



Prospective Study of Relative Weight and Risk of Breast Cancer: The Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987-1989

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Despite extensive research on obesity and breast cancer in recent decades, inconsistencies in the literature exist. The authors examined prospectively the relation between adult relative weight (weight (kg)/height (m)^{1.5}) and breast cancer risk in a cohort of 54,896 women aged 31-89 years who had previously participated in the Breast Cancer Detection Demonstration Project. During a mean follow-up period of 7 years, 226 of the premenopausal women and 1,198 of the postmenopausal women developed breast cancer. Analysis was performed using Cox proportional hazards regression methods with age as the underlying time variable and adjusted for the effects of potential confounders. Among postmenopausal women, the risk of breast cancer increased with increasing relative weight ($p < 0.05$ for trend); relative risk for the highest compared with the lowest quintile for relative weight was 1.3 (95% confidence interval (CI) 1.1-1.6). This association was modified by age at diagnosis, with relative risks of 1.1 (95% CI 0.8-1.4), 1.2 (95% CI 0.8-1.7), and 1.8 (95% CI 1.3-2.5), respectively, for women aged <60 , 60-64, and ≥ 65 years. The higher risk of breast cancer among the older and overweight women was largely confined to women whose weights were measured during the postmenopausal but not the premenopausal period. This risk pattern was observed among the naturally menopausal women, but was also apparent in the smaller group of women with bilateral oophorectomy or hysterectomy with one ovary retained. Among premenopausal women, adult relative weight was not associated with breast cancer risk. These findings suggest that the inconsistencies in the literature on obesity and breast cancer may be due in part to the differing age distribution of the populations studied. The authors conclude that prevention of obesity throughout adulthood, particularly after menopause, may help reduce breast cancer among older women. *Am J Epidemiol* 1996;143:985-95.

age factors; body weight; breast neoplasms; obesity; prospective studies; relative weight

The relation between obesity and the risk of breast cancer has been the subject of numerous investigations during recent decades (1). Obesity, as assessed by relative weight or the various indices of weight adjusted for height, has been associated with decreased breast cancer risk among younger or premenopausal women in most studies (2-12), but not all investigations (13-17). The most consistent finding has been an increase in breast cancer risk with increasing relative weight among older or postmenopausal women (2, 10, 18-22). However, this was not observed in two recent prospective studies in a relatively small group of postmenopausal women (13) and in a group of postmeno-

pausal women who were predominantly less than age 60 years (7). Thus, in spite of the large number of published data, the relation between obesity and the risk of breast cancer is still not clearly established.

In the current analysis, the effect of adult relative weight on the risk of breast cancer was examined in a prospective cohort of 54,896 women who had previously participated in the Breast Cancer Detection Demonstration Project (23). Due to the large sample size, and the availability of information on ages at menopause and at weight/height measurement, the cohort provided an opportunity for detailed examination of factors modifying the relative weight-breast cancer risk relation.

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Abbreviation: CI, confidence interval.

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MATERIALS AND METHODS

The Breast Cancer Detection Demonstration Project Follow-up Study Cohort

The study subjects are past participants in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening program conducted between

1973 and 1981 at 29 centers throughout the United States (23). In this program, which was jointly sponsored by the National Cancer Institute and the American Cancer Society, over 280,000 women received up to five annual breast cancer screenings, each consisting of a combination of physical examinations, mammography, and thermography. Beginning in 1979, a follow-up study on a subset of these women was further conducted by the National Cancer Institute. A total of 64,182 women were selected on the basis of their status at the last screening visit: women who had been diagnosed with breast cancer ($n = 4,275$) or who had nonmalignant or benign breast disease as a result of biopsies or other breast surgery performed ($n = 25,114$), and those who had been recommended by the project for biopsy or other breast surgery but did not have the procedure performed ($n = 9,628$). A sample of "normal" women who did not fall into the above three categories, and who were individually matched to those with breast cancer and benign breast disease on age and time at entry to the program, race, center, and length of participation in the program, was also selected ($n = 25,165$).

Data collection

The data used in this analysis were collected during the screening and the two completed phases of the ongoing follow-up study (figure 1). Demographic information was collected at entry into the screening program (1973–1981). The subjects' measured weight and height, and the ages at which they were measured, were obtained from the last examination performed during the screening visits. Weight was recorded to the nearest pound and was converted to kilograms, while height was recorded to the nearest inch and was converted to meters.

The first phase of the follow-up study involved the administration of a baseline interview and annual telephone interviews during the period 1979–1986. Data collected during the baseline interview included the following: family history of breast cancer in a first-degree relative; history of biopsies for benign breast

disease; use of female hormones or oral contraceptives; age at menarche; parity; age at first livebirth; date and reason for cessation of periods if no period was reported within the 3 months prior to the interview; and information on the surgical procedures of the breast and the removal of the uterus and/or ovaries. These data were updated, and vital status and change of address were ascertained in up to six annual follow-up telephone interviews. A further update, and collection of additional data on life-style factors, including smoking and alcohol use, were conducted during the second phase between 1987 and 1989 by means of a mailed questionnaire. All attempts were made to interview nonresponders to the mailed questionnaire by telephone. Extensive efforts were made throughout the study to locate women lost to follow-up, including attempted tracing through the National Center for Health Statistics National Death Index.

