A Prospective Study of Body Size in Different Periods of Life and Risk of Premenopausal Breast Cancer

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Abstract

The prevalence of obesity at all ages is increasing epidemically worldwide. Information on the association between premenopausal breast cancer and body size during childhood and teenage years is scarce. In 1991 to 1992, a prospective cohort study was assembled in Norway and Sweden. We included in the analysis presented here 99,717 premenopausal women. During the follow-up period, which ended in December 1999, 733 of these women developed a primary invasive breast cancer. Overweight and obesity [body mass index (BMI) > 25 kg/m^2] at enrolment was associated with a decreased risk of premenopausal breast cancer (P for linear trend = 0.007). Apparent associations between perceived body shape at age 7 and BMI at age 18, with heavier builds at both ages seemingly being protective for premenopausal breast cancer risk, lost their statistical significance after adjustment for BMI at cohort enrolment. Body size at age 7 was correlated with BMI at age 18 (r = 0.43); BMI at age 18 was correlated with adult BMI (r = 0.48). Changes in body size from age 7 or 18 to adulthood did not affect *per se* risk of premenopausal breast cancer risk. Height was related to risk, with a statistically significantly 30% reduced risk only in women shorter than 160 cm as compared with taller ones. The decreased risk of premenopausal breast cancer was observed in overweight and obese women without, but not in those with, a family history of breast cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(7):1121–7)

Introduction

The prevalence of overweight and obesity is increasing rapidly worldwide and affects more than one third of the population in certain countries such as the United States (1). Hence, any health outcome related to obesity may have a substantial impact on public health. One such outcome is breast cancer, currently the most common malignancy in women worldwide (2). A causal association between obesity and breast cancer incidence has been convincingly demonstrated in numerous epidemiologic investigations (1). More recent research has also revealed a complicated dual effect of obesity: a risk reduction before menopause and a risk increase after menopause (1). The hormonal mechanisms by which obesity affects breast cancer postmenopausally are increasingly well understood (1). In contrast, much less is known and understood about the role of obesity in younger women. Amenorrhea has been proposed as a possible mechanism by which obesity protects from breast cancer (1), but this hypothesis remains to be adequately tested empirically. Moreover, the possible role of obesity in childhood and adolescence is not fully known nor are the consequences of weight change during the early phases of adult life.

We present here results from a large, population-based cohort study carried out among premenopausal women in Norway and Sweden in relation to body size in three different periods of life (age 7, age 18, and adulthood) and breast cancer risk.

Subjects and Methods

Study Population. As described previously in detail (3, 4), the cohort was enrolled during 1991 and 1992. In Norway, a sample of 100,000 women born between 1943 and 1957 (34 to 49 years old) was randomly selected from the Central Population Register. This register records the addresses of all persons alive and residing in the country and the dates of death or migration to or from Norway since 1960. In Sweden, a sample of 96,000 women born between 1942 and 1962 (30 to 49 years old) and residing in the Uppsala Health Care Region (comprising about one sixth of the Swedish population) was randomly selected from the Swedish Central Population Registry at Statistics Sweden. In both Norway and Sweden, each individual is identified by their unique personal national registration

Received 11/25/03; revised 2/11/04; accepted 3/1/04.

Grant support: In Norway, the survey was supported by grants from the National Cancer Institute (grant CA 52449), the Norwegian Cancer Society (grant DNK 90050), and the Aakre Foundation. In Sweden, the survey was supported by the Swedish Council for Planning and Coordination of Research, Swedish Cancer Society, Organon, Pharmacia, Medical Products Agency, and Schering-Plough.
Dr. Weiderpass is supported by a grant from the Swedish Cancer Society.

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number, which encodes information on date of birth and gender (5).

A letter of invitation to participate in the study and a health survey questionnaire was sent to all women. In Norway, the questionnaire was mailed to 10 subgroups at regular intervals. In Sweden, two mailings were done: one in 1991 and one in 1992. The questions relevant to the analysis presented here were identical in the two countries. This common set of questions included a detailed assessment of body size and shape in different periods of life, oral contraceptive use, reproductive history, prevalent diseases, history of breast cancer in the mother and sister(s), and other lifestyle habits. To facilitate recall, a color brochure with pictures of almost all contraceptive pill packages ever sold in Norway and Sweden was sent to all women together with the letter of invitation.

