

ORIGINAL ARTICLE

# Growth Patterns and the Risk of Breast Cancer in Women

Martin Ahlgren, M.D., Mads Melbye, M.D., Dr.Med.Sci., Jan Wohlfahrt, M.Sc.,  
and Thorkild I. A. Sørensen, M.D., Dr.Med.Sci.

## 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.

From the Department of Epidemiology Research, Danish Epidemiology Science Center, Statens Serum Institut (M.A., M.M., J.W.); and the Danish Epidemiology Science Centre, Institute of Preventive Medicine, Copenhagen University Hospital (T.I.A.S.) — both in Copenhagen. Address reprint requests to Dr. Ahlgren at the Department of Epidemiology Research, Danish Epidemiology Science Center, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark, or at abk@ssi.dk.

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**M**OST 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,<sup>1</sup> whereas obese women have a reduced risk of breast cancer before menopause but an increased risk after menopause.<sup>2</sup> 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.<sup>3,4</sup>

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.<sup>3</sup> 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.<sup>4</sup>

### 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.<sup>5</sup> 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).<sup>6</sup> Adjustment was made for attained age (quadratic splines with “knots” for each five years) and for the calendar period (in five-year intervals).<sup>7</sup> 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 underlying

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).<sup>5</sup> 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.

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## RESULTS

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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 ( $\pm$ SD) age at the first measurement was  $7.2\pm 1.1$  years, and the median age at the last measurement was  $14.5\pm 2.0$  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<sup>1</sup> and with the inverse association between BMI and the risk of premenopausal breast cancer.<sup>8</sup> 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/m <sup>2</sup> )		
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<sup>9-18</sup> but not all<sup>12,19-23</sup> 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.<sup>24</sup> 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.<sup>15,16,25,26</sup> 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,<sup>27</sup> 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.<sup>2</sup> 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.<sup>28</sup> 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.<sup>27</sup>

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.<sup>29</sup> 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,<sup>30,31</sup> 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.<sup>32</sup>

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.<sup>33</sup> 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,<sup>34</sup> 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.<sup>35</sup> 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.

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