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Original Paper

Height and Breast Cancer Risk

A. Tavani,[1] C. Braga,[1] C. La Vecchia,[1,2] F. Parazzini,[1] R. Talamini[3] and S. Franceschi[3]

[1]Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan; [2]Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Via Venezian 1, 20133 Milan; and [3]Centro di Riferimento Oncologico, Via Pedemontana Occ.le, 33081 Aviano (Pordenone), Italy

The relationship between adult height and breast cancer risk was considered, combining data from two case–control studies, one conducted between 1983 and 1991 in northern Italy and the other between 1991 and 1994 in six Italian centres. Cases were 5984 women, below the age of 75 years, with histologically confirmed breast cancer, and controls were 5504 women admitted to hospital for a wide spectrum of acute, non-neoplastic, non-hormone-related diseases. No relationship was observed between height and the risk of breast cancer, with a multivariate odds ratio (OR) of 0.96 (95% confidence intervals (CI) 0.85–1.08) for the tallest women (height $\geq$ 166 cm) compared with the shortest (height < 156 cm). No significant heterogeneity was found across strata of age at diagnosis, education, body mass index, body weight, alcohol intake, age at menarche and menopause, parity, age at first birth, ever use of oral contraceptives and hormone replacement therapy, history of benign breast disease and family history of breast cancer. Thus, this study indicates that adult height is not appreciably related to breast cancer risk in this Italian population.

Key words: breast neoplasms, case–control studies, height, risk factors
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INTRODUCTION

IT HAS been suggested that adult height is related to the risk of breast cancer in women. In fact, height, age at menarche and breast tissue development are influenced by the endocrinological modifications during peripubertal and adolescent life, which may be critical for the development of breast cancer later in life [1, 2]. Childhood and adolescent energy and nutrient intake influence both maturation of ovarian function and adult height [3] and may influence subsequent breast cancer risk [1, 2]. A positive relationship between height and mammary gland mass is conceivable, since both are likely to reflect, to a certain extent, overall growth [1]. Thus, adult height might be an indicator of breast cancer risk.

The relationship of height to breast cancer has been extensively studied, but epidemiological evidence is controversial [1, 2, 4, 5]. An ecological study of 24 populations showed a significant correlation between height and breast cancer incidence, largely influenced by Japanese women [6]. Prospective studies reported either a modest positive association [7–13], or no association [14–17]. Case–control studies also found inconsistent results, showing either an increased risk of breast cancer in taller women [18–24], or no association [25–31]. When separate analyses were conducted in pre- and postmenopausal women, at least two case–control studies [32, 33] and one cohort study [34] found a positive association between height and breast cancer risk in post- but not in premenopausal women, but one case–control study [35] found no association in either condition. Another case–control study [36] showed a slightly increased risk in taller women younger than 65 years and a lower risk in taller women aged 65 years or older. It is unclear, however, whether any differential effect reflects the potential influence of menopausal status and/or cohort of birth.

The issue is thus still open to debate. A recent American case–control study [37], including more than 1500 women younger than 45 years, showed a direct relationship between height and breast cancer, with a 46% higher risk of the disease among women in the highest quartile of height (> 167 cm) compared with women in the lowest quartile (< 159 cm). However, another recent case–control study [38], conducted in the U.S.A., Canada and Israel on more than 5300 incident breast cancer cases, found no association with height, overall or in specific risk factor subgroups.

Correspondence to A. Tavani.
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Thus, to obtain further information on the issue, we analysed the relationship between height and breast cancer risk using combined data from two large case–control studies conducted between 1983 and 1994 in Italy. Part of the data of these studies has already been published [29, 39].

PATIENTS AND METHODS

The data were derived from two case–control studies of breast cancer, the first conducted between January 1983 and May 1991 in the greater Milan area [40], and the second between June 1991 and February 1994 [29, 39] in six Italian areas: greater Milan, the province of Pordenone, the urban area of Genoa and the province of Forlì, in northern Italy; the province of Latina, in central Italy; and the urban area of Naples, in southern Italy. The interviewers were centrally trained and the structured questionnaires were tested for reliability and reproducibility [41, 42]. On average, in both studies, less than 4% of cases and controls approached for interview refused to participate.

Cases were 5984 women aged 22–74 years (median age 54 years) with incident (i.e. diagnosed within the year before interview), histologically confirmed breast cancer, admitted to the major teaching and general hospitals in the areas under surveillance.

Controls were 5504 women aged 15–74 years (median age 55 years), residing in the same geographical areas and admitted to the same network of hospitals where cases had been identified, for a wide spectrum of acute conditions unrelated to known or potential risk factors for breast cancer. Of these, 27% had traumatic conditions (mostly fractures and sprains), 32% non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 17% were admitted for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 24% for other miscellaneous illnesses, such as eye, ear, nose and throat and dental disorders. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic diseases.