Measurement of Exposure. Information about anthropometric measures is based on the questionnaire administered at cohort enrolment. Women were asked about their perceived body shape at age 7 as compared with other girls of the same age. They classified themselves as very thin, thin, average, fat, and very fat. They were also asked about their weight at age 18 and at study enrolment and their adult height (cm). Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). We calculated BMI at age 18 and at study enrolment. We created an indicator variable on the difference in body size between age 7 and adulthood with the following categories:

(a) remained thin: was thin/very thin at age 7 and had a BMI < 20 kg/m^2 at both age 18 and 1 year before interview;
(b) decreased weight: had average body shape at age 7 and had a BMI < 20 kg/m^2 at age 18 or 1 year before interview or was fat/very fat at age 7 and had a BMI < 25 kg/m^2 at age 18 or 1 year before interview;
(c) remained at an average body weight: had average body shape at age 7 and a BMI between 20 and 25 kg/m^2 at age 18 and 1 year before interview;
(d) increased weight: was thin/very thin at age 7 and had a BMI ≥ 20 kg/m^2 at age 18 or 1 year before interview or had average body size at age 7 and a BMI > 25 kg/m^2 at age 18 or 1 year before interview; and
(e) remained fat: was over the average in body shape, was fat/very fat at age 7, and had a BMI > 25 kg/m^2 at age 18 and/or 1 year before interview.

We also calculated the changes in BMI between age 18 and entry to the study and classified this difference (BMI units) as decreased, increased up to 1.4 units, increased 1.5 to 4.0 units, and increased >4.0 units.

Information on menopausal status was obtained from the questionnaire. We have no information about menopausal status after start of follow-up. Only women who reported a natural menopause or a bilateral oophorectomy at cohort enrolment were considered as postmenopausal. All other women were considered as premenopausal, regardless of hysterectomy or use of hormonal replacement therapy until age 50 (mean age of natural menopause in these populations), and censored from all analyses. Only breast cancers diagnosed before age 50 were considered as relevant outcome in the present analysis.

Information on self-perceived physical activity levels at age 14, age 30, and at cohort enrolment was collected as scores from 1 (lowest level of physical activity) to 5 (highest level of physical activity). Subsequently, the variables were compiled into three levels for each age period: low (scores 1 and 2), middle (scores 3 and 4), and high (score 5).

To identify women who had possible anovulatory cycles, we asked how many years after menarche their periods became regular. The answers were classified as <1 year, 1 to 3 years, >3 years, never, and I do not know. We considered those who answered ''never'' as having irregular menstrual cycles. We also asked women if they had ever tried to become pregnant for a period of >1 year without succeeding and considered those who answered ''yes'' as probably having an infertility problem.

Follow-up. Follow-up was performed through links between the cohort data set and various population-based registries. This was possible by use of the national registration numbers present in the cohort data set and in all national registers. We obtained information on the date of death for deceased persons from the death registers and on the date of emigration from the registers of population migration. The national cancer registers, established in the 1950s in both countries, provided data on prevalent cancer cases at cohort enrolment and incident cancers diagnosed in cohort during follow-up. These registries are estimated to be almost complete (6, 7).

The start of follow-up was defined by the return of the questionnaire in 1991 or 1992. The follow-up ended on December 31, 1999, at emigration, death, or primary breast cancer diagnosis, whichever occurred first. Of the 100,000 invited women in Norway, 57,582 (57.6%) returned a completed questionnaire as did 49,259 (51.3%) of the 96,000 invited women in Sweden. Thus, the overall crude participation rate was 54.5% (106,841 of 196,000). During follow-up, 789 women emigrated and 1,360 died.

For the analysis presented here, we further excluded 15 women who were dead or had emigrated before we started follow-up, 1,663 women who had been reported as having an invasive cancer before study enrolment, 237 women without any information on weight during their lifetime, and 5,209 women reporting being postmenopausal (see criteria above) at cohort enrolment. In summary, 99,717 women were included altogether in the analysis presented here.

Statistical Methods. We calculated relative hazards using the Cox proportional hazard models (8), considering anthropometric measures as the independent variable and premenopausal breast cancer as the dependent variable. We interpreted relative hazards as estimates of relative risks (RR) with 95% confidence intervals (CI). The comparison group is specified in each table.

