle that often takes advantage of lymphangioscintigraphy to detect possible spread outside the axilla. It seems likely that more accurate diagnosis and surgical treatment of for example the internal mammary nodes could lead to improved prognosis for patients with tumors located in the medial half of the breast. The impact on survival after radiotherapeutical treatment of the internal mammary nodes in women with medially located tumors is the subject of an ongoing EORCT trial.[16]

Our results, however, would suggest that a better classification system and thus more accurate treatment allocation alone would not be sufficient to eliminate the observed survival differences by tumor location. Thus, in a restricted analysis of women with metastatic spread to the axillary lymph nodes the relative risk of dying remained significantly higher for women with a lower medial or lateral tumor compared to a tumor in the upper lateral quadrant. In this scenario all women were found to have metastatic spread and received similar therapy, including systemic therapy. Introduction of a different classification system based on *e.g.*, the sentinal node principle would not change the treatment regiment to these women. This observation indicates that other factors than nodal misclassification should be considered.

It is documented that a proper axillary dissection is important not only regarding staging of the disease but also with respect to the local tumor control.[1,17] Hence, women with tumors in the upper lateral quadrant are likely to have the most complete surgical management of the tumor burden where axillary Level I and II dissection is a standard procedure. Compared to these patients, women with other tumor locations that may have drainage also to other lymph nodes outside of Level I and II of the axilla, may have a higher likelihood of having regional undiscovered metastatic spread after standard surgical treatment. Undetected metastatic tissue could be placed in the internal mammary chain, or as isolated nodal involvement of Level III in the axilla (nodes that are not dissected as a standard procedure), or in other locations. Women with medial tumor location are more likely to have metastatic spread to the internal mammary nodes.[18–22] Thus, incomplete removal of tumor tissue among women with tumors located away from the axilla may explain why survival disadvantage is observed also among certain groups of axillary node positive patients who receive adjuvant treatment.

Some centers have evaluated whether more extended operations including internal mammary chain dissection can improve survival of the patients.[18–22] Based on these studies between 6% and 9% (in some old studies up to 19%) of the patients have been found to have metastases in the internal mammary chain and negative

TABLE II – DISTRIBUTION OF NODAL STATUS ACCORDING TO TUMOR SIZE AND QUADRANT LOCATION OF TUMOR[1]

Positive tumor nodes	Lateral		Medial	
	Upper	Lower	Upper	Lower
≤ 2cm				
0	5,519 (64.9)	1,483 (61.8)	2,360 (74.2)	821 (68.2)
1–3	2,236 (26.3)	673 (28.1)	631 (19.8)	285 (23.7)
4–9	595 (7.0)	192 (8.0)	156 (4.9)	73 (6.1)
>10	152 (1.8)	51 (2.1)	32 (1.0)	25 (2.1)
> 2, ≤ 5 cm				
0	2,651 (41.6)	642 (43.7)	1,047 (53.6)	320 (46.8)
1–3	2,126 (33.4)	478 (32.5)	586 (30.0)	230 (33.6)
4–9	1,198 (18.8)	270 (18.4)	244 (12.5)	105 (15.4)
>10	398 (6.2)	79 (5.4)	75 (3.8)	29 (4.2)
> 5 cm				
0	234 (22.7)	31 (17.3)	51 (25.5)	18 (28.1)
1–3	294 (28.6)	60 (33.5)	57 (28.5)	18 (28.1)
4–9	297 (28.9)	69 (38.5)	62 (31.0)	18 (28.1)
>10	204 (19.8)	19 (10.6)	30 (15.0)	10 (15.6)

[1]Patients with central tumors or missing information on tumor location, tumor size, or nodal status were excluded.–Presentation of 27,234 breast cancer patients with laterally or medially located tumors operated in Denmark 1977–1998. Tumor quadrant location, *n* (%).

TABLE III – ADJUSTED RELATIVE RISK OF DYING ACCORDING TO TUMOR QUADRANT LOCATION AND AXILLARY NODAL STATUS AMONG DANISH WOMEN WITH PRIMARY BREAST CANCER OPERATED 1977–1998[1]

	All[3] (n = 27,234)	Node + (n = 12,057)	Node – (n = 15,177)
Lateral			
Upper[2]	1	1	1
Lower	1.15 (1.09–1.22)	1.15 (1.07–1.24)	1.16 (1.05–1.27)
Medial			
Upper	1.17 (1.11–1.24)	1.08 (0.996–1.16)	1.30 (1.20–1.40)
Lower	1.21 (1.11–1.31)	1.21 (1.09–1.35)	1.21 (1.07–1.37)

[1]Relative risk of dying (95% CI) adjusted for number of positive nodes, tumor size, histologic grading, age at diagnosis, year of treatment, and protocol allocation.–[2]Reference category.–[3]Patients with central tumors or missing information on tumor size or nodal status are excluded.

axillary lymph nodes. Although some authors found a beneficial effect of the extended operation for women with medial tumors, the overall conclusion was that due to increased morbidity of the intensive procedure, it was not found recommendable.

Recent studies on sentinel node procedures have revealed that about 3% of breast cancer patients without positive axillary lymph nodes have metastatic nodes outside the axilla.[3,15] Our present study underlines that axillary nodal staging is insufficient in a proportion of women with breast cancer. The sentinel node technique may offer an attractive opportunity to identify women with primary lymph drainage to lymph nodes outside the axilla and thus lead to changed treatment procedures for some women. Based on the present results, however, such altered procedures may primarily be beneficial to women with upper medially located tumors. Unfortunately, a better classification of nodal status does not appear to remove the differential survival for all tumors in the breast. The differences in survival according to tumor location are substantial and suggest that other factors of prognostic importance need be considered. We cannot exclude that the biology of the tumors differ according to location in the breast but have no evidence to support such a notion. Rather, factors such as differences in the surgical efficacy of removing regional metastatic tissue might show important for the differential survival according to tumor location observed in the present study.

REFERENCES

1. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415–8.
2. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, Costa A, de Cicco C, Geraghty JG, Luini A, Sacchini V, Veronesi P. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997;349:1864–7.
3. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, Feldman S, Kusminsky R, Gadd M, Kuhn J, Harlow S, Beitsch P. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998;339:941–6.
4. Veronesi U, Paganelli G, Viale G, Galimberti V, Luini A, Zurrida S, Robertson C, Sacchini V, Veronesi P, Orvieto E, de Cicco C, Intra M, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. J Natl Cancer Inst 1999;91:368–73.
5. Krag D. Current status of sentinel lymph node surgery for breast cancer [editorial]. J Natl Cancer Inst 1999;91:302–3.
6. Turner-Warwick RT. The lymphatics of the breast. BMJ 1957;46: 574–82.
7. Vendrell-Torné E, Setoain-Quinquer J, Domenech-Torne FM. Study of normal mammary lymphatic drainage using radioactive isotopes. J Nucl Med 1972;13:801–5.
8. Zucali R, Mariani L, Marubini E, Kenda R, Lozza L, Rilke F, Veronesi U. Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. J Clin Oncol 1998;16:1363–6.
9. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG) A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988;27:627–43.
10. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–55.
11. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–8.
12. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 2000;320:474–9.
13. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997;89:939–47.
14. SAS Institute. SAS Technical Report P-229, SAS/STAT, Software: changes and enhancements, Release 6.07. Cary, NC: SAS Institute, 1992.
15. Jansen L, Doting MH, Rutgers EJ, de Vries J, Olmos RA, Nieweg OE. Clinical relevance of sentinel lymph nodes outside the axilla in patients with breast cancer. Br J Surg 2000;87:920–5.
16. Budach V, Mirimanoff R, Schnabel T. Radiation therapy group. EORCT organization activities and current research 2000–2001. Brussels: Francoise Meunier, 2000. 162–6.
17. Moore MP, Kinne DW. Axillary lymphadenectomy: a diagnostic and therapeutic procedure [editorial]. J Surg Oncol 1997;66:2–6.
18. Morrow M, Foster RS. Staging of breast cancer: a new rationale for internal mammary node biopsy. Arch Surg 1981;116:748–51.
19. Lacour J, Le MG, Hill C, Kramar A, Contesso G, Sarrazin D. Is it useful to remove internal mammary nodes in operable breast cancer? Eur J Surg Oncol 1987;13:309–14.
20. Le MG, Arriagada R, de Vathaire F, Dewar J, Fontaine F, Lacour J, Contesso G, Tubiana M. Can internal mammary chain treatment decrease the risk of death for patients with medial breast cancers and positive axillary lymph nodes? Cancer 1990;66:2313–8.
21. Veronesi U, Cascinelli N, Bufalino R, Morabito A, Greco M, Galluzzo D, Delle, Donne V, De Lellis R, Piotti P, Sacchini V. Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. Ann Surg 1983;198:681–4.
22. Meier P, Ferguson DJ, Karrison T. A controlled trial of extended radical mastectomy. Cancer 1985;55:880–91.

APPENDIX B

Effect of Breast-Conserving Therapy versus Radical Mastectomy on Prognosis for Young Women with Breast Carcinoma

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Supported by the Danish National Research Foundation, the United States Army (DAMD17-96-1-6321), and the Boel Foundation.

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The views expressed herein do not necessarily reflect the views of the U.S. Government.

Received August 1, 2003; revision received November 12, 2003; accepted November 17, 2003.

DOI 10.1002/cncr.20022

BACKGROUND. Among middle-aged and older women with early breast carcinoma, breast-conserving therapy (BCT) has been shown to have an effect on survival that is similar to that of modified radical mastectomy (RM). Nonetheless, it remains to be established whether BCT also is the optimal treatment option for early breast carcinoma in young women, because these women generally have more aggressive disease and a higher frequency of local recurrence compared with older women.
METHODS. We investigated a cohort of 9285 premenopausal women with primary breast carcinoma who were age < 50 years at diagnosis. These women were identified from a population-based Danish breast carcinoma database containing detailed information on patient and tumor characteristics, predetermined treatment regimens, and survival.
RESULTS. In total, 7165 patients (77.2%) were treated with RM, and 2120 patients (22.8%) were treated with BCT. We calculated the relative risk of death within the first 10 years after diagnosis according to surgical treatment and age, both before and after adjustment for known prognostic factors. No increased risk of death was observed among women who received BCT compared with women who underwent RM, regardless of age at diagnosis (< 35 years, 35–39 years, 40–44 years, or 45–49 years), despite the increased risk of local recurrence among young women. Restricting the analysis to women with small tumors (size < 2 cm) yielded similar results.
CONCLUSIONS. Despite having a higher rate of local recurrence, young women with breast carcinoma who receive BCT are similar to young women treated with RM in terms of survival. *Cancer* **2004;100:688–93.** © *2003 American Cancer Society.*

KEYWORDS: breast carcinoma, breast conserving therapy, radical mastectomy, surgical treatment, young age.

Breast-conserving therapy (BCT), in which surgery is restricted to removal of the clinically apparent tumor, generally is accepted as a treatment whose effectiveness is equal to that of modified radical mastectomy (RM) in early-stage breast carcinoma.[1,2] Nonetheless, this conclusion is based primarily on data from middle-aged or older women rather than very young women. Several findings suggest that very young women with early breast carcinoma may have unique features. Studies have demonstrated that young age is a risk factor for local recurrence among women who receive BCT.[3–6] Among women age < 35 years at diagnosis who receive BCT, 10-year local recurrence rates of ≥ 30% have been reported, compared with local recurrence rates of < 10% among middle-aged and older women.[7,8] There is debate over whether local recurrence in this respect is an independent negative prognostic factor or simply an indicator of aggressive

disease.[9–15] In cases of local recurrence within the residual breast after BCT, women generally are offered RM.[16] It is unknown whether such a 'two-stage' procedure is as effective as primary RM in terms of overall survival. Thus, it remains to be determined whether BCT, compared with RM, is a safe treatment option for young women with breast carcinoma, who experience local recurrence more frequently than do their older counterparts.

We previously found that young age at diagnosis is an independent negative prognostic factor for patients with primary breast carcinoma, but this negative effect was restricted to women who did not receive adjuvant cytotoxic treatment.[17] In the current study, we examined the effect (adjusted for expected mortality) of age on breast carcinoma survival according to the type of surgical treatment used. Analysis was performed using a large, comprehensive, population-based Danish breast carcinoma registry, which contained detailed information on clinical presentation, surgical treatment, predetermined adjuvant therapy, and follow-up status.

MATERIALS AND METHODS

Registration of Patients with Breast Carcinoma

In 1977, the Danish Breast Cancer Cooperative Group (DBCG) initiated nationwide prospective studies on the effects of breast carcinoma treatment. To date, four generations of treatment programs have been launched, including DBCG 77 (patient accrual from 1977 to 1982), DBCG 82 (patient accrual from 1982 to 1989), DBCG 89 (patient accrual from 1989 to 1998), and DBCG 99 (patient accrual since 1999). Because BCT was introduced in 1982, we restricted the current study to patients from the DBCG 82 and DBCG 89 programs. Furthermore, our primary objective was to evaluate the prognosis of young patients; therefore, we limited the study to premenopausal women (defined as women who had experienced menstruation within the preceding 12 months) age < 50 years at diagnosis.

In all programs, the primary surgical treatment for patients who were assigned to treatment protocols included either total mastectomy plus axillary dissection or lumpectomy plus axillary dissection and radiotherapy against residual breast. Standard adjuvant cytotoxic chemotherapy was used in all three programs (Table 1).[17,18] Patients were classified as either low risk or high risk according to histopathologic criteria. High-risk criteria during the investigation period included positive lymph nodes, tumor size > 5 cm, and (after 1989) histologic Grade II or III disease (according to the Bloom and Richardson grading system). Treatment allocation, which was independent of primary surgical treatment, is described in detail elsewhere.[17,18] In the 1980s, BCT was used only in a limited number of major departments as part of a randomized trial, whereas in the 1990s, BCT became a standard procedure.

TABLE 1
Overview of Postoperative Adjuvant Treatment Administered between 1982 and 1998 to Premenopausal, High-Risk Patients with Breast Carcinoma in Denmark

Treatment protocol	Treatment randomization
DBCG 82	CMF or CMF + radiotherapy; or CMF + tamoxifen
DBCG 89	
Patients with ER-positive disease	CMF or ovariectomy
Patients with ER-negative disease	CMF; or CEF; or CMF + pamidronate; or CEF + pamidronate

DBCG: Danish Breast Cancer Cooperative Group; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; ER: estrogen receptor; CEF: cyclophosphamide, epirubicin, and 5-fluorouracil.

Patients with bilateral breast carcinoma or inflammatory carcinoma, distant metastases, or contraindication against the planned postoperative therapy, as well as patients who were not treated according to the surgical guidelines, were not assigned to a protocol. These patients were known as the *miscellaneous group.*

Primary clinical and histopathologic data and data regarding postoperative adjuvant therapy and status at follow-up, including information on site of recurrence, have been registered by the DBCG secretariat based on specific case report forms submitted by departments of surgery, pathology, and oncology within Denmark. Comparison of the DBCG registry with the Danish Cancer Registry, which is considered nearly complete with respect to the reporting of breast carcinoma diagnoses among residents in Denmark, revealed a concordance rate of $> 95\%$ within the age group investigated in the current study.[19,20]

Registration of Vital Status

The Danish Civil Registration System (CRS) was established in 1968, and since then, a unique identification number has been assigned to each Danish resident. Individual information is kept using this personal identification number in all national registries, allowing accurate linkage of information between registries. The CRS registry maintains updated files on vital status. A detailed description of the information included in this registry is provided elsewhere.[21] Patient records in the DBCG registry were linked with records in the CRS registry to obtain complete information on vital status.

Statistical Analysis

Women with breast carcinoma diagnosed between January 1, 1982, and December 31, 1998, were included and followed for survival data until 10 years after diagnosis or until December 31, 2000 (whichever occurred first). The study was restricted to premenopausal women age < 50 years at diagnosis who had received either BCT or RM.

The overall death rate was modeled as a sum of two terms. The first term represented the age-and-calendar-specific expected mortality as a known time-dependent offset; expected mortality data was obtained from life tables for the overall female population in Denmark stratified by 5-year age groups and 5-year calendar periods.[22] The second term in the model was the exponential function of a linear expression that included the following categoric variables: an interaction term between surgical treatment type (BCT or RM) and age at diagnosis (by 5-year group); tumor size (≤ 2 cm, > 2 cm and ≤ 5 cm, or > 5 cm); number of positive lymph nodes (0, 1-3, 4-9, or ≥ 10); histologic grade (I, II, III, or nonductal carcinoma); protocol allocation (allocated, not treated according to surgical guidelines, or not allocated for other reasons); and year of diagnosis (1982-1988 or 1989-1998). This model can be viewed as a log-linear representation of the observed death rate minus the expected death rate—i.e., a log-linear model of the excess death rate. The expected number of deaths due to breast carcinoma accounts for only a small proportion of all expected deaths.[22] Therefore, the adjusted relative risks were interpreted as relative risks of death due to breast carcinoma. We chose to perform Poisson regression analysis, rather than Cox regression analysis, to facilitate additive adjustment for expected mortality.

All tests in the Poisson regression analyses were performed as likelihood ratio tests using Epicure software (Hirosoft International, Seattle, WA).[23] Tests for differences in the age-specific effects of surgical treatment between low-risk patients and high-risk patients receiving cytotoxic treatment were performed by including a three-way interaction term among surgical treatment (BCT or RM), age at diagnosis, and risk group. Associations between selected characteristics at diagnosis were analyzed using chi-square tests.

RESULTS

By January 1, 1999, 9285 premenopausal women age < 50 years with primary breast carcinoma were registered by the DBCG. The study cohort accounted for a total of 60,246 person-years of follow-up: 13,116 person-years in the BCT group and 47,130 person-years in the RM group. The median follow-up period was 7.1 years, and 32.6% of all patients were followed for 10 years. The distribution of patients according to surgical treatment type, age at diagnosis, tumor characteristics, and protocol allocation is provided in Table 2. A total of 7165 patients (77.2%) were treated with RM, compared with 2120 patients (21.8%) treated with BCT. Until 1989, BCT was offered only in randomized trials; consequently, the overall rate of BCT use was relatively low. Compared with women age > 35 years at diagnosis, women age < 35 years were more likely to have tumors > 2 cm in size ($P = 0.007$) and lymph

TABLE 2
Distribution, According to Surgical Treatment Type, Age at Diagnosis, Tumor Characteristics, and Risk-Group Allocation, of 9285 Premenopausal Women with Primary Breast Carcinoma Who Underwent Surgery in Denmark between 1982 and 1998

	Surgical treatment (%)	
Characteristic	Mastectomy	Breast-conserving treatment
All patients	7165 (77.2)	2120 (22.8)
Age at diagnosis (yrs)		
< 35	500 (69.5)	219 (30.5)
35–39	1126 (75.9)	357 (24.1)
40–44	2355 (78.3)	654 (21.7)
45–49	3184 (78.2)	890 (21.8)
Tumor size (cm)		
≤ 2	3662 (69.5)	1611 (30.5)
> 2 and ≤ 5	2817 (86.1)	455 (13.9)
> 5	589 (97.8)	13 (2.2)
No information	97 (70.3)	41 (29.7)
Positive lymph nodes		
0	3516 (72.2)	1351 (27.8)
1–3	2147 (78.9)	574 (21.1)
4–9	1025 (91.3)	98 (8.7)
≥ 10	356 (93.2)	26 (6.8)
No information	121 (63.0)	71 (37.0)
Histologic grade		
I	1676 (74.3)	580 (25.7)
II/III	3962 (78.9)	1061 (21.1)
ND	1527 (76.1)	479 (23.9)
Estrogen receptor status		
Positive	3054 (74.7)	1036 (25.3)
Negative	1610 (75.7)	516 (24.3)
No information	2501 (81.5)	568 (18.5)
Protocol allocation		
1982 protocol	3450 (87.2)	506 (12.8)
1989 protocol	3715 (69.7)	1614 (30.3)
Risk group		
Low	3054 (72.5)	1156 (27.5)
High	3192 (84.1)	603 (15.9)
Not treated according to guidelines[a]	568 (64.4)	314 (35.6)
Not allocated for other reasons[b]	351 (88.2)	47 (11.8)

ND: patients with nonductal carcinoma or without available histologic grading information.
[a] Patients who were not allocated because surgical treatment did not follow guidelines.
[b] Patients who were not allocated due to medical contraindications, bilateral or inflammatory breast carcinoma, or distant metastases.

TABLE 3
Adjusted Estimates of Relative Risk of Death (with 95% Confidence Intervals) for Women Receiving Breast-Conserving Therapy Relative to Patients Undergoing Radical Mastectomy, by Age at Diagnosis, Tumor Size, and Protocol Allocation[a]

	All patients (n = 9000)[b]				Tumor size ≤ 2 cm (n = 5195)				Protocol TM82 (n = 350)[c]			
	Mastectomy (n = 6971)		BCT (n = 2029)		Mastectomy (n = 3620)		BCT (n = 1575)		Mastectomy (n = 170)		BCT (n = 180)	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Age at diagnosis (yrs)												
< 35	1 (ref.)	488	0.87 (0.64–1.19)	203	1 (ref.)	219	1.05 (0.71–1.54)	147	1 (ref.)	12	1.09 (0.35–3.40)	15
35–39	1 (ref.)	1094	1.02 (0.78–1.34)	343	1 (ref.)	598	0.77 (0.53–1.12)	254	1 (ref.)	31	1.37 (0.53–3.54)	36
40–44	1 (ref.)	2273	0.80 (0.62–1.04)	629	1 (ref.)	1197	0.72 (0.51–1.02)	496	1 (ref.)	50	2.07 (0.82–5.22)	66
45–49	1 (ref.)	3116	0.66 (0.50–0.88)[d]	854	1 (ref.)	1606	0.56 (0.38–0.83)	679	1 (ref.)	77	1.44 (0.60–3.49)	63

BCT: breast-conserving therapy; RR: relative risk; CI: confidence interval; ref.: referent group.
[a] Data from 9000 Danish women with primary breast carcinoma diagnosed between 1982 and 1988. Relative risk estimates are adjusted for tumor size, lymph node status, histologic grade, estrogen receptor status, year of treatment, and protocol allocation.
[b] Two hundred eighty-five patients were excluded because of missing information on tumor size or lymph node status.
[c] Patients randomized to breast-conserving therapy versus radical mastectomy.
[d] $P < 0.05$.

node–positive disease ($P = 0.002$). Younger patients also were more likely to receive BCT ($P < 0.001$). Overall, compared with women in the RM group, women in the BCT group were significantly more likely to have tumors < 2 cm in size ($P < 0.001$) and lymph node–negative disease ($P < 0.001$).

To evaluate the independent, age-specific effect of surgical treatment type on breast carcinoma–specific survival, we performed a multivariate analysis (with patients placed into 5-year age groups) that included surgical treatment, tumor size, axillary lymph node status, histologic grade, year of treatment, and protocol allocation (Table 3). Women who underwent RM were selected to be the reference group. All adjusted relative risk estimates for women receiving BCT were equal to or less than the reference values; this finding indicates that BCT was not associated with reduced survival. Among patients ages 45–49 years, the adjusted estimates of relative risk of death were significantly lower in the BCT group (relative risk, 0.66; 95% confidence interval [CI], 0.50–0.88) compared with the RM group. Restricting the analysis to small tumors (size < 2 cm) or to patients randomized to BCT versus RM (protocol TM82) did not change the results. Analysis of patients receiving BCT indicated a 5.2-fold greater incidence (15.4% vs. 3.0%) of local recurrence in the breast within 5 years of diagnosis among women age < 35 years compared with women ages 45–49 years.

To evaluate the effects of adjuvant cytotoxic therapy in relation to age at diagnosis and surgical treatment type, we allowed for an interaction between age at diagnosis and low-risk status (low-risk patients received no adjuvant systemic treatment; $n = 4210$) versus high-risk status + adjuvant cytotoxic treatment ($n = 2935$) (Table 4). We observed a nonsignificant trend toward reduced survival with decreasing age among patients in the BCT group who did not receive adjuvant cytotoxic treatment ($P = 0.26$). No trend was observed among patients who received adjuvant cytotoxic treatment.

TABLE 4
Adjusted Estimates of Relative Risk of Death (with 95% Confidence Intervals) for Patients Receiving Breast-Conserving Therapy Relative to Patients Undergoing Radical Mastectomy, by Age at Diagnosis and Adjuvant Treatment Use[a]

	RR (95% CI)			
	Low-risk patients receiving no adjuvant treatment (n = 4210)		High-risk patients receiving adjuvant cytotoxic treatment (n = 2935)	
	Mastectomy (n = 3054)	BCT (n = 1156)	Mastectomy (n = 2486)	BCT (n = 449)
Age at diagnosis (yrs)				
< 35	1 (ref.)	1.31 (0.77–2.22)	1 (ref.)	0.73 (0.44–1.22)
35–39	1 (ref.)	1.18 (0.74–1.90)	1 (ref.)	0.69 (0.43–1.12)
40–44	1 (ref.)	0.94 (0.59–1.48)	1 (ref.)	0.81 (0.54–1.21)
45–49	1 (ref.)	0.63 (0.33–1.21)	1 (ref.)	0.64 (0.41–1.01)

RR: relative risk; CI: confidence interval; BCT: breast-conserving therapy; ref.: referent group.
[a] Data from 7145 Danish women with primary breast carcinoma diagnosed between 1982 and 1998. Relative risk estimates are adjusted for tumor size, lymph node status, histologic grade, estrogen receptor status, year of treatment, and protocol allocation.

DISCUSSION

Among younger women, we found that long-term survival was similar for those who received BCT and

those who underwent RM. Previous studies evaluating these treatment regimens have reported similar results, but these studies included a very limited number of women age < 40 years and consequently are not as conclusive in their findings on younger women.[1,2] The current study included more than 9000 women age < 50 years who received either BCT or RM; 1483 of these women were diagnosed at ages 35–39 years, and 719 were diagnosed at age < 35 years.

Our finding is reassuring since young women with breast carcinoma generally have a particularly poor prognosis.[24–26] Specifically, young women who receive BCT are more likely to experience local recurrence, as also noted in the current study, in which younger patients who received BCT were more than five times as likely to experience local recurrence compared with their middle-aged counterparts. Although this finding could be explained in part by the failure to control for the increased frequency of advanced disease among younger patients,[27–29] we previously found young age to be an independent negative prognostic factor.[17]

Despite efforts to adjust for differences in prognostic factor profiles between the BCT and RM groups, residual confounding cannot be ruled out. As expected, women who received BCT had a significantly lower incidence of advanced disease as measured by tumor size and lymph node status. This finding may explain why superior survival was observed in the BCT group regardless of age at diagnosis. Nonetheless, the results remained unchanged when the analysis was restricted to women with tumors < 2 cm in size; in this group of women, the risk of selection bias is expected to be reduced, and therefore, the credibility of the result is enhanced. Furthermore, an updated analysis of patients randomized to either RM or BCT[30] revealed no trend toward decreased survival among the youngest patients.

Bias would be introduced if the surgeon changed the criteria for offering BCT based on patient age. Thus, residual confounding may explain the apparent survival advantage observed among women ages 45–49 years who received BCT, because the proportion of women receiving BCT was smallest in this age group. However, women age < 35 years at diagnosis were less likely to have small tumors and negative lymph node status, and the proportion of women who received BCT was largest in this age group. Thus, selection bias (and, consequently, residual confounding) should not be any more apparent in this group. Nonetheless, BCT was found to be as beneficial as RM among young patients, indicating that young patients have similar survival irrespective of treatment type.

We performed additional stratified analyses that focused on the adjusted relative risk of death according to surgical method among women who did or did not receive adjuvant therapy. Among women who did not receive adjuvant therapy, the risk of death was not significantly greater for patients who received BCT compared with patients who underwent RM in any of the age categories; however, overall, there was a nonsignificant trend toward poorer prognosis with decreasing age. In theory, if substantial residual confounding were present in the BCT group, then the observed trend toward reduced survival among younger patients who received BCT could hide true risks for very young patients who received BCT without adjuvant treatment. Among women who received BCT with adjuvant cytotoxic treatment, no association between age and survival was found. We previously observed decreased survival among young women who did not receive adjuvant cytotoxic therapy,[17] and the International Consensus Panel on the Treatment of Primary Breast Cancer recently changed its recommendation to include age < 35 years as a sufficient criterion for systemic chemotherapy, irrespective of disease stage.[31] Such treatment reduces the risk of distant metastases and disease recurrence and thus must be expected to decrease the likelihood of observing any trend toward diminished survival among very young women with BCT-treated early breast carcinoma in the future.

The use of BCT has steadily become more common over the last few decades. As might be expected, younger patients typically choose BCT more often than do older patients. Although the high frequency of local recurrence among younger patients represents a problem in itself, the current study did not find survival to be significantly different for young women who received BCT compared with those who underwent RM. Based on the results of the current study, however, adherence to the international recommendation of systemic chemotherapy in addition to surgery for very young women does appear to be justified.

REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233–1241.
2. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227–1232.
3. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet.* 1991;338:327–331.

4. Harrold EV, Turner BC, Matloff ET, et al. Local recurrence in the conservatively treated breast cancer patient: a correlation with age and family history. *Cancer J Sci Am.* 1998;4: 302–307.
5. Elkhuizen PH, Voogd AC, van den Broek LC, et al. Risk factors for local recurrence after breast-conserving therapy for invasive carcinomas: a case-control study of histological factors and alterations in oncogene expression. *Int J Radiat Oncol Biol Phys.* 1999;45:73–83.
6. Mirza NQ, Vlastos G, Meric F, et al. Predictors of locoregional recurrence among patients with early-stage breast cancer treated with breast-conserving therapy. *Ann Surg Oncol.* 2002;9:256–265.
7. Touboul E, Buffat L, Belkacemi Y, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys.* 1999;43:25–38.
8. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for Stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol.* 2001;19:1688–1697.
9. Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol.* 1994;12:2229–2234.
10. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 2000;355:1757–1770.
11. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997;337:949–955.
12. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet.* 1999; 353:1641–1648.
13. Koscielny S, Tubiana M. Link between local recurrence and distant metastases in human breast cancer. *Int J Radiat Oncol Biol Phys.* 1999;45:245–246.
14. Rouzier R, Extra JM, Carton M, et al. Primary chemotherapy for operable breast cancer: incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. *J Clin Oncol.* 2001;19:3828–3835.
15. Vrieling C, Collette L, Fourquet A, et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer.* 2003;39:932–944.
16. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. *Breast Cancer Res Treat.* 1998;49:69–78.
17. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. *Br Med J.* 2000;320:474–479.
18. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). A description of the register of the nation-wide programme for primary breast cancer. *Acta Oncol.* 1988;27:627–647.
19. Storm HH. The Danish Cancer Registry, a self-reporting national cancer registration system with elements of active data collection. *IARC Sci Publ.* 1991;95:220–236.
20. Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. *Cancer Causes Control.* 2000;11:669–674.
21. Melbye M, Wohlfahrt J, Olsen JH, et al. Induced abortion and the risk of breast cancer. *N Engl J Med.* 1997;336:81–85.
22. Danmarks Statistik. Statistical ten-year review. Copenhagen: Danmarks Statistik, 1996.
23. al Saati T, Clamens S, Cohen-Knafo E, et al. Production of monoclonal antibodies to human estrogen-receptor protein (ER) using recombinant ER (RER). *Int J Cancer.* 1993;55:651–654.
24. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med.* 1986;315:559-563.
25. Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer.* 1996;77:97–103.
26. Winchester DP, Osteen RT, Menck HR. The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age. *Cancer.* 1996;78:1838–1843.
27. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? *J Natl Cancer Inst Monogr.* 1994;16:35–42.
28. Remvikos Y, Magdelenat H, Dutrillaux B. Genetic evolution of breast cancers. III. Age-dependent variations in the correlations between biological indicators of prognosis. *Breast Cancer Res Treat.* 1995;34:25–33.
29. Walker RA, Lees E, Webb MB, Dearing SJ. Breast carcinomas occurring in young women (< 35 years) are different. *Br J Cancer.* 1996;74:1796–1800.
30. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr.* 1992;11: 19–25.
31. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer. *J Clin Oncol.* 2001;19:3817–3827.

