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Incidence and Mortality of Breast Cancer Related to Body Height and Living Conditions During Childhood and Adolescence

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The nutritional component during childhood and adolescence that contributes to variation in adult height may be associated with the subsequent risk of breast cancer in women. Municipalities in three Norwegian counties were ranked and divided in three categories according to resident women's height, where variation in height is assumed to reflect variation in nutritional living conditions during childhood and adolescence. For each county observed number of incident cases (1975–1984) and deaths (1966–1987) of breast cancer in "short", "medium" and "tall" municipalities were compared with the expected number computed from the national rates. An analogous analysis was done, comparing incidence and mortality between 18 Norwegian counties, but using county-specific infant mortality for the period 1921–1935 as an alternative indicator of living conditions. There was a consistent positive association between height in municipalities and breast cancer incidence (overall *P* trend = 0.02) and mortality (overall *P* trend = 0.05). For infant mortality between counties, there was no association with breast cancer. In populations where variation in height reflects variation in nutritional living conditions during childhood and adolescence, there may be a positive association between height and risk and mortality of breast cancer.
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INTRODUCTION

AN ASSOCIATION between adult height and risk of breast cancer may be related to variation in nutritional energy, maybe predominantly acting during peri-pubertal growth, a period during which height is determined and breast tissue is developed [1–4]. In affluent societies, however, with reduced variability in living conditions during childhood and adolescence, variation in height may primarily reflect genetic variation, and no clear association with breast cancer may be expected [5], as has been demonstrated in the Nurses' Health Study [6]. In less homogeneous populations, and among persons who have suffered caloric restriction during a particular period of growth [7–9], a nutritional contribution may be important for the variability in height. Hence, a Norwegian cohort study could show that the positive association between height and breast cancer risk was confined to women who had their peri-pubertal growth during a period of national nutritional restriction (World War II) [9, 10]. The positive association with height may be attributed to differences in caloric energy, resulting in lower breast cancer rates among shorter women, among whom a greater proportion may have suffered caloric restriction during childhood and adolescence.

In this study we further explore the hypothesis that height, as an indicator of living conditions at a young age, is positively associated with the risk and mortality of breast cancer. We have partly used differences in mean height between women residing in different municipalities as a proxy indicator for living conditions. In addition, we have used the variation in infant mortality between counties as such an indicator, and tested the hypothesis that infant mortality on a county level is negatively associated with the subsequent risk and mortality of breast cancer.

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PATIENTS AND METHODS

Between 1974 and 1978 all women between 35 and 49 years of age and samples of women aged 20–34 who were living in three separate counties in Norway were invited to participate in a health screening examination. The screening included a questionnaire and standardised measurements of blood pressure, height and weight, and a nonfasting blood sample was drawn from each subject. The screening and its results have been described [11, 12], and a 12-year follow-up of height and risk of breast cancer has been reported [9].

Since adult height may reflect living conditions during childhood [13], we ranked municipalities in each of the three counties according to the height of resident women, categorised into "short", "medium", and "tall", using height as an indicator to discriminate living conditions during childhood and adolescence between municipalities. We applied the reported incidence of breast cancer to the Cancer Registry by municipality, for the period 1975–1984 [14], and compared the observed number of cases with the expected number, computed from the national rates, to provide estimates of relative risk (age-standardised incidence ratios, SIR) of breast cancer for each category of height.

The SIR is presented with 95% confidence limits, using Mantel–Haenszel χ^2 statistics, and Mantel's extension test has been used to assess any trend in association between short, medium and tall municipalities [15]. In addition to incidence, an identical procedure was followed in relation to mortality rates of breast cancer, where the effect of height by municipality is presented as age-standardised mortality ratios (SMR). For mortality, however, we had access to, and applied number of deaths for the 22-year period 1966–1987 [16].

Table 1. Age-standardised incidence ratio (SIR) of breast cancer, according to mean height among women in municipalities, in three Norwegian counties. Incidence of breast cancer 1975–1984. *Population as per* 31 *December* 1979