We kept the following covariables in the final multivariate models: age at cohort enrolment (as a continuous variable in years), a combined variable with parity (0, 1, 2, or ≥3 children) and age at first birth (<21, 22 to 24, or ≥25 years), age at menarche (as a continuous variable), use of oral contraceptives (current, former, or never used

at cohort entry), history of breast cancer in the mother or sister(s), and total duration of breast-feeding (as a continuous variable in months). Because these variables were all repeatedly reported as being associated with premenopausal breast cancer (9), we kept them in the models although they did not affect the association between anthropometric measures and breast cancer in our data. In addition, we included the country of residence (Norway/Sweden) in multivariate models because breast cancer incidence varies slightly. The variables on physical activity were not kept in the final model because they did not alter risk estimates meaningfully but in fact worsened model fitting.

We analyzed BMI at cohort enrolment and breast cancer risk both with inclusion of all women and following exclusion of women who probably had long periods of anovulation as indicated by irregular menses, infertility, or both. We did so because long periods of anovulation might indicate polycystic ovarian syndrome, a possible risk factor for breast cancer, which is also associated with obesity (10, 11).

Possible interactions were evaluated by including appropriate product terms in the models. The responsible Data Inspection Boards and Ethical Committees in both countries approved the study design, and all women gave their informed consent to participate in the study.

Results

Characteristics of the study population are given in Table 1. During follow-up, a total of 733 incident breast cancers occurred among women who were premenopausal at entry and <50 years old at breast cancer diagnosis. The mean age at study entry was 40.1 years both for the study population and for the breast cancer cases. The mean age at diagnosis of breast cancer was 44.7 years.

Characteristics of the study participants according to body size and shape are given in Table 2. The mean height and weight of the women who developed breast cancer and those who did not were rather similar at cohort enrolment. Almost 9,000 (9.2%) women considered themselves to have been either fat or very fat at age 7. Of them, 1,716 (1.8%) were still overweight or obese until cohort enrolment (with BMI $\geq$ 25 kg/m^2). The prevalence of overweight or obesity (BMI $\geq$ 25 kg/m^2) increased from 4.9% (n = 4,531) at age 18 to 22.7% (n = 22,018) at cohort enrolment. During the same period, over 24,000 (26.1%) women increased their BMI by $\geq$4 units. Body size at age 7 was moderately correlated with BMI at age 18 (r = 0.43) and weakly correlated with BMI at cohort enrolment (r = 0.26). BMI at age 18 was moderately correlated with BMI at cohort enrolment (r = 0.48).

Women who considered themselves fat/very fat at age 7 had a lower risk of premenopausal breast cancer of about 30% (RR 0.69, 95% CI 0.50-0.93) compared with women of average size (Table 3). However, after including a term for BMI at cohort enrolment in the model, the decrease in risk was no longer statistically significant (RR 0.73, 95% CI 0.53-1.01; P for trend = 0.49). Likewise, women with BMI $\geq$ 25 kg/m^2 at age 18 were at lower breast cancer risk (RR 0.74, 95% CI 0.59-0.91) as compared with leaner

Table 1. Characteristics of the Norwegian and Swedish Women's Lifestyle and Health Cohort Study and of the incident cases of breast cancer during follow-up until the end of 1999

Characteristics	Norway	Sweden	Total
No. of women	53,448	46,269	99,717
Age (y) at cohort entry, mean (range)	40.9 (34-49)	39.3 (30-49)	40.1
Person-years of follow-up until outcome or censoring	360,801	311,634	672,436
No. of women with invasive breast cancer diagnosed before age 50 (premenopausal)	426	307	733
Age (y) at diagnosis of breast cancer (diagnosed before age 50), mean (range)	44.8 (36-50)	44.4 (30-50)	44.7

Table 2. Body size and shape in different periods of life in the Women's Lifestyle and Health Study