APPENDIX C

Int. J. Cancer: **107,** 997–1000 (2003)

Publication of the International Union Against Cancer

BIRTH WEIGHT AND RISK OF BREAST CANCER IN A COHORT OF 106,504 WOMEN

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The possible association between prenatal factors and breast cancer has been discussed for more than a decade. Birth weight has been used commonly as a proxy measure for intrauterine growth. Whereas some previous studies have found support for an association between birth weight and breast cancer, others have been inconclusive or found no association. We investigated the relationship between birth weight and risk of female breast cancer in a cohort of 106,504 Danish women. Birth weights were obtained from school health records on girls born between 1930–1975. Information on breast cancer came from linking the cohort with the Danish Cancer Registry and the Danish Breast Cancer Cooperative Groups Registry. A total of 2,334 cases of primary breast cancer were diagnosed in the cohort during 3,255,549 person-years of follow-up among women with birth weight between 500–6,000 g. Of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older. A significant association between birth weight and breast cancer was found equivalent to an increase in risk of 9% per 1,000 g increase in birth weight (95% CI 2–17). The increase was observed for all age groups, representing both pre- and postmenopausal women, and irrespective of tumor characteristics. Adjustment for age at first birth and parity did not influence the results. Birth weight is positively associated with risk of breast cancer, indicating that prenatal factors are important in the etiology of breast cancer.

Key words: *breast cancer; birth weight; oestrogen; prenatal factors; epidemiology; cohort*

In 1990, Trichopoulos hypothesized that breast cancers may originate in utero.[1] The idea is based on the assumption that endogenous estrogens are important in the etiology of breast cancer, and that the first exposure of the mammary gland to high concentrations of estrogens (10–100 times the oestrogen levels achieved later in life) occurs in utero.[1] At this early stage, the mammary gland is largely undifferentiated and may be particularly susceptible to influences that could increase the risk of cancer through accelerated cell growth or by being more prone to exogenous carcinogenic stimuli.[1] Studies have shown that birth weight is associated with oestrogen levels during pregnancy, which suggests that birth weight is a useful proxy measure of intrauterine oestrogen measure.[2–4]

Studies on the association between birth weight and risk of breast cancer have, however, yielded somewhat conflicting results. Overall, the available literature on birth weight is suggestive of an intrauterine effect on later risk of breast cancer especially for premenopausal ages, but the evidence is in many cases based either on studies with small sample sizes or on data of recalled events that occurred many decades earlier.[5–20]

We explore the relation between birth weight and risk of breast cancer in a very large population-based cohort of women for whom birth weights were recorded early in life.

MATERIAL AND METHODS

Study population

The study cohort consisted of 161,063 girls born between 1930–1975 who attended school in Copenhagen, Denmark. In this period school health records were kept for all pupils. The health records were filled in by nurses or physicians in the school health services on a yearly basis from school start until the child left school. Either or both parents accompanied their child to the first visit, at which they reported the child's birth weight. The complete records are now kept at the Copenhagen City Archives and contain information on *e.g.* the child's name and date of birth, birth weight and the mother's name.

The Danish Civil Registration System (CRS) was established 1 April 1968. All residents and newborns in Denmark have been given a unique 10-digit person identification number (the CRS-number). The CRS-number is stored along with information on name, place of birth, and parental identity on all Danish residents. It is updated daily with respect to vital and migration status. All other national registries in Denmark, which record individual information, are based on the CRS number, thus serving as a unique key for linkage studies. Information from the CRS was used to generate a population-based relational database, the Birth Order Study database (BOS), containing information on all men and women born during the period 1 January 1935 to 31 December 1998, who have been assigned a CRS-number.[21] This database contains close to complete information on sibships of children, parity of women and links between family members. The completeness of the linkage between mother and child in BOS was estimated to 97.3% for children born before 1968, and complete information for children born hereafter.[22]

Information from the school health records was computerized and linked to the CRS matching on birth date and name. This resulted in the identification of CRS-numbers for 141,481 girls (88%). The lack of identification of the remaining 12% is partly due to death (1%), emigration, and change of surname at the time of marriage, before 1 April 1968. Of the 141,468 girls with a CRS-number 106,504 (75%) had information on birth weight.

Ascertainment of cases

Information on incident breast cancer cases was obtained from the Danish Cancer Registry and from the Danish Breast Cancer Cooperative Groups Registry. The Danish Cancer Registry was established in 1942 and is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since

Grant sponsor: Department of the US Army; Grant sponsor: Danish Cancer Society; Grant sponsor: Danish National Research Foundation; Grant sponsor: Dagmar Marshall Foundation.

The authors certify that they have not entered into any agreement that could interfere with their access to the data on the research, nor upon their ability to analyze the data independently, to prepare manuscripts, and to publish them.

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Received 3 February 2003; Revised 2 July 2003; Accepted 4 July 2003

DOI 10.1002/ijc.11481

1943.[23] The Danish Breast Cancer Cooperative Groups Registry (DBCG) was established in late 1976 for the purpose of standardizing and evaluating the treatment of breast cancer in Denmark.[24] In addition to information from the Danish Cancer Registry, DBCG contains information on tumor size and histology, oestrogen receptor status, nodal status and subsequent treatment.

STATISTICAL METHODS

The association between birth weight and breast cancer risk was estimated in a cohort design using log-linear Poisson regression. Follow-up for breast cancer began 1 April 1968, or the date of birth, which ever came last, and continued until a diagnosis of cancer, death, emigration or 31 August 2000, whichever came first.

Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60) and calendar period in 5-year intervals.[25] In additional analyses, adjustments were made for age at first birth (nulliparous, 12–19, 20–24, 25–29, 30–34, 35+) and parity (0,1,2,3,4+).

The relative risk (rate ratio) increase per 1,000 g increase in birth weight was estimated by treating birth weight categorized in intervals of 100 g as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. The log-linear assumptions underlying the trend estimation of birth weight were checked in 2 ways. Firstly, by a likelihood ratio test comparing the models with birth weight treated as a continuous and a categorical variable, respectively. Second, by evaluating the effect of including a quadratic term in the trend analysis.

Poisson regression was used instead of Cox regression because of the computational efficiency in large datasets. Estimation using Cox regression with age as the underlying time variable gave identical estimates of the main trend and the confidence interval.

Information on tumor characteristics was available from 1977. Estimation of the increase in breast cancer risk according to tumor diameter (<2 cm; 2–5 cm; ≥5 cm; missing or diagnosed before 1977), nodal status (negative; positive; missing or diagnosed before 1977) and oestrogen receptor status (negative; positive; missing or diagnosed before 1977) by 1,000 g increase in birth weight was carried out as a competing risks analysis, *i.e.*, with censoring as above but counting only the selected case category as cases.

All analyses were carried out using the SAS statistical software release 8.02 (specifically the PROC GENMOD procedure).[26]

RESULTS

A total of 2,340 cases of primary breast cancer were diagnosed in the cohort during 3,266,070 years of follow-up. Women with recorded birth weights ≥6,000 g or ≤500 g were excluded from the analyses due to a high risk of misclassification in these extreme groups.

Number of breast cancer cases and person-years of follow-up by age, calendar period, birth cohort and birth weight category for women remaining in the analysis are shown in Table I. A total of 2,334 cases of primary breast cancer were diagnosed in the restricted cohort during 3,255,549 years of follow-up and of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older.

In our main analysis we found a significant positive association between birth weight and breast cancer equivalent to a 9% increase in risk per 1,000 g increase in birth weight (95% CI = 2% to 17%). If all registered birth weights were included in the analysis (*i.e.*, including birth weight registered as being below 501 g or above 5,999 g) the increase in risk was 8% per 1,000 g (95% CI = 1% to 16%). Data and trend are shown on Figure 1.

Table II shows the increase in breast cancer risk by 1,000 g increase in birth weight stratified by age. The risk increase by birth weight did not vary with age (p = 0.30). Analysis of the linear trend according to year of birth and period likewise showed no variation (data not shown).

To investigate the association with tumor characteristics we used additional data from DBCG on tumor size (<2 cm: n = 1,132, 2–5 cm: n = 680, ≥ 5 cm: n = 159, missing: n = 363) nodal status (node neg: n = 1,097, node pos: n = 859, missing: n = 378) and oestrogen receptor status (ER pos: n = 1,087, ER neg: n = 469, missing: n = 778). Estimating the increase in risk of breast cancer according to tumor characteristics by 1,000 g increase in birth weight showed no systematic differences in the

TABLE I – NUMBER OF BREAST CANCER CASES AND PERSON YEARS OF FOLLOW-UP

Cohort characteristics	Cases (%)	Person years / 1,000 (%)
	(n = 2,334)	(n = 3,256)
Age		
0–39	375 (16.1)	2,305.6 (70.8)
40–44	453 (19.4)	347.9 (10.7)
45–49	584 (25.0)	281.2 (8.6)
50–54	502 (21.5)	199.0 (6.1)
55–59	325 (13.9)	98.2 (3.0)
60 +	95 (4.1)	23.6 (0.7)
Calendar period		
1968–1979[1]	145 (6.2)	1,187.7 (36.5)
1980–1989	624 (26.7)	1,022.8 (31.4)
1990 +	1,565 (67.1)	1,045.1 (32.1)
Birth cohort		
1930–1939	587 (25.2)	322.1 (9.9)
1940–1949	1,387 (59.4)	1,249.8 (38.4)
1950–1959	325 (13.9)	83.3 (25.5)
1960 +	35 (1.5)	853.3 (26.2)
Birth weight		
501–1,499 g	5 (0.2)	13.5 (0.4)
1,500–2,499 g	125 (5.4)	191.6 (5.9)
2,500–2,999 g	305 (13.1)	522.6 (16.1)
3,000–3,499 g	846 (36.3)	1,207.5 (37.1)
3,500–3,999 g	717 (30.7)	938.5 (28.8)
4,000–4,499 g	248 (10.6)	298.0 (9.2)
4,500–5,999 g	88 (3.8)	83.8 (2.6)

[1]Follow-up began 1 April 1968.

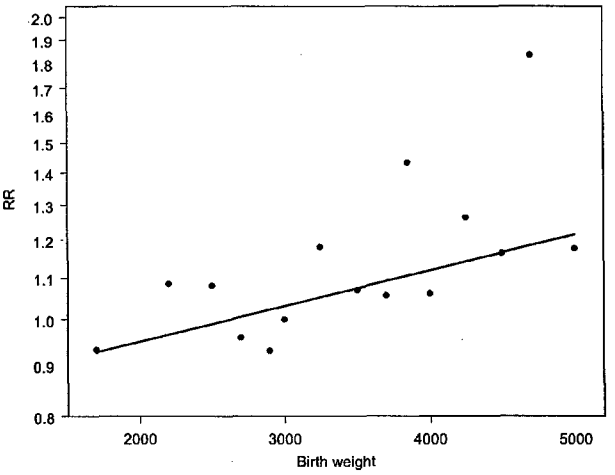

FIGURE 1 – Adjusted relative risk of breast cancer in birth weight intervals of 200 g compared to women with a birth weight between 3,000–3,199 g. Due to small numbers at the end of the distributions we have grouped the birth weights into the following categories: <2,000 g, 2,000–2,399 g, 2,400–2,599 g, 2,600–2,799 g, 2,800–2,999 g, ..., 4,600–4,799 g, ≥4,800 g. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment was made for age and calendar period.

TABLE II – INCREASE IN BREAST CANCER RISK PER 1000 G INCREASE IN BIRTH WEIGHT ACCORDING TO AGE

Age (years)	Cases (n = 2,334)	$RR_{per\ 1000\ g}$ (95% CI)[1]	
0–39	375	1.07 (0.90–1.28)	$p = 0.30$[2]
40–44	453	1.08 (0.92–1.26)	
45–49	584	1.20 (1.04–1.38)	
50–54	502	1.08 (0.92–1.25)	
55–59	325	1.09 (0.91–1.31)	
60 +	95	0.77 (0.56–1.07)	
Overall		1.09 (1.02–1.17)	

[1]Adjusted for calendar period.–[2]Test for difference, *i.e.* test for interaction between age and birth weight trend. Similar analysis but with binary age groups (< 50 years and ≥ 50 years) revealed no difference in trend according to age, $p = 0.29$.

trend by tumor characteristics at diagnosis. The increase in risk of being diagnosed with a tumor <2 cm by 1,000 g increase in birth weight was 1.09 (0.99–1.20), 0.98 (0.86–1.11) for tumors between 2–5 cm, and 1.21 (0.93–1.58) for tumors ≥5 cm. Likewise was the increase in risk by 1,000 g increase in birth weight for nodal positive tumors 1.03 (0.91–1.15) and 1.07 (0.96–1.18) for nodal negative tumors. For oestrogen receptor positive tumors the increase in risk was 1.03 (0.88–1.20) and for oestrogen receptor negative tumors 1.01 (0.91–1.12).

To further validate the results three additional analyses were carried out. Firstly, parity and age at first birth were known for women born in 1935 and later. No confounding effect was found when adjusting for these factors. Restricting the cohort to women where parity and age at first birth were known the increase in risk by 1,000 g increase in birth weight was similar the increase in risk for whole cohort (RR = 9% per 1,000 g, 95% CI = 2%–17%). Adjusting for parity and age did not change this estimate. Secondly, some of the identified women had missing information on birth weight. Their breast cancer risk did not vary significantly from women with known birth weight, $RR_{unknown\ vs.\ known} = 0.94$ (95% CI = 0.86–1.03). Thirdly, the estimation was based on the assumption that the association between birth weight and breast cancer can be described by a trend. Goodness-of-fit tests gave no indication that this assumption was inadequate.

DISCUSSION

Based on a cohort of 106,504 women we documented a statistically significant association between birth weight and breast cancer. Thus, risk of breast cancer increased by 9% per 1,000 g increase in birth weight. This finding is in agreement with the currently prevailing hypothesis that intrauterine factors contribute to the development of breast cancer in adulthood.

Whereas some previous studies have found support for an association between birth weight and breast cancer,[5–9,20] others have been inconclusive or observed no association.[9–19] Thus, 3 recent smaller cohort studies found a positive but non-significant association with high birth weight.[10–12] A significant positive association was found in a Norwegian case-control study (373 cases of breast cancer),[7] whereas a similarly designed Swedish study (1,068 cases) failed to document a significant association with birth size indicators.[13] Based on 2 different case-control studies, Sanderson and colleagues[9] reported a positive association between birth weight and risk of breast cancer in premenopausal women in the US, but not in postmenopausal women. The association in premenopausal women was supported by Innes and McCormack,[5,20] but others found no such association.[15–18] Based on recalled birth weights reported by adult women and their mothers, Michels et al.[6] found significant evidence to support a positive association between extreme birth weight and risk of breast cancer, not only in younger women but also later in life. The reason why some previous studies failed to find an association may partly be due to the fact that the independent effect of birth weight seems to be rather small, and the studies thus lacked power due to their size.

Analysis of the magnitude of the trend per 1,000 g increase in birth weight has only been reported in one previous study[10] that followed 3,447 women who gave rise to 177 breast cancers. The authors also found a linear increased risk of breast cancer with increased birth weight with a hazard ratio of 22% per 1,000 g (95% CI 10–65). Three other studies have reported significant trends,[6,7,20] but did not calculate the magnitude of the trend.

In contrast to most previous studies our study had sufficient power to detect weak associations and avoided, to a large extent, potentials for bias of the results. We based our cohort on all children attending schools in a well defined area of Denmark and followed them for as much as 70 years through our national registries. These registries contain continuously updated mandatory registrations of vital status, emigration and cancer diagnoses. The social structure of the Danish health care system that provides equal access to health care further diminished possibilities for bias. Measures of birth weight were recorded decades before and independent of possible breast cancer diagnosis, making differential misclassification unlikely. Furthermore, birth weight was recorded at an early age, which limited potentials for recall bias.[27] We were not able to adjust birth weight for gestational age. Studies have suggested, however, that prematurity is associated with an increased risk of breast cancer[28] and controlling for gestational age would then likely have tended to strengthen the association with birth weight.[13]

The size of this study made it possible to perform estimations in subgroups. It has previously been suggested that the association with birth weight is strongest for premenopausal women.[5,9] We found, however, the effect of birth weight to be similar in all age groups (Table II). The association with birth weight according to tumor characteristics has not previously been investigated. We found no systematic differences in the association by tumor characteristics. This suggests that the association with birth weight is a general phenomenon and not restricted to tumors with specific characteristics.

Adjustment for parity and age at first birth had no impact on our results. Parity and age at first birth reflects the hormonal and cellular changes after pregnancies as well as maternal social status. Based on this result we found in line with others[20] no indication of confounding by social status although both birth weight and breast cancer have been associated with social factors.[29]

The biological explanation for an association between birth weight and later risk of breast cancer remains to be established. Involvement of hormones, particularly estrogens, in the carcinogenesis has received much attention as the mammary gland is exposed to very high concentrations of estrogens *in utero*.[30] Studies have shown that birth weight is correlated with oestrogen levels during pregnancy,[2–4] and birth weight has therefore typically been used as a proxy measure of intra-uterine oestrogen exposure. As the intra-uterine hormonal milieu is very complex, however, it is likely that other exposures, *e.g.*, IGF and insulin, which are also correlated with birth weight, could be equally important.

In conclusion, we found a small but significant association between birth weight and risk of breast cancer, which supports the hypothesis that prenatal factors are involved in the pathogenesis of breast cancer.

REFERENCES

1. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990;335:939–40.
2. McFadyen IR, Worth HG, Wright DJ, Notta SS. High oestrogen excretion in pregnancy. Br J Obstet Gynaecol 1982;89:994–9.

3. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990;1:247–50.
4. Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000;11:315–9.
5. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152:1121–8.
6. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC. Birthweight as a risk factor for breast cancer. Lancet 1996;348: 1542–6.
7. Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, Stuver SO. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002;86:89–91.
8. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001;93:60–2.
9. Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, Daling JR. Perinatal factors and risk of breast cancer. Epidemiology 1996;7:34–7.
10. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, Barker DJ. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001;85: 1680–4.
11. Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A, Hulthen L. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193–8.
12. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000;83:964–8.
13. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71–6.
14. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015–8.
15. Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397–407.
16. Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988;57:437–9.
17. Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER, Baron JA, Trichopoulos D, Willett WC. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:207–10.
18. Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84–8.
19. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001;91:248–51.
20. McCormack VA, dos SS, I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003;326:248.
21. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997;89:939–47.
22. Westergaard T. Birth order and cancer risk. PhD-thesis, University of Copenhagen. Copenhagen: Department of Epidemiology Research, Danish Epidemiology Science Center, 1997. 1–82.
23. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. Dan Med Bull 1997;44:535–9.
24. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988;27:627–47.
25. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356–65.
26. SAS/STAT. User's guide, version 8. vol. 1–3. SAS Publishing, 2003.
27. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997;145:58–67.
28. Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. J Natl Cancer Inst 2000;92:840–1.
29. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37(Suppl):S4–66.
30. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.

APPENDIX D

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Growth Patterns and the Risk of Breast Cancer in Women

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ABSTRACT

BACKGROUND

Adult height and body-mass index influence the risk of breast cancer in women. Whether these associations reflect growth patterns of the fetus or growth during childhood and adolescence is unknown.

METHODS

We investigated the association between growth during childhood and the risk of breast cancer in a cohort of 117,415 Danish women. Birth weight, age at menarche, and annual measurements of height and weight were obtained from school health records. We used the data to model individual growth curves. Information on vital status, age at first childbirth, parity, and diagnosis of breast cancer was obtained through linkages to national registries.

RESULTS

During 3,333,359 person-years of follow-up, 3340 cases of breast cancer were diagnosed. High birth weight, high stature at 14 years of age, low body-mass index (BMI) at 14 years of age, and peak growth at an early age were independent risk factors for breast cancer. Height at 8 years of age and the increase in height during puberty (8 to 14 years of age) were also associated with breast cancer. The attributable risks of birth weight, height at 14 years of age, BMI at 14 years of age, and age at peak growth were 7 percent, 15 percent, 15 percent, and 9 percent, respectively. No effect of adjusting for age at menarche, age at first childbirth, and parity was observed.

CONCLUSIONS

Birth weight and growth during childhood and adolescence influence the risk of breast cancer.

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N Engl J Med 2004;351:1619-26.

Most studies of body size and the risk of breast cancer have shown that tall women have an increased risk of breast cancer regardless of menopausal status,[1] whereas obese women have a reduced risk of breast cancer before menopause but an increased risk after menopause.[2] The extent to which these associations in adults reflect growth patterns in early life is unknown. A better understanding of the association between early growth patterns and the risk of breast cancer could improve our knowledge of the mechanisms of the disease and could be important for prevention.

We explored possible associations among birth weight, childhood and pubertal growth, and breast cancer in a large, population-based cohort study of women for whom height and weight had been recorded annually during the school years.

METHODS

STUDY POPULATION

We based our study on a cohort of women born from 1930 through 1975 who had undergone regular health examinations in school in the municipality of Copenhagen. A manual register of the school health records lists 161,063 girls. The records include information on annual measurements of weight and height, age at menarche, and birth weight as reported by the parents. Information from these school health records was computerized and linked by name and date of birth to the Danish Civil Registration System (CRS).

Since April 1, 1968, the CRS has assigned a unique 10-digit personal identification number (the CRS number) to all residents and newborns in Denmark. The CRS number permits linkage with information from other registries. CRS numbers were identified for 141,393 girls (88 percent) but were missing in the remainder — mainly because of emigration, death, or changes in surnames before 1968. Information from the CRS was also used to determine the variables of parity and age at each delivery of a child for cohort members.[3,4]

Information about cases of invasive breast cancer occurring through 1997 was obtained from the Danish Cancer Registry, and information about cases from 1998 through 2001 was obtained from the registry of the Danish Breast Cancer Cooperative Group. The Danish Cancer Registry is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943.[3] For women under 70 years of age at diagnosis, more than 95 percent of cases have been registered in the clinical Danish Breast Cancer Cooperative Group database.[4]

STATISTICAL ANALYSIS

Weight and height at 8, 10, 12, and 14 years of age were estimated by linear interpolation of the last measurement before the birthday and the first measurement after the birthday. If no measurements after the 14th birthday existed but the measurements at ages 8, 10, and 12 were known, the level at 14 years of age was predicted by best subset regression performed with the use of Stata software, version 8.0.[5] Body-mass index (BMI) was the weight in kilograms divided by the square of the height in meters.

Age at peak growth was defined as the age between pairs of subsequent measurements that indicated the maximal growth rate in height. We estimated the growth rate between two measurements as a weighted average of the change in height between the two measurements (the interval has a weight of one half of the weighted average) and the change in both adjacent intervals (which have weights of one quarter and one quarter of the weighted average). With only one adjacent interval, the weights were two thirds and one third of the weighted average, respectively. Age at peak growth was estimated for girls with five or more measurements and in whom the maximal growth rate was estimated to be 3.5 cm per year or more.

Follow-up for the diagnosis of breast cancer began for all subjects at 14 years of age or on April 1, 1968, whichever came last, and continued until a diagnosis of breast cancer, death, emigration, or August 31, 2001 (the end of follow-up), whichever came first. The association with breast cancer was estimated according to a cohort design with the use of a log-linear Poisson regression model (SAS, version 8).[6] Adjustment was made for attained age (quadratic splines with "knots" for each five years) and for the calendar period (in five-year intervals).[7] In additional analyses, adjustments were made for age at first childbirth and parity.

Differences according to attained age and the difference in the effect of the change in height and BMI according to age intervals during childhood were evaluated by likelihood-ratio tests of heterogeneity. Trends were estimated by treating the categorized variables (assigned the median within the category) as continuous variables. The underly-

ing log-linear assumptions were checked against a categorical model with the use of likelihood-ratio tests.

Information about age at menarche had not been computerized originally along with measurements of birth weight, weight, and height. Therefore, we manually retrieved school health records in a nested, case–cohort design on all 2005 women who were born from 1940 to 1970 in whom breast cancer developed during follow-up and a cohort of 5500 randomly chosen women who were stratified according to birth cohort in accordance with the distribution of cases. Information on age at menarche was retrieved for 3610 of the women, of whom 950 had breast cancer.

Analyses involving age at menarche were performed with the use of Cox regression, with attained age as the underlying time variable and with birth cohort as stratum variable. The Cox regression analyses (with robust estimation of variance to avoid overestimation of the precision due to the oversampling of cases) were performed with the use of the STCOX procedure (Stata statistical software, version 8).[5] Follow-up was as in the Poisson regression.

We estimated the population attributable risk for each variable in scenarios in which each woman was assigned the median value in the lowest category (in the case of birth weight and height at 14 years of age) or the highest category (in the case of BMI at 14 years and age at peak growth) (Table 1). The population attributable risks were estimated for each variable on the basis of the distribution of risk factors presented in Table 1 and the relative risks (estimated from the trend) for the median value of each quintile.

RESULTS

In our cohort of 141,393 girls who had CRS numbers, there were 1,128,505 sets of measurements of weight and height. Overall, 89 percent of the girls had 5 to 12 measurements (median, 8). The median (±SD) age at the first measurement was 7.2±1.1 years, and the median age at the last measurement was 14.5±2.0 years. We limited all subsequent analyses to the 117,415 women with complete information on weight and height at 8, 10, 12, and 14 years of age as well as age at peak growth. In this cohort, 3340 cases of breast cancer were observed during 3,333,359 person-years of follow-up.

As Table 1 shows, the age at menarche (data were available for 3610 women), the estimated age at peak growth, and the BMI at 14 years of age were inversely associated with the relative risk of breast cancer. Birth weight (data were available for 91,601 women) and height at 14 years of age showed a positive association with the relative risk of breast cancer. No change in effect was found when we adjusted for parity and age at first childbirth.

We investigated whether growth in any specific age interval influenced the risk of breast cancer. We used the age at peak growth to subdivide the period from 8 to 14 years of age into the following three intervals: from 8 years of age until the peak year, during the peak year, and from the peak year until 14 years of age. The peak year was defined as the 12-month period beginning 6 months before the estimated age at peak growth. Increase in height was significantly associated with the relative risk of breast cancer within all age intervals after adjustment for the BMI at 14 years of age, age at peak growth, and attained age and calendar period (Table 2). The relative risk per increase in height was similar in the three age intervals between 8 and 14 years of age (P=0.33), whereas the relative risk was significantly higher for changes in height between 8 and 14 years of age than for changes in height before the age of 8 (P=0.01).

The BMI, adjusted for height at age 14, age at peak growth, and attained age and calendar period, was significantly associated with the relative risk of breast cancer within all the age intervals (Table 2). However, the increase in risk per increase in BMI was similar in the three intervals from 8 to 14 years of age (P=0.77). Also, the increase in risk was similar for changes in the BMI between 8 and 14 years of age and changes in the BMI before the age of 8 (P=0.10). No association was found between weight (unadjusted for height) at any age and the risk of breast cancer (data not shown).

The correlation coefficients for each of the five variables in Table 1 as well as height and BMI at 8 years of age were all less than 0.4 with three exceptions: height at the ages of 8 and 14 (0.88), BMI at the ages of 8 and 14 (0.74), and age at menarche and age at peak growth (0.60). The correlation coefficients for birth weight were all less than 0.20.

After further mutual adjustment (Table 3), birth weight, height at 8 years of age, height increase between 8 and 14 years of age, and the BMI at 14 years of age remained independently associated

Table 1. Adjusted Relative Risk of Breast Cancer According to Birth Weight, Age at Peak Growth, Age at Menarche, and Height and BMI at 14 Years of Age in the Cohort of 117,415 Women.*

Variable	No. of Cases	Relative Risk (95% CI)
Birth weight (kg)†		
Median of each quintile		
2.5	381	1.00‡
3.0	392	0.98 (0.85–1.13)
3.4	668	1.06 (0.93–1.20)
3.6	150	1.05 (0.87–1.27)
4.0	483	1.17 (1.02–1.33)
Trend per kg	2074	1.10 (1.01–1.20)
Age at peak growth (yr)		
Median of each quintile		
10.4	568	1.00‡
11.3	727	1.04 (0.93–1.16)
12.0	703	0.94 (0.84–1.05)
12.8	657	0.86 (0.77–0.96)
13.5	685	0.84 (0.75–0.93)
Trend per yr	3340	0.97 (0.96–0.98)
Age at menarche (yr)§		
Median of each quintile		
11.9	193	1.00‡
12.6	201	1.03 (0.85–1.26)
13.2	209	1.09 (0.90–1.33)
13.7	183	0.94 (0.77–1.15)
14.4	164	0.83 (0.67–1.02)
Trend per yr	950	0.96 (0.92–1.00)

with breast cancer, with trends similar to those presented in Tables 1 and 2. Similar analyses in the nested case–cohort design, where age at menarche was known, revealed that adjustment for age at menarche did not affect these associations.

The association between age at peak growth and breast cancer was enhanced after adjustment for all growth variables except age at menarche, which did not affect the association. Age at menarche was not associated with the relative risk of breast cancer after adjustment for the pubertal growth factors (Table 3).

To evaluate the effect of these variables on the population, we calculated population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases would be diminished by 7 percent. Similar figures for height at 14 years of age, BMI at 14 years of age, and age at peak growth were 15 percent, 15 percent, and 9 percent, respectively.

DISCUSSION

With the use of a very large collection of school health records combined with effective follow-up, we found that high birth weight, early age at peak growth, high stature at 14 years of age, low BMI at 14 years of age, and high growth rate in childhood — particularly around puberty — were all independent risk factors for breast cancer. Our results are in accord with the positive association between adult height and premenopausal and postmenopausal risks of breast cancer[1] and with the inverse association between BMI and the risk of premenopausal breast cancer.[8] However, we also identified specific periods of early growth that are important to the risk of breast cancer.

Table 1. (Continued.)