Height (cm)	Municipality	Population	Observed	Expected	SIR	95% Confidence limit	
Oppland County							
Short (≤ 162.5)	8	19083	122	169.9	0.72	0.58–0.88	
Medium (162.6–163.3)	8	27032	200	214.6	0.93	0.80–1.07	*P* trend = 0.13
Tall (≥ 163.4)	8	41849	318	333.5	0.95	0.84–1.06	
Sogn og Fjordane County							
Short (≤ 162.9)	8	14995	87	117.0	0.74	0.59–0.92	
Medium (163.0–163.5)	9	20621	137	150.3	0.91	0.78–1.07	*P* trend = 0.007
Tall (≥ 163.6)	8	15866	130	134.5	0.97	0.80–1.18	
Finnmark County							
Short (≤ 158.5)	7	7508	27	44.5	0.61	0.47–0.67	
Medium (158.6–159.4)	6	7168	27	40.6	0.67	0.52–0.89	*P* trend = 0.21
Tall (≥ 159.5)	7	23198	106	139.1	0.76	0.66–0.88	
Total—three counties							
Short	23	41586	236	331.4	0.71	0.62–0.82	
Medium	23	54821	364	405.5	0.80	0.71–0.90	
Tall	24	80913	554	607.1	0.91	0.83–0.99	*P* trend = 0.02
Total	70	177320	1154	1344.0	0.86	0.81–0.92	

Infant mortality may also be used as an indicator for living conditions during childhood [17]. This could be done specifically for municipalities in only one county (Finnmark). Instead, we therefore used infant mortality in each of the 18 counties (excluding the city of Oslo) of Norway, assuming differences in infant mortality between counties for the time period 1921–1935 [18] might be a reasonable indicator for living conditions during childhood. We ranked counties, and divided them into categories of "low", "medium", and "high" infant mortality. Analogous to the methods used for height, the observed incidence of breast cancer between 1975 and 1984, and mortality between 1966 and 1987 for each category of infant mortality, was compared to the expected number, based on national rates, to provide age-adjusted estimates of relative risk (SIRs and SMRs).

RESULTS

Table 1 shows the age-adjusted SIRs for participating municipalities in each of the screened counties, according to categories of resident women's height. It shows that overall, the incidence in these counties is lower than the national incidence of breast cancer. Within counties, however, there appears to be a consistent pattern, where taller municipalities have a higher incidence of breast cancer than shorter municipalities, although there is an overlap between confidence limits. The trend is similar for each county, but the test for trend is statistically significant ($P = 0.007$) only in one of the counties (Sogn og Fjordane). By pooling the counties, the precision of the relative risks is improved, and the overall test for trend between categories of height is statistically significant ($P = 0.02$).

Although information on municipality of residence at birth was not complete, a similar analysis was done using place of birth as indicator of living conditions during childhood and adolescence. The results did not materially differ (data not shown) from those based on municipality of residence as an indicator.

Table 2 shows an analogous analysis of breast cancer mortality for the period 1966–1987 in the same municipalities. The results replicate those of incidence, but the strong positive association between height and incidence in Sogn og Fjordane is not present with respect to mortality.

In Table 3 infant mortality rates by county for the period 1921–1935 has been used as an alternative indicator of living conditions, and related to incidence (1975–1984) and mortality (1966–1987) of breast cancer. Table 3 does not show any association between infant mortality and the age-adjusted estimates of either incidence or mortality of breast cancer.

DISCUSSION

In this study, there was a positive association between mean height on the municipal level and incidence and mortality of breast cancer. With the exception of certain municipalities in one county (Finnmark), demographic characteristics do not suggest that this finding can be attributed to genetic differences which may be associated with height. We therefore assume that variability in mean height between women in different municipalities is more likely to reflect variation in nutritional living conditions during childhood and adolescence. Despite an overlap in the confidence limits between the estimates of relative risk, there was a consistent trend from short to tall municipalities, giving an overall statistically significant trend.

Several prospective studies have found a positive association between height and breast cancer incidence [3, 4, 7–9] and mortality [4]. A large American study [6], however, showed no clear relation with height, and it is of interest to understand the basis for this discrepancy between studies. Height has been related to living conditions during childhood and adolescence, and in particular, variation in height may reflect variation in nutrition [1, 2]. Simultaneously, it has been proposed that adult height in industrialised societies primarily reflects genetic variation, and nutritional variability is too little to contribute to variation in height [5]. This may apply to participants in the Nurses Health Study [6], in whom difference in height to a

Table 2. Age-standardised mortality ratio (SMR) of breast cancer, according to mean height among women in municipalities, in three Norwegian counties. Mortality of breast cancer 1966–1987. Population as per 31 December 1979