Characteristics	Study Population, No. (%)	Breast Cancer Cases, No. (%)
Perceived body shape at age 7		
Very thin	11,272 (11.5)	92 (12.9)
Thin	23,042 (23.6)	164 (23.0)
Average	54,364 (55.7)	411 (57.6)
Fat/very fat	8,997 (9.2)	46 (6.5)
Mean (SD) adult height	166.3 (5.7)	167.0 (5.6)
BMI (kg/m^2) at age 18		
<20	41,091 (44.2)	330 (47.9)
20-24.9	47,329 (50.9)	327 (47.5)
≥25	4,531 (4.9)	32 (4.6)
Mean (SD) weight at cohort enrolment	64.1 (10.3)	63.4 (10.1)
BMI (kg/m^2) at cohort enrolment		
<20	13,494 (13.9)	123 (17.2)
20-24.9	61,474 (63.4)	466 (65.1)
25-29.9	17,411 (18.0)	104 (14.5)
≥30	4,607 (4.7)	23 (3.2)
Mean (SD) BMI at cohort enrolment	23.2 (3.5)	22.7 (3.3)
Difference in body size and shape between age 7 and adulthood*		
Remained thin	6,260 (6.7)	54 (7.9)
Decreased weight	19,939 (21.3)	156 (22.6)
Remained at average weight	22,464 (24.0)	178 (25.8)
Increased weight	43,153 (46.2)	294 (42.7)
Remained fat	1,716 (1.8)	7 (1.0)
Adult BMI change (difference between age 18 and 1 year before recruitment)		
Decreased	17,623 (19.2)	140 (20.6)
Increased 0-1.4	16,217 (17.6)	131 (19.3)
Increased 1.5-4.0	34,158 (37.1)	259 (38.1)
Increased >4.0	24,047 (26.1)	150 (22.0)

Table 3. Risk of premenopausal breast cancer according to body size and shape

Characteristics	No. of Cases/ Non-cases	Age-Adjusted RR	95% CI	Multivariate RR*	95% CI	Multivariate RR†	95% CI
Perceived body shape at age 7							
Very thin	92/11,180	1.13	0.90-1.41	1.13	0.90-1.43	1.08	0.85-1.38
Thin	164/22,878	0.94	0.79-1.13	0.94	0.78-1.13	0.90	0.74-1.09
Average	411/54,364	1.0 (reference)	—	1.0 (reference)	—	1.0 (reference)	—
Fat/very fat	46/8,951	0.69	0.51-0.93	0.69	0.50-0.93	0.73	0.53-1.01
P for linear trend		0.10		0.11		0.49	
BMI (kg/m^2) at age 18							
<20	330/40,761	1.07	0.92-1.25	1.06	0.90-1.24	1.03	0.87-1.21
20-24.9	327/47,002	1.0 (reference)	—	1.0 (reference)	—	1.0 (reference)	—
≥25	32/4,499	0.75	0.61-0.92	0.74	0.59-0.91	0.90	0.66-1.24
P for linear trend		0.004		0.004		0.60	
BMI at age 18 per unit increase		0.96	0.93-0.99	0.96	0.93-0.99	0.98	0.95-1.02
BMI (kg/m^2) at cohort enrolment							
<20	123/13,371	1.22	1.00-1.49	1.20	0.98-1.47	1.16	0.94-1.44
20-24.9	466/61,008	1.0 (reference)	—	1.0 (reference)	—	1.0 (reference)	—
25-29.9	104/17,307	0.80	0.65-0.99	0.79	0.63-0.99	0.82	0.65-1.04
≥30	23/4,584	0.68	0.45-1.04	0.62	0.40-0.97	0.66	0.40-1.07
P for linear trend		0.0003		0.0003		0.007	
BMI at cohort enrolment per unit increase		0.96	0.94-0.98	0.96	0.94-0.98	0.96	0.94-0.99
Adult height (cm)							
<160	54/10,258	0.67	0.50-0.90	0.70	0.50-0.93	0.72	0.54-0.97
160-164	186/26,647	0.89	0.73-1.07	0.88	0.72-1.06	0.89	0.73-1.08
165-169	251/31,694	1.0	Reference	1.0	Reference	1.0	Reference
170-174	180/21,860	1.05	0.86-1.27	0.99	0.81-1.20	1.00	0.82-1.22
≥175	57/7,258	1.01	0.76-1.35	0.90	0.67-1.21	0.91	0.67-1.23
P for trend		0.003		0.02		0.03	

*Multivariate adjustment for age at enrolment, parity, age at first birth, oral contraceptive use, age at menarche, family history of breast cancer, total duration of breast-feeding, and country of residence.
†Same model as above, with additional covariates: (a) adult BMI in the analysis of perceived body shape at age 7, BMI at age 18, and height and (b) body shape at age 7 and BMI at age 18 in the analysis of adult BMI.

women, but the association was attenuated after adjustment for BMI at cohort enrolment (RR 0.90, 95% CI 0.66-1.24).