Variable	No. of Cases	Relative Risk (95% CI)
Height at age 14 (cm)		
Median of each quintile		
151.1	733	1.00‡
156.2	678	1.07 (0.96–1.19)
159.8	682	1.18 (1.06–1.31)
162.9	600	1.15 (1.03–1.28)
167.6	647	1.51 (1.36–1.68)
Trend per 5 cm	3340	1.11 (1.08–1.15)
BMI at age 14 (kg/m²)		
Median of each quintile		
16.7	644	1.00‡
18.1	692	0.96 (0.86–1.07)
19.1	736	1.02 (0.92–1.13)
20.3	711	0.99 (0.89–1.10)
22.4	557	0.84 (0.75–0.94)
Trend per unit	3340	0.97 (0.96–0.98)

* All variables were adjusted for age and calendar period except age at menarche, which was adjusted for birth cohort instead of calendar period owing to the case–cohort design. BMI denotes body-mass index (calculated as the weight in kilograms divided by the square of the height in meters), and CI confidence interval. Adjustment for parity and age at first childbirth did not markedly change the trend estimates. Trends are for each increase of one in the unit specified.
† Birth weight was known for 91,601 of the 117,415 women for whom complete information was available on height, weight, and age at peak growth, and breast cancer developed in 2074.
‡ This group served as the reference group.
§ Information on age at menarche was collected with use of a case–cohort design for 3610 women, and of these, breast cancer developed in 950.

Birth weight, a proxy for in utero growth and prenatal exposure, has been studied by several authors, and most[9-18] but not all[12,19-23] have found support for an association between birth weight and breast cancer. In a previous study of women from the same population but without information on subsequent growth, we also found a significant association.[24] In the present study, we found that the association of breast cancer with birth weight is independent of the effect of subsequent growth patterns and the timing of puberty on the risk of breast cancer.

Four studies have explored the association between pubertal growth and the risk of breast cancer in cohorts where actual measurements of weight and height were obtained, although on a much more limited scale than in our study.[15,16,25,26] In agreement with these studies, we found the BMI at 8, 10, 12, and 14 years of age to be inversely associated with the risk of breast cancer. We used height at 14 years of age, which serves as a good proxy for adult height,[27] to confirm the finding of a direct association between adult height and risk of breast cancer. Our finding of an 11 percent increase in risk for every 5 cm increase in height was similar to the results of a very large study of adults.[2] Our data allowed us to investigate whether the influence of final height was modified by the growth pattern. Height at 8 years of age and the increase in height around puberty were both associated with breast cancer, but the latter was stronger, suggesting that pubertal growth has a special effect on the risk of breast cancer. In contrast, analyses of the BMI did not reveal any time interval in which changes in the BMI were of special importance.

We found a linear trend between a lower age at peak growth and an increased risk of breast cancer, which was independent of other measures. Adult height is weakly linked to age at peak growth and age at menarche, and it is possible that different factors control these variables. Age at peak growth probably reflects the initiation of puberty. A Nor-

Table 2. Adjusted Relative Risk of Breast Cancer According to Change in Height and BMI during Various Periods in Childhood.*

Period in Childhood	Height		BMI	
	Relative Risk per 5-cm Increase (95% CI)†	P Value‡	Relative Risk per 1-Unit Increase (95% CI)§	P Value‡
<8 Yr old	1.11 (1.07–1.15)	0.01	0.94 (0.91–0.97)	0.10
8–14 Yr old	1.17 (1.09–1.25)		0.96 (0.93–0.99)	
8–Peak yr	1.18 (1.08–1.27)	0.33	0.95 (0.91–0.99)	0.77
Peak yr	1.15 (0.97–1.36)		0.96 (0.90–1.02)	
Peak yr–14 yr old	1.10 (1.00–1.20)		0.97 (0.93–1.02)	

* Peak year is defined as the 12-month time period beginning 6 months before the estimated age at peak growth. BMI denotes body-mass index, and CI confidence interval.

† Adjustments were made for attained age and calendar period, age at peak growth, and BMI at 14 years of age.

‡ P values for the difference in relative risk were derived from the likelihood-ratio test of heterogeneity.

§ Adjustments were made for attained age and calendar period, age at peak growth, and height at 14 years of age.

wegian study showed that the risk of breast cancer increased by 4 percent for each year that age at menarche decreased.[28] We also found that age at menarche was associated with a risk of breast cancer, but not when age at peak growth was included in the analysis. Thus, previous findings could show that age at menarche is a proxy for age at peak growth or that both reflect the importance of age at the onset of puberty. Another indication of the importance of puberty was our finding that the increase in height between 8 and 14 years of age conferred a higher risk of breast cancer than the increase in height that accrued up to 8 years of age.

We did not have information on the women's status with respect to family history of breast cancer, history of benign breast disease, and hormone-replacement therapy. Although these factors influence the risk of breast cancer, they are unlikely to vary according to childhood height and weight and, as such, do not confound our estimates. Another limitation of our study was the inability to analyze adult weight and BMI. Thus, whereas adolescent height is closely correlated with adult height and hence is well elucidated in this study, weight has a weaker correlation. In a large population-based British cohort, height at 16 years of age had a correlation of 0.92 with height at 33 years of age, as compared with a correlation with weight of 0.63.[27]

To illustrate the quantitative contributions of the growth factors to the overall risk of breast cancer, we also calculated the population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases of breast cancer would have been diminished by 7 percent. Similarly, lowest quintiles of height at 14 years of age and highest quintile of BMI at 14 years of age and of age at peak growth would have resulted in a 15 percent, 15 percent, and 9 percent decrease in cases, respectively.

Our study had sufficient power to detect weak but relevant associations, and it avoided various sources of bias. Information on birth weight and the measurements of height and weight was recorded during school years, making differential misclassification unlikely. The validity of parents' reports of their children's birth weights is very high.[29] We based our cohort on all children attending schools in a well-defined area of Denmark and followed them through our national registries. The Danish social structure further diminished any risk of diagnostic bias, because free and equal access to health care is provided for all citizens.

The biologic background for our findings needs to be elucidated, and mechanistic models including modified susceptibility seem warranted. Within the past century, adult height and the prevalence of obesity have increased and the age at menarche has decreased,[30,31] indicating that changes in some environmental conditions are important and probably interact with genetic factors. Nutritional status, for example, is related to an increased gain in height in childhood and earlier onset of puberty.[32]

An increase in the total number of menstrual cycles during a lifetime may explain the association between the early onset of puberty (and thus early age at peak growth) and an increased risk of breast cancer. However, this explanation may be too simple. Even a two-year delay in age at menarche would result in only a limited number of "lost" menstrual cycles in the context of the total number of cycles in a lifetime. The breast epithelium undergoes final differentiation at first pregnancy, and it is a generally held belief that differentiated cells are less prone to carcinogenic effects than undifferentiated cells.[33] Whereas some differentiation of breast epithelium occurs before the first pregnancy, breast cells present before menarche are probably the least differentiated. Since the female breast begins developing well before the start of

Table 3. Association between Growth Variables and Breast Cancer, According to Age.

Growth Variable	Relative Risk (95% CI)*			P Value¶
	All Ages	Age <50 yr	Age ≥50 yr	
Birth weight†	1.10 (1.01–1.21)	1.14 (1.01–1.28)	1.05 (0.91–1.21)	0.39
Age at peak growth‡	0.94 (0.91–0.97)	0.90 (0.86–0.95)	0.98 (0.93–1.03)	0.03
Age at menarche§	0.99 (0.91–1.07)	0.98 (0.88–1.08)	1.01 (0.87–1.17)	0.74
Height at age 8‡	1.11 (1.07–1.15)	1.11 (1.05–1.17)	1.11 (1.05–1.17)	0.62
Height increase age 8 to age 14‡	1.17 (1.09–1.25)	1.15 (1.05–1.27)	1.18 (1.07–1.30)	0.74
BMI age 14‡	0.95 (0.93–0.97)	0.96 (0.94–0.99)	0.94 (0.92–0.97)	0.22

* The relative risk is per 1-kg increase in birth weight, per 1-year increase in age at peak growth and age at menarche, per 5-cm increase in height, and per 1-unit increase in body-mass index (BMI). CI denotes confidence interval.
† Adjusted for age at peak growth, height at 8 years of age, height increase from 8 to 14 years of age, and BMI at 14 years of age. Further adjustment for age at menarche did not markedly change the estimate.
‡ Mutually adjusted. Further adjustment for birth weight and age at menarche did not markedly change the estimate.
§ Adjusted for age at peak growth, height at age 8, height increase from age 8 to age 14, and BMI at age 14. Further adjustment for birth weight did not markedly change the estimate.
¶ P values represent the difference in relative risk according to attained ages.

menstrual cycles,[34] it is possible that the age at peak growth is really an indicator of the age at which the breast starts growing and, hence, influences the risk of breast cancer.

Our finding that a high BMI protects against breast cancer contrasts with studies showing that overweight in girls is associated with early menarche.[35] Our findings suggest that the effect of childhood obesity on breast cancer does not occur by means of a contribution to the acceleration of puberty, because early menarche has the opposite effect of obesity. However, the estrogens produced by adipose tissue may promote differentiation of the breast epithelium.

Overall, our results provide evidence that factors influencing fetal, childhood, and adolescent growth are important independent risk factors for breast cancer in adulthood. Therefore, the exposures or conditioning processes during these periods are of particular importance in relation to adult breast cancer.

Supported by grants from the U.S. Department of Defense Congressionally Directed Medical Research Programs, the Danish Medical Research Council, the Danish National Research Foundation, and the Danish Cancer Society.

REFERENCES

1. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001;23:313-42.
2. Tretli S. Height and weight in relation to breast cancer morbidity and mortality: a prospective study of 570,000 women in Norway. Int J Cancer 1989;44:23-30.
3. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry — history, content, quality and use. Dan Med Bull 1997;44:535-9.
4. Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000;11:669-74.
5. Stata base reference manual, version 8. College Station, Tex.: Stata Press, 2003.
6. SAS/STAT user's guide, version 8. Cary, N.C.: SAS Institute, 2003.
7. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356-65.
8. Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev 2001;10:15-32.
9. Andersson SW, Bengtsson C, Hallberg L, et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193-8.
10. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000;152:1121-8.
11. Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a risk factor for breast cancer. Lancet 1996;348:1542-6.
12. Sanderson M, Williams MA, Malone KE, et al. Perinatal factors and risk of breast cancer. Epidemiology 1996;7:34-7.
13. Vatten LJ, Maehle BO, Lund Nilsen TI, et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002;86:89-91.
14. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001;93:60-2.
15. Hilakivi-Clarke L, Forsen T, Eriksson JG, et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001;85:1680-4.
16. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000;83:964-8.
17. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015-8.
18. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001;91:248-51.
19. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71-6.
20. Sanderson M, Williams MA, Daling JR, et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397-407.
21. Le Marchand L, Kolonel LN, Myers BC,

Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988;57:437-9.
22. 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;11:207-10.
23. Sanderson M, Shu XO, Jin F, et al. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-8.
24. Ahlgren M, Sorensen TIA, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003;107:997-1000.
25. Herrinton LJ, Husson G. Relation of childhood height and later risk of breast cancer. Am J Epidemiol 2001;154:618-23.
26. Le Marchand L, Kolonel LN, Earle ME, Mi MP. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988;128:137-52.
27. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. Am J Clin Nutr 1997;66:1094-101.
28. Kvale G, Heuch I. Menstrual factors and breast cancer risk. Cancer 1988;62:1625-31.
29. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997;145:58-67.
30. Petersen TA, Rasmussen S, Madsen M. BMI of Danish school children measured during the periods 1986/1987–1996/1997 compared to Danish measurement in 1971/1972. Ugeskr Laeger 2002;164:5006-10. (In Danish.)
31. Rasmussen S, Petersen TA, Madsen M. Body height of 6 15-year-old school children measured in the period 1986/1987 to 1996/1997 compared with Danish measurements in 1971/1972. Ugeskr Laeger 2002;164:5011-5. (In Danish.)
32. He Q, Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res 2001;49:244-51.
33. Russo J, Russo IH. Cellular basis of breast cancer susceptibility. Oncol Res 1999;11:169-78.
34. Howard BA, Gusterson BA. Human breast development. J Mammary Gland Biol Neoplasia 2000;5:119-37.
35. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974;185:949-51.

APPENDIX E

uncertain until we know how endovascular repair fares over decades. In addition, "small incision" and laparoscopic techniques have been developed, and further studies will be needed to clarify their roles.

Meanwhile, patient management should be guided by what we already know. Small aneurysms should be kept under surveillance with periodic ultrasonographic measurements — every two to three years for those smaller than 4.0 cm, and every six months for larger aneurysms. Elective repair should be considered for abdominal aortic aneurysms measuring 5.5 cm or larger. If the patient is a candidate for either open or endovascular repair, referral to a randomized trial is the best option.

From the Center for Epidemiological and Clinical Research, Veterans Affairs Medical Center, Minneapolis.

1. Prinssen M, Verhoeven ELG, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351:1607-18.
2. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet 2004;364:843-8.
3. Hallett JW Jr, Marshall DM, Petterson TM, et al. Graft-related complications after abdominal aortic aneurysm repair: reassurance from a 36-year population-based experience. J Vasc Surg 1997;25:277-86.
4. Johnston KW, Canadian Society for Vascular Surgery Aneurysm Study Group. Nonruptured abdominal aortic aneurysm: six-year follow-up results from the multicenter prospective Canadian aneurysm study. J Vasc Surg 1994;20:163-70.
5. Lederle FA, Wilson SE, Johnson GR, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1437-44.
6. Collin J, Murie JA. Endovascular treatment of abdominal aortic aneurysms: a failed experiment. Br J Surg 2001;88:1281-2.
7. Cronenwett JL, Seeger JM. Withdrawal of article by the FDA after objection from Medtronic. J Vasc Surg 2004;40:209-10.
8. Anderson PL, Arons RR, Moskowitz AJ, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. J Vasc Surg 2004;39:10-9.
9. Lee WA, Carter JW, Upchurch G, Seeger JM, Huber TS. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. J Vasc Surg 2004;39:491-6.
10. Laheij RJ, Buth J, Harris PL, Moll FL, Stelter WJ, Verhoeven EL. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms: intermediate-term follow-up results of a European collaborative registry (EUROSTAR). Br J Surg 2000;87:1666-73.
11. Vallabhaneni SR, Harris PL. Lessons learnt from the EUROSTAR registry on endovascular repair of abdominal aortic aneurysm repair. Eur J Radiol 2001;39:34-41.
12. Beard JD, Thomas SM. Mid-term results of the RETA registry. Br J Surg 2002;89:520. abstract.
13. Carpenter JP, Baum RA, Barker CF, et al. Durability of benefits of endovascular versus conventional abdominal aortic aneurysm repair. J Vasc Surg 2002;35:222-8.
14. Peppelenbosch N, Buth J, Harris PL, van Marrewijk C, Fransen G. Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. J Vasc Surg 2004;39:288-97.
15. Ouriel K, Srivastava SD, Sarac TP, et al. Disparate outcome after endovascular treatment of small versus large abdominal aortic aneurysm. J Vasc Surg 2003;37:1206-12.
16. The United Kingdom Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1445-52.

Breast Cancer — Early Life Matters

Karin B. Michels, Sc.D., and Walter C. Willett, M.D., Dr.P.H.

Despite improved treatment, mortality rates from breast cancer remain high, partly because of the increasing incidence of the disease. Understanding the causes of breast cancer could ultimately lead to its prevention. Many observations point to early life as a susceptible period in mammary carcinogenesis. Early menarche, late first delivery, and ionizing radiation during early life are documented risk factors. High stature, which to a certain extent is determined by childhood nutrition, has consistently been associated with an increase in the risk of breast cancer.[1]

Studies in animals also indicate that the mammary gland is most vulnerable to carcinogenic influences before a woman's first delivery, when many of the cells in the breast differentiate to assume their intended function.[2] Since some differentiation is likely to occur during the development of the mammary glands and sexual maturation, the period between conception and mammary-gland development may be one of particular sensitivity. Among survivors of atomic bomb explosions, the excess relative risk of breast cancer was greatest among girls who were exposed before 10 years of age.[3]

In their study of growth patterns in a Danish population, reported in this issue of the *Journal*, Ahlgren and colleagues[4] found that high birth weight, rapid growth around the time of mammary-gland development, high stature, and low body-mass index during adolescence were independent risk factors for breast cancer later in life. Interestingly, the investigators found that after they had accounted for the growth pattern during childhood and adolescence, the age at menarche was not related to the

risk of breast cancer. The strengths of this study are its considerable size and the unbiased source of the data on early life, which were abstracted from school health records. The findings of Ahlgren et al. add to a substantial literature indicating that there is a positive association between birth weight and the risk of breast cancer,[5] primarily before menopause, and that childhood adiposity is inversely associated with the risk of breast cancer.

An association between the risk of breast cancer and the rate of growth during adolescence has been suggested previously, but these new data are the most convincing. An important new finding from the current study is that rapid growth between 8 and 14 years of age carries an additional risk of breast cancer independent of a woman's final height. Although information on risk factors during adult life was not available in this study, others have found that the body-mass index during early adulthood is inversely related to the risk of breast cancer but that weight gain during adulthood and higher body mass after menopause are associated with an increased risk of breast cancer among postmenopausal women.[6] Thus, a key question that was not addressed by this study is the independent contribution of the body-mass index in childhood and early adulthood to the risk of breast cancer.

How does this observation from Denmark relate to trends occurring elsewhere? Among the most dramatic and well-documented changes are those in Japan, where a large increase in height has been observed over the past five decades, presumably primarily because of a change in diet. This increase in height has been followed by a steady increase in the rate of breast cancer (Fig. 1). Generally, the world population has become taller over time, especially during the past century. At least part of the increasing incidence of breast cancer may be attributable to this growth.

Currently available data paint a complex picture of the lifetime body build associated with the lowest risk of breast cancer: one would want to be born light, to grow slowly but steadily into a chubby, short child, and to maintain one's fat mass until one reached menopause, at which point, one would want to shed the excess pounds immediately in order to keep the risk of breast cancer low. However, we should not necessarily interpret these associations as directly causal. Low birth weight and short stature could be related to genetically determined low levels of insulin-like growth factor 1 or other growth factors that affect breast cells later during adulthood; if so, modifying birth weight, which may just be an early marker of hormonal effects, might not change the risk of breast cancer. One must also bear in mind that higher birth weight,

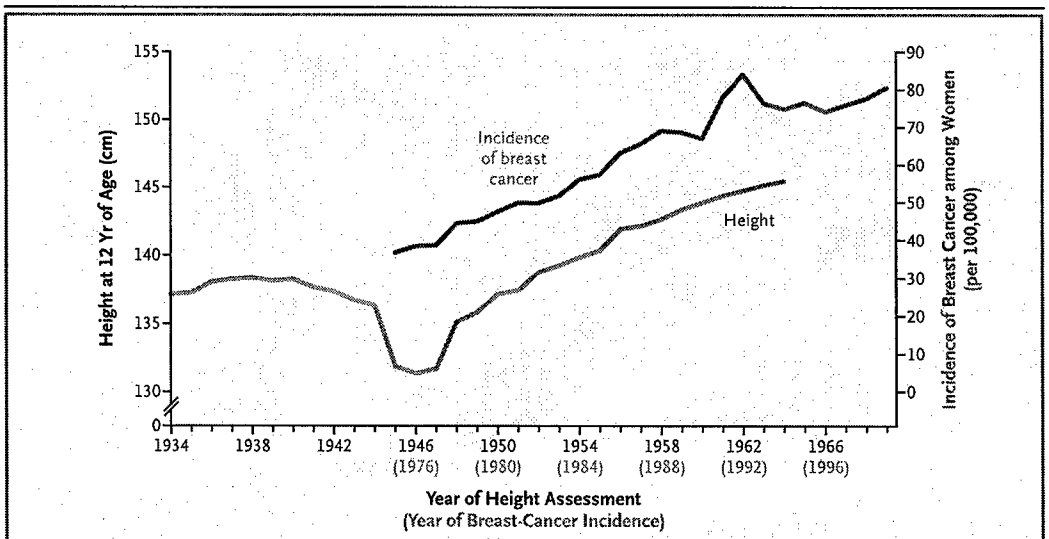

Figure 1. Relation between Height at 12 Years of Age among Japanese Girls and the Incidence of Breast Cancer 30 Years Later among Japanese Women 40 to 44 Years of Age.

Data are from Takahashi[7] and the Research Group for Population-Based Cancer Registration in Japan.[8]

higher stature, and lower body-mass index during adolescence are related to lower risks of cardiovascular disease and diabetes.[9] Thus, modifying these factors in an effort to reduce the risk of breast cancer, even if they were causal, might not be desirable for overall health. A rapid rate of growth during early adolescence, however, may be of particular interest as a potentially modifiable risk factor, since it does not, as yet, seem advantageous for other health outcomes.

We still face the challenge of discovering the biologic pathways underlying the observed associations. Growth factors are likely to play a role, because they affect susceptible mammary tissue. When the mammary gland matures, it undergoes rapid cell division, increasing the opportunities for mutations to occur — opportunities that may be further increased by an accelerated rate of growth. The identification of biologic mechanisms that could translate into practical preventive strategies is even more important. One factor that has been related to the rate of growth in children is animal protein. Milk has been hypothesized to be a factor in the rapid changes in growth among Japanese girls, in part because of its protein content, but also because of its high content of many anabolic hormones. Recent findings have confirmed that milk consumption does increase the circulating levels of insulin-like growth factor 1 and is associated with higher stature.[10] Understanding how these and other factors are related to childhood growth and to the risk of breast cancer will not be an easy task, but it is one that deserves serious attention.

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1. 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;152:514-27.
2. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 1982;2:5-73.
3. Land CE. Studies of cancer and radiation dose among atomic bomb survivors: the example of breast cancer. JAMA 1995;274:402-7.
4. Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA. Growth patterns and the risk of breast cancer in women. N Engl J Med 2004;351:1619-26.
5. McCormack VA, dos Santos Silva I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003;326:248.
6. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407-11.
7. Takahashi E. Growth and environmental factors in Japan. Hum Biol 1966;38:112-30.
8. The Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2004;34:352-6.
9. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:938-41.
10. Hoppe C, Udam TR, Lauritzen L, Molgaard C, Juul A, Michaelsen KF. Animal protein intake, serum insulin-like growth factor I, and growth in healthy 2.5-y-old Danish children. Am J Clin Nutr 2004;80:447-52.

Dynamic Mitral Regurgitation — More Than Meets the Eye

Robert A. Levine, M.D.

Recollections of early medical training conjure up images of the master clinician standing beside the exercising patient, keenly observing the effects of disease. Exercise stress testing is a cornerstone of the evaluation of dynamic coronary insufficiency, providing diagnosis and prognosis. Valvular heart disease, in contrast, has been considered relatively static and has been managed largely on the basis of resting evaluation. Current clinical guidelines indicate that there is conflicting evidence regarding exercise testing in valvular disease and that no efficacy has been established; advocates suggest exploring the dynamics of the ventricle, not the valve.

Ischemic mitral regurgitation consequent to myocardial infarction, however, is characteristically dynamic and sensitive to changes in ventricular size, shape, and loading that restrict closure of the mitral leaflet. In this issue of the *Journal*, Piérard and Lancellotti[1] make that point in a new way by showing that patients who present with acute pulmonary edema subsequently have large exercise-induced increases in mitral regurgitation and related pulmonary pressures. The authors have associated this exercise physiology with an adverse prognosis. Exercise can therefore unmask the true severity of what might otherwise be considered a mild lesion.

Pulmonary edema has three basic causes: increased alveolar-capillary permeability, decreased alveolar pressure, and increased pulmonary-capillary pressure (with or without increased interstitial

APPENDIX F

BIRTH WEIGHT AND GROWTH DURING SCHOOL YEARS AND RISK OF CANCER

Epidemiological Studies Based On A Danish Cohort Of 325,218 Children

PhD Thesis

University of Copenhagen, 2004

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The present thesis is based on the following studies referred to by their Roman numerals:

I: Ahlgren M, Sørensen TIA, Wohlfahrt J, Haflidadóttir Á, Holst C, Melbye M.
Birth weight and risk of breast cancer in a cohort of 106,504 women.
International Journal of Cancer 2003; 107: 997-1000.

II: Ahlgren M, Wohlfahrt J, Sørensen TIA, Melbye M.
Birth weight and risk of cancer.
Submitted.

III: Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA.
Growth Patterns and the Risk of Breast Cancer in Women.
New England Journal of Medicine 2004; 351: 1619-26.

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CONTENTS

1 ACKNOWLEDGEMENTS

The work presented in this thesis was carried out during my employment at the Department of Epidemiology Research at Statens Serum Institut, 2000-2004.

First of all, I would like to thank my supervisors for their encouragement, constructive criticism and support. I am especially grateful to Mads Melbye, who let me be part of the outstanding epidemiological research environment at Statens Serum Institut. I furthermore owe many thanks to Thorkild I.A. Sørensen for letting me use the computerized data from the school health records.

I am indebted to Jan Wohlfahrt, not just for being my SAS guru, but also for many fruitful discussions on the design of this study and interpretation of its results.

There would furthermore not have been a thesis without Lisa and Henrik Hjalgrim, who lured me into the world of epidemiology, and who have been my good friends for many years.

Many thanks go to my many good colleagues and friends at the Department of Epidemiology Research. In particular, I would like to thank Annemette, Birgitte, Charlotte, Helle, Nete, and Jeppe for always having time to share the ups and downs of life.

Frederiksberg, November 2004
Martin Ahlgren

The projects presented in this thesis were supported by grants from the U.S. Department of Defense Congressionally Directed Medical Research Programs, the Danish Medical Research Council, the Danish National Research Foundation, the Danish Cancer Society, Augustinus Fonden, Dagmar Marshalls Fond, Fabrikant Einar Willumsens Mindelegat, Aase og Ejner Danielsens Fond, Else og Mogens Wedell-Wedellsborgs Fond, and Andersen-Isted Fonden.

2 BACKGROUND

2.1 INTRODUCTION

Breast cancer is the most common cancer in Danish women, with more than 3,500 new cases diagnosed every year (1). The associations between adult anthropometrical measures and breast cancer are well established, but the extent to which these associations are reflections of specific growth patterns of the fetus, in childhood and adolescence is not resolved.

The breast in women goes through four major growth phases over a lifetime (2), all of which have been suggested to be critical in relation to possibly malignant transformation. The formation of the breast begins in early fetal life and at birth it is morphologically identical in boys and girls. Not until puberty does sexual dimorphism occur under the influence of sex hormones. The breast in women grows due to an increase in stromal tissue and through an extension of the breast epithelium. However, not until pregnancy does the breast undergo final maturation into a lactating organ. Involution occurs following weaning and the breast resumes its resting stage, with some residual increase in size of functional glandular units. At menopause the breast undergoes major involution in which both the glandular epithelium and the connective stroma regress and are replaced by fat tissue.

Looking for biological processes that operate during these "critical" time periods therefore has a sound biological background, and many factors have been examined for their importance in breast cancer etiology. In the following overview focus will be on previous studies of early life exposures.

2.2 IN-UTERO GROWTH AND RISK OF CANCER

In 1990, Trichopolous hypothesized that part of a woman's breast cancer risk profile is caused by exposures exerting their influence in-utero. The hypothesis is based on the findings that estrogen levels during pregnancy vary between individuals and that the undifferentiated mammary gland in-utero is exposed to high concentrations of estrogens (10-100 times the estrogen levels achieved later in life) (3). Estrogens are mammotropic, as well as being established growth factors, and as such they induce cell proliferation (4). Rapid cell division per se may affect risk of breast cancer without genotoxicity by increasing the probability of irreparable DNA damage (5). High levels of estrogen during pregnancy could thus give rise to an increased number of cells "susceptible" to later carcinogenic stimuli, e.g. by priming the mammary tissue for excessive responses at puberty or during early adult life (6). Studies have shown that high estrogen levels during pregnancy are associated with high birth weight, which suggests that birth weight is a useful proxy of intrauterine estrogen measure (7-9).

Studies on the association between birth weight and risk of breast cancer have, however, yielded somewhat conflicting results. Overall, the available literature on birth weight is suggestive of an intrauterine effect on later risk of breast cancer, especially for premenopausal ages, but the evidence is in many cases based either on studies with small sample sizes or on data of recalled events that occurred many decades earlier (10-25). Previous studies are presented in Table 1 on page 9.

A significantly positive association was found in a Norwegian case-control study (373 cases of breast cancer) (12), whereas a similarly designed Swedish study (1,068 cases) failed to document a significant association with birth size indicators (18). Based on two different case-control studies, Sanderson and colleagues reported a positive association between birth weight and risk of breast cancer in premenopausal women in the US, but not in postmenopausal women (14). The association in premenopausal women was supported by Innes and McCormack (10;25), but others found no such association (20-23). Based on recalled birth weights reported by adult women and their mothers, Michels and colleagues found significant evidence to support a positive association between extreme birth weight and risk of breast cancer, not only in younger women but also later in life (11). Analysis of the magnitude of the trend per 1,000 g increase in birth weight has only been reported in one previous study (15) that followed a cohort of 3,447 women of whom 177 women developed breast cancer. Hilakivi-Clarke and colleagues found a linear increased risk of breast cancer with birth weight with a hazard ratio of 22% pr 1,000 g (95% CI –10% to 65%). Three other studies have likewise reported a significant trend (11;12;25), but did not calculate the magnitude of the trend.

Table 1. Previous studies on the association between birth weight and breast cancer.

Author	Size	Findings
Case-control studies		
Ekbom, 1992 (19)	458 cases & 1,197 controls	Non-significant trend
Ekbom, 1997 (18)	1,068 cases & 2,727 controls	No trend
Hubinette, 2001 (24)	87 same sex twin pairs	Non-sign. association with high birth weight
Innes, 2000 (10)	481 cases & 2,861 controls	OR 3.3 for >4,500 g vs. 2,500-2,999 g
Kaijser, 2001 (13)	90 cases & 90 controls	Twin study
Le Marchand, 1988 (21)	74 cases & 245 controls	No trend
Michels, 1996 (11)	550 cases & 1,478 controls	Significant positive trend OR 0,6 for < 2,500 vs. >=4,000 g
Sanderson, 1996 (14)	Premenopausal women: 630 cases & 864 controls	Premenopausal women: Non-sign trend. OR=1.7 for 4 kg vs. 2.5 kg
	Postmenopausal women: 212 cases & 330 controls	Postmenopausal women: No trend
Sanderson, 1998 (20)	448 cases & 399 controls	No trend
Sanderson, 2002 (23)	288 cases & 350 controls	No trend
Titus-Ernstoff, 2002 (22)	1,716 cases & 1,886 controls	No trend
Vatten, 2002 (12)	373 cases & 1,150 controls	OR 1.4 for Q1 vs. Q4
Cohort studies		
Andersson, 2001 (16)	62 cases in 1,080 women	Non-significant trend
Hilakivi-Clarke, 2001 (15)	177 cases in 3,447 women	Positive non-significant trend (Hazard Ratio=1.22 pr. kg)
McCormack, 2003 (25)	63 cases in 5,358 women	Significant trend
Stavola, 2000 (17)	37 cases in 2,221 women	Non-significant trend

The findings of an association between birth weight and breast cancer have led researchers to hypothesize that birth weight could be a risk factor for other cancers as well, and especially for hormone-related cancers. As for studies on breast cancer, these studies require large cohorts with a long follow-up time and the number of studies exploring the association between birth weight and other cancers is thus still limited to few cancer sites, primarily prostate and testicular cancer (Table 2 on page 11).