Analytical cohort

Of the 64,182 women selected for participation in the follow-up study, 9,286 were excluded from the analyses for the following reasons: 4,996 with first breast cancer diagnosed before the start of the follow-up, that is, at or before the baseline interview, as representing prevalent cases; 120 who had died before the baseline interview; 2,632 who had no baseline interview, and thus, were no longer followed; 105 with bilateral prophylactic mastectomy at or before the baseline interview who were no longer considered at risk of developing breast cancer; one woman who had inconsistent baseline and last interview dates; 1,310 women with missing information on weight and height; 10 who reported that they had never menstruated or had inconsistent information on cessation of periods; and 112 who reported natural or surgical menopause but had missing ages at menopause. Several women were included in one or more of the above exclusion categories. The final analytical cohort consisted of 54,896 women, with 1,424 who subsequently developed breast cancer after the baseline interview.

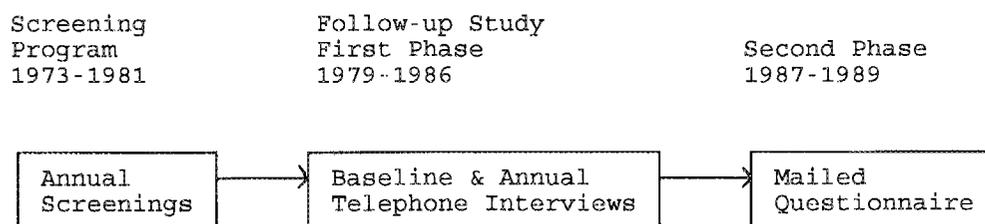


FIGURE 1. The data collection phases of the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987–1989.

Ascertainment of breast cancer cases

Self-reports of breast cancer and reports of breast cancer on death certificates and from relatives for those lost to follow-up were matched to pathology reports. Of the 1,424 breast cancer cases, 1,309 were confirmed by pathology reports. Because 91.4 percent of the self-reported cancers for which pathology reports were available were confirmed to be cancers, the 115 self-reported cancers for which no pathology reports were available were also included as cases. Self-reported cancers shown by pathology reports to be of uncertain benign or malignant condition ($n = 6$) or to be noncarcinomas ($n = 12$) were not considered as cases, and they were included with the noncases in the current analyses.

Data analyses

The breast cancer incidence of this cohort was examined by Cox proportional hazards regression methods using age as the underlying time metric (24). Subjects entered the cohort at the age attained at the date of their baseline interview, and left the cohort at the age attained at the date of their exit from the study. The case's exit date was either the date of first breast cancer diagnosis ($n = 1,384$), or, if unknown, the date of death reported on death certificate ($n = 40$). The exit date for the noncases ($n = 53,472$) was based on the following descending order of priority: 1) date of second prophylactic mastectomy for women who had their second prophylactic mastectomy during follow-up ($n = 33$); 2) date of death if they had died ($n = 1,969$); 3) date of the update interview during the second phase of the study ($n = 45,507$); 4) date of the last contact for women who did not complete the second phase interview but who had been contacted and were known to be alive ($n = 1,736$) or who were either ill or refused to be reinterviewed ($n = 4,170$); and 5) date of the last available interview for those who could not be contacted ($n = 57$). Thus, through the second phase of the study (1987-1989), the follow-up rate for this analytical cohort was 89.1 percent (48,933 out of 54,896).

The relative weight indices of weight (kg)/height (m)^{1.5} and weight (kg)/height (m)² (Quetelet index), which serve as a measure of obesity, were the primary variables of interest. Based on the distributions of the entire analytical cohort, the subjects were categorized into quintiles of the relative weight indices. Quintile-trend variables were also constructed by assigning the scores of 0-4 to the quintiles. As a measure of association with breast cancer risk, the relative risks for the four upper quintiles compared with the lowest (reference) quintile were estimated from the regression coef-

ficients of the indicator variables constructed for the upper quintiles. To adjust for possible differences among the study center populations, all analyses were performed stratified by center. For all relative risks, 95 percent confidence intervals were computed, and all p values were two-tailed. The analyses were performed with the use of the PHREG procedure in the Statistical Analysis System (SAS) software package (25).