BMI at cohort enrolment was inversely associated with risk of breast cancer in premenopausal women (multivariate RR 0.62, 95% CI 0.40-0.97; *P* for trend = 0.0003). We found ~2-fold gradient in risk between the lowest and the highest categories of BMI, and women with a BMI ≥ 30 kg/m^2 at enrolment had a 38% lower RR compared with women with a BMI between 20 and 25 kg/m^2. In a multivariate model having BMI at enrolment adjusted for measures of body size at age 7 and BMI at age 18, the risk reduction among women who were fat/very fat was slightly attenuated (RR 0.66, 95% CI 0.40-1.07; *P* for trend = 0.007). When BMI at cohort enrolment was modeled as a continuous variable, each one-unit increment of BMI reduced breast cancer risk by 4%.

BMI at cohort enrolment was positively associated with a history of irregular menses ($P < 0.001$) but not with evidence of infertility ($P = 0.95$). We repeated the analyses on adult BMI (Table 3) after the exclusion of 3,051 women with irregular menses (of which 19 developed breast cancer during follow-up), 3,561 women with infertility (36 developed breast cancer), and 233 women with both irregular menses and infertility (2 developed breast cancer). The risk estimates were largely identical: in the full multivariate model, women who were obese had RR = 0.65 (95% CI 0.40-1.07) compared with those who had a BMI = 20 to 25 kg/m^2. When BMI was modeled as a continuous variable, risk reduction per unit increase was still 4% (95% CI 0.94-0.99).

Women taller than 160 cm had a 30% increased breast cancer risk as compared with shorter women (Table 3). However, there was no evidence of a linear association between height and premenopausal breast cancer (RR 1.02, 95% CI 1.00-1.03 for increase in 1 cm height).

We did a stratified analysis to further clarify whether body shape during different periods of life—and adult height—could mutually confound or modify the effects on breast cancer risk (Table 4). We found no clear evidence of significant interaction between these characteristics. The most salient finding in this analysis was the consistently reduced risk among women who were overweight or obese (BMI ≥ 25 kg/m^2) at cohort entry, particularly among those reporting being fat/very fat during childhood, and some indication—although not statistically significant—of a reduced risk among women who were fat/very fat at childhood (Table 4). Among tall women (measuring ≥170 cm), there was no significant effect of BMI on breast cancer risk, whereas in short women (<162 cm), the risk reduction was clearest in heavy women (BMI ≥ 25 kg/m^2; Table 4).

Table 4. Risk of premenopausal breast cancer according to body size at enrolment stratified by perceived body shape at age 7 and adult height

	BMI (kg/m^2) at Cohort Enrolment								
	<20			20-24.9			≥25		
	No. of Cases/ Non-cases	Multivariate RR*	95% CI	No. of Cases/ Non-cases	Multivariate RR*	95% CI	No. of Cases/ Non-cases	Multivariate RR*	95% CI
Body shape in childhood									
Very thin/thin	62/7,702	1.06	0.80-1.41	162/20,841	1.03	0.85-1.26	26/4,641	0.75	0.49-1.14
Average	56/4,972	1.44	1.08-1.94	270/35,062	1.0 (reference)		77/1,2447	0.82	0.63-1.06
Fat/very fat	2/385	0.67	0.17-2.70	22/3,893	0.75	0.49-1.17	20/4,324	0.60	0.37-0.95
P for interaction = 0.30									
Adult height (cm)									
≤161	18/2,332	0.96	0.58-1.60	77/11,661	0.87	0.68-1.15	22/4,906	0.59	0.39-0.95
162-169	73/7,056	1.30	0.99-1.72	230/30,691	1.0 (reference)		62/10,986	0.75	0.57-1.01
≥170	32/3,966	1.00	0.68-1.49	159/18,669	1.09	0.87-1.32	43/6,003	0.84	0.61-1.22
P for interaction = 0.29									

*Multivariate adjustment for age at enrolment, parity, age at first birth, oral contraceptive use, age at menarche, family history of breast cancer, total duration of breast-feeding, and country of residence.