In a Swedish cohort study of women the authors found a linear association with cancer (16). However, when analyzing non-hormonal and hormonal cancers separately, the authors only found a significant trend for non-hormonal cancers. The study, although of a cohort design, was limited in strength due to its size (262 cases). Ovarian cancer was studied by Barker and colleagues who did not find an association with birth weight and mortality from ovarian cancer in a small UK cohort (26). In one study of prostate cancer an association with birth weight was found (27), but bigger and more recent studies have, however, reported only a non-significant association (28;29) or failed to find associations at all (30;31). In contrast, studies on testicular cancer have consistently found both high and low birth weight to be risk factors (32-38). As for studies on other cancers an increased risk of renal cell cancer was observed among men with a birth weight greater than 3,500 g in a case-control study by Bergstrom (39), whereas no association was found in women. The association between birth weight and risk of colorectal cancer showed a nonlinear association in a case-control study by Sandhu and colleagues (40) with children of both low and high birth weight being at increased risk.

Table 2. Previous studies on the association between birth weight and cancer other than breast cancer.

Author	Cancer site	Type*	Size	Findings
Akre , 1996 (33)	Testis	RE	232 cases 904 controls	V-shape association
Brown, 1986 (32)	Testis	RE	197 cases 201 controls	Association with low birth weight Controls were men with other cancers
Moller, 1997 (34)	Testis	RE	96 cases 98 controls	V-shape association
Rasmussen, 2003 (37)	Testis	BI	144 cases in 337,249 men	No association. Mean follow-up 4.8 years
Richiardi, 2002 (36)	Testis	BI	628 cases 2,309 controls	V-shape association
Richiardi, 2003 (38)	Testis	BI	371 cases 1,238 controls	V-shape association
Sabroe, 1998 (35)	Testis	BI	307 cases 704 controls	No association. Controls were not checked for survival past infancy
Boland, 2003 (31)	Prostate	BI	192 cases 374/384 controls	Two control groups. No significant findings
Ekbom, 1996 (28)	Prostate	BI	250 cases 691 controls	No association with birth weight
Ekbom, 2000 (29)	Prostate	BI	834 cases 1,880 controls	No association with birth weight
Platz, 2003 (30)	Prostate	RE	545 cases in 21,140 men	No association with birth weight
Tibblin, 1995 (27)	Prostate	BI	21 cases in 366 men	Association with high birth weight
Bergstrom, 2001 (39)	Kidney	RE	648 cases 900 controls	Association with high birth weight in men but not in women
Barker, 1995 (26)	Ovary	BI	41 cases in 5,585 women	No association between birth weight and mortality from ovarian cancer
Sandhu, 2002 (40)	Colo-rectal	RE	52 cases in 11857 men and women	V-shape association
Andersson, 2001 (16)	Overall	BI	262 cases in 1,080 women	Significantly positive trend to overall cancer

* Type specifies whether analyses of birth weight were based on birth records (BI) from e.g. midwives or hospitals or whether the birth weight was retrospectively reported (RE).

2.3 Growth During School Years And Risk Of Breast Cancer

Numerous studies have described an association between adult body build and breast cancer risk. A recent extensive review by Gunnell and colleagues has concluded that consistent evidence supports the hypothesis that tall women are at increased risk of both pre- and postmenopausal breast cancer (41). The exact magnitude of the association is somewhat difficult to calculate since many different cut-off points have been used (41). However the biggest study so far, a cohort study of 570,000 Norwegian women, found an increase in relative risk of breast cancer between 1.28 and 1.42 per 15 cm increase in height for pre- and post-menopausal women respectively (42).

Adult obesity has furthermore been shown to have an association with breast cancer. The effect of obesity is, however, opposite in pre-menopausal and post-menopausal breast cancer. Thus obesity is associated with a reduced risk of pre-menopausal breast cancer, but with an increased risk for post-menopausal breast cancer (43).

Adult height, and to some extent obesity, is determined by prepubescent and pubescent growth (44), and it is therefore highly relevant to focus on growth patterns during puberty in an attempt to better understand the association between body size and breast cancer.

The extent to which the associations with adult anthropometrical measures can be traced back to growth patterns in childhood and adolescence is still not fully understood. Epidemiological studies in this field have been constrained by the availability of sufficiently large and old cohorts with data gathered prospectively. It has been especially difficult to find cohorts consisting of women with repeated measurements of weight and/or height during puberty.

To our knowledge, only four studies published so far have explored the association between pubertal growth measurements and breast cancer risk in cohorts where actual measurements of weight and height were obtained (15;17;45;46). Two of these studies were case-control studies, and the largest is a study by Le Marchand and colleagues with 580 cases and 2,528 controls (46). The authors had access to actual measurements of height of women aged 24 years or younger, however, only one measurement per women, which meant that they had 154 or less cancers in every separate 5-year age group presented. They found a negative association between adolescent body mass and premenopausal breast cancer, but the analyses only reached statistical significance in girls aged 10-14 years. Analyses of height indicated an increased risk for the tallest girls in all age groups, but statistical significance was not reached. The results of the study were not modified by adjustment for age at first birth, parity or socioeconomic indicators.

In a study by Herrinton and Husson, the authors had access to repeated measurements for every individual (214 cases and 214 controls). However, due to the size of the cohort (less than 150 cases with measurements in each 3-year age-group) their study had limited statistical power. They found that in the age-group 15-18 years, tall-for-age was a risk factor for breast cancer (45). In a cohort study by Stavola and colleagues (37 cases in a cohort of 2,221 women) the authors had access to repeated measurements of weight and height throughout childhood and adult life (17). They, however, only used the measurements for age 7 in their analyses and no univariate analyses of height were reported. In another cohort study (177 cases among 3,447 women), Hilakivi-Clarke and colleagues found that at each age, from 7 to 15 years, the girls who later developed breast cancer were taller and had lower body mass than the other girls (15).

The above studies are supported by studies where the anthropometrical variables were obtained retrospectively (23;47-54). Thus most (47-51) but not all (52;53) of these studies have an inverse association between BMI and breast cancer in the pubertal period. A positive association with height in the pubertal period was likewise found in most (47-50) but not all studies (23;54).

In summary, studies have suggested that prenatal growth may be of importance to risk of cancer. However, further characterization of this association is warranted. For instance, it is not known whether high birth weight confers an increased risk of all or only certain types of cancers. Similarly it is not known whether the proposed association between adult anthropometrical measures and risk of cancer can be traced back to early life growth patterns. For breast cancer it seems pertinent to access the independent contributions to risk from growth in-utero, in childhood and during adolescence.

3 STUDY OBJECTIVES

3.1 AIM

The aim of the present PhD thesis was to characterize the association between anthropometrical markers of growth and cancer. The thesis addresses the significance of birth weight for all cancers, whereas the significance of growth during school years is addressed specifically for breast cancer. Here the aim was to study whether the well-known association between adult stature and risk of breast cancer could be explained by particular events during childhood and adolescence.

3.2 HYPOTHESES

- High birth weight is associated with increased risk of breast cancer
- The possible association between high birth weight and increased risk of breast cancer is a generalized phenomenon for cancer at all sites
- Growth during school years modifies breast cancer risk

4 DATA SOURCES

4.1 THE DANISH CIVIL REGISTRATION SYSTEM

A nationwide civil register system (CRS) was established on 1 April 1968 and all residents and newborns in Denmark have since been given a unique 10-digit person identification number (the CRS number). The CRS number is stored along with information on name, place of birth, and parental identity on all Danish residents. It is updated daily with respect to vital and migration status. All national registries in Denmark recording individual information use the CRS number, which thus serves as a unique key for linkage studies.

In the Department of Epidemiology Research, information from the CRS has previously been used to generate a population-based relational database, the Birth Order Study database (BOS), containing information on all men and women born during the period 1 January 1935 to 31 December 1998, who have been assigned a CRS number (55). This database contains close to complete information on sibships of children, parity of women and links between family members. The completeness of the linkage between mother and child in the BOS database was estimated to 97.3% for children born before 1968, and close to 100% for children born hereafter (56).

4.2 SCHOOL HEALTH RECORDS

The study cohort is based on a population of 161,063 girls and 164,155 boys born between 1930 and 1975 who attended school in the municipality of Copenhagen, Denmark. In this period school health records maintained by nurses or physicians in the school health services were kept for all pupils. The records contain information on annual measurements of weight and height as well as information on age at menarche and birth weight. To a varying degree the records furthermore contain information on childhood infections, vaccinations and general health in pre-school years with annual updates throughout school years. The records had pre-printed fields to be answered by the people working in the health service; however, the exact fields on the records have changed slightly over the years. To begin with the schools in the City of Copenhagen had their own type of records, but in 1949 a law was passed standardizing the records countrywide.

4.3 THE DANISH CANCER REGISTRY

The Danish Cancer Registry (DCR) was established in 1942 and is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943 (57;58). Notifications to the registry are forwarded from hospital departments countrywide including departments of histopathology and departments of forensic medicine, and only a small proportion of cases (1-2%) are based on death certificate information alone (1). Until 1978 all cancers were coded according to 7th International Classification of Diseases (ICD-7), but thereafter according to the International Classification of Diseases for Oncology (ICD-O). To maintain comparability throughout the DCR's history, cancers coded according to ICD-O have also been coded according to ICD-7.

4.4 THE DANISH BREAST CANCER COOPERATIVE GROUPS REGISTRY

The Danish Breast Cancer Cooperative Group (DBCG) was established in 1976 by The Danish Surgical Society with the purpose of standardizing and evaluating the treatment of breast cancer in Denmark (59). A clinical database was formed, which contains information submitted from all Danish departments of surgery, histopathology, radiotherapy and medical oncology involved in the treatment of breast cancer. In studies on breast cancer information from the DBCG database supplements the DCR, as it contains more detailed information on tumor size and histology, i.e. estrogen receptor status, nodal status, and treatment. The database is updated daily.

5 METHODS

5.1 THE STUDY COHORT

Information on the school health records regarding name, day of birth, birth weight and annual measurements of weight and height was computerized and linked to the CRS matching on birth date and name at The Institute of Preventive Medicine. The CRS numbers for 141,393 girls (88%) and 145,140 boys (88%) were identified, and these children thus comprised our main study cohort (Table 3, page 19). The lack of identification of the remaining 12% is partly due to death, emigration, and change of surname at the time of marriage, before 1 April 1968.

Table 3. CRS numbers identified for children in the school health records according to birth year.

	Men (N=164,155)		**Women (N=161,063)**	
Birth Year	**Known CRS number**	**Unknown CRS number (%)**	**Known CRS number**	**Unknown CRS number (%)**
1930-1934	14,776	3,952 (21.10)	14,527	3,729 (20.43)
1935-1939	19,451	4,332 (18.21)	18,858	4,418 (18.98)
1940-1944	23,009	4,364 (15.94)	22,631	4,338 (16.09)
1945-1949	23,173	3,222 (12.21)	22,755	3,302 (12.67)
1950-1954	16,943	1,572 (8.49)	16,635	1,846 (9.99)
1955-1959	14,195	712 (4.78)	13,611	953 (6.54)
1960-1964	11,736	346 (2.86)	11,287	582 (4.90)
1965-1969	10,674	171 (1.58)	10,320	219 (2.08)
1970-1975	10,984	344 (3.04)	10,771	195 (1.78)
All	145,140	19,015 (11,60)	141,393	19,582 (12,16)

5.2 *EXPOSURE VARIABLES*

5.2.1 *Birth weight*

Typically either or both parents accompanied their child to the first visit at the school health services, at which they reported the child's birth weight. Before 1941 most schools used health records without a preprinted space for information on birth weight, but information on birth weight was still found in most records in the birth cohorts 1935-39 (Table 4, page 20). In our study population of children with a CRS number, information on birth weight was available for 106,504 girls (75%) and 110,825 boys (76%).

Table 4. Distribution of birth weights among children with known CRS number according to birth cohort.

	Men (N=145,140)		Women (N=141,393)	
Birth Year	**Known birth weight**	**Unknown birth weight (%)**	**Known birth weight**	**Unknown birth weight (%)**
1930-1934	1	14,775 (99.99)	296	14,231 (97.96)
1935-1939	11,282	8,169 (42.00)	10,388	8,470 (44.91)
1940-1944	20,403	2,606 (11.33)	19,869	2,762 (12.20)
1945-1949	21,377	1,796 (7.75)	20,867	1,888 (8.30)
1950-1954	15,489	1,454 (8.58)	14,328	2,307 (13.87)
1955-1959	12,835	1,360 (9.58)	12,276	1,335 (9.81)
1960-1964	10,541	1,195 (10.18)	10,157	1,130 (10.01)
1965-1969	9,407	1,267 (11.87)	9,184	1,136 (11.01)
1970-1975	9,328	1,656 (15.08)	9,140	1,631 (15.14)
All	110,825	34,315 (23.65)	106,504	34,889 (24,68)

5.2.2 Height and weight

Information on annual measurements of weight and height was used for women in *Study III.* Unlike for birth weight the school health records had preprinted space for measurements of weight and height on all editions. The number of height/weight measurements in the cohort totals 2,448,172 ~ an average of 7.5 measurements per child. Only children born from 1970 to 1975 have fewer than 7 measurements on average. The children in the cohort are between 5 and 17 years of age when measured, however only few children have measurements from their 5th year, and the number of measurements from 6-year-olds equals 37% of the number of measurements from 7-year-olds. Ninety-four percent of all measurements are on children between the age of 7 and 15 years of age, and 87% of all children have between 6 and 12 measurements.

Measurements of weight and height were not done according to individual birth dates. We therefore calculated weight and height at ages 8, 10, 12 and 14 by linear interpolation of the last measurements before the birthday and the first measurement after the birthday. Weight and height at ages 8, 10, 12 and 14 years were estimated by linear interpolation of the last measurements before the birthday and first measurement after the birthday. If no measurements after the 14th birthday existed but the levels at ages 8, 10 and 12 were known, the level at age 14 was predicted by best subset regression performed in STATA (60). BMI at ages 8, 10, 12 and 14 was calculated as weight (kilo) divided by squared height (meter) at the respective ages. Table 5 page 22 presents the distribution of weight, height and BMI in the cohort.

5.2.3 Age at peak growth

Due to the nature of the dataset with repeated measurements of height over time, we were able to estimate age at peak growth. Age at peak growth was defined as the age in the middle of the two measurements where the maximum growth rate in height was observed. The growth rate between two measurements was estimated as a weighted average of change in height between the two measurements (weight: ½) and the change in the two adjacent intervals (weight: ¼). With only one adjacent interval the weights were ⅔ and ⅓, respectively. If the growth rate peaked two or more times the latest was chosen as a maximum. Age at peak growth was estimated in women with 5 or more measurements (129,303 women) and where the maximum growth rate was estimated to be 3.5 cm per year or higher (Table 5, page 22).

5.2.4 Age at menarche

The school health records did not have a preprinted space for registration of menarche before 1950, and this information is thus sparse for earlier birth cohorts. However, from 1940 this information was begun to appear regularly in the records. Information on age at menarche was not originally computerized along with information on birth weight and measurements of height and weight. We therefore chose to retrieve the school health records in a nested case-cohort design to look for information on age at menarche. At the Department of Epidemiology Research we manually retrieved and computerized information on menarche on all 2,005 women born from 1940 to 1970 who later developed breast cancer and 2,200, 1,650, 550, 550, 200, 200 and 200 randomly chosen women from the birth cohort strata 1940-44, 1945-49, 1950-54, 1955-59, 1960-1964, 1965-69 and 1970+ respectively (Table 5, page 22).

Table 5. Distribution of growth variables in the cohort.

Variable	N	Median	Std. dev.
Height			
Age 8	129,205	126.7	5.5
Age 10	131,457	137.2	6.2
Age 12	129,745	149.0	7.3
Age 14	126,818	159.4	6.5
Weight			
Age 8	129,204	25.5	3.7
Age 10	131,465	31.6	5.2
Age 12	129,745	39.8	7.2
Age 14	126,818	49.5	7.8
BMI			
Age 8	129,202	15.8	1.5
Age 10	131,456	16.7	1.9
Age 12	129,742	17.8	2.2
Age 14	126,811	19.4	2.4
Indicators of puberty			
Age at peak growth	129,229	12.0	1.3
Age at menarche	3,778	13.1	1.0

5.3 *Outcome Variables*

All persons in the main study cohort were linked to the Danish Cancer Registry (DCR) on the basis of the CRS-number in order to identify incident cases of cancer. In all three studies a diagnosis of cancer was identified on the basis of the ICD-7 coding. We used the DBCG database as an additional source of information for two reasons. Firstly, as previously noted it supplements the DCR with tumor characteristics. Secondly, at the time of linkage the DCR was only complete until 31 December 1997 whereas the DBCG database was complete until 31 August 2001.

5.4 *Statistical Methods*

5.4.1 *Study I - "Birth weight and risk of breast cancer"*

The association between birth weight and incidence of breast cancer was estimated in a cohort design using log-linear Poisson regression. Follow-up for breast cancer began 1 April 1968, or the date of birth, whichever came last, and continued until a diagnosis of cancer, death, emigration, or 31 August 2000, whichever came first.

Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60 years) and calendar period in 5-year intervals (61). In additional analyses, adjustments were made for age at first birth (nulliparous, 12-19, 20-24, 25-29, 30-34, 35+ years) and parity (0, 1, 2, 3, 4+ children).

The relative risk (rate ratio) increase per 1,000 g increase in birth weight was estimated by treating birth weight categorized in intervals of 100 g as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. The log-linear assumptions underlying the trend estimation of birth weight were checked in two ways. Firstly, by a likelihood ratio test comparing the models with birth weight treated as a continuous and a categorical variable, respectively. Secondly, we evaluated the effect of including a quadratic term in the trend analysis.

Estimation of the increase in breast cancer risk according to tumor diameter (< 2 cm; 2-5 cm; $\geq$ 5 cm; missing or diagnosed before 1977), nodal status (negative; positive; missing or diagnosed before 1977) and estrogen receptor status (negative; positive; missing or diagnosed before 1977) by 1,000 g increase in birth weight was performed as a competing risks analysis, i.e. with censoring as above but counting only the selected case category as cases.

Poisson regression was used instead of Cox regression because of the computational efficiency in large datasets when analyzing time-dependent variables such as parity and age at first birth. All analyses were carried out using the SAS statistical software release 8.02 (specifically the PROC GENMOD procedure) (62).

5.4.2 Study II – "Birth weight and risk of cancer"

The association between birth weight and cancer was estimated in a cohort design using log-linear Poisson regression. Follow-up for cancer began 1 April 1968 or at age 6 years, whichever came last, and continued until a diagnosis of cancer, death, emigration, or 31 December 1997, whichever came first. In additional analyses, adjustments were made for age at first birth (nulliparous, 12-19, 20-24, 25-29, 30-34, 35+ years) and parity (0, 1, 2, 3, 4+ children).

The association between birth weight and cancer risk was analyzed in two different models. A linear spline model with 3,500 g as knot was estimated in order to investigate the association in low and high birth weights. If these two trend estimates could be considered equal (based on a likelihood ratio test) an overall trend was estimated. The relative risk (rate ratio) increase per 1,000 g increase in birth weight was estimated by treating birth weight categorized in intervals (501-2,499 g, 2,500-2,999 g, 3,000-3,499 g, 3,500-3,999 g, 4,000-4,499 g, 4,500-5,999 g) as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category.

Trends for different sites were compared using inverse-variance weighted regression using PROC GENMOD in SAS and based on the site-specific trend estimates and standard error. This approach was used instead of a competing risks approach (63), as the dataset became too large even with Poisson regression due to the many competing risks and the refined adjustment for age and calendar period. The main difference between the two is that in the first approach patients with two different cancers are included twice compared to once in the latter approach. The trends for different sites were furthermore compared using inverse-variance weighted regression with a common fixed effect and a random site effect with PROC MIXED in SAS. There was no indication of a random site effect.

5.4.3 Study III – "Growth Patterns and the Risk of Breast Cancer in Women"

The main analyses were performed in a cohort of 117,415 women for whom information was known on weight and height at ages 8, 10, 12 and 14 years as well as age at peak growth. The association with breast cancer was estimated in a cohort design using log-linear Poisson regression (PROC GENMOD procedure in SAS v. 8.02 statistical software) (11).

Follow-up for breast cancer began at age 14 years or on 1 April 1968, whichever came last, and continued until a diagnosis of cancer, death, emigration, or 31 August 2001, whichever came first. Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60 years) and calendar period in 5-year intervals (12). In additional analyses, adjustments were made for age at first birth (nulliparous, 12-19, 20-24, 25-29, 30-34, 35+ years) and parity (0, 1, 2, 3, 4+ children).

Trends were estimated by treating the categorized variables as continuous variables. The numerical value assigned to a given category was chosen as the median of the distribution of the variable within the category. The log-linear assumptions underlying the trend estimation of the variable were checked by a likelihood ratio test comparing the models with the variable treated as a continuous and a categorical variable, respectively.

Analyses involving age at menarche from the nested case-cohort design were performed using Cox regression with age as the underlying time variable and with birth cohort as strata variable. The Cox regression analyses (with robust estimation of variance to avoid overestimation of the precision due to the design-induced over sampling of cases) were performed using the STCOX procedure in STATA v. 8 statistical software (60). Follow-up and covariates were as in the Poisson regression, however, as birth cohort had to be included by design it was viewed as a substitute for calendar period. To validate this substitution we repeated some of the Poisson regressions with birth cohort instead of calendar period and obtained very similar results.

6 RESULTS

6.1 STUDY I - "BIRTH WEIGHT AND RISK OF BREAST CANCER"

A total of 2,334 cases of primary breast cancer were diagnosed in this cohort during 3,255,549 person-years of follow-up. Of these, 922 (40%) were diagnosed with breast cancer at the age of 50 years or older. Women with recorded birth weights greater than or equal to 6,000 g or less than or equal to 500 g were excluded from the analyses due to a high risk of misclassification in these extreme groups (N=344).

We found a linear association between birth weight and breast cancer equivalent to a RR=1.09 (95% CI 1.02 to 1.17%) per 1,000 g increase in birth weight (Figure 1, page 28).

The risk increase by birth weight did not vary with age (Table 6, page 28). Analysis of the linear trend according to year of birth and period likewise showed no variation. Estimating the increase in risk of breast cancer according to tumor characteristics at diagnosis by 1,000 g increase in birth weight revealed no systematic differences. Furthermore no confounding effect was found when adjusting for parity and age at first birth.

For some of the identified women information on birth weight was missing. Their breast cancer risk did not vary significantly from women with known birth weight, $RR_{unknown\ vs\ known}$=0.94 (95% CI, 0.86 to 1.03). The estimation was based on the assumption that the association between birth weight and breast cancer can be described by a trend. Goodness-of-fit tests gave no indication that this assumption was inadequate.

Figure 1. Relative risk of breast cancer according to birth weight.

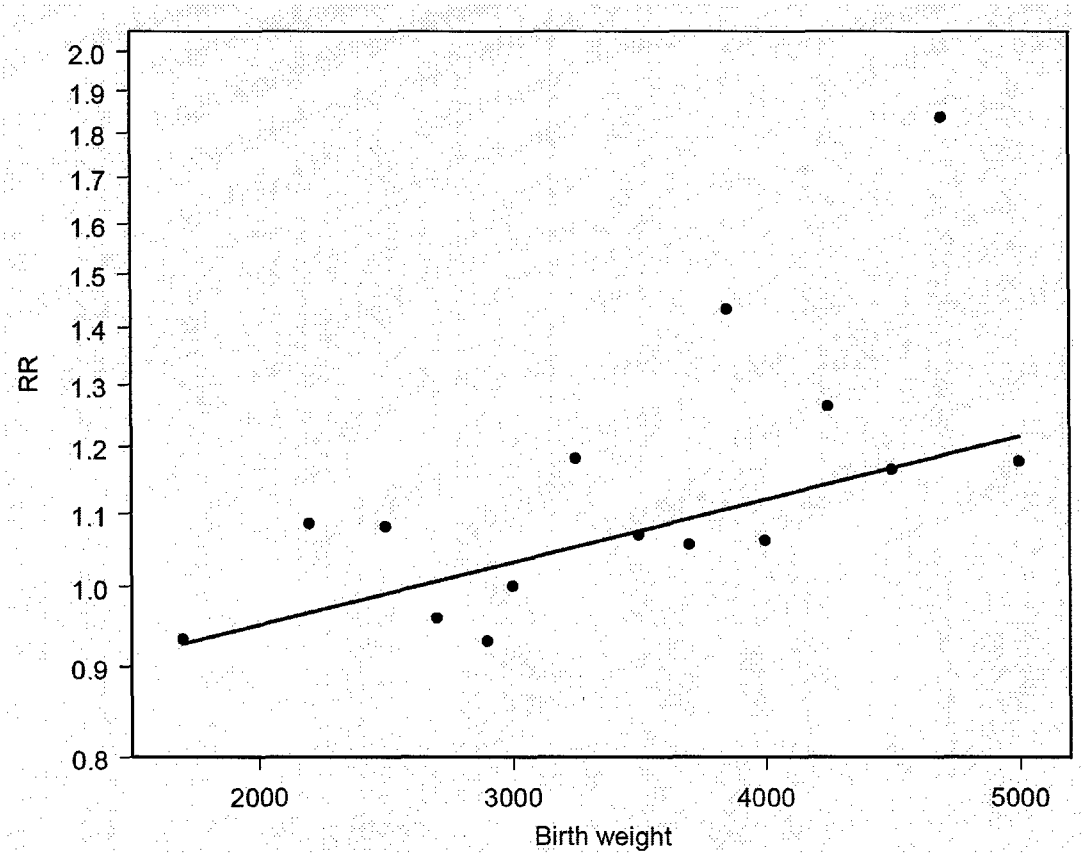


Table 6. Breast cancer risk per 1,000 g increase in birth weight according to age.

Age (years)	Cases	$RR_{per\ 1,000\ g}$ (95% CI)	
0 – 39	375	1.07 (0.90 – 1.28)	
40 – 44	453	1.08 (0.92 – 1.26)	
45 – 49	584	1.20 (1.04 – 1.38)	$p_{diff} = 0.30^*$
50 – 54	502	1.08 (0.92 – 1.25)	
55 – 59	325	1.09 (0.91 – 1.31)	
60 +	95	0.77 (0.56 – 1.07)	
Overall	2,334	1.09 (1.02 – 1.17)	

* Test for difference, i.e. test for interaction between age and birth weight trend. Similar analysis but with binary age groups (< 50 years and ≥ 50 years) revealed no difference in trend according to age, p = 0.29

6.2 *Study II – "Birth Weight Risk Of And Cancer"*

A total of 106,504 women and 110,825 men had recorded birth weights. Persons with recorded birth weights greater than or equal to 6,000 g or less than or equal to 500 g were excluded from the analyses due to a high risk of misclassification in these extreme groups (N_{women}=344 and N_{men}=369). A total of 7,529 cases of primary invasive cancer were diagnosed in the remaining cohort during 5,858,074 person-years of follow-up.

Table 7 on page 30 presents the association between birth weight and incidence of site-specific cancer (adjusted for age and calendar period). Trends were calculated for children with birth weights < 3,500 g (LBW), children with birth weights >3,500 g (HBW) and for all children.

V-shaped associations were observed for prostate, testicular, and bladder cancers and for multiple myeloma and non-Hodgkin's lymphoma, and inverse V-shaped associations were observed for Hodgkin's lymphoma, and cancers of the kidney and the larynx. If the trends for LBW and HBW children were significantly different no common trend was calculated. This was the case for prostate and testicular cancer and for Hodgkin's lymphoma. When analyzing difference in trends for all cancers (excluding only testis cancer, prostate cancer and Hodgkin's lymphoma) we found that the site-specific trends were not significantly different (p=0.59) from each other. Analyses of all cancers combined (excluding testis cancer, prostate cancer and Hodgkin's lymphoma) showed a significantly positive association between birth weight and cancer equivalent to a RR=1.10 (95% CI 1.05 to 1.15%) per 1,000 g increase in birth weight (Figure 2, page 31).

Analyses according to attained age showed a similar trend with birth weight (p=0.91) for age under 50 years ($RR_{age<50}$=1.10; 95% CI 1.04 to 1.17) when compared to age 50 years or older ($RR_{age>=50}$=1.10; 95% CI 1.01 to 1.19). Analyses according to sex also showed a similar trend with birth weight (p=0.45) for men (RR_{men}=1.13; 95% CI 1.04 to 1.22) and women (RR_{women}=1.09; 95% CI 1.03 to 1.15). Parity and age at first birth were known for women born in 1935 and later. No confounding effect was found when adjusting for these factors.

The above findings were consistent when cancers were analyzed according to hormonal etiology (Figure 3, page 32). Thus for male cancers of hormonal etiology (prostate and testicular cancer) different trends in LBW and HBW children was found (RR_{LBW}=0.63 (95% CI: 0.49-0.80) and RR_{HBW}=1.29 (95% CI: 0.89-1.88). For all other cancers in males a common trend of R=1.12 (95% CI: 1.02-1.21) could be estimated. In women, no difference was seen between cancers with a hormonal etiology (breast, cervical, uterine and ovarian cancers) and other cancers ($RR_{Women\ hormonal}$=1.08 (95% CI: 0.99-1.17) and $RR_{Women\ all\ other}$ =1.09 (95% CI: 1.01-1.18)).

Table 7. Birth weight and relative risk of cancer. Adjusted for age and calendar period.