In the multivariate regression analyses, potential confounders were included as indicator variables: education (high school or less, some college/college graduate, postgraduate work, unknown), age at first livebirth (nulliparous, <20, 20-24, 25-29, ≥ 30 years, unknown), parity (nulliparous, 1-2, ≥ 3 , unknown), age at menarche (≤ 12 , 13-14, ≥ 15 years, unknown), history of breast cancer in a first-degree relative (no, yes, unknown), prior biopsies indicating benign breast disease (no, yes), and female menopausal hormone use during the period not more than 5 years before menopause for the postmenopausal women (no, yes, unknown); the latter three variables were treated as time-dependent. Because the results obtained with the use of a separate indicator for missing data are similar to those found excluding women with missing data, only the results for the former are presented. Smoking and drinking (obtained retrospectively at the second phase interview) and oral contraceptive use (treated as a time-dependent variable) did not materially alter the results, and thus were not included in the final regression models.

Based on all available interviews during the follow-up period, women were classified as premenopausal if they reported having a menstrual period in the 3 months prior to each interview. Because menopausal status could change over the follow-up period, women were considered to be postmenopausal at the reported age at period cessation if they had natural menopause, or if it was not known whether menopause was natural or surgical, and at the age at bilateral oophorectomy if they had undergone that procedure. Menopausal status is less certain for women who did not have bilateral oophorectomy, but who had hysterectomy with at least one ovary retained ($n = 9,254$) or had unknown ovarian status ($n = 485$), or who reported cessation of periods due to radiation treatment or other reasons not including pregnancy or irregularity ($n = 335$). For this group of women, menopause was considered to have occurred at the following ages: 1) the median age of natural menopause of the BCDDP cohort, i.e., 52.75 years for women whose ages at hysterectomy or at cessation of periods due to radiation treatment were missing or were reported as <52.75 years; and 2) the ages at hysterectomy and at period cessation, respectively, for women whose ages

at hysterectomy and at period cessation due to radiation treatment were ≥ 52.75 years. Thus, of the 54,896 women in this cohort, 5,668 (10.3 percent) remained as premenopausal, 37,380 (68.1 percent) remained as postmenopausal, whereas 11,848 (21.6 percent) changed from pre- to postmenopausal over the follow-up period.

The pre- and postmenopausal women were studied separately by using the age at menopause established above as a time-dependent indicator variable which suppressed women in the analysis according to their menopausal status. Thus, for the separate pre- and postmenopausal analyses, only cases who were pre- or postmenopausal at diagnosis were counted, and each case's risk set included women of the same age who were pre- or postmenopausal at that age, who had not exited from the study, and were alive and free from breast cancer. In addition, a woman whose menopausal status changed over the study period could be included in both the pre- and postmenopausal analyses, and a case could be included among the noncases of a risk set at an earlier age. The same approach was adopted to perform analyses among pre- and postmenopausal women further stratified in a time-dependent fashion by the age at diagnosis, and for the postmenopausal women, by the timing of weight measurement, age at menopause, and the duration of the period since menopause. The proportional hazards assumption for the relative weight variable was examined by including an interaction term, relative weight \times age at diagnosis of the risk set's case, in the regression models.

RESULTS

The analytical cohort of 54,896 women, aged 31–89 years at baseline, was followed for an average period of 7.2 years (range 0.01–10.3 years), for a total of 396,661 person-years. Eighty-seven percent of the women were white and 5 percent were black, and 85 percent had completed ≥ 12 years of education. At the time of diagnosis, there were 226 premenopausal and 1,198 postmenopausal breast cancer cases. Among the premenopausal cases, 12, 55, 30, and 3 percent, respectively, were diagnosed at ages <45 , 45–49, 50–54, and ≥ 55 years, while among the postmenopausal cases, 17, 23, 23, 18, and 19 percent, respectively, were diagnosed at age <55 , 55–59, 60–64, 65–69, and ≥ 70 years.

Risk estimates by menopausal status

The age- and multivariate-adjusted relative risks of breast cancer by menopausal status for the quintiles of relative weight (weight (kg)/height (m)^{1.5}) are shown in table 1. Among premenopausal women, there was no evidence for an association between relative weight and breast cancer risk. By contrast, among postmenopausal women, a modest increase in risk with increasing relative weight was observed ($p < 0.05$ for trend); the multivariate-adjusted relative risk for the highest quintile compared with the lowest quintile was 1.3 (95 percent confidence interval (CI) 1.1–1.6).

Similar results were observed by quintile of Quetelet index (kg/m²) (<21.0 , 21.0–22.6, 22.7–24.3, 24.4–27.3, and ≥ 27.4) (data not shown). However, the

TABLE 1. Relative risks of breast cancer according to quintiles of relative weight by menopausal status: the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987–1989

Menopausal status	Relative weight quintile*					χ^2 trend	<i>p</i> value
	1 <26.8	2 26.8–28.8	3 28.9–31.0	4 31.1–34.6	5 ≥ 34.7		
Premenopausal (<i>n</i> = 226)							
No. of cases	63	51	44	34	34		
Relative risk							
Age adjusted†	1.0§	1.0	1.0	0.8	0.8	1.81	0.18
Multivariate‡	1.0§	1.0	1.0	0.9	0.9	0.24	0.62
95% confidence interval		0.7–1.4	0.7–1.5	0.6–1.4	0.6–1.4		
Postmenopausal (<i>n</i> = 1,198)							
No. of cases	207	237	239	248	267		
Relative risk							
Age adjusted	1.0§	1.1	1.1	1.0	1.2	1.23	0.27
Multivariate	1.0§	1.2	1.1	1.1	1.3	4.74	0.03
95% confidence interval		1.0–1.4	0.9–1.3	0.9–1.3	1.1–1.6		

* Based on quintiles of the entire analytical cohort (kg/m^{1.5}).