Next, we analyzed breast cancer risk in relation to changes in body size and shape over time. After adjusting for BMI at cohort enrolment, we found no evidence of associations between changes in perceived body shape in childhood to body shape in adulthood or changes in BMI from age 18 to cohort enrolment. Weight loss since age 18 was not associated with any significant change in breast cancer risk (Table 5).

There were 4,885 women in the cohort who reported having a family history of breast cancer (mother and/or a sister affected). Among these women, 72 developed breast cancer during follow-up. The decreased risk of breast cancer in premenopausal women with high a BMI (≥30 kg/m^2) was limited to those without any family history of breast cancer. No such reduction was seen in obese women with a family history of breast cancer in first-degree relatives, although this stratified analysis was hampered by small numbers (low statistical power; Table 6).

Discussion

In this large prospective study, we found evidence of an inverse association between adult BMI and risk of premenopausal breast cancer. Apparent associations between perceived body shape at age 7 and BMI at age 18 and risk, with heavier builds at both ages seemingly being protective, lost their statistical significance after adjustment for adult BMI. Body size at age 18 was moderately correlated with BMI in adulthood. Changes in body size from age 7 or 18 to adulthood did not affect the premenopausal breast cancer risk once BMI at cohort enrolment was taken into account. Height was related to risk in a nonlinear fashion, with a statistically significantly reduced risk only in women shorter than 160 cm as compared with those of normal or tall height. We found weak evidence that the effect of adult BMI was stronger in women who were short and had no family history of breast cancer.

Table 5. Risk of premenopausal breast cancer according to modifications in body size and shape in different periods of life

Characteristics	No. of Cases/ Non-cases	Age-Adjusted RR	95% CI	Multivariate RR*	95% CI	Multivariate RR†	95% CI
Difference in body size and shape between age 7 and adulthood (age 18 and age at cohort enrolment)							
Remained thin	54/6,206	1.09	0.81-1.47	1.07	0.79-1.44	0.96	0.70-1.32
Decreased weight	156/19,783	0.95	0.79-1.14	0.93	0.77-1.13	0.94	0.77-1.13
Remained at an average weight	178/22,286	1.0 (reference)	—	1.0 (reference)	—	1.0 (reference)	—
Increased weight	294/42,859	0.87	0.73-1.03	0.87	0.73-1.03	0.97	0.80-1.17
Remained fat	7/1,709	0.61	0.29-1.28	0.60	0.29-1.28	0.78	0.36-1.68
P for linear trend		0.03		0.06		0.94	
Adult BMI change (difference between age 18 and at recruitment)							
Decreased in BMI	140/17,483	0.91	0.71-1.16	0.90	0.70-1.15	0.89	0.69-1.14
Increased 0-1.4	131/16,086	1.0 (reference)	—	1.0 (reference)	—	1.0 (reference)	—
Increased 1.5-4.0	259/33,899	0.90	0.74-1.10	0.91	0.75-1.11	0.98	0.80-1.20
Increased >4.0	150/23,897	0.74	0.59-0.92	0.76	0.60-0.95	0.95	0.72-1.25
P for linear trend		0.04		0.07		0.37	

*Multivariate adjustment for age at enrolment, parity, age at first birth, oral contraceptive use, age at menarche, family history of breast cancer, total duration of breast-feeding, and country of residence.
†Same model as above, adding BMI at enrolment as an additional covariate.

Table 6. Risk of premenopausal breast cancer in women with and without family history of breast cancer according to body size and shape at cohort enrolment

	Family History of Breast Cancer			No Family History of Breast Cancer		
	No. of Cases/ Non-cases	Multivariate RR*	95% CI	No. of Cases/ Non-cases	Multivariate RR*	95% CI
BMI (kg/m^2) at cohort enrolment						
<20	14/616	1.40	0.76-2.57	109/12,738	1.17	0.95-1.46
20-24.9	46/2,941	1.0 (reference)	—	420/58,080	1.0 (reference)	—
25-29.9	11/798	0.92	0.47-1.79	93/16,513	0.77	0.61-0.98
≥30	4/226	0.96	0.30-3.13	19/4,358	0.58	0.36-0.95
P for linear trend		0.37			0.0004	
P for interaction between BMI and presence of family history of breast cancer = 0.40						

*Multivariate adjustment for age at enrolment, parity, age at first birth, oral contraceptive use, age at menarche, family history of breast cancer, total duration of breast-feeding, and country of residence.