Cancer site	N	RR pr. kg (95% CI) (Birth weight < 3,500 g)	RR pr. kg (95% CI) (Birth weight > 3,500 g)	RR pr. kg (95% CI) (All birth weights)
Men, specific sites				
Prostate	56	0.56 (0.27-1.18)	2.76 (1.10-6.97)	-
Testis	443	0.64 (0.50-0.83)	1.16 (0.76-1.75)	-
Women, specific sites				
Breast	1,842	1.15 (1.00-1.33)	1.02 (0.83-1.26)	1.10 (1.01-1.21)
Cervix	515	1.07 (0.83-1.39)	1.00 (0.66-1.52)	1.05 (0.89-1.24)
Ovary	276	0.97 (0.69-1.36)	0.93 (0.52-1.67)	0.96 (0.76-1.20)
Uterus	143	0.95 (0.59-1.53)	1.13 (0.54-2.37)	1.01 (0.73-1.38)
Men and women, specific sites				
Bladder	269	0.85 (0.59-1.23)	1.68 (1.08-2.63)	1.14 (0.90-1.44)
Brain	473	1.16 (0.87-1.54)	1.15 (0.97-1.38)	1.15 (0.97-1.38)
Colon and rectum	520	1.03 (0.79-1.34)	0.95 (0,65-1.38)	1.00 (0.85-1.18)
Hodgkin's Lymphoma	141	1.52 (0.89-2.61)	0.27 (0.09-0.79)	-
Kidney	175	1.69 (0.99-2.89)	0.86 (0.46-1.63)	1.26 (0.94-1.68)
Larynx	95	2.14 (0.97-4.73)	0.85 (0.37-1.95)	1.37 (0.92-2.03)
Leukemia	219	1.16 (0.76-1.76)	0.98 (0.55-1.76)	1.09 (0.84-1.41)
Liver and gallbladder	83	0.94 (0.49-1.82)	1.31 (0.55-3.11)	1.08 (0.71-1.64)
Lung	658	1.18 (0.92-1.51)	1.36 (1.01-1.84)	1.26 (1.08-1.46)
Malignant melanoma	555	1.08 (0.84-1.41)	1.34 (0.95-1.90)	1.18 (1.00-1.39)
Multiple myeloma	51	0.87 (0.37-2.03)	2.09 (0.79-5.52)	1.29 (0.75-2.21)
Non Hodgkin's Lymphoma	291	0.89 (0.63-1.25)	1.55 (0.98-2.44)	1.16 (0.87-1.54)
Other cancers	578	0.85 (0.67-1.09)	1.36 (0.97-1.91)	1.02 (0.87-1.20)
Pancreas	120	1.36 (0.73-2.50)	1.03 (0.47-2.26)	1.21 (0.84-1.74)
Pharynx	115	0.62 (0.38-1.02)	0.95 (0.43-2.12)	0.72 (0.51-1.01)
Stomach and esophagus	201	1.23 (0.78-1.93)	0.88 (0.48-1.61)	1.07 (0.82-1.41)

Figure 2. Relative risk of cancer at all sites (excluding prostate and testicular cancer as well as for Hodgkin's lymphoma) according to birth weight. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment was made for age and calendar period.

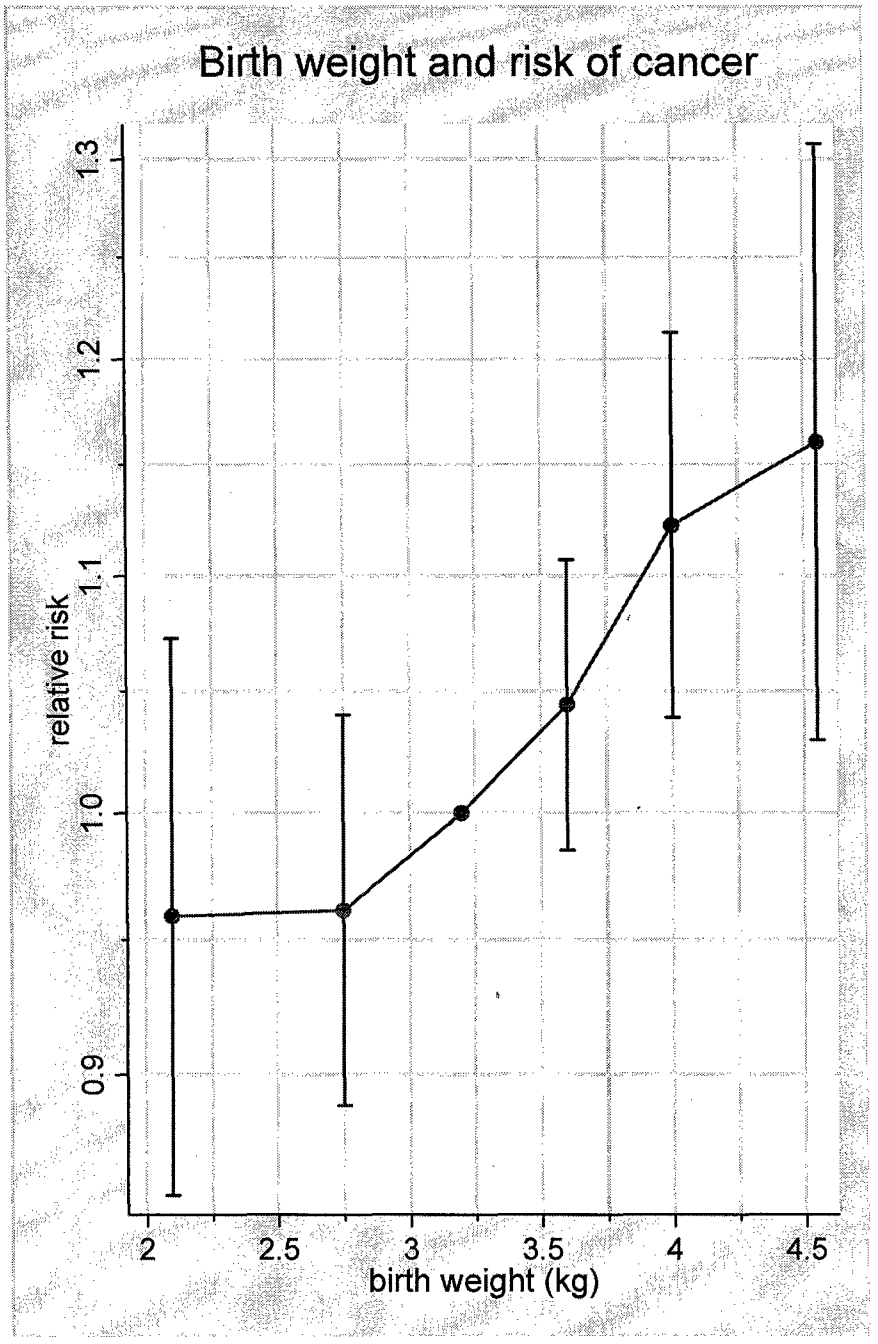
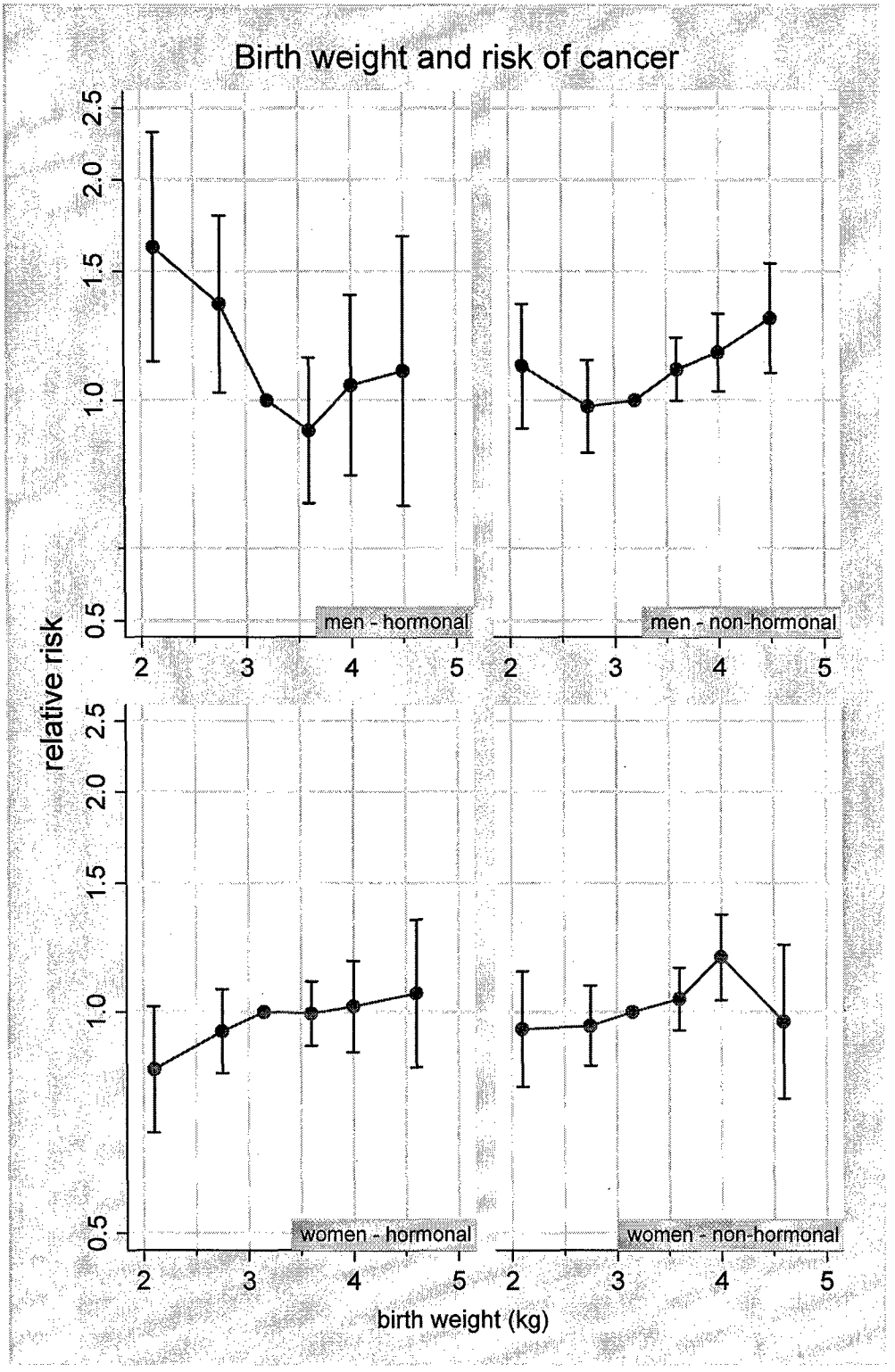


Figure 3. Birth weight and relative risk of cancer for hormonal and non-hormonal cancers in men and women respectively. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment was made for age and calendar period.



6.3 *Study III – "Growth Patterns and the Risk of Breast Cancer in Women"*

In the cohort of 117,415 women 3,340 cases of breast cancer were observed during 3,333,359 person-years of follow-up. Relative risk of breast cancer according to birth weight, age at peak growth, age at menarche, height at age 14 and BMI at age 14 are presented in Table 8 on page 34. All variables in the table were adjusted for age and calendar period, except for age at menarche, which for technical reasons was adjusted for birth cohort instead of calendar period. Analysis of birth weight was performed on the 91,601 women for whom birth weight was known within the cohort of 117,415 women. Birth weight was positively associated with breast cancer with a RR=1.10 per 1,000 g increase in birth weight (95% CI: 1.01 to 1.20).

The estimated age at peak growth was negatively associated with breast cancer, with a RR=0.93 per 1-year increase in age at peak growth (95% CI: 0.91 to 0.96). Age at menarche was likewise negatively associated with breast cancer, with a RR=0.96 (95% CI: 0.92 to 1.00) per 1-year increase in age at peak growth. Height at age 14 was positively associated with breast cancer with a RR=1.11 per 5 cm increase in height (95% CI: 1.08 to 1.15). BMI at age 14 was negatively associated with breast cancer with a RR=0.97 per BMI (95% CI: 0.96 to 0.98). No association was found with weight at any age and breast cancer.

No confounding effect was found when adjusting the trends presented in Table 8 (page 34) for parity and age at first birth.

Table 8. Adjusted[#] relative risk (RR) of breast cancer according to birth weight, age at peak growth, age at menarche, height at age 14 and BMI at age 14.

Cohort (N=117.415)	cases	RR (95% CI)
birth weight[*] (median of quintiles)		
2.5 kg	381	1 (ref)
3.0 kg	392	0.98 (0.85-1.13)
3.4 kg	668	1.06 (0.93-1.20)
3.6 kg	150	1.05 (0.87-1.27)
4.0 kg	483	1.17 (1.02-1.33)
trend pr. kg[§]	2,074	1.10 (1.01-1.20)
age at peak growth (median of quintiles)		
10.4 year	568	1 (ref)
11.3 year	727	1.04 (0.93-1.16)
12.0 year	703	0.94 (0.84-1.05)
12.8 year	657	0.86 (0.77-0.96)
13.5 year	685	0.84 (0.75-0.93)
trend pr. year[§]	3,340	0.97 (0.96-0.98)
age at menarche[¤] (median of quintiles)		
11.9 year	193	1 (ref)
12.6 year	201	1.03 (0.85-1.26)
13.2 year	209	1.09 (0.90-1.33)
13.7 year	183	0.94 (0.77-1.15)
14.4 year	164	0.83 (0.67-1.02)
trend pr. year[§]	950	0.96 (0.92-1.00)
height at age 14 (median of quintiles)		
151.1 cm	733	1 (ref)
156.2 cm	678	1.07 (0.96-1.19)
159.8 cm	682	1.18 (1.06-1.31)
162.9 cm	600	1.15 (1.03-1.28)
167.6 cm	647	1.51 (1.36-1.68)
trend pr. 5 cm[§]	3,340	1.11 (1.08-1.15)
BMI at age 14 (median of quintiles)		
16.7 kg/m²	644	1 (ref)
18.1 kg/m²	692	0.96 (0.86-1.07)
19.1 kg/m²	736	1.02 (0.92-1.13)
20.3 kg/m²	711	0.99 (0.89-1.10)
22.4 kg/m²	557	0.84 (0.75-0.94)
trend pr. kg/m²[§]	3,340	0.97 (0.96-0.98)

* Birth weight was only known for 91,601 of the 117,415 women.

¤ Based on a nested subcohort of 3610 women with known age at menarche.

§ Adjustment for parity and age at first birth did not markedly change the trend estimates.

All variables were adjusted for age and calendar period, except for age at menarche, which for technical reasons was adjusted for birth cohort instead of calendar period as described in the methods section

To further utilize the longitudinal nature of the data we investigated whether growth in any specific age interval had a special impact on breast cancer risk by decomposing the association with height at age 14 as associations with height at age 8 and increments in height between age 8 and age 14. We used the estimated age at peak growth to subdivide the age interval between 8 and 14 years of age into the following individual categories: "age 8 until peak year", "peak year" and "peak year until age 14" (Table 9, page 35).

Increase in height was significantly associated with breast cancer within all three age intervals after adjustment for BMI at age 14, age at peak growth, age and calendar period. The relative risk per increase in height was similar in all three age-intervals (p=0.33), whereas the relative risk was significantly higher for changes in height between age 8 and age 14 compared to height at age 8 (p=0.01). We furthermore modeled BMI in age intervals as described above with height. BMI adjusted for height at age 14, age at peak growth, age and calendar period was significantly associated with breast cancer within all three age intervals. However, the increase in relative risk per increase in BMI was similar in all three age intervals (p=0.77), and the increase in relative risk was furthermore similar for changes in BMI between age 8 and age 14 compared to BMI at age 8 (p=0.10).

Table 9. Adjusted relative risk (95% CI) of breast cancer according to pubertal growth.

	AGE 8 YEARS	AGE 8 TO PEAK YEAR	PEAK YEAR	PEAK YEAR TO AGE 14	AGE 8 TO AGE 14	
Height*			p_{diff}=0.33			
trend pr. 5 cm	1.10 (1.06-1.15)	1.18 (1.08-1.27)	1.15 (0.97-1.36)	1.10 (1.00-1.20)		
trend pr. 5 cm	1.11 (1.07-1.15)				1.17 (1.09-1.25)	p_{diff}=0.01
BMI#			p_{diff}=0.77			
trend pr. kg/m²	0.93 (0.90-0.97)	0.95 (0.91-0.99)	0.96 (0.90-1.02)	0.97 (0.93-1.02)		
trend pr. kg/m²	0.94 (0.91-0.97)				0.96 (0.93-0.99)	p_{diff}=0.10

* Adjusted for age, calendar period as well as age at peak growth and BMI at age 14.
\# Adjusted for age, calendar period as well as age at peak growth and height at age 14.

Table 10 on page 36 presents mutually adjusted relative risks of breast cancer according to birth weight, age at peak growth, age at menarche, height at age 8, height difference between age 8 and age 14 and BMI at age 14. Birth weight, height at age 8, height increase between age 8 and age 14

and BMI at age 14 remained after further adjustment independently associated with breast cancer with trends similar to those presented in Table 8 and Table 9. Adjustment for age at menarche did not affect these associations. The effect of age at peak growth was enhanced after adjustment for other growth factors, primarily due to adjustment for height and BMI. Adjustment for age at menarche did not affect the association between age at peak growth and breast cancer, whereas age at menarche was not associated with breast cancer after adjustment for the pubertal growth factors. Only age at peak growth had a significantly different association in women younger than 50 years (RR=0.90 per year; 95% CI: 0.86 to 0.95 compared to women 50 years or older (RR=0.98 per year; 95% CI: 0.93 to 1.03) (p=0.03).

Table 10. Associations between growth variables and breast cancer.

	ALL AGES	AGE < 50 YEAR	AGE >= 50	test for difference according to age
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	
birth weight* trend pr. kg	1.10 (1.01-1.21)	1.14 (1.01-1.28)	1.05 (0.91-1.21)	p=0.39
age at peak growth¤ trend pr. year	0.94 (0.91-0.97)	0.90 (0.86-0.95)	0.98 (0.93-1.03)	p=0.03
age at menarche# trend pr. year	0.99 (0.91-1.07)	0.98 (0.88-1.08)	1.01 (0.87-1.17)	p=0.74
height age 8¤ trend pr. 5 cm	1.11 (1.07-1.15)	1.11 (1.05-1.17)	1.11 (1.05-1.17)	p=0.62
height increase age 8 to age 14¤ trend pr. 5 cm	1.17 (1.09-1.25)	1.15 (1.05-1.27)	1.18 (1.07-1.30)	p=0.74
BMI age 14¤ trend pr. kg/m²	0.95 (0.93-0.97)	0.96 (0.94-0.99)	0.94 (0.92-0.97)	p=0.22

* Adjusted for age at peak growth, height at age 8, height increase age 8 to age 14 and BMI at age 14. Further adjustment for age at menache did not markedly change the estimate.

Adjusted for age at peak growth, height at age 8, height increase age 8 to age 14 and BMI at age 14. Further adjustment for birth weight did not markedly change the estimate.

¤ Mutually adjusted. Further adjustment for birth weight and age at menache did not markedly change the estimate.

7 CONCLUSIONS DRAWN FROM THE STUDIES

7.1 STUDY I - "BIRTH WEIGHT AND RISK OF BREAST CANCER"

- A linear significant association between birth weight and incidence of breast cancer equivalent to 9% increase in risk per 1,000 g increase in birth weight
- The association did not vary with age at diagnosis, and no systematic differences were seen according to tumor characteristics
- No confounding effect by parity or age at first birth was seen

7.2 STUDY II – "BIRTH WEIGHT AND RISK OF CANCER"

- Most cancers were found to have a positive linear association with birth weight
- Exceptions were testicular and prostate cancer that showed a V-shaped association and Hodgkin's lymphoma that showed an inverse V-shaped association with birth weight
- The trends for the individual cancer sites (excluding the three exceptions) were not statistically different from an overall trend of 10% increase in risk per 1,000 gram increase in birth weight
- This trend was the same in men and women and in all age groups. No confounding effect was found of age at first birth or parity in women

7.3 STUDY III – "GROWTH PATTERNS AND THE RISK OF BREAST CANCER IN WOMEN"

- High birth weight, early age at peak growth, high stature and low BMI at 14 years of age were all found to be independent risk factors for breast cancer
- Both height achieved at age 8 years and increment in height during puberty (age 8-14 years) were associated with breast cancer, however, the latter association was significantly stronger
- No confounding by age at menarche, age at first birth or parity was observed

8 DISCUSSION OF METHODOLOGY

8.1 SELECTIONS BIAS

The study cohort was based on all children born between 1930 and 1970 who attended school in the City of Copenhagen, Denmark. Records from all schools, public as well as private, have been kept. However, only children that could be identified in the CRS by match on birth date and name were included in the analyses (88%). Lack of identification was partly due to death, emigration, and change of surname at time of marriage, before 1 April 1968. This could thus have induced some selection bias. The studies were fully registry-based, thus selection bias in relation to differential willingness to participate is not relevant. Information on vital status throughout follow-up was obtained from the Danish Civil Registration System, which is a mandatory and daily updated system. Loss to follow-up is therefore virtually non-existing.

8.2 INFORMATION BIAS

8.2.1 Exposure misclassification

Birth weights were reported by the parents and recorded at an early age which limited potential recall bias (64). All information on the school health records were furthermore recorded decades prior to and independently of possible cancer diagnosis, making differential misclassification of exposure unlikely.

A small proportion of children (0.3%), however, had recorded birth weights of less than 500 g or more than 6,000 g. In analyses of birth weight, these children was excluded, as they were likely to have been erroneous. Exclusion was chosen in preference to correction of all extreme values, as this would have led to a regression towards the mean.

Time of menarche is by nature difficult to determine precisely. Still in contrast to many previous studies the date of menarche was recorded in the following year in the present investigation, reducing the likelihood of significant bias.

8.2.2 Detection bias

Cases in all three studies were ascertained in the Danish Cancer Registry, which is believed to be virtually complete in relation to diagnosis of incident cancers in Denmark (57). As a supplement to the Danish Cancer Registry the DBCG database was also used. The differences in registration between the DBCG register and the Danish Cancer Registry have been described previously (65). The authors concluded that the difference between the two data sources is almost entirely restricted

to women older than 70 years at diagnosis. For women under 70 years of age at diagnosis the completeness of case registration in the DBCG database is >95% compared with the Danish Cancer Registry, which thus has little influence on the present studies due to the age distribution in the cohort. Access to health care in Denmark has always been free and equal, which limits the risk of socio-economically related detection bias.

8.3 CONFOUNDING

We were not able to adjust the analyses of the effect of birth on cancer risk for the effect of gestational age. A study by Ekbom and colleagues has suggested that prematurity is associated with an increased risk of breast cancer (66), but it has since been refuted in an enlarged study (67). Gestational age, however, may not be important if it is the number of susceptible cells that accounts for the observed associations.

Furthermore, we were unable to adjust for the effect of smoking. Smoking exhibits a parent-offspring association, maternal smoking reduces birth weight, and smoking is a strong risk factor for certain cancers (e.g. nasopharyngeal, stomach, liver, pancreas and kidney cancer). Thus, lack of possibility to control for smoking limits the interpretation for these cancers. However, we note with interest that the association between birth weight and smoking associated cancers was similar to that found for cancers not associated with smoking, implying that control for smoking in the mother and the offspring would expectedly strengthen the association.

Socio-economic status could potentially also have acted as a confounder in our analyses. However, if the confounding effect was strong one should imagine that adjustment for age at first birth and parity had an effect, which was not observed in our study.

9 DISCUSSION OF FINDINGS

Denmark provides excellent opportunities for registry-based research, due to the long existence of reliable and nationwide registers. Combining information from a number of these registries we have aimed to characterize the association between anthropometrical markers of early exposures and cancer in a series of investigations. Specifically, we addressed the significance of birth weight for risk of all types of cancer, and for breast cancer we moreover conducted a detailed analysis of the significance of growth during school years.

In *Study I* we documented a statistically significant linear association between birth weight and risk of breast cancer. Thus, the risk of breast cancer increased by 9% per 1,000 g increase in birth weight (Figure 1, page 28). This finding is in agreement with the currently prevailing hypothesis that intrauterine factors contribute to the development of breast cancer in adulthood (3) and in line with many previous studies, although some inconsistencies exist (10-25;68).

The size of *Study I* made it possible to perform estimations in many subgroups of breast cancer, some of which have not been studied earlier. It has been suggested that the association with birth weight is strongest for premenopausal women (10;14). Interestingly, however, we found the association to be equally strong for pre- and postmenopausal women (Table 6, page 28). The association with birth weight according to tumor characteristics at the time of diagnoses has not previously been investigated. We found no systematic differences in the association by tumor characteristics. Together these findings suggest that the association between birth weight and breast cancer risk is not restricted to certain types of breast tumors but rather applies to breast cancer in general.

Consistent with this interpretation, adjustment for parity and age at first birth had no impact on the association between birth weight and breast cancer risk. Parity and age at first birth reflect the hormonal and cellular changes following pregnancies as well as maternal social status. Thus, based on this result we found in line with others (25) no indication of confounding by social status, although both birth weight and breast cancer have been associated with social factors (69).

The finding of high birth weight being a general risk factor for all types of breast cancers – not only for e.g. estrogen receptor positive breast cancers - raises this question: Is birth weight associated with risk of all cancers? To our knowledge, the only previous study addressing the association between overall risk of cancer and birth weight was a Swedish cohort study of women. In that investigation a linear association with overall incidence of cancer was found (16). However,

the study was limited in size, and when cancers were analyzed in subgroups, the authors got somewhat inconsistent results. Studies between birth weight and risk of ovarian, renal and colon cancer have likewise been inconsistent (26;39;40).

In *Study II* we analyzed the association between birth weight and cancer at all sites using two different statistical approaches. The first of these focused on trends in either the lower or the upper end of the birth weight spectrum. This was done to assure that any V-shaped association was not overlooked. In the second series of analyses, we studied whether there was an overall trend between birth weight and risk of cancer.

We found that prostate and testicular cancer had a significant V-shaped association with birth weight, whereas Hodgkin's lymphoma had a significant inverse V-shaped association to birth weight (Table 7, page 30). Non-linear associations were found for some other cancers, but they were not significantly departing from linearity, and we thus we assumed linear associations in the estimation of a common trend. This common trend was found to fit a linear trend of a 10-percent (95% CI from 5 percent to 15 percent) risk increase per 1,000 g increase in birth weight (Figure 2, page 31). Interestingly, this trend was of similar magnitude as the trend observed for the two male hormonal cancers (prostate and testis) in their category of high birth weight children.

In subsequent analyses we found that the overall trend in cancer risk was the same in all age groups and in both sexes. This latter observation is important as is indicates that the trend in risk for all cancers combined cannot be explained by breast cancer, the largest single group of cancers. Adjustment for parity and age at first birth did not further change the results when analyzing female-specific cancers separately.

High birth weight therefore seems to act as a common risk factor for most if not all cancers, whereas low birth weight may be "protective" for all cancers with the possible exception of prostate and testicular cancer. The observed V-shaped association between birth weight and prostate and testicular cancer has been observed by others which adds credibility to the existence of a true non-linear association with birth weight for these cancers (27;30-38;70).

To our knowledge no studies have examined the possible association between birth weight and risk of Hodgkin's lymphoma, making our finding of a V-shaped association to birth weight more uncertain. This finding could be real, but in our study it stands out as the only such significant association in the entire group of cancers.

The experience from previous studies as well as *Study II* underlines the necessity of a very large study material to address the effect of birth weight on cancer in general. While there seems to be a

true association between birth weight and cancer risk, however, the magnitude of the association is small. Even in our cohort of nearly 6 million person-years of follow-up and 7,529 cancer outcomes, some cancers were still relatively rare, and findings would have been inconsistent if they were reported by a single cancer site at a time. Clearly, previous inconsistencies in studies on birth weight and cancer risk can to a large degree be explained by small sample sizes.

The possibility that in-utero growth has a uniform effect on risk of cancer at almost all sites is intriguing. It could be explained by the existence of a common pathway, with the added conditioning by one or more opposing factors influencing risk of male hormone-related cancers. The common pathway could establish a "base cancer risk" on which other later risk factors would have independent influence.

Several exposures have been shown to be associated with birth size, and particular attention has been paid to estrogen, IGF-I and insulin levels in the mother during pregnancy (7-9;71). The focus on particularly estrogens in the carcinogenesis has received much attention in breast cancer research as the mammary gland is exposed to very high concentrations of estrogens in utero (4). However, as birth weight seems to be important for almost all cancers, it is very likely that other still unknown factors are critical to this association.

Furthermore, how does birth size modulate cancer risk? It has been suggested that breast cancer risk increases with increasing numbers of relevant susceptible stem cells (3). Breast density (which acts as a proxy for mammary gland mass) has been associated with breast cancer risk (72) and kidney size in adults has also been associated with birth weight (73).

We believe that this model could be broadened to include most, if not all, types of cancer, and that accordingly large babies could have an increased cancer risk due to persistently increased number of susceptible cells. Specifically, the association between birth weight and cancer risk could either reflect a simple correlation between birth weight and number of cells or reflect that factors governing birth weight are also associated with an increased cancer risk, e.g. by initiating a multistep carcinogenesis.

Such a hypothesis fits well with our findings from *Study III.* Here we found a clear association between high birth weight and risk of breast cancer, independently of the effect of subsequent growth patterns. It is therefore reasonable to interpret the effect of fetal growth on breast cancer risk as being a particular effect unrelated to later growth and timing of puberty. Thus the effect of birth weight is not just a proxy for later growth.

Growth during childhood and adolescence is by nature correlated with final *adult* stature (44), and it can be difficult to disentangle the contributions of the different components of growth to the

risk of breast cancer. It is well-known that adult height is positively associated with both pre- and post-menopausal breast cancer (41), whereas high BMI is associated with a reduced pre-menopausal breast cancer, but with an increased risk of post-menopausal breast cancer (74).

As described in the *Introduction* only four previous studies have hitherto explored the association between pubertal growth measurements and breast cancer risk in cohorts where actual measurements of weight and height were obtained (15;17;45;46).

In agreement with these studies we found BMI at ages 8, 10, 12 and 14 years to be inversely associated with breast cancer risk (Table 8, 34). Using height at age 14 years, which serves as a good proxy for adult height since most girls have concluded their growth spurt by this age, we also confirmed an association between adult height and breast cancer risk (Table 8, 34). In fact, our finding of an increment in the relative risk of 11% per 5 cm increase in height was similar to results from a very large previous study on *adult* stature (42).

The nature of our dataset with repeated annual measurements allowed us to investigate whether the importance of final height was modified by the growth pattern. We found that height at age 8 and the increment in height during puberty (8-14 years) were both independently associated with breast cancer, but that the latter association was statistically significantly stronger, suggesting a separate contribution from pubertal growth (Table 9, page 35). In contrast our analyses of BMI did not reveal any time-interval in which changes in BMI was of special importance in relation to breast cancer risk.

Furthermore, we found a linear trend between decreasing age at peak growth as well as decreasing age at menarche and risk of breast cancer, which was independent of the effect of other anthropometrical measures (Table 10, page 36).

Adult height is only to some extent linked to ages at peak growth and menarche, and it is possible that different factors control these variables. Early growth spurt has previously been reported to be a risk factor in one (75) but not in another study (47). Age at peak growth and age at menarche most likely reflect the initiation of puberty. Age at menarche was in a Norwegian study found to increase breast cancer risk by 4% for each year of decrease in age at menarche (76). In our study, age at menarche was also found to be associated with breast cancer, but only age at peak growth contributed statistically significantly to breast cancer risk in the final multivariate model (which included age at peak growth, age at menarche, BMI at age 14, height at age 8 and increment in height between age 8 and age 14 years).

Thus, previous findings of an effect of age at menarche on breast cancer risk could reflect that age at menarche serves as a proxy for age at peak growth. Alternatively and perhaps more likely, age at menarche and age at peak growth may be so closely correlated and be proxies for the initiation of puberty that their effects on breast cancer risk in essence reflect the significance of onset of puberty. If the reported age at menarche is less precise than the estimated age at peak growth, this may explain why the latter factor over-rules the former. Another indication of the importance of puberty was our finding that centimeters accumulated between age 8 and 14 years conferred a higher risk of breast cancer than those accumulated up to age 8 years.

