

Adult height and risk of breast cancer: a possible effect of early nutrition

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Summary The relationship of breast cancer to early reproductive development and height suggests that fetal and childhood nutrition may be important in its aetiology. Caloric restriction sufficient to reduce adult height may reduce breast cancer risk. During World War II (WWII) there was a marked reduction in average caloric intake in Norway that resulted in greater nutritional diversity. We hypothesized that a positive association between height and risk of breast cancer would be stronger among women who were born during this period than among women born before or after the war. A total of 25 204 Norwegian women were followed up for approximately 11 years, and 215 incident cases of breast cancer were registered. We found the strongest positive association between height and breast cancer among women born during WWII: women in the tallest tertile (>167 cm) had a relative risk of 2.5 (95% confidence interval = 1.2–5.5) compared with the shortest (\leq 162 cm). Among women born before or after the war we found no clear association with height. The association with height in the WWII cohort may imply a role for early nutrition in breast cancer aetiology. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

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Early menarche (Kelsey et al, 1993) and adult stature (de Waard, 1975; Tretli, 1989; Vatten and Kvinnsland, 1990) are positively associated with breast cancer risk. In populations characterized by nutritional diversity, differences in adult height may reflect differences in childhood nutrition (Willett, 1998). The relationship to early reproductive development and adult height may therefore indicate that nutrition at a young age can be important for future breast cancer risk (MacMahon, 1975).

During gestation, maternal nutritional deprivation may restrict fetal (Godfrey et al, 1996; Thame et al, 1997) and childhood growth (Cacciari et al, 2000), and the offspring may end up shorter as adults than their genetic potential would indicate (Karlberg and Luo, 2000; Luo et al, 2000; Rona and Chinn, 1995). Some studies have shown a positive association between birth weight and future risk of breast cancer (Ekbom et al, 1992; Michels et al, 1996; Sanderson et al, 1996; Stavola et al, 2000; Kaijser et al, 2001). Other studies have, however, shown no association between indicators of birth size and risk of breast cancer (Ekbom et al, 1997; Le Marchand et al, 1988).

In Norway, there was an overall reduction in average caloric intake during World War II, from 3475 kcal daily in 1939, to a minimum of 2700 kcal in late 1944 and early 1945 (Galtung-Hansen, 1947; Strøm, 1948). Among women who were born during that period, nutritional diversity was likely to be greater, both during intra-uterine life and early childhood, than among women who were born before or after the war. We therefore hypothesized that a positive association between height and risk of breast cancer would be stronger among women who were born during World War II. We used information from a cohort of 25 204 Norwegian women to test this hypothesis in a prospective study.

MATERIALS AND METHODS

This study includes 25 204 women born between 1925 and 1965 who participated in the Nord-Trøndelag Health Survey between 1984 and 1986 (Holmen and Midthjell, 1990). All residents in Nord-Trøndelag country aged 20 years or older were invited to participate in a brief health examination that included anthropometric measurements and self-administered questionnaires that provided information on medical history and lifestyle factors.

The participants were followed from the date of entry to the study (between January 1984 to April 1986) until the date of cancer diagnosis (of all sites), death, emigration, or the cut-off date of 1 January 1996, whichever occurred first. The unique identification number of every citizen in Norway enabled linkage to the national Cancer Registry in order to identify incident cases of cancer. To achieve a high degree of completeness and data quality, the material of the Cancer Registry is matched against the Register of Deaths at Statistics Norway. For all cancer cases registered since 1953, 84.7% are histologically verified and only 1.7% of the diagnoses are based on death certificate alone (Cancer Registry of Norway, 1998).

We used the Cox proportional hazards model (Kleinbaum, 1995) to compute incidence rate ratios (RRs) of breast cancer associated with adult height by year of birth. Height was categorized into tertiles according to the distribution of the total population (cut-off = 162 cm and 167 cm), while year of birth was categorized into five birth cohorts. The first birth cohort ranged from January 1925 to December 1929, and the second from January 1930 to December 1934. Since Norway was occupied between 9 April 1940 and 8 May 1945, the fourth birth cohort (i.e. the World War II cohort) ranged from July 1940 to December 1945, and consequently the third ranged from January 1935 to June 1940. The last birth cohort included all women born in January 1946 or later. In the stratified analysis of these youngest women (born in 1946 or later) we adjusted for age at study entry in

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three categories (< 30, 30–34, and ≥ 35 years). Further multivariate analyses were conducted to assess potential confounding by body mass index (BMI), smoking, and physical activity.

All statistical analyses were performed using the statistical software SPSS for Windows (Release 10.0.5, Copyright © SPSS Inc., 1989–1999).

RESULTS

During almost 12 years of follow-up (median = 11.0 years) we observed a total of 276 239 person-years, and 215 incident cases of breast cancer were registered. Mean age at study entry was 39.5 years (range = 20–61 years) and mean age at diagnosis of breast cancer was 53.4 years (range = 31–70 years).