Our finding of a protective effect of adult BMI on premenopausal breast cancer risk is in accordance with a growing body of evidence from numerous investigations (1). In a recent analysis of pooled data from prospective cohort studies (12), women with a BMI ≥ 31 kg/m^2 had a RR of premenopausal breast cancer of 0.54 (95% CI 0.34-0.85) as compared with those with a BMI < 21 kg/m^2. In our study, this association was closely similar and seemed to stand independent of body size at an early age. We had no opportunity to explore whether perinatal anthropometry—relevant because birth weight is a potential breast cancer risk factor (13, 14), which has been demonstrated to carry a U-shaped relationship with adult BMI (15)—confounded the relationship. The mechanisms linking adult obesity to premenopausal breast cancer are not fully known (1). Although an increased frequency of anovulatory menstrual cycles has been repeatedly invoked, empirical support for this theory is scant (1, 16). In our data, the association with adult BMI was not influenced by the exclusion of women who reported irregular menses and/or infertility. However, even when women are ovulating regularly, obesity may be associated with luteal insufficiency as shown by decreased levels of progestins or other changes in the sex steroid profile (16). The suggested effect modifiers of the association between adult BMI and risk in our data—height and family history of breast cancer—awaits confirmation or rejection and biological interpretation in future studies.

In two previous cohort studies, BMI during adolescence and young adulthood was associated with a 25% to 40% decrease in premenopausal breast cancer risk (17, 18). In case-control studies, heavier weight during young adulthood was associated with 20% to 30% decrease in premenopausal breast cancer (19-24), increased risk in one study (25), and no association in other studies (26, 27). Data on the influence of childhood obesity on premenopausal breast cancer risk are scarce, and an association is far from established (1). In the Nurses' Health Study, recalled body fatness at age 10 was associated with a decreased risk of breast cancer (28). In contrast to our findings, this relationship remained statistically significant even after adjustment for body fatness at age 30.

In a recent case-control study in twins, the risk of premenopausal breast cancer was increased for women who were less obese than their twin at age 10 among dizygotic twins but not among monozygotic twins (29). This indicates that the potential impact of childhood obesity operates through environmental rather than genetic pathways. Excessive prepubertal body fat might slow adolescent physical growth (28), allowing more time for repair of DNA damage occurring in the highly proliferating adolescent breast epithelium (30). Data from a study by Li et al. (31) suggest that risk is lower among women who reach their maximum adult height at a later age independently of age at menarche, supporting the notion that slow physical maturation might be beneficial with regard to breast cancer development.

In the limited number of studies of premenopausal breast cancer risk, adult weight gain was associated with a 30% reduction in risk (21-23). The apparent inverse association in our data was, however, completely explained by BMI at enrolment.

As reported previously by others (32, 33), we also found height to be positively associated with increased breast cancer risk, albeit in a nonlinear fashion. Possible mechanisms suggested to explain this association include energy intake (because in rodents, energy restriction has been associated with decreased mammary tumor rates) and circulating insulin-like growth factor-I levels during childhood, both associated with adult height (9).

Our study presents strengths and limitations. The strengths include those inherent to a prospective cohort study such as lack of recall and selection bias (34).

Furthermore, we collected detailed information on anthropometric measure during different periods of life and on potential confounders. Because we used self-administered questionnaires to assess body size in different periods of life, exposure measurement error or recall error could be substantial especially concerning childhood body build. However, if exposure measurement error occurred, it should be nondifferential with regard to case status.

In summary, body size at childhood and early adulthood as well as weight gain are related to premenopausal breast cancer risk chiefly as predictors of adult body size (18). In contrast, BMI in adulthood is one of the strongest predictors of premenopausal breast cancer thus far established and one of the few that are potentially modifiable. Nevertheless, no public heath message can be meaningfully founded on this association, because overweight and obesity increase overall mortality even before menopause and also increase the

risk of breast cancer as women become postmenopausal. Hence, the main scientific challenge now is to understand the biological mechanisms by which obesity prevents malignant transformation of breast tissue in younger women. Our data do not support the hypothesis that anovulation is likely to play an important role in this process.

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Cancer Epidemiol Biomarkers Prev 2004;13:1121-1127.