The biological background for our findings in relation to growth and breast cancer risk is clearly complex. Since it is obvious that neither height nor leanness or early puberty *per se* causes cancer, underlying mechanisms should be considered. Within the past century adult height and prevalence of obesity have increased, and age at menarche has decreased (77;78), indicating that changes in environmental conditions are of importance, probably operating in interaction with well known genetic factors. The effect of height on risk of breast cancer has been suggested mediated through IGF-I, as IGF-I is strongly correlated with height (79). Levels of IGF-I have furthermore been found to be risk factors for breast cancer in some (80), although not all, studies (81).

The positive association between height and cancer risk could reflect the influence of calorie intake during childhood (82;83). Similar findings have come from a study of the Boyd Orr cohort in England. According to this study, persons with high energy intake in childhood had a higher mortality from cancers (84). Animal studies confirm this finding, as rat experiments have shown energy restriction early in life to result in a reduced risk of development of different types of cancer (85).

Increased total number of menstrual cycles over a lifetime has been suggested as an explanation as to why early puberty is associated with increased breast cancer risk (86). However, this may be too simple an explanation. Thus, even an up to two-year delay in age of menarche would only result in a very limited number of "lost" menstrual cycles compared with the total number of lifetime cycles. Another explanation could be that early age of menarche increases the time interval until first pregnancy. The breast undergoes significant transformation at first pregnancy with final differentiation of the breast epithelium (2). Early menarche thus leaves the undifferentiated breast cells exposed to possible carcinogenic stimuli for a longer period of a time (87;88).

Our study was entirely registry-based, so we had no possibilities of directly testing biological hypotheses. Our finding that high BMI is protective for breast cancer is somewhat contradictive to studies showing that overweight in girls is associated with earlier menarche (89). This suggests that the effect of childhood obesity on breast cancer is not caused by an induction of early menarche, and consequently an acceleration of puberty as early menarche has an opposite effect of obesity. Importantly, even though high pubertal BMI seems to offer protection towards breast cancer, our results should not be interpreted in favor of early obesity as a way of reducing breast cancer risk, as obesity correlates with all-cause-mortality when it persists into adulthood (90).

In conclusion, the results from *Study I* strengthen previous findings of an association between birth weight and the risk of breast cancer. The study is furthermore the first to show that the effect of birth weight is equally important in all histological subtypes of breast cancer.

In *Study II* we found a positive linear association with birth weight and cancer at most sites, many of which had never previously been studied. Only prostate and testicular cancer revealed a significant V-shaped association with birth weight, whereas Hodgkin's lymphoma had a significant inverse V-shaped association to birth weight. Importantly, the association with birth weight for all other cancer sites (except only prostate and testis cancer and Hodgkin's lymphoma) was found to be uniform and to fit a linear trend similar to the trend found for breast cancer in *Study I*. We therefore hypothesize that the biological explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway, with some superimposed opposing factor(s) influencing male hormonal cancer.

In *Study III* we found that high birth weight is an independent risk factor for breast cancer not linked to the effects of growth patterns during adolescence or to final stature. Also early puberty as indicated by early age at peak growth was found to independently increase the risk of breast cancer.

We found that tallness and leanness at any age during puberty was associated with an increased breast cancer risk. However, there was an additional effect of growth during puberty. Compared with known risk factors such as age at first birth and parity, the association with pubertal growth was of greater magnitude and independent hereof, indicating that the exposures or conditioning processes during this period of life are of particular importance in relation to adult breast cancer risk.

10 SUMMARY IN ENGLISH

Breast cancer is the most common cancer in Danish women, with more than 3,500 new cases diagnosed every year. The associations between adult anthropometrical measures and breast cancer are well established, but the extent to which these associations are reflections of specific growth patterns of the fetus, in childhood and adolescence is not resolved.

The aim of the present PhD thesis was to characterize the association between anthropometrical markers of growth and cancer. Based on three studies, the thesis addresses the significance of birth weight for all cancers, whereas the significance of growth during school years is addressed specifically for breast cancer.

The studies were based on a cohort of girls and boys born between 1930 and 1975. During this period, all pupils in the Copenhagen municipality underwent regular health examinations in the School Health Service, for which nurses or physicians filled in records. A manual register of school health records covering this period has been kept representing a total of 161,063 girls and 164,155 boys. The records include information on annual measurements of weight and height as well as information on age at menarche and birth weight as reported by the parents at the first school health examination. Information from these school health records was computerized and linked to the Danish Civil Registration System matching on birth date and name. Information on incident breast cancer cases was obtained from the Danish Cancer Registry and the registry of the Danish Breast Cancer Cooperative Group.

The longitudinal nature of the data offered a unique possibility to model individual growth curves and calculate age at peak growth. For a sub-cohort of women information on age at menarche was available. Information on birth characteristics, vital status, age at first childbirth, parity, and possible diagnosis of breast cancer was obtained on all cohort members through linkages to national registries.

The results from Study I strengthen previous findings of an association between birth weight and the risk of breast cancer. The study is furthermore the first to show that the effect of birth weight is equally important in all histological subtypes of breast cancer.

In Study II we found that the association with birth weight is not specific for breast cancer, but observed for cancer at all sites. Prostate and testicular cancer revealed a significant V-shaped association with birth weight, whereas Hodgkin's lymphoma had a significant inverse V-shaped association with birth weight. Importantly, the association with birth weight for all other cancer sites was found to be uniform and to fit a linear trend similar to the trend found for breast cancer in Study I. We therefore hypothesize that the biological explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway, with some superimposed opposing factor(s) influencing male hormonal cancer.

In Study III we found that high birth weight is an independent risk factor for breast cancer not linked to the effects of growth patterns during adolescence or to final stature. Also early puberty as indicated by early age at peak growth was found to independently increase the risk of breast cancer.

We found that tallness and leanness at any age during puberty was associated with an increased breast cancer risk. However, there was an additional effect of growth during puberty. Compared with known risk factors such as age at first birth and parity, the association with pubertal growth was of greater magnitude and independent hereof, indicating that the exposures or conditioning processes during this period of life are of particular importance in relation to adult breast cancer risk. The importance of final stature may thus be seen as a general effect with an additional effect of the growth attained during puberty.

11 DANSK RESUMÉ

Brystkræft er den hyppigste kræftform blandt danske kvinder med flere end 3500 nye årlige tilfælde. Det er velkendt, at høje kvinder har øget risiko for brystkræft, men vægten har ligeledes betydning for risikoen for brystkræft. Således har overvægtige kvinder en øget risiko for brystkræft efter menopausen, men en mindsket risiko for brystkræft inden menopausen. Det er dog ikke særligt velbeskrevet, i hvilken udstrækning disse sammenhænge med højde og vægt i voksenårene afspejler vækst i fosterlivet, barndommen og puberteten.

Målet med denne ph.d.-afhandling har derfor været at karakterisere sammenhængen mellem vækst og kræftudvikling nøjere. Afhandlingen er bygger på tre studier, der studerer betydningen af fødselsvægt (som udtryk for vækst i fosterlivet) for udviklingen af alle kræftformer, og ydermere betydningen af vækst i børne- og ungdomsårene for udviklingen af brystkræft.

Undersøgelserne er baseret på helbredsoplysningerne fra en unik samling af skolehelbredskort fra 325.631 københavnske skoleelever, født mellem 1930 og 1975. Disse helbredskort blev udfyldt ved de almindelige årlige besøg hos skolelægen og indeholder information om barnets navn, årlige højde- og vægtmålinger, fødselsvægt, fødselsdato samt for pigernes vedkommende alder ved første menstruation. De årlige målinger af højde og vægt giver os en enestående mulighed for at beregne individuelle vækstkurver og alder ved vækstspurt.

Ved hjælp af børnenes fødselsdato og navn har vi fundet frem til CPR-nummeret på de fleste af børnene. Derfor har vi kunnet finde frem til hvilke børn, der efterfølgende udviklede kræft, ved at indhente oplysninger fra Cancerregisteret og den kliniske database hos "Danish Breast Cancer Cooperative Group" ved hjælp af CPR-nummeret. Alder ved første fødsel og antal børnefødsler for pigerne har vi ligeledes kunne beregne ved brug af oplysninger fra CPR-registeret.

Resultaterne i Studie I styrker tidligere undersøgelsers fund af, at høj fødselsvægt er forbundet med øget risiko for brystkræft, mens en lav fødselsvægt er forbundet med lav risiko. Studiet er ydermere det første til at vise, at denne sammenhæng er den samme for alle typer af brystkræft, uafhængig af østrogen-receptor status eller spredningsgrad ved diagnosetidspunktet.

I Studie II fandt vi, at høj fødselsvægt ikke kun er en risikofaktor for brystkræft, men for stort set alle kræftformer, og at lav fødselsvægt er forbundet med lav risiko for de fleste kræftformer. De eneste undtagelser var, at lav fødselsvægt også var en risikofaktor for prostata- og testikelkræft, mens høj fødselsvægt var beskyttende mod Hodgkins lymfom. Sammenhængen mellem høj fødselsvægt og lav risiko for Hodgkins lymfom er ikke tidligere beskrevet og kan være et tilfældigt fund. Ydermere fandt vi, at sammenhængen mellem fødselsvægt og risikoen for at udvikle alle former for kræft (undtagen de førnævnte tre undtagelser) var af samme størrelsesorden. Baseret på disse resultater fremsætter vi derfor en ny hypotese: Sammenhængen mellem fødselsvægt og kræft skyldes en fælles biologisk årsag, men en eller flere yderligere faktorer har betydning for prostata- og testikelkræft.

Resultaterne i Studie III styrker tidligere fund af, at høje piger har en øget risiko for brystkræft. Desuden kunne vi vise, at piger, der var tynde i skoleårene, havde en øget risiko for senere at få brystkræft, både før og efter menopausen. Særligt vigtigt var imidlertid fundet af, at høj fødselsvægt er en risikofaktor for brystkræft, uafhængig af den senere vækst i børne- og ungdomsårene og uafhængigt af den opnåede sluthøjde. Samtidig viser vores resultater, at den højdevækst der sker i puberteten er af særlig betydning for senere brystkræftrisiko. Tidlig pubertet i sig selv, bestemt ved alder ved vækstspurt, var også en uafhængig risikofaktor for brystkræft. De fundne sammenhænge i alle tre studier var uafhængige af alder ved første fødsel og antal børnefødsler, begge kendte risikofaktorer for brystkræft.

12 REFERENCES

(1) Danish National Board of Health. Cancer Incidence in Denmark 1998. Statistical Office 2002.

(2) Howard BA, Gusterson BA. Human breast development. J Mammary Gland Biol Neoplasia 2000; 5(2):119-137.

(3) Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990; 335(8695):939-940.

(4) Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993; 15(1):48-65.

(5) Cohen SM, Ellwein LB. Cell proliferation in carcinogenesis. Science 1990; 249(4972):1007-1011.

(6) Anbazhagan R, Gusterson BA. Prenatal factors may influence predisposition to breast cancer. Eur J Cancer 1994; 30A(1):1-3.

(7) McFadyen IR, Worth HG, Wright DJ, Notta SS. High oestrogen excretion in pregnancy. Br J Obstet Gynaecol 1982; 89(12):994-999.

(8) Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990; 1(3):247-250.

(9) Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000; 11(3):315-319.

(10) Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152(12):1121-1128.

(11) Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ et al. Birthweight as a risk factor for breast cancer. Lancet 1996; 348(9041):1542-1546.

(12) Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002; 86(1):89-91.

(13) Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001; 93(1):60-62.

(14) Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E et al. Perinatal factors and risk of breast cancer. Epidemiology 1996; 7(1):34-37.

(15) Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001; 85(11):1680-1684.

(16) Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001; 84(9):1193-1198.

(17) Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000; 83(7):964-968.

(18) Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997; 89(1):71-76.

(19) Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992; 340(8826):1015-1018.

(20) Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998; 12(4):397-407.

(21) Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988; 57(4):437-439.

(22) Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER et al. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002; 11(2):207-210.

(23) Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT et al. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002; 86(1):84-88.

(24) Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: A study among like-sexed twins. Int J Cancer 2001; 91(2):248-251.

(25) McCormack VA, dos SS, I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003; 326(7383):248.

(26) Barker DJ, Winter PD, Osmond C, Phillips DI, Sultan HY. Weight gain in infancy and cancer of the ovary. Lancet 1995; 345(8957):1087-1088.

(27) Tibblin G, Eriksson M, Cnattingius S, Ekbom A. High birthweight as a predictor of prostate cancer risk. Epidemiology 1995; 6(4):423-424.

(28) Ekbom A, Hsieh CC, Lipworth L, Wolk A, Ponten J, Adami HO et al. Perinatal characteristics in relation to incidence of and mortality from prostate cancer. BMJ 1996; 313(7053):337-341.

(29) Ekbom A, Wuu J, Adami HO, Lu CM, Lagiou P, Trichopoulos D et al. Duration of gestation and prostate cancer risk in offspring. Cancer Epidemiol Biomarkers Prev 2000; 9(2):221-223.

(30) Platz EA, Giovannucci E, Rimm EB, Curhan GC, Spiegelman D, Colditz GA et al. Retrospective analysis of birth weight and prostate cancer in the Health Professionals Follow-up Study. Am J Epidemiol 1998; 147(12):1140-1144.

(31) Boland LL, Mink PJ, Bushhouse SA, Folsom AR. Weight and length at birth and risk of early-onset prostate cancer (United States). Cancer Causes Control 2003; 14(4):335-338.

(32) Brown LM, Pottern LM, Hoover RN. Prenatal and perinatal risk factors for testicular cancer. Cancer Res 1986; 46(9):4812-4816.

(33) Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO. Testicular nonseminoma and seminoma in relation to perinatal characteristics. J Natl Cancer Inst 1996; 88(13):883-889.

(34) Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes Control 1997; 8(6):904-912.

(35) Sabroe S, Olsen J. Perinatal correlates of specific histological types of testicular cancer in patients below 35 years of age: a case-cohort study based on midwives' records in Denmark. Int J Cancer 1998; 78(2):140-143.

(36) Richiardi L, Akre O, Bellocco R, Ekbom A. Perinatal determinants of germ-cell testicular cancer in relation to histological subtypes. Br J Cancer 2002; 87(5):545-550.

(37) Rasmussen F, Gunnell D, Ekbom A, Hallqvist J, Tynelius P. Birth weight, adult height, and testicular cancer: cohort study of 337,249 Swedish young men. Cancer Causes Control 2003; 14(6):595-598.

(38) Richiardi L, Askling J, Granath F, Akre O. Body size at birth and adulthood and the risk for germ-cell testicular cancer. Cancer Epidemiol Biomarkers Prev 2003; 12(7):669-673.

(39) Bergstrom A, Lindblad P, Wolk A. Birth weight and risk of renal cell cancer. Kidney Int 2001; 59(3):1110-1113.

(40) Sandhu MS, Luben R, Day NE, Khaw KT. Self-reported birth weight and subsequent risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2002; 11(9):935-938.

(41) Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001; 23(2):313-342.

(42) Tretli S. Height and weight in relation to breast cancer morbidity and mortality. A prospective study of 570,000 women in Norway. Int J Cancer 1989; 44(1):23-30.

(43) van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000; 152(6):514-527.

(44) Proos LA. Anthropometry in adolescence--secular trends, adoption, ethnic and environmental differences. Horm Res 1993; 39 Suppl 3:18-24.

(45) Herrinton LJ, Husson G. Relation of childhood height and later risk of breast cancer. Am J Epidemiol 2001; 154(7):618-623.

(46) Le Marchand L, Kolonel LN, Earle ME, Mi MP. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988; 128(1):137-152.

(47) Swerdlow AJ, De Stavola BL, Floderus B, Holm NV, Kaprio J, Verkasalo PK et al. Risk factors for breast cancer at young ages in twins: an international population-based study. J Natl Cancer Inst 2002; 94(16):1238-1246.

(48) Brinton LA, Swanson CA. Height and weight at various ages and risk of breast cancer. Ann Epidemiol 1992; 2(5):597-609.

(49) Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer 1999; 85(11):2400-2409.

(50) Magnusson C, Baron J, Persson I, Wolk A, Bergstrom R, Trichopoulos D et al. Body size in different periods of life and breast cancer risk in post-menopausal women. Int J Cancer 1998; 76(1):29-34.

(51) Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L. Childhood and recent eating patterns and risk of breast cancer. Cancer Detect Prev 1986; 9(1-2):47-58.

(52) Pryor M, Slattery ML, Robison LM, Egger M. Adolescent diet and breast cancer in Utah. Cancer Res 1989; 49(8):2161-2167.

(53) Franceschi S, Favero A, La Vecchia C, Baron AE, Negri E, Dal Maso L et al. Body size indices and breast cancer risk before and after menopause. Int J Cancer 1996; 67(2):181-186.

(54) Coates RJ, Uhler RJ, Hall HI, Potischman N, Brinton LA, Ballard-Barbash R et al. Risk of breast cancer in young women in relation to body size and weight gain in adolescence and early adulthood. Br J Cancer 1999; 81(1):167-174.

(55) Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997; 89(13):939-947.

(56) Westergaard T. Birth Order and Cancer Risk. PhD-thesis, University of Copenhagen 1997; Copenhagen: Department of Epidemiology Research, Danish Epidemiology Science Center:1-82.

(57) Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997; 44(5):535-539.

(58) 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(4):359-364.

(59) Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988; 27(6A):627-647.

(60) Stata v. 8.0 Base Reference Manual (4 volumes). Stata Press, 2003.

(61) Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995; 6(4):356-365.

(62) SAS/STAT User's Guide, Version 8, Volumes 1, 2, and 3. SAS Publishing, 2003.

(63) Wohlfahrt J, Andersen PK, Melbye M. Multivariate competing risks. Stat Med 1999; 18(9):1023-1030.

(64) Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997; 145(1):58-67.

(65) Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000; 11(7):669-674.

(66) Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. J Natl Cancer Inst 2000; 92(10):840-841.

(67) Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, birth weight, and subsequent risk of female breast cancer. Br J Cancer 2003; 89(9):1664-1666.

(68) Ahlgren M, Sorensen T, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003; 107(6):997-1000.

(69) Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001; 37 Suppl 8:S4-66.

(70) Andersson SO, Baron J, Wolk A, Lindgren C, Bergstrom R, Adami HO. Early life risk factors for prostate cancer: a population-based case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 1995; 4(3):187-192.

(71) Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. Diabetes Care 1994; 17(7):640-648.

(72) Trichopoulos D, Lipman RD. Mammary gland mass and breast cancer risk. Epidemiology 1992; 3(6):523-526.

(73) Hughson M, Farris AB, III, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. Kidney Int 2003; 63(6):2113-2122.

(74) Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev 2001; 10(1):15-32.

(75) Li CI, Malone KE, White E, Daling JR. Age when maximum height is reached as a risk factor for breast cancer among young U.S. women. Epidemiology 1997; 8(5):559-565.

(76) Kvale G, Heuch I. Menstrual factors and breast cancer risk. Cancer 1988; 62(8):1625-1631.

(77) Rasmussen S, Petersen TA, Madsen M. [Body height of 6-15-year-old school children measured in the period 1986/1987 to 1996/1997. Compared with Danish measurements in 1971/1972]. Ugeskr Laeger 2002; 164(43):5011-5015.

(78) Petersen TA, Rasmussen S, Madsen M. [BMI of Danish school children measured during the periods 1986/1987--1996/1997 compared to Danish measurement in 1971/1972]. Ugeskr Laeger 2002; 164(43):5006-5010.

(79) Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J Clin Endocrinol Metab 1994; 78(3):744-752.

(80) Bruning PF, Van Doorn J, Bonfrer JM, van Noord PA, Korse CM, Linders TC et al. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer 1995; 62(3):266-270.

(81) Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998; 351(9113):1393-1396.

(82) Davey SG, Hart C, Upton M, Hole D, Gillis C, Watt G et al. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. J Epidemiol Community Health 2000; 54(2):97-103.

(83) Nilsen TI, Vatten LJ. Adult height and risk of breast cancer: a possible effect of early nutrition. Br J Cancer 2001; 85(7):959-961.

(84) Frankel S, Gunnell DJ, Peters TJ, Maynard M, Davey SG. Childhood energy intake and adult mortality from cancer: the Boyd Orr Cohort Study. BMJ 1998; 316(7130):499-504.

(85) Ross MH, Bras G. Lasting influence of early caloric restriction on prevalence of neoplasms in the rat. J Natl Cancer Inst 1971; 47(5):1095-1113.

(86) Clavel-Chapelon F. Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer Causes Control 2002; 13(9):831-838.

(87) Rosenberg L. Induced abortion and breast cancer: more scientific data are needed. J Natl Cancer Inst 1994; 86(21):1569-1570.

(88) Russo J, Russo IH. Susceptibility of the mammary gland to carcinogenesis. II. Pregnancy interruption as a risk factor in tumor incidence. Am J Pathol 1980; 100(2):497-512.

(89) Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974; 185(4155):949-951.

(90) Jeffreys M, McCarron P, Gunnell D, McEwen J, Smith GD. Body mass index in early and mid-adulthood, and subsequent mortality: a historical cohort study. Int J Obes Relat Metab Disord 2003; 27(11):1391-1397.

13 PAPER I

Ahlgren M, Sørensen TIA, Wohlfahrt J, Haflidadóttir Á, Holst C, Melbye M.

Birth weight and risk of breast cancer in a cohort of 106,504 women.

International Journal of Cancer 2003; 107: 997-1000.

Int. J. Cancer: **107,** 997–1000 (2003)

Publication of the International Union Against Cancer

BIRTH WEIGHT AND RISK OF BREAST CANCER IN A COHORT OF 106,504 WOMEN

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The possible association between prenatal factors and breast cancer has been discussed for more than a decade. Birth weight has been used commonly as a proxy measure for intrauterine growth. Whereas some previous studies have found support for an association between birth weight and breast cancer, others have been inconclusive or found no association. We investigated the relationship between birth weight and risk of female breast cancer in a cohort of 106,504 Danish women. Birth weights were obtained from school health records on girls born between 1930–1975. Information on breast cancer came from linking the cohort with the Danish Cancer Registry and the Danish Breast Cancer Cooperative Groups Registry. A total of 2,334 cases of primary breast cancer were diagnosed in the cohort during 3,255,549 person-years of follow-up among women with birth weight between 500–6,000 g. Of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older. A significant association between birth weight and breast cancer was found equivalent to an increase in risk of 9% per 1,000 g increase in birth weight (95% CI 2–17). The increase was observed for all age groups, representing both pre- and postmenopausal women, and irrespective of tumor characteristics. Adjustment for age at first birth and parity did not influence the results. Birth weight is positively associated with risk of breast cancer, indicating that prenatal factors are important in the etiology of breast cancer.

Key words: *breast cancer; birth weight; oestrogen; prenatal factors; epidemiology; cohort*

In 1990, Trichopoulos hypothesized that breast cancers may originate in utero.[1] The idea is based on the assumption that endogenous estrogens are important in the etiology of breast cancer, and that the first exposure of the mammary gland to high concentrations of estrogens (10–100 times the oestrogen levels achieved later in life) occurs in utero.[1] At this early stage, the mammary gland is largely undifferentiated and may be particularly susceptible to influences that could increase the risk of cancer through accelerated cell growth or by being more prone to exogenous carcinogenic stimuli.[1] Studies have shown that birth weight is associated with oestrogen levels during pregnancy, which suggests that birth weight is a useful proxy measure of intrauterine oestrogen measure.[2–4]

Studies on the association between birth weight and risk of breast cancer have, however, yielded somewhat conflicting results. Overall, the available literature on birth weight is suggestive of an intrauterine effect on later risk of breast cancer especially for premenopausal ages, but the evidence is in many cases based either on studies with small sample sizes or on data of recalled events that occurred many decades earlier.[5–20]

We explore the relation between birth weight and risk of breast cancer in a very large population-based cohort of women for whom birth weights were recorded early in life.

MATERIAL AND METHODS

Study population

The study cohort consisted of 161,063 girls born between 1930–1975 who attended school in Copenhagen, Denmark. In this period school health records were kept for all pupils. The health records were filled in by nurses or physicians in the school health services on a yearly basis from school start until the child left school. Either or both parents accompanied their child to the first visit, at which they reported the child's birth weight. The complete records are now kept at the Copenhagen City Archives and contain information on *e.g.* the child's name and date of birth, birth weight and the mother's name.

The Danish Civil Registration System (CRS) was established 1 April 1968. All residents and newborns in Denmark have been given a unique 10-digit person identification number (the CRS-number). The CRS-number is stored along with information on name, place of birth, and parental identity on all Danish residents. It is updated daily with respect to vital and migration status. All other national registries in Denmark, which record individual information, are based on the CRS number, thus serving as a unique key for linkage studies. Information from the CRS was used to generate a population-based relational database, the Birth Order Study database (BOS), containing information on all men and women born during the period 1 January 1935 to 31 December 1998, who have been assigned a CRS-number.[21] This database contains close to complete information on sibships of children, parity of women and links between family members. The completeness of the linkage between mother and child in BOS was estimated to 97.3% for children born before 1968, and complete information for children born hereafter.[22]

Information from the school health records was computerized and linked to the CRS matching on birth date and name. This resulted in the identification of CRS-numbers for 141,481 girls (88%). The lack of identification of the remaining 12% is partly due to death (1%), emigration, and change of surname at the time of marriage, before 1 April 1968. Of the 141,468 girls with a CRS-number 106,504 (75%) had information on birth weight.

Ascertainment of cases

Information on incident breast cancer cases was obtained from the Danish Cancer Registry and from the Danish Breast Cancer Cooperative Groups Registry. The Danish Cancer Registry was established in 1942 and is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since

Grant sponsor: Department of the US Army; Grant sponsor: Danish Cancer Society; Grant sponsor: Danish National Research Foundation; Grant sponsor: Dagmar Marshall Foundation.

The authors certify that they have not entered into any agreement that could interfere with their access to the data on the research, nor upon their ability to analyze the data independently, to prepare manuscripts, and to publish them.

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Received 3 February 2003; Revised 2 July 2003; Accepted 4 July 2003

DOI 10.1002/ijc.11481

1943.[23] The Danish Breast Cancer Cooperative Groups Registry (DBCG) was established in late 1976 for the purpose of standardizing and evaluating the treatment of breast cancer in Denmark.[24] In addition to information from the Danish Cancer Registry, DBCG contains information on tumor size and histology, oestrogen receptor status, nodal status and subsequent treatment.

STATISTICAL METHODS

The association between birth weight and breast cancer risk was estimated in a cohort design using log-linear Poisson regression. Follow-up for breast cancer began 1 April 1968, or the date of birth, which ever came last, and continued until a diagnosis of cancer, death, emigration or 31 August 2000, whichever came first.

Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60) and calendar period in 5-year intervals.[25] In additional analyses, adjustments were made for age at first birth (nulliparous, 12–19, 20–24, 25–29, 30–34, 35+) and parity (0,1,2,3,4+).

The relative risk (rate ratio) increase per 1,000 g increase in birth weight was estimated by treating birth weight categorized in intervals of 100 g as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. The log-linear assumptions underlying the trend estimation of birth weight were checked in 2 ways. Firstly, by a likelihood ratio test comparing the models with birth weight treated as a continuous and a categorical variable, respectively. Second, by evaluating the effect of including a quadratic term in the trend analysis.

Poisson regression was used instead of Cox regression because of the computational efficiency in large datasets. Estimation using Cox regression with age as the underlying time variable gave identical estimates of the main trend and the confidence interval.

Information on tumor characteristics was available from 1977. Estimation of the increase in breast cancer risk according to tumor diameter (<2 cm; 2–5 cm; ≥5 cm; missing or diagnosed before 1977), nodal status (negative; positive; missing or diagnosed before 1977) and oestrogen receptor status (negative; positive; missing or diagnosed before 1977) by 1,000 g increase in birth weight was carried out as a competing risks analysis, *i.e.*, with censoring as above but counting only the selected case category as cases.

All analyses were carried out using the SAS statistical software release 8.02 (specifically the PROC GENMOD procedure).[26]

RESULTS

A total of 2,340 cases of primary breast cancer were diagnosed in the cohort during 3,266,070 years of follow-up. Women with recorded birth weights ≥6,000 g or ≤500 g were excluded from the analyses due to a high risk of misclassification in these extreme groups.

Number of breast cancer cases and person-years of follow-up by age, calendar period, birth cohort and birth weight category for women remaining in the analysis are shown in Table I. A total of 2,334 cases of primary breast cancer were diagnosed in the restricted cohort during 3,255,549 years of follow-up and of these, 922 (40%) were diagnosed with primary breast cancer at the age of 50 years or older.

In our main analysis we found a significant positive association between birth weight and breast cancer equivalent to a 9% increase in risk per 1,000 g increase in birth weight (95% CI = 2% to 17%). If all registered birth weights were included in the analysis (*i.e.*, including birth weight registered as being below 501 g or above 5,999 g) the increase in risk was 8% per 1,000 g (95% CI = 1% to 16%). Data and trend are shown on Figure 1.

Table II shows the increase in breast cancer risk by 1,000 g increase in birth weight stratified by age. The risk increase by birth weight did not vary with age (p = 0.30). Analysis of the linear trend according to year of birth and period likewise showed no variation (data not shown).

To investigate the association with tumor characteristics we used additional data from DBCG on tumor size (<2 cm: n = 1,132, 2–5 cm: n = 680, ≥ 5 cm: n = 159, missing: n = 363) nodal status (node neg: n = 1,097, node pos: n = 859, missing: n = 378) and oestrogen receptor status (ER pos: n = 1,087, ER neg: n = 469, missing: n = 778). Estimating the increase in risk of breast cancer according to tumor characteristics by 1,000 g increase in birth weight showed no systematic differences in the

TABLE I – NUMBER OF BREAST CANCER CASES AND PERSON YEARS OF FOLLOW-UP

Cohort characteristics	Cases (%)	Person years / 1,000 (%)
	(n = 2,334)	(n = 3,256)
Age		
0–39	375 (16.1)	2,305.6 (70.8)
40–44	453 (19.4)	347.9 (10.7)
45–49	584 (25.0)	281.2 (8.6)
50–54	502 (21.5)	199.0 (6.1)
55–59	325 (13.9)	98.2 (3.0)
60 +	95 (4.1)	23.6 (0.7)
Calendar period		
1968–1979[1]	145 (6.2)	1,187.7 (36.5)
1980–1989	624 (26.7)	1,022.8 (31.4)
1990 +	1,565 (67.1)	1,045.1 (32.1)
Birth cohort		
1930–1939	587 (25.2)	322.1 (9.9)
1940–1949	1,387 (59.4)	1,249.8 (38.4)
1950–1959	325 (13.9)	83.3 (25.5)
1960 +	35 (1.5)	853.3 (26.2)
Birth weight		
501–1,499 g	5 (0.2)	13.5 (0.4)
1,500–2,499 g	125 (5.4)	191.6 (5.9)
2,500–2,999 g	305 (13.1)	522.6 (16.1)
3,000–3,499 g	846 (36.3)	1,207.5 (37.1)
3,500–3,999 g	717 (30.7)	938.5 (28.8)
4,000–4,499 g	248 (10.6)	298.0 (9.2)
4,500–5,999 g	88 (3.8)	83.8 (2.6)

[1]Follow-up began 1 April 1968.