† Relative risk from a proportional hazards model with age as the underlying time variable and stratified by study center.

‡ Relative risk adjusted for education, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, and benign breast disease, and, for postmenopausal women, female menopausal hormone use not more than 5 years before menopause.

§ Reference category.

magnitudes of the relative risk estimates for weight (kg)/height (m)^{1.5} were slightly higher than those for the Quetelet index and, for either index, were not altered after the further adjustment for height. Furthermore, in this cohort, weight (kg)/height (m)^{1.5} compared with Quetelet index was more highly correlated with weight ($r = 0.93$ vs. 0.88) but was slightly less correlated with height ($r = 0.06$ vs. -0.07). Thus, only the results based on the weight (kg)/height (m)^{1.5} index (hereafter referred to as relative weight) are presented.

The age-adjusted relative risks of breast cancer in relation to relative weight were not materially altered after the adjustment for the breast cancer risk factors of education, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, benign breast disease, and, for the postmenopausal women, the use of female menopausal hormones (table 1). When the relative weight-breast cancer relation was further examined within levels of these factors, the effects of relative weight were not modified in any material way. For the premenopausal women but not the postmenopausal women, the pro-

portions of in situ and smaller tumors were found to be slightly higher among those who were in the lowest compared with the higher quintiles of relative weight. However, there was no apparent modification of the relative weight-breast cancer relation by tumor size among both the pre- and postmenopausal women (data not shown).

Effect modification by age at diagnosis and menopausal status

In a multivariate proportional hazards model, the coefficient for the linear interaction term between relative weight and the age at diagnosis was positive for premenopausal ($\beta = 0.006$, $p = 0.12$) and postmenopausal women ($\beta = 0.002$, $p < 0.01$). Non-linear effects of these interactions, examined by orthogonal polynomials, were found to be nonsignificant. To further explore the modification effects of the age at diagnosis on the association between relative weight and breast cancer risk, the women were stratified into different age groups (table 2). To ensure approximately even distribution of the number of cases for the

TABLE 2. Multivariate-adjusted relative risk of breast cancer according to quintiles of relative weight by age at diagnosis and menopausal status: the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987-1989

Menopausal status	Relative weight quintile*					χ^2 trend	p value
	1 <26.8	2 26.8-28.8	3 28.9-31.0	4 31.1-34.6	5 ≥34.7		
Premenopausal†							
<49 years							
No. of cases	38	20	17	14	17		
Relative risk‡	1.0§	0.7	0.8	0.7	0.8	1.07	0.30
95% confidence interval		0.4-1.2	0.4-1.3	0.4-1.2	0.4-1.4		
≥49 years							
No. of cases	25	31	27	20	17		
Relative risk	1.0§	1.4	1.5	1.2	1.1	0.05	0.82
95% confidence interval		0.8-2.4	0.8-2.6	0.7-2.3	0.6-2.1		
Postmenopausal							
<60 years							
No. of cases	102	121	79	86	93		
Relative risk	1.0§	1.2	0.8	0.9	1.1	0.42	0.52
95% confidence interval		0.9-1.6	0.6-1.1	0.7-1.2	0.8-1.4		
60-64 years							
No. of cases	48	51	58	59	63		
Relative risk	1.0§	1.0	1.1	1.0	1.2	0.57	0.45
95% confidence interval		0.7-1.5	0.7-1.6	0.7-1.5	0.8-1.7		
≥65 years							
No. of cases	57	65	102	103	111		
Relative risk	1.0§	1.1	1.6	1.5	1.8	13.60	0.0002
95% confidence interval		0.8-1.6	1.1-2.2	1.1-2.1	1.3-2.5		

* Based on quintiles of the entire analytical cohort (kg/m^{1.5}).

† Stratified by median age.

‡ Relative risk from a proportional hazards model with age as the underlying time variable, stratified by study center, and adjusted for education, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, and benign breast disease, and, for postmenopausal women, female menopausal hormone use not more than 5 years before menopause.

§ Reference category.

comparison groups, the small sample of premenopausal women was stratified at the median age of 49 years. The risk of breast cancer was associated with relative weight in a negative direction among the younger women but in a positive direction among the older women, but neither association was statistically significant.