Both questionnaires included information on personal characteristics and habits, anthropometric variables (self-reported adult height and weight), education and other socioeconomic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, gynaecological and obstetric data, related medical history, and history of use of oral contraceptives and hormone replacement therapy. The most recent questionnaire included more details on diet and physical activity. All interviews for cases and controls were conducted in hospital.

Data analysis

Odds ratios (ORs) of breast cancer, and the corresponding 95% confidence intervals (CI) for height were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood [43]. Three models were considered: the first (A) included terms for study/centre and quinquennia of age (10 levels); the second (B) included further terms for education ($<7/7$–$11/>11$ years), body mass index ($<23.2/23.2$–$26.5/>26.5$, approximate tertiles), age at menarche ($<13/\geq 13$ years) and parity (nulliparae/1/≥ 2 children); the third (C) included additional terms for alcohol intake ($0/>0$–$<3/>3$ drinks per day), smoking status (never/current/ex-smokers), use of oral contraceptives and hormone replacement therapy (never/ever), history of benign breast disease (no/yes) and family history of breast cancer in a first degree relative (no/yes).

RESULTS

Table 1 gives the distribution of breast cancer cases and the comparison group according to height (approximate quintiles), and the corresponding ORs derived from the three models. All the ORs were close to unity. The estimates for the highest (>165 cm) versus the lowest height quintile (<156 cm) were 1.05 after adjustment for study/centre and age, and 0.96 with further allowance for all identified potential confounding factors. Women who were ≥ 170 cm tall had an OR of 0.87 (95% CI 0.75–1.01) compared with those in the lowest quintile of height. The OR for 5 cm increment was 0.98 (95% CI 0.95–1.01).

The Spearman correlation coefficients with height were 0.11 for education, −0.11 for body mass index, 0.03 for age at menarche and −0.05 for parity (all $P<0.001$). However, the inclusion of terms for these covariates in the regression model did not change the risk estimates.

The risk of breast cancer with height in separate strata of selected covariates, including socioeconomic factors, body mass index, body weight, total alcohol intake, menstrual and reproductive factors, use of exogenous female hormones, history of benign breast disease and family history of breast cancer, i.e. the best recognised risk factors for breast cancer, is shown in Table 2. There was no significant interaction with breast cancer risk in any subgroup.

Table 1. *Distribution of* 5984 *breast cancer cases and* 5504 *controls, and corresponding odds ratios (OR) with their* 95% *confidence intervals (CI) according to height, Italy,* 1983–1994

			OR (95% CI)*		
	Breast cancers	Controls	A	B	C
Height (cm)					
<156	1171	1089	1†	1†	1†
156–159	837	724	1.08 (0.95–1.23)	1.03 (0.90–1.17)	1.00 (0.88–1.15)
160–162	1540	1424	1.01 (0.91–1.13)	0.99 (0.88–1.11)	0.98 (0.88–1.10)
163–165	1134	1090	0.98 (0.87–1.10)	0.93 (0.83–1.05)	0.92 (0.81–1.04)
≥166	1286	1169	1.05 (0.93–1.17)	0.97 (0.87–1.10)	0.96 (0.85–1.08)
	16	8			
χ^2 trend			0.0048	0.9725	1.5463
5 cm increment			1.00 (0.97–1.03)	0.98 (0.95–1.01)	0.98 (0.95–1.01)

*Estimates from multiple logistic regression equations, including terms for study/centre and age (A), plus education, body mass index, age at menarche and number of births (B), plus oral contraceptives, hormone replacement therapy, history of benign breast disease, family history of breast cancer, alcohol intake and smoking status (C). †Reference category.

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer cases in various strata of height according to selected covariates, Italy, 1983–1994