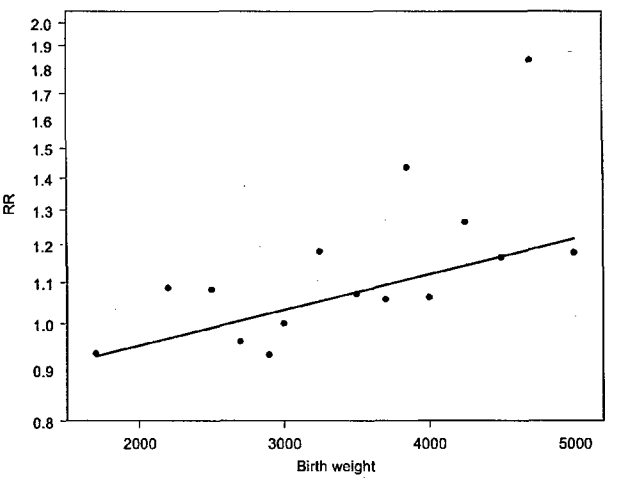

FIGURE 1 – Adjusted relative risk of breast cancer in birth weight intervals of 200 g compared to women with a birth weight between 3,000–3,199 g. Due to small numbers at the end of the distributions we have grouped the birth weights into the following categories: <2,000 g, 2,000–2,399 g, 2,400–2,599 g, 2,600–2,799 g, 2,800–2,999 g, ..., 4,600–4,799 g, ≥4,800 g. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment was made for age and calendar period.

TABLE II – INCREASE IN BREAST CANCER RISK PER 1000 G INCREASE IN BIRTH WEIGHT ACCORDING TO AGE

Age (years)	Cases (n = 2,334)	$RR_{per\ 1000\ g}$ (95% CI)[1]	
0–39	375	1.07 (0.90–1.28)	$p = 0.30$[2]
40–44	453	1.08 (0.92–1.26)	
45–49	584	1.20 (1.04–1.38)	
50–54	502	1.08 (0.92–1.25)	
55–59	325	1.09 (0.91–1.31)	
60 +	95	0.77 (0.56–1.07)	
Overall		1.09 (1.02–1.17)	

[1]Adjusted for calendar period.–[2]Test for difference, *i.e.* test for interaction between age and birth weight trend. Similar analysis but with binary age groups (< 50 years and ≥ 50 years) revealed no difference in trend according to age, $p = 0.29$.

trend by tumor characteristics at diagnosis. The increase in risk of being diagnosed with a tumor <2 cm by 1,000 g increase in birth weight was 1.09 (0.99–1.20), 0.98 (0.86–1.11) for tumors between 2–5 cm, and 1.21 (0.93–1.58) for tumors ≥5 cm. Likewise was the increase in risk by 1,000 g increase in birth weight for nodal positive tumors 1.03 (0.91–1.15) and 1.07 (0.96–1.18) for nodal negative tumors. For oestrogen receptor positive tumors the increase in risk was 1.03 (0.88–1.20) and for oestrogen receptor negative tumors 1.01 (0.91–1.12).

To further validate the results three additional analyses were carried out. Firstly, parity and age at first birth were known for women born in 1935 and later. No confounding effect was found when adjusting for these factors. Restricting the cohort to women where parity and age at first birth were known the increase in risk by 1,000 g increase in birth weight was similar the increase in risk for whole cohort (RR = 9% per 1,000 g, 95% CI = 2%–17%). Adjusting for parity and age did not change this estimate. Secondly, some of the identified women had missing information on birth weight. Their breast cancer risk did not vary significantly from women with known birth weight, $RR_{unknown\ vs.\ known} = 0.94$ (95% CI = 0.86–1.03). Thirdly, the estimation was based on the assumption that the association between birth weight and breast cancer can be described by a trend. Goodness-of-fit tests gave no indication that this assumption was inadequate.

DISCUSSION

Based on a cohort of 106,504 women we documented a statistically significant association between birth weight and breast cancer. Thus, risk of breast cancer increased by 9% per 1,000 g increase in birth weight. This finding is in agreement with the currently prevailing hypothesis that intrauterine factors contribute to the development of breast cancer in adulthood.

Whereas some previous studies have found support for an association between birth weight and breast cancer,[5–9,20] others have been inconclusive or observed no association.[9–19] Thus, 3 recent smaller cohort studies found a positive but non-significant association with high birth weight.[10–12] A significant positive association was found in a Norwegian case-control study (373 cases of breast cancer),[7] whereas a similarly designed Swedish study (1,068 cases) failed to document a significant association with birth size indicators.[13] Based on 2 different case-control studies, Sanderson and colleagues[9] reported a positive association between birth weight and risk of breast cancer in premenopausal women in the US, but not in postmenopausal women. The association in premenopausal women was supported by Innes and McCormack,[5,20] but others found no such association.[15–18] Based on recalled birth weights reported by adult women and their mothers, Michels et al.[6] found significant evidence to support a positive association between extreme birth weight and risk of breast cancer, not only in younger women but also later in life. The reason why some previous studies failed to find an association may partly be due to the fact that the independent effect of birth weight seems to be rather small, and the studies thus lacked power due to their size.

Analysis of the magnitude of the trend per 1,000 g increase in birth weight has only been reported in one previous study[10] that followed 3,447 women who gave rise to 177 breast cancers. The authors also found a linear increased risk of breast cancer with increased birth weight with a hazard ratio of 22% per 1,000 g (95% CI 10–65). Three other studies have reported significant trends,[6,7,20] but did not calculate the magnitude of the trend.

In contrast to most previous studies our study had sufficient power to detect weak associations and avoided, to a large extent, potentials for bias of the results. We based our cohort on all children attending schools in a well defined area of Denmark and followed them for as much as 70 years through our national registries. These registries contain continuously updated mandatory registrations of vital status, emigration and cancer diagnoses. The social structure of the Danish health care system that provides equal access to health care further diminished possibilities for bias. Measures of birth weight were recorded decades before and independent of possible breast cancer diagnosis, making differential misclassification unlikely. Furthermore, birth weight was recorded at an early age, which limited potentials for recall bias.[27] We were not able to adjust birth weight for gestational age. Studies have suggested, however, that prematurity is associated with an increased risk of breast cancer[28] and controlling for gestational age would then likely have tended to strengthen the association with birth weight.[13]

The size of this study made it possible to perform estimations in subgroups. It has previously been suggested that the association with birth weight is strongest for premenopausal women.[5,9] We found, however, the effect of birth weight to be similar in all age groups (Table II). The association with birth weight according to tumor characteristics has not previously been investigated. We found no systematic differences in the association by tumor characteristics. This suggests that the association with birth weight is a general phenomenon and not restricted to tumors with specific characteristics.

Adjustment for parity and age at first birth had no impact on our results. Parity and age at first birth reflects the hormonal and cellular changes after pregnancies as well as maternal social status. Based on this result we found in line with others[20] no indication of confounding by social status although both birth weight and breast cancer have been associated with social factors.[29]

The biological explanation for an association between birth weight and later risk of breast cancer remains to be established. Involvement of hormones, particularly estrogens, in the carcinogenesis has received much attention as the mammary gland is exposed to very high concentrations of estrogens *in utero*.[30] Studies have shown that birth weight is correlated with oestrogen levels during pregnancy,[2–4] and birth weight has therefore typically been used as a proxy measure of intra-uterine oestrogen exposure. As the intra-uterine hormonal milieu is very complex, however, it is likely that other exposures, *e.g.*, IGF and insulin, which are also correlated with birth weight, could be equally important.

In conclusion, we found a small but significant association between birth weight and risk of breast cancer, which supports the hypothesis that prenatal factors are involved in the pathogenesis of breast cancer.

REFERENCES

1. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990;335:939–40.
2. McFadyen IR, Worth HG, Wright DJ, Notta SS. High oestrogen excretion in pregnancy. Br J Obstet Gynaecol 1982;89:994–9.

3. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990;1:247–50.
4. Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000;11:315–9.
5. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152:1121–8.
6. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC. Birthweight as a risk factor for breast cancer. Lancet 1996;348: 1542–6.
7. Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, Stuver SO. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002;86:89–91.
8. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001;93:60–2.
9. Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, Daling JR. Perinatal factors and risk of breast cancer. Epidemiology 1996;7:34–7.
10. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, Barker DJ. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001;85: 1680–4.
11. Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A, Hulthen L. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193–8.
12. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000;83:964–8.
13. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71–6.
14. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015–8.
15. Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397–407.
16. Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988;57:437–9.
17. Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER, Baron JA, Trichopoulos D, Willett WC. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:207–10.
18. Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84–8.
19. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001;91:248–51.
20. McCormack VA, dos SS, I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003;326:248.
21. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997;89:939–47.
22. Westergaard T. Birth order and cancer risk. PhD-thesis, University of Copenhagen. Copenhagen: Department of Epidemiology Research, Danish Epidemiology Science Center, 1997. 1–82.
23. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. Dan Med Bull 1997;44:535–9.
24. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988;27:627–47.
25. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356–65.
26. SAS/STAT. User's guide, version 8. vol. 1–3. SAS Publishing, 2003.
27. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997;145:58–67.
28. Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. J Natl Cancer Inst 2000;92:840–1.
29. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37(Suppl):S4–66.
30. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.

14 PAPER II

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Birth weight and risk of cancer.

Submitted.

BIRTH WEIGHT
AND RISK OF CANCER

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WORD COUNTS:

Abstract: 334 Text: 2697

KEYWORDS:

Birth weight, cancer, epidemiology, population based, cohort study, prenatal exposure

ABSTRACT

Background:

It is well established, that prenatal biological processes are important for the development of some childhood cancers, whereas less is known regarding their influence on adult cancer risk. Of interest, birth weight has been associated with risk of breast and testicular cancer, whereas studies of e.g. prostate cancer are less conclusive. Lack of appropriate materials has limited the possibilities to address whether prenatal exposures are important for the development of cancer in general.

Methods:

We investigated the relationship between birth weight and risk of cancer in a Danish cohort of 106,504 women and 110,825 men born between 1930 and 1975. Birth weights were obtained from school health records and information on cancer was obtained by linking the cohort with the Danish Cancer Registry. Follow-up was done from 1 April 1968 until 31 December 1997. A total of 7,529 cases of primary invasive cancer were diagnosed in the cohort during 5,858,074 person-years of follow-up.

Results:

Analyses of site-specific cancers revealed that most cancers have a positive linear association to birth weight. Departures from a linear association were statistically significant for testicular and prostate cancers that showed a V-shaped association and Hodgkin's lymphoma that showed an inverse V-shaped association to birth weight. Excluding the three exceptions, the trends for the individual cancer sites were not statistically different from an overall trend of RR=1.10 (95% CI 1.05 to 1.15) pr. 1,000 gram increase in birth weight. This trend was the same in men and women and in all age groups. No confounding effect was found of age at first birth and parity in women.

Conclusion:

Birth weight has a linear association with cancer risk in general with 10 percent increase in risk per 1000 g increase in weight. Few cancers showed non-linear associations with birth weight, among which a V-shaped association for cancers of the prostate and the testis was particularly striking. We hypothesize that the biological explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway, with some superimposed opposing factor(s) influencing male hormonal cancer.

INTRODUCTION

It is well established that prenatal biological processes are important for the development of childhood leukemia (1), whereas less is known regarding their influence on adult cancer risk. Reports focusing in particular on the association between birth weight and risk of adult cancer have found some support for this hypothesis (2;3). However, testing this hypothesis in adults with sufficient power requires large cohorts with a long follow-up time. The number of studies on this topic is still limited to few cancers sites, and the focus has primarily been on cancers influenced by hormonal factors, e.g. breast, prostate and testicular cancer.

So far only one cohort study has addressed the importance of birth weight for the development of cancer in general. In their study of Swedish women, Andersson and colleagues found a linear association with overall incidence of cancer. However, when analyzing non-hormonal and hormonal cancers separately, only a significant trend for non-hormonal cancers was found (4). The study was limited in strength due to its size (262 cases with known birth weights).

A positive association between birth weight and risk of breast cancer has been established by several researchers including ourselves, although some have reached different conclusions (4-20). Other female cancers have been sparsely studied. Barker and colleagues found no association with birth weight and mortality from ovarian cancer in a small UK cohort (21).

In one study of prostate cancer an association with birth weight was found (22), but bigger and more recent studies have, however, reported only a non-significant association (23;24) or failed to find associations at all (25;26). In contrast, studies on testicular cancer have consistently found that both high and low birth weight is a risk factor (27-33).

An increased risk of renal cell cancer was observed among men with a birth weight greater than 3500 g in a case-control study by Bergstrom (34), whereas no association was found in women. The association between birth weight and risk of incident colorectal cancer showed a nonlinear association in a case-control study by Sandhu and colleagues (35) with children of both low and high birth weight being at increased risk.

In the present study we explored the association between birth weight and risk of adult cancer in a very large population-based cohort of Danish women and men born between 1930 and 1975 in whom birth weights were recorded early in life.

MATERIAL AND METHODS

Study population

The study is based on a cohort of children born between 1930 and 1975. In this period a school health record was kept for all pupils in the Copenhagen minicipality. Records for 161,063 girls and 164,155 boys who attended school in Copenhagen have been kept. These records were filled in by nurses or physicians in the school health services and include information on e.g. name and birth weight.

Linkage

The Danish Civil Registration System (CRS) was established 1 April 1968, and all residents and newborns in Denmark have since been given a unique 10-digit person identification number (CRS-number). The CRS-number is stored along with information on name, place of birth, and parental identity on all Danish residents. It is updated daily with respect to vital and migration status. All other national registries in Denmark, which record individual information, are based on the CRS number, thus serving as a unique key for linkage studies.

Information from the CRS was used to generate a population-based relational database, the Birth Order Study (BOS) database, containing information on all men and women born between 1 January 1935 and 31 December 1998, who have been assigned a CRS-number (36). This database contains close to complete information on sibships of children, parity of women and links between family members. The completeness of the linkage between mother and child in the BOS database was estimated to 97.3% for children in the cohort born before 1968, and complete information for children born hereafter (37).

Information from the school health records was computerized and linked to the CRS matching on birth date and name. CRS-numbers were identified for 141,393 girls (88%) and 145,140 boys (88%). For the present analysis, parity and age at first birth during follow-up for women were obtained by linkage with the BOS database.

Ascertainment of cases

Information on incident cancer cases was obtained from the Danish Cancer Registry, which was established in 1942 and is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943 (38).

Statistical methods

The association between birth weight and incidence of cancer was estimated in a cohort design using log-linear Poisson regression with the PROC GENMOD procedure in the SAS statistical software release 8.02 (39). Poisson regression was used instead of Cox regression because of computational efficiency. Follow-up for a specific cancer began 1 April 1968 or at age 6 years, whichever came last, and continued until a diagnosis of the specific cancer, death, emigration, or 31 December, 1997, whichever came first.

Adjustment was made for age (quadratic splines with knots: 35, 40, 45, 50, 55 and 60 years) and calendar period in 5-year intervals (40). In additional analyses, adjustments were made for age at first birth (nulliparous, 12-19, 20-24, 25-29, 30-34, 35+ years) and parity (0, 1, 2, 3, 4+ children).

The association between birth weight and cancer risk was analyzed in two different models. A linear spline model with 3500 g as knot was estimated in order to investigate the linearity of the association in birth weights being lower or higher than 3500 g. If these two trend estimates could be considered equal (based on a likelihood ratio test) an overall trend was estimated. The trends were estimated by treating birth weight categorized in intervals (501-2499 g, 2500-2999 g, 3000-3499 g, 3500-3999 g, 4000-4499 g, 4500-5999 g) as a continuous variable. The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category.

Trends for different sites were compared using inverse-variance weighted regression by means of PROC GENMOD in SAS and based on the site-specific trend estimates and standard error. This approach was used instead of a competing risks approach (41) as the dataset became too large even with Poisson regression due to the many competing risks and the refined adjustment for age and calendar period. The main difference between the two approaches is that in the first approach patients with two different cancers are included twice compared with once in the latter approach. The trends for different sites were furthermore compared using inverse-variance weighted regression with a common fixed effect and a random site effect with PROC MIXED in SAS. There was no indication of a random site effect.

RESULTS

A total of 106,504 women and 110,825 men had recorded birth weights. Persons with recorded birth weights greater than or equal to 6000 g or less than or equal to 500 g were excluded from the analyses due to a high risk of misclassification in these extreme groups (N_{women}=344 and N_{men}=369). A total of 7,529 cases of primary invasive cancer were diagnosed in the remaining cohort during 5,858,074 person-years of follow-up. Table 1 shows Number of cancer cases and person-years of follow-up by age, calendar period and birth cohort.

Table 2 presents the association between birth weight and incidence of site-specific cancer (adjusted for age and calendar period). Trends have been calculated for children with birth weights < 3,500 g (LBW), children with birth weights >3,500 g (HBW) and for all children.

V-shaped associations were observed for prostate, testicular, and bladder cancers and for multiple myeloma and non-Hodgkin's lymphoma, and inverse V-shaped associations were observed for Hodgkin's lymphoma, and cancers of the kidney and the larynx. If the trends for LBW and HBW children were significantly different no common trend was calculated. This was the case for prostate and testicular cancer and for Hodgkin's lymphoma (Table 2).

When analyzing the difference in trends for all cancers (excluding testis cancer, prostate cancer and Hodgkin's lymphoma) we found that the site-specific trends were not significantly different (p=0.59) from each other. Analyses of all cancers combined (excluding only testis cancer, prostate cancer and Hodgkin's lymphoma) showed a significantly positive association between birth weight and cancer equivalent to a RR=1.10 (95% CI 1.05 to 1.15%) per 1,000 g increase in birth weight (Figure 1). Analyses according to attained age showed a similar birth weight trend (p=0.91) for age under 50 years ($RR_{age<50}$=1.10; 95% CI 1.04 to 1.17) when compared to age 50 years or older ($RR_{age>=50}$=1.10; 95% CI 1.01 to 1.19). Analyses according to sex also showed a similar birth weight trend (p=0.45) in men (RR_{men}=1.13; 95% CI 1.04 to 1.22) and women (RR_{women}=1.09; 95% CI 1.03 to 1.15). Parity and age at first birth were known for women born in 1935 and later. No confounding effect was found when adjusting for these factors.

The above findings were consistent when cancers were analyzed according to hormonal etiology. Thus for male cancers of hormonal etiology (prostate and testicular cancer) different trends in LBW and HBW children were found (RR_{LBW}=0.63 (95% CI: 0.49-0.80) and RR_{HBW}=1.29 (95% CI: 0.89-1.88). For all other cancers in males a common trend of R=1.12 (95% CI: 1.02-1.21) could be estimated. In women, no difference was seen between cancers with a hormonal etiology (breast, cervical, uterine and ovarian cancers) and other cancers ($RR_{Women\ hormonal}$=1.08 (95% CI: 0.99-1.17) and $RR_{Women\ all\ other}$ =1.09 (95% CI: 1.01-1.18)).

DISCUSSION

The intrauterine period has been hypothesized to be a critical time window in relation to exposures associated with chronic diseases as well as cancer. Testing this hypothesis with sufficient power in relation to cancer has, however, yielded several challenges. Previously most of the evidence has come from studies of a number of hormone-related cancers i.e. prostate, testicular and breast cancer.

Using birth weight as a proxy variable we have explored the possible association between intrauterine exposure and cancer in a Danish cohort of 106,505 women and 110,663 men born between 1930 and 1975. The size of the present study made it possible to perform separate analyses of several cancers not previously investigated.

We analyzed the association between birth weight and cancer in two different models, one focusing on trends in either the lower or the upper end of the distribution of birth weights, and another addressing whether there was an overall trend between birth weight and risk of cancer. Only prostate and testicular cancer revealed a significant V-shaped association to birth weight, whereas Hodgkin's lymphoma had a significant inverse V-shaped association to birth weight. Similar non-linear associations were found for some other cancers, but they were not significantly departing from linearity, wherefore we assumed linear associations in the estimation of a common trend.

The association with birth weight for all other cancer sites was found to be similar and to fit a linear trend of a 10 percent (95% CI from 5 percent to 15 percent) increase in cancer risk per 1,000 g increase in birth weight. Interestingly, this trend was comparable to the trend observed for the two male hormonal cancers (prostate and testis) in their category of high birth weight children.

In additional analyses we found that the association to be the same in all age groups and in both sexes. Adjustment for parity and age at first birth did not change the conclusion when analyzing female-specific cancers separately. High birth weight therefore seems to act as a common risk factor for almost all if not all cancers, whereas low birth weight is "protective" for all cancer except prostate and testicular cancer. Birth weight was positively associated with risk of Hodgkin's lymphoma in children with low birth weight but with an inverse association in the group of children with high birth weight. Whereas this finding could be real it stands out as the only such statistically significant association in the entire group of cancers, and it needs confirmation.

Apart from studies on testicular, prostate, and breast cancer, few studies have been conducted on the association between cancer and birth weight. Similar to several previous reports we found a linear association between breast cancer and birth weight (4-20). We found a V-shaped association

between birth weight and prostate and testicular cancer. This thus strengthens the previous findings of a non-linear relation with birth weight for these cancers (22;25-33;42).

The only study addressing the association between overall risk of cancer and birth has been a Swedish cohort study of women were the authors found a linear association with overall incidence of cancer (4). However, when analyzing cancers in subgroups the authors got somewhat inconsistent results. Results on ovarian, renal and colon cancer have likewise been inconsistent (21;34;35).

The experience from previous as well as the present study underlines the necessity of a very large study material to address the effect of birth weight on cancer in general. Even in our cohort of nearly 6 million person-years of follow-up and 7,529 cancer outcomes, some cancers were still relatively rare due to the age distribution in the cohort. Clearly, previous inconsistencies should to a large degree be explained by small sample sizes.

The possibility that in-utero growth has an equal effect on risk of cancer at almost all if not all sites is intriguing. It could be explained by the existence of a common pathway with one or more opposing factors influencing male hormone-related cancers. The common pathway could establish a "base risk" on which other later risk factors would have independent influence. Several exposures have been shown to be associated with size at birth, and focus has especially been on levels of estrogen, IGF-1 and insulin in the mother during pregnancy, but other still unknown factors may very well show to be important (43;44).

The question is how birth size modulates cancer risk? It has been suggested that breast cancer risk correlates with number of stem cells (3). We believe that this model could be broadened to include most if not all types of cancer, and that accordingly large babies could have an increased cancer risk due to persistently increased number of susceptible cells.

Specifically, the association between birth weight and cancer risk could either reflect a simple correlation between birth weight and number of cells or reflect that factors that govern birth weight are also associated with an increased cancer risk, e.g. by initiating a multistep carcinogenesis.

Our study had several strengths due to design and size. The Danish national health registries contain continuously updated mandatory registrations of e.g. vital status, emigration and cancer diagnoses, which enabled us to follow our cohort members for almost 70 years. The social structure of the Danish health care system further diminished risk of for bias, as equal access to health care is provided for all citizens. Birth weights were reported by the parents and recorded at an early age

which has been found to be very accurate in relation to recall (45). Birth weights were furthermore recorded decades prior to and independently of possible cancer diagnosis, making differential misclassification unlikely.

We were not able to adjust birth weight for gestational age, which, however, may not be important if it is the number of susceptible cells that accounts for the observed associations. Furthermore, we were unable to adjust for the effect of smoking. Smoking exhibits a parent-offspring association, maternal smoking reduces birth weight, and smoking is a strong risk factor for certain cancers, so lack of possibility to control for smoking therefore limits the interpretation for smoking associated cancers. However, we note with interest that the association between birth weight and smoking associated cancers was similar to that found for cancers not associated with smoking implying that control for smoking in the mother and the offspring would expectedly strengthen the association.

In conclusion, our results strongly suggest that prenatal biological processes are important in the pathogenesis of all cancers. For most cancers, the risk increased in a linear manner with increasing birth weight, the only clear exception being male cancers with a hormonal etiology (prostate and testis) where a V-shaped association with birth weight was found. We hypothesize that the biological explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway, with some opposing factor(s) influencing male hormonal cancer.

Table 1. Total number of cancer cases and person-years of follow-up by age, calendar period and birth cohort

Cohort Characteristics	Cases (%) (Total = 7,529)		Person-years / 1,000 (%) (Total = 5,858)	
Age				
0 - 39	2,534	(33.7)	4,319.4	(73.7)
40 - 44	1,265	(16.8)	638.1	(10.9)
45 - 49	1,540	(20.5)	489.4	(8.4)
50 - 54	1,377	(18.3)	294.6	(5.0)
55 - 59	742	(9.9)	108.4	(1.9)
60 +	71	(0.9)	8.2	(0.1)
Calendar Period*				
1968 - 1972	270	(3.6)	841.0	(14.4)
1973 - 1977	513	(6.8)	964.9	(16.5)
1978 - 1982	847	(11.2)	1,026.5	(17.5)
1983 - 1987	1,228	(16.3)	1,033.4	(17.6)
1988 - 1992	1,906	(25.3)	1,010.9	(17.3)
1993 - 1997	2,765	(36.7)	981.3	(16.8)
Birth Cohort				
1930 - 1934	41	(0.5)	7.9	(0.1)
1935 - 1939	1,780	(23.6)	597.3	(10.2)
1940 - 1944	2,462	(32.7)	1,124.2	(19.2)
1945 - 1949	1,733	(23.2)	1,190.2	(20.3)
1950 - 1954	716	(9.5)	849.0	(14.5)
1955 - 1959	412	(5.5)	721.4	(12.3)
1960 - 1964	212	(2.8)	580.8	(9.9)
1965 - 1975	173	(2.3)	787.3	(13.4)

* Follow-up began on 1 April 1968 and ended on 31 December 1997

Table 2. Birth weight and relative risk of cancer. Adjusted for age and calendar period.

Cancer site	N*	RR pr. kg (95% CI) Birth weight < 3,500 g	RR pr. kg (95% CI) Birth weight > 3,500 g	RR pr. kg (95% CI) All birth weights
Men				
Prostate	56	0.56 (0.27–1.18)	2.76 (1.10–6.97)	–
Testis	443	0.64 (0.50–0.83)	1.16 (0.76–1.75)	–
Women				
Breast	1,842	1.15 (1.00–1.33)	1.02 (0.83–1.26)	1.10 (1.01–1.21)
Cervix	515	1.07 (0.83–1.39)	1.00 (0.66–1.52)	1.05 (0.89–1.24)
Ovary	276	0.97 (0.69–1.36)	0.93 (0.52–1.67)	0.96 (0.76–1.20)
Uterus	143	0.95 (0.59–1.53)	1.13 (0.54–2.37)	1.01 (0.73–1.38)
Men and women				
Bladder	269	0.85 (0.59–1.23)	1.68 (1.08–2.63)	1.14 (0.90–1.44)
Brain	473	1.16 (0.87–1.54)	1.15 (0.97–1.38)	1.15 (0.97–1.38)
Colon and rectum	520	1.03 (0.79–1.34)	0.95 (0,65–1.38)	1.00 (0.85–1.18)
Hodgkin's lymphoma	141	1.52 (0.89–2.61)	0.27 (0.09–0.79)	–
Kidney	175	1.69 (0.99–2.89)	0.86 (0.46–1.63)	1.26 (0.94–1.68)
Larynx	95	2.14 (0.97–4.73)	0.85 (0.37–1.95)	1.37 (0.92–2.03)
Leukemia	219	1.16 (0.76–1.76)	0.98 (0.55–1.76)	1.09 (0.84–1.41)
Liver and gallbladder	83	0.94 (0.49–1.82)	1.31 (0.55–3.11)	1.08 (0.71–1.64)
Lung	658	1.18 (0.92–1.51)	1.36 (1.01–1.84)	1.26 (1.08–1.46)
Malignant melanoma	555	1.08 (0.84–1.41)	1.34 (0.95–1.90)	1.18 (1.00–1.39)
Multiple myeloma	51	0.87 (0.37–2.03)	2.09 (0.79–5.52)	1.29 (0.75–2.21)
Non-Hodgkin's lymphoma	291	0.89 (0.63–1.25)	1.55 (0.98–2.44)	1.16 (0.87–1.54)
Other cancers	578	0.85 (0.67–1.09)	1.36 (0.97–1.91)	1.02 (0.87–1.20)
Pancreas	120	1.36 (0.73–2.50)	1.03 (0.47–2.26)	1.21 (0.84–1.74)
Pharynx	115	0.62 (0.38–1.02)	0.95 (0.43–2.12)	0.72 (0.51–1.01)
Stomach and esophagus	201	1.23 (0.78–1.93)	0.88 (0.48–1.61)	1.07 (0.82–1.41)

* Persons with more than one cancer are counted twice.

FIGURE 1

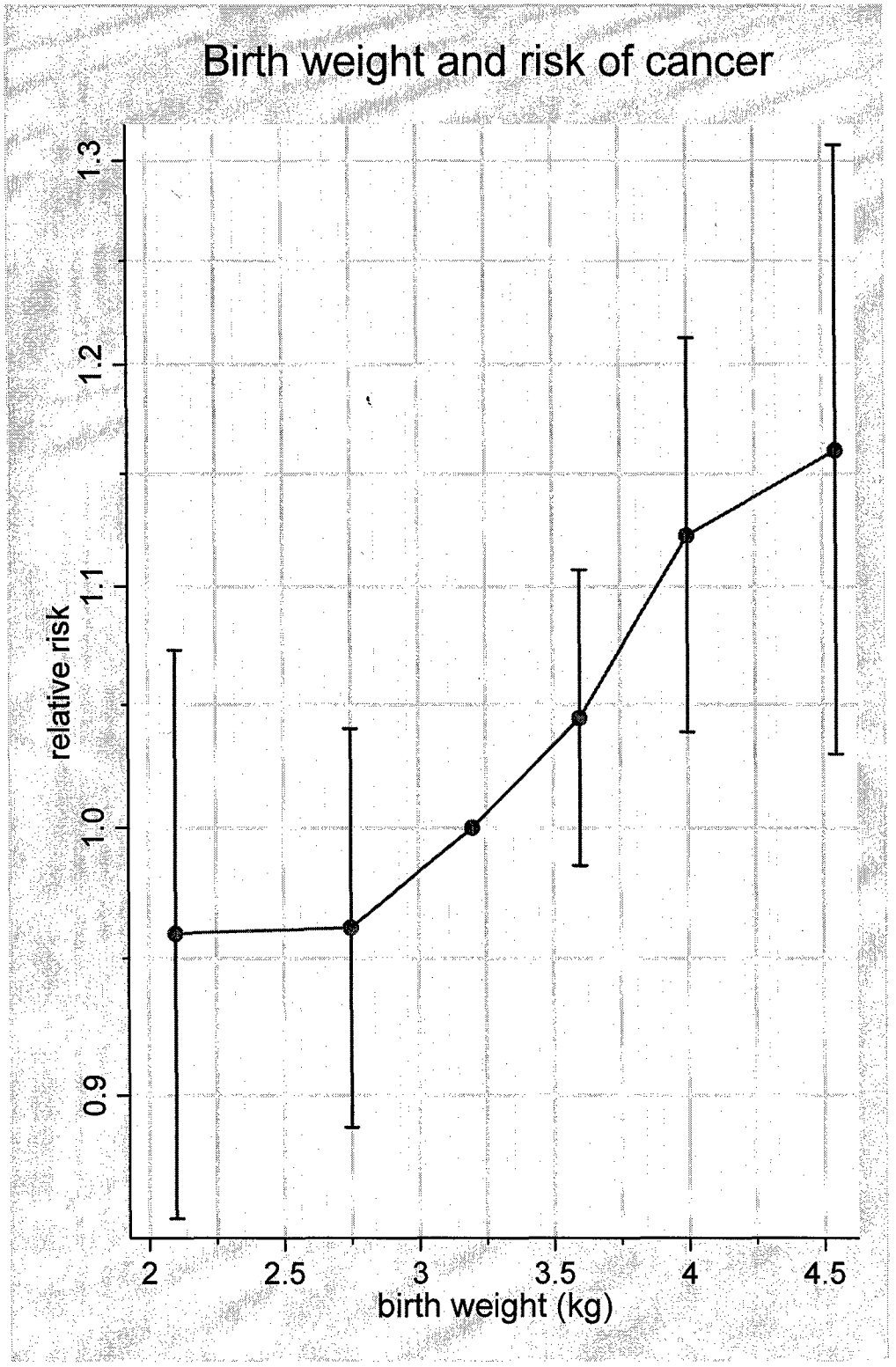
Birth weight and risk of cancer
relative risk
0.9
1.0
1.1
1.2
1.3
2
2.5
3
3.5
4
4.5
birth weight (kg)

FIGURE LEGEND

Figure 1

Birth weight and relative risk of all cancers combined (excluding testis cancer, prostate cancer and Hodgkin's lymphoma). The numerical value assigned to a given category was chosen as the median of the distribution of birth weight within the category. Adjustment was made for age and calendar period.