Among the postmenopausal women, the relative weight-breast cancer association was modified by age. This effect was observed for different age categorizations. Because breast cancer risk was only found to increase significantly with increasing relative weight among women aged 65 years or older ($p < 0.001$ for trend), and there were relatively few breast cancer cases among women aged <55 or ≥ 70 years, results are only presented for the age categories <60 , $60-64$, and ≥ 65 years (table 2). The multivariate-adjusted relative risks for the highest quintile compared with the lowest quintile for relative weight were 1.1 (95 percent CI 0.8-1.4), 1.2 (95 percent CI 0.8-1.7), and 1.8 (95 percent CI 1.3-2.5) for women aged <60 , $60-64$, and ≥ 65 years, respectively.

Effect modification by age at diagnosis and type of menopause among postmenopausal women

The majority of the postmenopausal women were naturally menopausal (58.3 percent). For this overall group of women, a trend of an increase in risk of breast cancer with increasing relative weight was observed ($p < 0.01$); the multivariate-adjusted relative risk for the highest quintile compared with the lowest quintile was 1.6 (95 percent CI 1.2-2.1) (data not shown). In a multivariate proportional hazards model, the coefficient for the interaction term between relative weight and the age at diagnosis was positive, but was not statistically significant ($\beta = 0.001$, $p = 0.29$). However, when stratified by age (table 3), the corresponding relative risk was higher for women ≥ 65 years than for women <65 years of age (multivariate-adjusted relative risk = 1.8 (95 percent CI 1.2-2.9) vs. 1.5 (95 percent CI 1.1-2.0)), with the trend significant only across the quintiles for women aged ≥ 65 years ($p < 0.01$).

An age modification of the relative weight-breast cancer association was observed for the group of women who had bilateral oophorectomy (20.6 percent) or hysterectomy with unilateral oophorectomy (18.8 percent). The interaction term between relative weight and the age at diagnosis was statistically significant for both groups ($\beta = 0.004$, $p < 0.01$ for bilateral oophorectomy, and $\beta = 0.005$, $p < 0.05$ for hysterectomy with unilateral oophorectomy). Although there was a pattern of an increase in risk with increasing relative weight for women aged ≥ 65 years

but a decrease in risk with increasing relative weight for women <65 years in both groups (table 3), the trends were not statistically significant, probably reflecting the further reduction of the sample size due to stratification. In the case of the smaller group of women for whom it was not known whether they had a natural or surgical menopause (0.7 percent), or who had hysterectomy with unknown ovarian status (1 percent) or radiation treatment (0.7 percent), the results are too unstable to provide any meaningful interpretation (data not shown). The relative risk estimates presented for the overall group of postmenopausal women in table 1, however, remained unchanged when these women with less certain menopausal status were excluded.

Effect of timing of weight measurement among naturally menopausal women

Over the follow-up period, 21.6 percent of the women changed from pre- to postmenopausal status. As a result, the weight measurements of some of the postmenopausal women were obtained during the premenopausal period and some during the postmenopausal period. To examine the effects of this timing of weight measurement with respect to the changing menopausal status, the postmenopausal women were divided into two groups using a time-dependent indicator variable for the menopausal status at the time of weight measurement. Results are only presented for the larger group of naturally menopausal women (table 4). The risk of breast cancer was not associated with relative weight for the women with weight measurements during the premenopausal period and who were also predominantly less than 65 years of age. By contrast, the higher risk was confined to those women with weight measurements during the postmenopausal period. In this subgroup of women, risk was further observed to be higher for women with older age at diagnosis; the multivariate-adjusted relative risk for the highest quintile compared with the lowest quintile for relative weight was 1.9 (95 percent CI 1.2-2.9) for women aged ≥ 65 years vs. 1.6 (95 percent CI 1.1-2.4) for women <65 years of age, with a significant trend across the quintiles in both age groups ($p < 0.05$). The interaction term between relative weight and the age at diagnosis, when added to the multivariate model, was positive, but was not statistically significant ($\beta = 0.0001$, $p = 0.94$). Similar relative risk estimates were obtained when this group of women was stratified by the median age at weight measurement, thus reflecting the high correlation between the ages at diagnosis and at weight measurement ($r = 0.97$).

TABLE 3. Multivariate-adjusted relative risk of breast cancer according to quintiles of relative weight among postmenopausal women by age at diagnosis and type of menopause: the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987-1989