	(OR(95% CI))*					
Height	156–159 cm	160–162 cm	163–165 cm	> 165 cm	χ^2 trend	*P*
Study						
1	1.1 (0.9–1.3)	1.0 (0.9–1.2)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	0.75	0.39
2	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.10	0.75
Age (years)						
< 45	1.0 (0.7–1.3)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	0.9 (0.7–1.2)	1.76	0.18
45–54	1.2 (0.9–1.6)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	1.2 (1.0–1.5)	0.70	0.40
55–64	1.0 (0.8–1.3)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	1.52	0.22
≥ 65	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	0.9 (0.7–1.1)	0.12	0.73
Education (years)						
< 7	1.1 (0.9–1.3)	1.0 (0.9–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	2.16	0.14
7–11	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	0.06	0.80
≥ 12	1.0 (0.7–1.4)	1.0 (0.8–1.4)	0.9 (0.6–1.2)	1.1 (0.8–1.5)	0.08	0.78
Body mass index (kg/m^2)						
< 23.2	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.05	0.83
23.2–26.5	1.0 (0.8–1.2)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	1.78	0.18
> 26.5	1.1 (0.9–1.4)	1.0 (0.9–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.00	0.98
Body weight (kg)						
< 59	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.8 (0.6–1.0)	1.0 (0.8–1.3)	0.42	0.51
59–67	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.9 (0.7–1.3)	0.45	0.50
> 67	1.2 (0.9–1.5)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.2)	1.19	0.28
Total alcohol intake (drinks/day)						
Abstainers	1.0 (0.8–1.3)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.73	0.39
< 1.36	1.0 (0.8–1.2)	1.0 (0.9–1.3)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	0.25	0.62
≥ 1.36	1.1 (0.9–1.4)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.33	0.57
Age at menarche (years)						
< 13	1.2 (1.0–1.4)	1.1 (0.9–1.3)	0.9 (0.8–1.1)	1.0 (0.9–1.3)	0.25	0.62
≥ 13	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.71	0.40
Menopausal status						
Pre + peri	1.1 (0.9–1.4)	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.9 (0.8–1.1)	2.86	0.09
Post	1.0 (0.8–1.1)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.8–1.1)	0.01	0.94
Age at menopause (years)						
< 50	1.0 (0.8–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.56	0.45
≥ 50	0.9 (0.7–1.1)	1.1 (0.9–1.3)	0.9 (0.8–1.1)	0.9 (0.7–1.1)	0.79	0.37
Number of births						
0	0.9 (0.7–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.3)	0.9 (0.7–1.2)	0.41	0.52
1	0.9 (0.7–1.2)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	0.38	0.54
≥ 2	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.18	0.68
Age at first birth (years)						
< 20	1.4 (0.8–2.4)	1.1 (0.7–1.7)	0.9 (0.5–1.5)	1.2 (0.7–2.0)	0.00	0.95
20–24	1.2 (0.9–1.5)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.0 (0.9–1.3)	0.01	0.92
25–29	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.8 (0.6–1.0)	0.9 (0.8–1.2)	0.95	0.33
≥ 30	1.0 (0.7–1.4)	1.0 (0.8–1.4)	1.2 (0.8–1.6)	1.0 (0.8–1.4)	0.24	0.63
Oral contraceptive use						
Never	1.0 (0.9–1.1)	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	0.72	0.39
Ever	1.2 (0.8–1.7)	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.0 (0.7–1.4)	0.44	0.51
Hormone replacement therapy use						
Never	1.0 (0.9–1.2)	1.0 (0.9–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	1.83	0.18
Ever	1.0 (0.6–1.8)	1.0 (0.6–1.7)	1.1 (0.7–1.8)	1.2 (0.7–2.1)	0.64	0.42
History of benign breast disease						
No	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	2.01	0.16
Yes	1.8 (1.2–2.8)	1.2 (0.9–1.7)	1.0 (0.7–1.5)	1.5 (1.0–2.1)	0.48	0.49
Family history of breast cancer						
No	1.0 (0.9–1.2)	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	0.61	0.44
Yes	0.8 (0.5–1.3)	0.8 (0.5–1.3)	0.7 (0.4–1.1)	0.7 (0.5–1.2)	2.03	0.15

*Estimates from multiple logistic regression equations, including terms for study/centre, age, education, body mass index, age at menarche and number of births. The reference category consisted of women with the lowest height (< 156 cm).

DISCUSSION

The results in this study, based on a large number of cases, indicate no association between adult height and breast cancer risk.

Some nutrient and caloric restriction was frequent in Italy, mainly before and during the second world war, which corresponded to the childhood and/or adolescence of women aged over 60 years in the 1990s, and among people with lower levels of education. However, we found no association with height in the overall dataset, nor differences across strata of age, education, or other covariates of interest. Indeed, positive associations between height and breast cancer did not selectively emerge in those countries where energy intake might have been limited during growth, and the largest increases in risk were observed in studies from the U.S.A. [18, 44].

Previous findings based on part of this dataset showed a significant association between body mass index and breast cancer risk in post-, but not in premenopausal women [39], and no meaningful relationship with breast size [45]. Both factors were not significantly correlated with height (Spearman correlation coefficients were 0.09 for height with body mass index and 0.06 for height with breast size). The inclusion of terms for these covariates reduced the risk estimates for height; however, height had no influence on breast cancer risk when several strata of body mass index were considered. Likewise, the introduction of weight into the model did not materially modify any of the estimates for height (OR for 5 cm increment 0.97).

The limitations and strengths of this study are common to other hospital-based case–control studies [46]. Although this study was not population-based, cases were identified in the major teaching and general hospitals of the area under surveillance; only acute conditions, unrelated to known or potential risk factors for breast cancer in this population, were included in the comparison group and the participation of cases and controls was almost complete. A potentially more important limitation lies in the fact that measures of height were not validated, and self-reported height is known to be somewhat overestimated [47, 48], although there is no reason to assume different recall on the basis of disease status. The similar interview settings provide further reassurance against potential information bias. The results were similar in the two studies, and the potential confounding effect of several covariates was allowed for in the analysis, but there was no material modification of the risk estimates.

Thus, this large dataset provides evidence that height is not a major determinant of breast cancer risk in Italian women, even in strata of major selected covariates. Minor effects remain possible, but are unlikely to be of material influence or public health relevance in this population.

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