REFERENCE LIST

(1) Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H et al. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. Am J Epidemiol 2003; 158(8):724-735.

(2) Ekbom A. Growing evidence that several human cancers may originate in utero. Semin Cancer Biol 1998; 8(4):237-244.

(3) Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990; 335(8695):939-940.

(4) Andersson SW, Bengtsson C, Hallberg L, Lapidus L, Niklasson A, Wallgren A et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001; 84(9):1193-1198.

(5) Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152(12):1121-1128.

(6) Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ et al. Birthweight as a risk factor for breast cancer. Lancet 1996; 348(9041):1542-1546.

(7) Vatten LJ, Maehle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002; 86(1):89-91.

(8) Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001; 93(1):60-62.

(9) Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E et al. Perinatal factors and risk of breast cancer. Epidemiology 1996; 7(1):34-37.

(10) Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001; 85(11):1680-1684.

(11) Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000; 83(7):964-968.

(12) Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997; 89(1):71-76.

(13) Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992; 340(8826):1015-1018.

(14) Sanderson M, Williams MA, Daling JR, Holt VL, Malone KE, Self SG et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998; 12(4):397-407.

(15) Le Marchand L, Kolonel LN, Myers BC, Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988; 57(4):437-439.

(16) Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER et al. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002; 11(2):207-210.

(17) Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT et al. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002; 86(1):84-88.

(18) Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: A study among like-sexed twins. Int J Cancer 2001; 91(2):248-251.

(19) McCormack VA, dos SS, I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003; 326(7383):248.

(20) Ahlgren M, Sorensen T, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003; 107(6):997-1000.

(21) Barker DJ, Winter PD, Osmond C, Phillips DI, Sultan HY. Weight gain in infancy and cancer of the ovary. Lancet 1995; 345(8957):1087-1088.

(22) Tibblin G, Eriksson M, Cnattingius S, Ekbom A. High birthweight as a predictor of prostate cancer risk. Epidemiology 1995; 6(4):423-424.

(23) Ekbom A, Hsieh CC, Lipworth L, Wolk A, Ponten J, Adami HO et al. Perinatal characteristics in relation to incidence of and mortality from prostate cancer. BMJ 1996; 313(7053):337-341.

(24) Ekbom A, Wuu J, Adami HO, Lu CM, Lagiöu P, Trichopoulos D et al. Duration of gestation and prostate cancer risk in offspring. Cancer Epidemiol Biomarkers Prev 2000; 9(2):221-223.

(25) Platz EA, Giovannucci E, Rimm EB, Curhan GC, Spiegelman D, Colditz GA et al. Retrospective analysis of birth weight and prostate cancer in the Health Professionals Follow-up Study. Am J Epidemiol 1998; 147(12):1140-1144.

(26) Boland LL, Mink PJ, Bushhouse SA, Folsom AR. Weight and length at birth and risk of early-onset prostate cancer (United States). Cancer Causes Control 2003; 14(4):335-338.

(27) Brown LM, Pottern LM, Hoover RN. Prenatal and perinatal risk factors for testicular cancer. Cancer Res 1986; 46(9):4812-4816.

(28) Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO. Testicular nonseminoma and seminoma in relation to perinatal characteristics. J Natl Cancer Inst 1996; 88(13):883-889.

(29) Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes Control 1997; 8(6):904-912.

(30) Sabroe S, Olsen J. Perinatal correlates of specific histological types of testicular cancer in patients below 35 years of age: a case-cohort study based on midwives' records in Denmark. Int J Cancer 1998; 78(2):140-143.

(31) Richiardi L, Akre O, Bellocco R, Ekbom A. Perinatal determinants of germ-cell testicular cancer in relation to histological subtypes. Br J Cancer 2002; 87(5):545-550.

(32) Rasmussen F, Gunnell D, Ekbom A, Hallqvist J, Tynelius P. Birth weight, adult height, and testicular cancer: cohort study of 337,249 Swedish young men. Cancer Causes Control 2003; 14(6):595-598.

(33) Richiardi L, Askling J, Granath F, Akre O. Body size at birth and adulthood and the risk for germ-cell testicular cancer. Cancer Epidemiol Biomarkers Prev 2003; 12(7):669-673.

(34) Bergstrom A, Lindblad P, Wolk A. Birth weight and risk of renal cell cancer. Kidney Int 2001; 59(3):1110-1113.

(35) Sandhu MS, Luben R, Day NE, Khaw KT. Self-reported birth weight and subsequent risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2002; 11(9):935-938.

(36) Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997; 89(13):939-947.

(37) Westergaard T. Birth Order and Cancer Risk. PhD-thesis, University of Copenhagen 1997; Copenhagen: Department of Epidemiology Research, Danish Epidemiology Science Center:1-82.

(38) Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997; 44(5):535-539.

(39) SAS/STAT User's Guide, Version 8, Volumes 1, 2, and 3. SAS Publishing, 2003.

(40) Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995; 6(4):356-365.

(41) Wohlfahrt J, Andersen PK, Melbye M. Multivariate competing risks. Stat Med 1999; 18(9):1023-1030.

(42) Andersson SO, Baron J, Wolk A, Lindgren C, Bergstrom R, Adami HO. Early life risk factors for prostate cancer: a population-based case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 1995; 4(3):187-192.

(43) Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. Diabetes Care 1994; 17(7):640-648.

(44) Kaijser M, Granath F, Jacobsen G, Cnattingius S, Ekbom A. Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data. Epidemiology 2000; 11(3):315-319.

(45) Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997; 145(1):58-67.

15 PAPER III

Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA.

Growth Patterns and the Risk of Breast Cancer in Women.

New England Journal of Medicine 2004; 351: 1619-26.

ORIGINAL ARTICLE

Growth Patterns and the Risk of Breast Cancer in Women

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ABSTRACT

BACKGROUND

Adult height and body-mass index influence the risk of breast cancer in women. Whether these associations reflect growth patterns of the fetus or growth during childhood and adolescence is unknown.

METHODS

We investigated the association between growth during childhood and the risk of breast cancer in a cohort of 117,415 Danish women. Birth weight, age at menarche, and annual measurements of height and weight were obtained from school health records. We used the data to model individual growth curves. Information on vital status, age at first childbirth, parity, and diagnosis of breast cancer was obtained through linkages to national registries.

RESULTS

During 3,333,359 person-years of follow-up, 3340 cases of breast cancer were diagnosed. High birth weight, high stature at 14 years of age, low body-mass index (BMI) at 14 years of age, and peak growth at an early age were independent risk factors for breast cancer. Height at 8 years of age and the increase in height during puberty (8 to 14 years of age) were also associated with breast cancer. The attributable risks of birth weight, height at 14 years of age, BMI at 14 years of age, and age at peak growth were 7 percent, 15 percent, 15 percent, and 9 percent, respectively. No effect of adjusting for age at menarche, age at first childbirth, and parity was observed.

CONCLUSIONS

Birth weight and growth during childhood and adolescence influence the risk of breast cancer.

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N Engl J Med 2004;351:1619-26.

MOST STUDIES OF BODY SIZE AND THE risk of breast cancer have shown that tall women have an increased risk of breast cancer regardless of menopausal status,[1] whereas obese women have a reduced risk of breast cancer before menopause but an increased risk after menopause.[2] The extent to which these associations in adults reflect growth patterns in early life is unknown. A better understanding of the association between early growth patterns and the risk of breast cancer could improve our knowledge of the mechanisms of the disease and could be important for prevention.

We explored possible associations among birth weight, childhood and pubertal growth, and breast cancer in a large, population-based cohort study of women for whom height and weight had been recorded annually during the school years.

METHODS

STUDY POPULATION

We based our study on a cohort of women born from 1930 through 1975 who had undergone regular health examinations in school in the municipality of Copenhagen. A manual register of the school health records lists 161,063 girls. The records include information on annual measurements of weight and height, age at menarche, and birth weight as reported by the parents. Information from these school health records was computerized and linked by name and date of birth to the Danish Civil Registration System (CRS).

Since April 1, 1968, the CRS has assigned a unique 10-digit personal identification number (the CRS number) to all residents and newborns in Denmark. The CRS number permits linkage with information from other registries. CRS numbers were identified for 141,393 girls (88 percent) but were missing in the remainder — mainly because of emigration, death, or changes in surnames before 1968. Information from the CRS was also used to determine the variables of parity and age at each delivery of a child for cohort members.[3,4]

Information about cases of invasive breast cancer occurring through 1997 was obtained from the Danish Cancer Registry, and information about cases from 1998 through 2001 was obtained from the registry of the Danish Breast Cancer Cooperative Group. The Danish Cancer Registry is considered close to complete with respect to cases of malignant diseases diagnosed in Denmark since 1943.[3] For women under 70 years of age at diagnosis, more than 95 percent of cases have been registered in the clinical Danish Breast Cancer Cooperative Group database.[4]

STATISTICAL ANALYSIS

Weight and height at 8, 10, 12, and 14 years of age were estimated by linear interpolation of the last measurement before the birthday and the first measurement after the birthday. If no measurements after the 14th birthday existed but the measurements at ages 8, 10, and 12 were known, the level at 14 years of age was predicted by best subset regression performed with the use of Stata software, version 8.0.[5] Body-mass index (BMI) was the weight in kilograms divided by the square of the height in meters.

Age at peak growth was defined as the age between pairs of subsequent measurements that indicated the maximal growth rate in height. We estimated the growth rate between two measurements as a weighted average of the change in height between the two measurements (the interval has a weight of one half of the weighted average) and the change in both adjacent intervals (which have weights of one quarter and one quarter of the weighted average). With only one adjacent interval, the weights were two thirds and one third of the weighted average, respectively. Age at peak growth was estimated for girls with five or more measurements and in whom the maximal growth rate was estimated to be 3.5 cm per year or more.

Follow-up for the diagnosis of breast cancer began for all subjects at 14 years of age or on April 1, 1968, whichever came last, and continued until a diagnosis of breast cancer, death, emigration, or August 31, 2001 (the end of follow-up), whichever came first. The association with breast cancer was estimated according to a cohort design with the use of a log-linear Poisson regression model (SAS, version 8).[6] Adjustment was made for attained age (quadratic splines with "knots" for each five years) and for the calendar period (in five-year intervals).[7] In additional analyses, adjustments were made for age at first childbirth and parity.

Differences according to attained age and the difference in the effect of the change in height and BMI according to age intervals during childhood were evaluated by likelihood-ratio tests of heterogeneity. Trends were estimated by treating the categorized variables (assigned the median within the category) as continuous variables. The underly-

ing log-linear assumptions were checked against a categorical model with the use of likelihood-ratio tests.

Information about age at menarche had not been computerized originally along with measurements of birth weight, weight, and height. Therefore, we manually retrieved school health records in a nested, case–cohort design on all 2005 women who were born from 1940 to 1970 in whom breast cancer developed during follow-up and a cohort of 5500 randomly chosen women who were stratified according to birth cohort in accordance with the distribution of cases. Information on age at menarche was retrieved for 3610 of the women, of whom 950 had breast cancer.

Analyses involving age at menarche were performed with the use of Cox regression, with attained age as the underlying time variable and with birth cohort as stratum variable. The Cox regression analyses (with robust estimation of variance to avoid overestimation of the precision due to the oversampling of cases) were performed with the use of the STCOX procedure (Stata statistical software, version 8).[5] Follow-up was as in the Poisson regression.

We estimated the population attributable risk for each variable in scenarios in which each woman was assigned the median value in the lowest category (in the case of birth weight and height at 14 years of age) or the highest category (in the case of BMI at 14 years and age at peak growth) (Table 1). The population attributable risks were estimated for each variable on the basis of the distribution of risk factors presented in Table 1 and the relative risks (estimated from the trend) for the median value of each quintile.

RESULTS

In our cohort of 141,393 girls who had CRS numbers, there were 1,128,505 sets of measurements of weight and height. Overall, 89 percent of the girls had 5 to 12 measurements (median, 8). The median (±SD) age at the first measurement was 7.2±1.1 years, and the median age at the last measurement was 14.5±2.0 years. We limited all subsequent analyses to the 117,415 women with complete information on weight and height at 8, 10, 12, and 14 years of age as well as age at peak growth. In this cohort, 3340 cases of breast cancer were observed during 3,333,359 person-years of follow-up.

As Table 1 shows, the age at menarche (data were available for 3610 women), the estimated age at peak growth, and the BMI at 14 years of age were inversely associated with the relative risk of breast cancer. Birth weight (data were available for 91,601 women) and height at 14 years of age showed a positive association with the relative risk of breast cancer. No change in effect was found when we adjusted for parity and age at first childbirth.

We investigated whether growth in any specific age interval influenced the risk of breast cancer. We used the age at peak growth to subdivide the period from 8 to 14 years of age into the following three intervals: from 8 years of age until the peak year, during the peak year, and from the peak year until 14 years of age. The peak year was defined as the 12-month period beginning 6 months before the estimated age at peak growth. Increase in height was significantly associated with the relative risk of breast cancer within all age intervals after adjustment for the BMI at 14 years of age, age at peak growth, and attained age and calendar period (Table 2). The relative risk per increase in height was similar in the three age intervals between 8 and 14 years of age ($P=0.33$), whereas the relative risk was significantly higher for changes in height between 8 and 14 years of age than for changes in height before the age of 8 ($P=0.01$).

The BMI, adjusted for height at age 14, age at peak growth, and attained age and calendar period, was significantly associated with the relative risk of breast cancer within all the age intervals (Table 2). However, the increase in risk per increase in BMI was similar in the three intervals from 8 to 14 years of age ($P=0.77$). Also, the increase in risk was similar for changes in the BMI between 8 and 14 years of age and changes in the BMI before the age of 8 ($P=0.10$). No association was found between weight (unadjusted for height) at any age and the risk of breast cancer (data not shown).

The correlation coefficients for each of the five variables in Table 1 as well as height and BMI at 8 years of age were all less than 0.4 with three exceptions: height at the ages of 8 and 14 (0.88), BMI at the ages of 8 and 14 (0.74), and age at menarche and age at peak growth (0.60). The correlation coefficients for birth weight were all less than 0.20.

After further mutual adjustment (Table 3), birth weight, height at 8 years of age, height increase between 8 and 14 years of age, and the BMI at 14 years of age remained independently associated

Table 1. Adjusted Relative Risk of Breast Cancer According to Birth Weight, Age at Peak Growth, Age at Menarche, and Height and BMI at 14 Years of Age in the Cohort of 117,415 Women.*

Variable	No. of Cases	Relative Risk (95% CI)
Birth weight (kg)†		
Median of each quintile		
2.5	381	1.00‡
3.0	392	0.98 (0.85–1.13)
3.4	668	1.06 (0.93–1.20)
3.6	150	1.05 (0.87–1.27)
4.0	483	1.17 (1.02–1.33)
Trend per kg	2074	1.10 (1.01–1.20)
Age at peak growth (yr)		
Median of each quintile		
10.4	568	1.00‡
11.3	727	1.04 (0.93–1.16)
12.0	703	0.94 (0.84–1.05)
12.8	657	0.86 (0.77–0.96)
13.5	685	0.84 (0.75–0.93)
Trend per yr	3340	0.97 (0.96–0.98)
Age at menarche (yr)§		
Median of each quintile		
11.9	193	1.00‡
12.6	201	1.03 (0.85–1.26)
13.2	209	1.09 (0.90–1.33)
13.7	183	0.94 (0.77–1.15)
14.4	164	0.83 (0.67–1.02)
Trend per yr	950	0.96 (0.92–1.00)

with breast cancer, with trends similar to those presented in Tables 1 and 2. Similar analyses in the nested case–cohort design, where age at menarche was known, revealed that adjustment for age at menarche did not affect these associations.

The association between age at peak growth and breast cancer was enhanced after adjustment for all growth variables except age at menarche, which did not affect the association. Age at menarche was not associated with the relative risk of breast cancer after adjustment for the pubertal growth factors (Table 3).

To evaluate the effect of these variables on the population, we calculated population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases would be diminished by 7 percent. Similar figures for height at 14 years of age, BMI at 14 years of age, and age at peak growth were 15 percent, 15 percent, and 9 percent, respectively.

DISCUSSION

With the use of a very large collection of school health records combined with effective follow-up, we found that high birth weight, early age at peak growth, high stature at 14 years of age, low BMI at 14 years of age, and high growth rate in childhood — particularly around puberty — were all independent risk factors for breast cancer. Our results are in accord with the positive association between adult height and premenopausal and postmenopausal risks of breast cancer[1] and with the inverse association between BMI and the risk of premenopausal breast cancer.[8] However, we also identified specific periods of early growth that are important to the risk of breast cancer.

Table 1. (Continued.)

Variable	No. of Cases	Relative Risk (95% CI)
Height at age 14 (cm)		
Median of each quintile		
151.1	733	1.00‡
156.2	678	1.07 (0.96–1.19)
159.8	682	1.18 (1.06–1.31)
162.9	600	1.15 (1.03–1.28)
167.6	647	1.51 (1.36–1.68)
Trend per 5 cm	3340	1.11 (1.08–1.15)
BMI at age 14 (kg/m²)		
Median of each quintile		
16.7	644	1.00‡
18.1	692	0.96 (0.86–1.07)
19.1	736	1.02 (0.92–1.13)
20.3	711	0.99 (0.89–1.10)
22.4	557	0.84 (0.75–0.94)
Trend per unit	3340	0.97 (0.96–0.98)

* All variables were adjusted for age and calendar period except age at menarche, which was adjusted for birth cohort instead of calendar period owing to the case–cohort design. BMI denotes body-mass index (calculated as the weight in kilograms divided by the square of the height in meters), and CI confidence interval. Adjustment for parity and age at first childbirth did not markedly change the trend estimates. Trends are for each increase of one in the unit specified.
† Birth weight was known for 91,601 of the 117,415 women for whom complete information was available on height, weight, and age at peak growth, and breast cancer developed in 2074.
‡ This group served as the reference group.
§ Information on age at menarche was collected with use of a case–cohort design for 3610 women, and of these, breast cancer developed in 950.

Birth weight, a proxy for in utero growth and prenatal exposure, has been studied by several authors, and most[9-18] but not all[12,19-23] have found support for an association between birth weight and breast cancer. In a previous study of women from the same population but without information on subsequent growth, we also found a significant association.[24] In the present study, we found that the association of breast cancer with birth weight is independent of the effect of subsequent growth patterns and the timing of puberty on the risk of breast cancer.

Four studies have explored the association between pubertal growth and the risk of breast cancer in cohorts where actual measurements of weight and height were obtained, although on a much more limited scale than in our study.[15,16,25,26] In agreement with these studies, we found the BMI at 8, 10, 12, and 14 years of age to be inversely associated with the risk of breast cancer. We used height at 14 years of age, which serves as a good proxy for adult height,[27] to confirm the finding of a direct association between adult height and risk of breast cancer. Our finding of an 11 percent increase in risk for every 5 cm increase in height was similar to the results of a very large study of adults.[2] Our data allowed us to investigate whether the influence of final height was modified by the growth pattern. Height at 8 years of age and the increase in height around puberty were both associated with breast cancer, but the latter was stronger, suggesting that pubertal growth has a special effect on the risk of breast cancer. In contrast, analyses of the BMI did not reveal any time interval in which changes in the BMI were of special importance.

We found a linear trend between a lower age at peak growth and an increased risk of breast cancer, which was independent of other measures. Adult height is weakly linked to age at peak growth and age at menarche, and it is possible that different factors control these variables. Age at peak growth probably reflects the initiation of puberty. A Nor-

Table 2. Adjusted Relative Risk of Breast Cancer According to Change in Height and BMI during Various Periods in Childhood.*

Period in Childhood	Height		BMI	
	Relative Risk per 5-cm Increase (95% CI)†	P Value‡	Relative Risk per 1-Unit Increase (95% CI)§	P Value‡
<8 Yr old	1.11 (1.07–1.15)	0.01	0.94 (0.91–0.97)	0.10
8–14 Yr old	1.17 (1.09–1.25)		0.96 (0.93–0.99)	
8–Peak yr	1.18 (1.08–1.27)	0.33	0.95 (0.91–0.99)	0.77
Peak yr	1.15 (0.97–1.36)		0.96 (0.90–1.02)	
Peak yr–14 yr old	1.10 (1.00–1.20)		0.97 (0.93–1.02)	

* Peak year is defined as the 12-month time period beginning 6 months before the estimated age at peak growth. BMI denotes body-mass index, and CI confidence interval.

† Adjustments were made for attained age and calendar period, age at peak growth, and BMI at 14 years of age.

‡ P values for the difference in relative risk were derived from the likelihood-ratio test of heterogeneity.

§ Adjustments were made for attained age and calendar period, age at peak growth, and height at 14 years of age.

wegian study showed that the risk of breast cancer increased by 4 percent for each year that age at menarche decreased.[28] We also found that age at menarche was associated with a risk of breast cancer, but not when age at peak growth was included in the analysis. Thus, previous findings could show that age at menarche is a proxy for age at peak growth or that both reflect the importance of age at the onset of puberty. Another indication of the importance of puberty was our finding that the increase in height between 8 and 14 years of age conferred a higher risk of breast cancer than the increase in height that accrued up to 8 years of age.

We did not have information on the women's status with respect to family history of breast cancer, history of benign breast disease, and hormone-replacement therapy. Although these factors influence the risk of breast cancer, they are unlikely to vary according to childhood height and weight and, as such, do not confound our estimates. Another limitation of our study was the inability to analyze adult weight and BMI. Thus, whereas adolescent height is closely correlated with adult height and hence is well elucidated in this study, weight has a weaker correlation. In a large population-based British cohort, height at 16 years of age had a correlation of 0.92 with height at 33 years of age, as compared with a correlation with weight of 0.63.[27]

To illustrate the quantitative contributions of the growth factors to the overall risk of breast cancer, we also calculated the population attributable risks under the assumption of causal associations. If all women had a birth weight in the lowest category (lowest quintile), the number of cases of breast cancer would have been diminished by 7 percent. Similarly, lowest quintiles of height at 14 years of age and highest quintile of BMI at 14 years of age and of age at peak growth would have resulted in a 15 percent, 15 percent, and 9 percent decrease in cases, respectively.

Our study had sufficient power to detect weak but relevant associations, and it avoided various sources of bias. Information on birth weight and the measurements of height and weight was recorded during school years, making differential misclassification unlikely. The validity of parents' reports of their children's birth weights is very high.[29] We based our cohort on all children attending schools in a well-defined area of Denmark and followed them through our national registries. The Danish social structure further diminished any risk of diagnostic bias, because free and equal access to health care is provided for all citizens.

The biologic background for our findings needs to be elucidated, and mechanistic models including modified susceptibility seem warranted. Within the past century, adult height and the prevalence of obesity have increased and the age at menarche has decreased,[30,31] indicating that changes in some environmental conditions are important and probably interact with genetic factors. Nutritional status, for example, is related to an increased gain in height in childhood and earlier onset of puberty.[32]

An increase in the total number of menstrual cycles during a lifetime may explain the association between the early onset of puberty (and thus early age at peak growth) and an increased risk of breast cancer. However, this explanation may be too simple. Even a two-year delay in age at menarche would result in only a limited number of "lost" menstrual cycles in the context of the total number of cycles in a lifetime. The breast epithelium undergoes final differentiation at first pregnancy, and it is a generally held belief that differentiated cells are less prone to carcinogenic effects than undifferentiated cells.[33] Whereas some differentiation of breast epithelium occurs before the first pregnancy, breast cells present before menarche are probably the least differentiated. Since the female breast begins developing well before the start of

Table 3. Association between Growth Variables and Breast Cancer, According to Age.

Growth Variable	Relative Risk (95% CI)*			P Value¶
	All Ages	Age <50 yr	Age ≥50 yr	
Birth weight†	1.10 (1.01–1.21)	1.14 (1.01–1.28)	1.05 (0.91–1.21)	0.39
Age at peak growth‡	0.94 (0.91–0.97)	0.90 (0.86–0.95)	0.98 (0.93–1.03)	0.03
Age at menarche§	0.99 (0.91–1.07)	0.98 (0.88–1.08)	1.01 (0.87–1.17)	0.74
Height at age 8‡	1.11 (1.07–1.15)	1.11 (1.05–1.17)	1.11 (1.05–1.17)	0.62
Height increase age 8 to age 14‡	1.17 (1.09–1.25)	1.15 (1.05–1.27)	1.18 (1.07–1.30)	0.74
BMI age 14‡	0.95 (0.93–0.97)	0.96 (0.94–0.99)	0.94 (0.92–0.97)	0.22

* The relative risk is per 1-kg increase in birth weight, per 1-year increase in age at peak growth and age at menarche, per 5-cm increase in height, and per 1-unit increase in body-mass index (BMI). CI denotes confidence interval.
† Adjusted for age at peak growth, height at 8 years of age, height increase from 8 to 14 years of age, and BMI at 14 years of age. Further adjustment for age at menarche did not markedly change the estimate.
‡ Mutually adjusted. Further adjustment for birth weight and age at menarche did not markedly change the estimate.
§ Adjusted for age at peak growth, height at age 8, height increase from age 8 to age 14, and BMI at age 14. Further adjustment for birth weight did not markedly change the estimate.
¶ P values represent the difference in relative risk according to attained ages.

menstrual cycles,[34] it is possible that the age at peak growth is really an indicator of the age at which the breast starts growing and, hence, influences the risk of breast cancer.

Our finding that a high BMI protects against breast cancer contrasts with studies showing that overweight in girls is associated with early menarche.[35] Our findings suggest that the effect of childhood obesity on breast cancer does not occur by means of a contribution to the acceleration of puberty, because early menarche has the opposite effect of obesity. However, the estrogens produced by adipose tissue may promote differentiation of the breast epithelium.

Overall, our results provide evidence that factors influencing fetal, childhood, and adolescent growth are important independent risk factors for breast cancer in adulthood. Therefore, the exposures or conditioning processes during these periods are of particular importance in relation to adult breast cancer.

Supported by grants from the U.S. Department of Defense Congressionally Directed Medical Research Programs, the Danish Medical Research Council, the Danish National Research Foundation, and the Danish Cancer Society.

REFERENCES

1. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001;23:313-42.
2. Tretli S. Height and weight in relation to breast cancer morbidity and mortality: a prospective study of 570,000 women in Norway. Int J Cancer 1989;44:23-30.
3. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. Dan Med Bull 1997;44:535-9.
4. Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000;11:669-74.
5. Stata base reference manual, version 8. College Station, Tex.: Stata Press, 2003.
6. SAS/STAT user's guide, version 8. Cary, N.C.: SAS Institute, 2003.
7. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356-65.
8. Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev 2001;10:15-32.
9. Andersson SW, Bengtsson C, Hallberg L, et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193-8.
10. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000;152:1121-8.
11. Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a risk factor for breast cancer. Lancet 1996;348:1542-6.
12. Sanderson M, Williams MA, Malone KE, et al. Perinatal factors and risk of breast cancer. Epidemiology 1996;7:34-7.
13. Vatten LJ, Maehle BO, Lund Nilsen TI, et al. Birth weight as a predictor of breast cancer: a case-control study in Norway. Br J Cancer 2002;86:89-91.
14. Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001;93:60-2.
15. Hilakivi-Clarke L, Forsen T, Eriksson JG, et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001;85:1680-4.
16. Stavola BL, Hardy R, Kuh D, Silva IS, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000;83:964-8.
17. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015-8.
18. Hubinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001;91:248-51.
19. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71-6.
20. Sanderson M, Williams MA, Daling JR, et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998;12:397-407.
21. Le Marchand L, Kolonel LN, Myers BC,

Mi MP. Birth characteristics of premenopausal women with breast cancer. Br J Cancer 1988;57:437-9.
22. 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;11:207-10.
23. Sanderson M, Shu XO, Jin F, et al. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-8.
24. Ahlgren M, Sorensen TIA, Wohlfahrt J, Haflidadottir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003;107:997-1000.
25. Herrinton LJ, Husson G. Relation of childhood height and later risk of breast cancer. Am J Epidemiol 2001;154:618-23.
26. Le Marchand L, Kolonel LN, Earle ME, Mi MP. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988;128:137-52.
27. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. Am J Clin Nutr 1997;66:1094-101.
28. Kvale G, Heuch I. Menstrual factors and breast cancer risk. Cancer 1988;62:1625-31.
29. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 1997;145:58-67.
30. Petersen TA, Rasmussen S, Madsen M. BMI of Danish school children measured during the periods 1986/1987–1996/1997 compared to Danish measurement in 1971/1972. Ugeskr Laeger 2002;164:5006-10. (In Danish.)
31. Rasmussen S, Petersen TA, Madsen M. Body height of 6 15-year-old school children measured in the period 1986/1987 to 1996/1997 compared with Danish measurements in 1971/1972. Ugeskr Laeger 2002;164:5011-5. (In Danish.)
32. He Q, Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res 2001;49:244-51.
33. Russo J, Russo IH. Cellular basis of breast cancer susceptibility. Oncol Res 1999;11:169-78.
34. Howard BA, Gusterson BA. Human breast development. J Mammary Gland Biol Neoplasia 2000;5:119-37.
35. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974;185:949-51.