Type of menopause	Relative weight quintile*					χ^2 trend	p value
	1 <26.8	2 26.8-28.8	3 28.9-31.0	4 31.1-34.6	5 ≥34.7		
Natural menopause							
<65 years							
No. of cases	79	104	79	81	95		
Relative risk†	1.0‡	1.4	1.1	1.1	1.5	2.22	0.14
95% confidence interval		1.0-1.8	0.8-1.5	0.8-1.5	1.1-2.0		
≥65 years							
No. of cases	32	39	61	50	57		
Relative risk	1.0‡	1.3	1.8	1.5	1.8	6.70	0.0097
95% confidence interval		0.8-2.1	1.2-2.8	0.9-2.3	1.2-2.9		
Bilateral oophorectomy							
<65 years							
No. of cases	34	34	29	33	30		
Relative risk	1.0‡	1.0	0.8	0.9	0.7	1.33	0.25
95% confidence interval		0.6-1.5	0.5-1.3	0.5-1.4	0.4-1.2		
≥65 years							
No. of cases	12	13	15	21	27		
Relative risk	1.0‡	1.2	1.2	1.4	1.9	2.97	0.08
95% confidence interval		0.5-2.7	0.5-2.6	0.7-2.9	0.9-3.8		
Hysterectomy with unilateral oophorectomy							
<65 years							
No. of cases	35	29	28	30	24		
Relative risk	1.0‡	0.8	0.7	0.7	0.6	3.50	0.061
95% confidence interval		0.5-1.3	0.4-1.2	0.4-1.2	0.4-1.0		
≥65 years							
No. of cases	12	10	23	29	24		
Relative risk	1.0‡	0.7	1.4	1.6	1.4	3.27	0.07
95% confidence interval		0.3-1.7	0.7-2.8	0.8-3.3	0.7-2.9		

* Based on quintiles of the entire analytical cohort (kg/m^{1.5}).

† Relative risk from a proportional hazards model with age as the underlying time variable, stratified by study center and adjusted for education, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, benign breast disease, and female menopausal hormone use not more than 5 years before menopause.

‡ Reference category.

Effects of age at menopause and duration of the postmenopausal period among naturally menopausal women with postmenopausal weight measurement

The higher risk of breast cancer in relation to relative weight for the subgroup of older naturally menopausal women with weight measurements during the postmenopausal period may be attributed to other menopausal factors besides age. This is because compared with women <65 years, those aged ≥65 years, as a group, were older at menopause (49.8 ± 4.7 vs. 48.4 ± 3.9 years, $p < 0.001$) and had a longer duration of the postmenopausal period between menopause and diagnosis (23.3 ± 7.7 vs. 13.6 ± 3.6 years, $p < 0.001$), in addition to being older at weight measurement (62.7 ± 5.8 vs. 52.1 ± 3.0 years, $p < 0.001$). Thus, to further examine the effects of these meno-

pausal factors, the women were stratified by the median age at menopause (50 years) and the median duration of the postmenopausal period (14 years) (table 5). The findings based on other cutpoints were similar and are not presented.

The multivariate-adjusted relative risks of breast cancer for women in the second to the fifth quintiles compared with the lowest quintile for relative weight ranged from 1.5 to 1.7 for women aged ≥50 years at menopause. In contrast, the corresponding relative risks were of lower magnitude for women aged <50 years at menopause, except in the highest quintile, where a similar relative risk of 1.7 (95 percent CI 1.1-2.7) was observed for either group of women. The risk of breast cancer in relation to relative weight was also higher for women with ≥14 years compared with <14 years for duration of the postmenopausal period.

TABLE 4. Multivariate-adjusted relative risk of breast cancer according to quintiles of relative weight among naturally menopausal women by timing of weight measurement*: the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987-1989

Timing of weight measurement	Relative weight quintile*					χ^2 trend	p value
	1 <26.8	2 26.8-28.8	3 28.9-31.0	4 31.1-34.6	5 ≥34.7		
Premenopausal weight							
No. of cases	38	50	36	31	33		
Relative risk†	1.0§	1.4	1.1	1.0	1.3	0.06	0.80
95% confidence interval		0.9-2.2	0.7-1.8	0.6-1.7	0.8-2.1		
Postmenopausal weight							
Age at diagnosis							
<65 years							
No. of cases	41	53	43	50	62		
Relative risk	1.0§	1.3	1.1	1.2	1.6	3.88	0.049
95% confidence interval		0.8-1.9	0.7-1.6	0.8-1.8	1.1-2.4		
≥65 years							
No. of cases	32	39	61	50	57		
Relative risk	1.0§	1.3	1.8	1.5	1.9	6.79	0.009
95% confidence interval		0.8-2.1	1.2-2.8	0.9-2.3	1.2-2.9		
Age at weight measurement 							
<59 years							
No. of cases	44	56	49	52	64		
Relative risk	1.0§	1.2	1.1	1.2	1.5	3.23	0.07
95% confidence interval		0.8-1.8	0.7-1.6	0.8-1.7	1.0-2.3		
≥59 years							
No. of cases	29	36	55	48	55		
Relative risk	1.0§	1.3	1.9	1.6	2.0	8.46	0.004
95% confidence interval		0.8-2.1	1.2-2.9	1.0-2.5	1.3-3.2		

* 118 women (1 case) were excluded from this analysis due to missing ages at weight/height measurement.

† Based on quintiles of the entire analytical cohort (kg/m^{1.5}).

‡ Relative risk from a proportional hazards model with age as the underlying time variable, stratified by study center, and adjusted for education, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, benign breast disease, and female menopausal hormone use not more than 5 years before menopause.