Height (cm)	Municipality	Population	Observed	Expected	SMR	95% Confidence limit	
Oppland County							
Short (≤ 162.5)	8	19 083	108	137.3	0.79	0.64–0.96	
Medium (162.6–163.3)	8	27 032	164	185.0	0.89	0.76–1.04	P trend = 0.05
Tall (≥ 163.4)	8	41 849	281	282.7	0.99	0.88–1.12	
Sogn og Fjordane County							
Short (≤ 162.9)	8	14 995	94	107.1	0.88	0.70–1.09	
Medium (163.0–163.5)	9	20 621	117	131.9	0.89	0.75–1.06	P trend = 0.16
Tall (≥ 163.6)	8	15 866	113	125.3	0.90	0.71–1.11	
Finnmark County							
Short (≤ 158.5)	7	7 508	21	36.9	0.57	0.43–0.78	
Medium (158–159.4)	6	7 168	23	33.6	0.68	0.52–0.92	P trend = 0.10
Tall (≥ 159.5)	7	23 198	87	111.3	0.78	0.68–0.92	
Total—three counties							
Short	23	41 586	223	281.3	0.71	0.63–0.81	
Medium	23	54 821	304	350.5	0.80	0.72–0.88	
Tall	24	80 913	481	519.3	0.91	0.84–0.98	P trend = 0.06
Total	70	177 320	1008	1151.1	0.88	0.84–0.93	

Table 3. Age-standardised incidence ratio (SIR) and age-standardised mortality ratio (SMR) of breast cancer in Norwegian counties, according to infant mortality between 1921 and 1935 (deaths per 1000 live births). Incidence of breast cancer 1975–1984, and mortality of breast cancer 1966–1987. Population as per 31 December 1979

			Incidence (1975–1984)			Mortality (1966–1987)		
Infant mortality	Counties	Population	Observed	Expected	SIR	Observed	Expected	SMR
Low (36–42)	6	575 585	4 285	4 414	0.97	3 738	3 823	0.98
Medium (43–47)	6	696 701	4 994	5 145	0.97	4 208	4 299	0.98
High (48–100)	6	499 246	3 699	3 854	0.96	3 299	3 295	1.00

lesser degree may reflect living conditions during growth than among participants in some of the other studies, who have been subject to caloric restriction during periods of their lives [7–9]. In this respect it is of interest to note that participants in another American study [3], which showed a positive association with height, were sampled in such a way as to include a relatively large proportion of subjects with an increased risk of malnutrition.

In this study we have made the assumption that variation in height on the municipality level may discriminate living conditions between communities, and that differences in incidence and mortality of breast cancer between municipalities may reflect differences in living conditions during a susceptible phase of a woman's life.

Can the estimated associations with height be explained by bias in the study design? We find it unlikely that our results can be ascribed to a differential selection of individuals, where taller women either live in, or move to areas which have a higher incidence of breast cancer due to other risk factors. Moreover, we regard the classification of municipalities into height categories to be reassuring, since measurements were standardised, and age distribution was approximately similar between communities. We cannot exclude the potential for confounding with other risk factors of breast cancer, and insufficient adjustment for age might be a problem, and since young women tend to be taller than older women the potential confounding with age would most likely bias the relative risk towards the null value.

However, the association between age at menarche and risk of breast cancer may justify a more detailed discussion of the relation between height and menarche. In stable, affluent populations, girls who mature early will be tall for their age at the onset of menarche, whereas a girl who matures later than average will be relatively short for her age at this time. Nevertheless, due to her longer growth period the late maturer will tend to end up taller than the early maturer [19]. Following menarche, early maturers will on average establish regular menstrual cycles within a shorter interval, whereas late maturers will have an extended period of irregular cycles [20]. On this background, taller women would be expected to have a lower breast cancer risk, due to their later age at menarche [21]. In populations of greater nutritional heterogeneity, this pattern may be modified. Women who have experienced caloric restriction during childhood are likely to have a later age at menarche as well as lower adult height.

Albanes and Winick have proposed that cancer risk is proportional to the number of proliferating cells, which both depends on the number of cells and the rate of cell division in the tissue [22]. Nutritional caloric energy during childhood and adolescence may modify the number of breast tissue cells by affecting hyperplastic growth, and caloric restriction may result in a smaller pool of cells that are at risk of malignant transformation. Alternatively, the influence of nutrition may be indirect, through its modifying effect on age at menarche and regularity of menstrual cycles. Thus, a higher rate of cell division (mitosis) in breast tissue cells may be expected among taller women, whom were well nourished during childhood, reached menarche early, and established regular menstrual cycles sooner than shorter women, who experienced caloric restriction during their childhood.

In this study we found a consistent positive association between height on the municipality level and risk and mortality of breast cancer, although the strong association with risk was absent for mortality in one county (Sogn og Fjordane). We used differences in infant mortality between counties as an alternative indicator for living conditions during childhood [17, 18], but were unable to find any relation with breast cancer for this indicator. Infant mortality on a community level was available in one county (Finnmark), for which the absence of any association with breast cancer was replicated (data not shown).

These findings suggest that living conditions (presumably nutritional) during childhood may be important for subsequent risk of breast cancer. The consistent positive association with height, and the lack of any association with infant mortality may imply that an effect is related to the pubertal growth spurt, a crucial period for height determination and breast tissue development.

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