We found no independent effect of height on the risk of breast cancer in the total population (age-adjusted *P*-trend = 0.6). However, in analyses stratified by birth cohort we found a strong positive association with height among the 3792 women (43 cases) who were born during World War II, where women in the tallest tertile of height (> 167 cm) had more than twice the risk of breast cancer compared with women in the shortest tertile (≤ 162 cm) (RR = 2.5; 95% CI = 1.2–5.5) (Table 1). For women in the other birth cohorts there was no significant association between height and breast cancer risk. Adjustment for BMI, smoking and physical activity did not change these results (data not shown).

DISCUSSION

In this prospective study of Norwegian women, we found that an association between adult height and breast cancer risk was confined to women who were born during World War II. Women in the highest tertile of height had more than twice the risk of breast cancer compared with women in the lowest tertile. Among women born before or after the war we found no clear association with height.

We adjusted for differences in body mass index, smoking, and physical activity. However, we had no information on age at menarche, age at first full-term pregnancy, and parity, and this may be a weakness of our study. Also, by stratifying cases according to

birth cohorts, the number of cases within each category of height was small, thereby reducing the precision of the results.

Recently, the association between indicators of birth size and breast cancer risk has received attention, and some studies have reported a positive association with birth weight (Ekbom et al, 1992; Michels et al, 1996; Sanderson et al, 1996; Stavola et al, 2000; Kaijser et al, 2001). Others, however, have not been able to confirm this finding (Ekbom et al, 1997; Le Marchand et al, 1988). For birth length or placenta weight, there have been no clear findings, but pre-eclampsia in the mother, which is associated with reduced fetal growth, appears to reduce the risk of breast cancer in the daughters (Ekbom et al, 1992; Ekbom et al, 1997; Sanderson et al, 1998).

In a previous Norwegian cohort study, there was a positive association between height and breast cancer risk among women whose peripubertal growth coincided with World War II (Vatten and Kvinnsland, 1990). Also, a large ecological study in Norway found that the incidence of breast cancer was lower than expected among women who experienced puberty during the war (Tretli and Gaard, 1996). In the present cohort we found no significant association with height among women who were born in the late 1920s or early 1930s, as would be predicted from the other two Norwegian studies. The cancer cases contributing to the effect of WWII in the present study and in the study by Vatten and Kvinnsland were mainly pre-menopausal. Tretli (1989) found, however, that the association between height and breast cancer did not substantially differ by age at diagnosis.

If fetal or childhood growth is important for a girl's prospects of developing breast cancer, one important set of biological mediators may be the insulin-like growth factors (IGFs) (Smith et al, 2000). The IGFs play an important role during the peripubertal growth spurt, and tallness is positively associated with plasma IGF-I levels (Juul et al, 1994). It is, however, unclear whether differences in IGF levels during early development are reflected in differences in adult IGF. Recently, two prospective studies of IGF-I measured in adult women found a positive association with risk of premenopausal, but not postmenopausal breast cancer (Hankinson et al, 1998; Toniolo et al, 2000).

In summary, this study shows a strong positive association between adult height and risk of breast cancer among the women

Table 1 Rate ratio (RR) with 95% confidence interval (CI) of breast cancer risk associated with tertiles of height stratified by birth cohort

Birth cohort	Tertiles of height ^a	No. of person-years	No. of cases	RR	95% CI
1925–1929	T1	16 793	37	1.0	–
	T2	9 467	20	0.9	0.5–1.6
	T3	4 870	6	0.5	0.2–1.1
1930–1934	T1	13 783	18	1.0	–
	T2	9 282	12	0.9	0.5–2.0
	T3	5 454	7	0.9	0.4–2.3
1935–1940 ^b	T1	11 933	10	1.0	–
	T2	11 510	8	0.8	0.3–1.9
	T3	8 416	10	1.3	0.5–3.1
1940–1945 ^b	T1	13 709	9	1.0	–
	T2	15 189	12	1.1	0.5–2.7
	T3	12 770	22	2.5	1.2–5.5
≥ 1946 ^c	T1	38 439	11	1.0	–
	T2	47 629	16	1.1	0.5–2.4
	T3	52 165	16	1.0	0.5–2.3

^aCut-off for tertiles of height = 162 cm and 167 cm; ^bCfr. time cut-off in 1940; see Materials and methods; ^cRR is adjusted for age at study entry (< 30, 30–34, and ≥ 35 years).

whose fetal growth coincided with the years of World War II. This period was characterized by general caloric restriction (Galtung-Hansen, 1947; Strøm, 1948) and a deceleration in the secular height gain observed before the war (Brundtland et al, 1980). We suggest that the strong association with height may reflect greater nutritional diversity during gestation among the mothers, implying a role for early nutrition in the aetiology of breast cancer.

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