§ Reference category.

|| Stratified by median age at weight measurement.

In a multivariate model, however, the interaction term between relative weight and either the age at menopause ($\beta = -0.002$, $p = 0.30$) or the duration of the postmenopausal period ($\beta = 0.001$, $p = 0.37$) was not statistically significant. These relative risk estimates are also similar in magnitude to those based on the ages at diagnosis and at weight measurement (table 4), and may reflect the high correlations between the duration of the postmenopausal period and the ages ($r = 0.83$ for age at diagnosis and $r = 0.79$ for age at weight measurement).

DISCUSSION

In this prospective cohort of 54,896 women, the risk of breast cancer was significantly and positively associated with adult relative weight among the postmenopausal women, thus confirming the risks reported in numerous predominantly case-control studies (4, 10, 11, 14-19, 21), but in contrast with the findings of two recent prospective studies (7, 13). However, as dem-

onstrated in this study, risk was further modified by age among the postmenopausal women. In contrast, the risk of breast cancer was not associated with adult relative weight among the premenopausal women. This finding is consistent with the findings of some studies (13, 15-17) but not in several case-control studies (11, 12) and prospective studies (2, 5, 7, 8).

There are several features of this study that should be considered before we discuss the findings. The relative risk estimates are based on the relative weight index of weight (kg)/height (m)^{1.5}, which has been found to be more highly correlated with weight but is less correlated with height compared with the more commonly used Quetelet index in this and other cohorts of women (17, 20, 26, 27). The findings are similar to those based on Quetelet index, the distribution of which is comparable with those of other cohorts, including that of the Nurses Health Study (7). However, as has been similarly reported by Swanson et al. (20), the weight (kg)/height (m)^{1.5} index is a

TABLE 5. Multivariate-adjusted relative risk of breast cancer according to quintiles of relative weight among naturally menopausal women with postmenopausal weight measurement by selected menopausal factors*: the Breast Cancer Detection Demonstration Project Follow-up Study, 1979 to 1987-1989

Menopausal status	Relative weight quintile†					χ^2 trend	p value
	1 <26.8	2 26.8-28.8	3 28.9-31.0	4 31.1-34.6	5 ≥34.7		
Age at menopause‡							
<50 years							
No. of cases	39	38	41	43	64		
Relative risk§	1.0	1.0	1.1	1.1	1.7	6.46	0.011
95% confidence interval		0.6-1.6	0.7-1.7	0.7-1.7	1.1-2.6		
≥50 years							
No. of cases	34	54	63	57	55		
Relative risk	1.0	1.5	1.7	1.5	1.7	4.42	0.036
95% confidence interval		1.0-2.4	1.1-2.7	1.0-2.4	1.1-2.7		
Duration of postmenopausal period¶							
<14 years							
No. of cases	41	51	46	49	61		
Relative risk	1.0	1.2	1.0	1.2	1.7	5.69	0.02
95% confidence interval		0.8-1.8	0.6-1.5	0.8-1.9	1.1-2.6		
≥14 years							
No. of cases	32	41	58	51	58		
Relative risk	1.0	1.3	1.7	1.5	1.9	6.80	0.009
95% confidence interval		0.8-2.1	1.1-2.7	1.0-2.3	1.2-2.9		

* 118 women (1 case) were excluded from this analysis due to missing ages at weight/height measurement.

† Based on quintiles of the entire analytical cohort (kg/m^2).

‡ Stratified by median age at menopause.

§ Relative risk from a proportional hazards model with age as the underlying time variable, stratified by study center, and adjusted for menopause, age at first livebirth, parity, age at menarche, history of breast cancer in a first-degree relative, benign breast disease, and female menopausal hormone use not more than 5 years before menopause.

|| Reference category.

¶ Stratified by median duration of the postmenopausal period (interval between menopause and diagnosis).

slightly stronger predictor of breast cancer risk in this cohort. There is a possibility that the findings may have been affected by a selection bias due to the loss to follow-up of 11 percent of the cohort. This would have occurred if those lost to follow-up included a large number of overweight or lean women, but it is unlikely that this would occur differentially between those who subsequently developed and did not develop breast cancer. Instead, a major strength of this study is the availability of information on age at menopause, and as a result, women were categorized according to their menopausal status with respect to age over the follow-up period. This time-dependent and more precise approach to the categorization of menopausal status may provide a better clarification of the differential risks of breast cancer by menopausal status. Furthermore, the findings are independent of the effects of known breast cancer risk factors, and there was no evidence of a modification in the effects of relative weight by these factors in any material way.

The conflicting findings in the literature on the relation between adult relative weight and breast cancer risk may be attributed to the age distributions as well as the sample size of the study group. Among the

small sample of premenopausal women in this study, the inverse association between relative weight and breast cancer risk, though not statistically significant, was only observed among the younger women (less than the median age of 49 years). This pattern of a less marked protective effect of adult relative weight on breast cancer risk with increasing age was similarly reported in the Nurses Health Study (7, 8), where the presence of a large proportion of premenopausal women less than 50 years of age may have facilitated the detection of a significant inverse association between relative weight and breast cancer risk. In the case of the postmenopausal women, the risk of breast cancer in relation to relative weight was of modest magnitude, but this was modified by the age at diagnosis. As shown in this study, the higher risk of breast cancer associated with relative weight was largely confined to women aged 65 years or older. Thus, a positive and significant association between relative weight and breast cancer risk may more likely to be found in this and other studies with a large number of postmenopausal women who were predominantly 65 years or older. In prospective studies where the postmenopausal women were predominantly aged less

than 60 years (7) or were small in numbers (13), a positive but nonsignificant association was the general finding.

Consistent with the findings in several studies (14, 15, 20), the higher risk of breast cancer in relation to relative weight was observed among the naturally postmenopausal women. The results of the few studies that have examined the relative weight-breast cancer relation in women with bilateral oophorectomy have been conflicting (8, 14, 28). Although this discrepancy may be attributed to the difference in hormonal profiles of women with surgical as opposed to natural menopause (29), it may also reflect an age effect (14-16, 28). As shown in this study, the risk of breast cancer was of higher magnitude among older naturally menopausal women, and a significant age modification of risk was apparent among the small sample of women with bilateral oophorectomy as well as those with hysterectomy but with at least one ovary retained.

The higher risk of breast cancer among the heavier and older postmenopausal women may be attributed to the effects of weight gain (7, 10, 11, 14, 22, 30-32). Similar to the prospective study of Tretli (2), breast cancer risk was found to be higher among those who were older at weight measurement. Although this study is limited by the availability of a single weight measurement obtained during adulthood, and because women who were aged 65 years or older as a group were heavier and had older ages at weight measurement compared with women who were less than 65 years of age, it is likely that the higher weight at older ages is largely due to the weight gained during adulthood. This is similarly reported in several case-control studies (10, 15, 16, 22, 32) where the postmenopausal breast cancer cases were not only heavier during adulthood, but had also gained more weight since adolescence compared with the controls.

In addition to degree of obesity, the relative weight-breast cancer relation may also reflect the timing of weight measurements. The higher risk of breast cancer was confined to overweight postmenopausal women whose weights were measured during the postmenopausal period. In contrast, breast cancer risk was not associated with the relative weights of the premenopausal women or of the younger postmenopausal women measured during the premenopausal period. These findings suggest that the risk of breast cancer may be related to the timing of obesity with respect to menopause, and may be explained by an underlying hormonal mechanism (33, 34). After menopause, estrogen is largely derived from the aromatization of androstenedione which occurs primarily in the adipose tissue. Because there is an increase in the deposition of adipose tissue with gain in weight during adulthood

(35), and weight is also associated with a decrease in the binding of estrogens to sex-hormone-binding globulin (36), overweight during the postmenopausal years may result in increased levels of biologically active estrogens, and consequently, a promotional effect on breast cancer development (34, 37). Prior to menopause, overweight may have little influence on the levels of estrogen which are primarily derived from the ovary (38), and thus may have little effect on breast cancer in pre- or younger postmenopausal women who were overweight during the premenopausal years.

Although the risk of breast cancer was higher for women with older age at menopause (28, 39), several studies (16, 21) as well as the present study do not show a significant interaction between relative weight and the age at menopause on breast cancer risk. However, as has been similarly noted by Kampert et al. (40), there is an indication of a less protective effect of an early age at menopause for the heavier naturally postmenopausal women in the highest quintile compared with women in the lower quintiles of relative weight. Furthermore, several studies (15, 28) have also noted that the higher risk of breast cancer in women with late menopause is most marked after age 70 years, which suggests that the duration of the period after menopause rather than age per se may have a more important effect on breast cancer risk. Similar to several case-control studies (14, 17, 39), the risk of breast cancer in this prospective study was higher in women with longer duration in the time period since menopause. However, the high correlation between the duration of the postmenopausal period and age precludes any definitive conclusion regarding their independent effect modifications. Nevertheless, these findings may suggest that women who were overweight for a prolonged period after menopause may be at increased risk for breast cancer. In accordance with the hormonal hypothesis, these effects may be attributed to the longer time of exposure to high levels of endogenous estrogens in overweight and older postmenopausal women.

Future prospective studies that examine the effects of weight and weight changes at various ages as well as during varying periods of life, and that take into account the changing menopausal status and other risk factors with age, may provide further confirmation of the findings observed in this study. In view of the findings obtained thus far, and because obesity is one of the few breast cancer risk factors amenable to change, obesity prevention may be an important measure for the prevention of breast cancer. The prevention of obesity throughout adulthood, particularly after menopause, may be especially relevant to the reduc-

tion of breast cancer among older postmenopausal women.

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