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Article *in* JAMA The Journal of the American Medical Association · November 1997

DOI: 10.1001/jama.1997.03550170037029

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Dual Effects of Weight and Weight Gain on Breast Cancer Risk

Zhiping Huang, MD, PhD; Susan E. Hankinson, ScD; Graham A. Colditz, MBBS, DrPH; Meir J. Stampfer, MD, DrPH; David J. Hunter, MBBS, ScD; JoAnn E. Manson, MD, DrPH; Charles H. Hennekens, MD; Bernard Rosner, PhD; Frank E. Speizer, MD; Walter C. Willett, MD, DrPH

Context.—Breast cancer is a major cause of mortality among women. It is important to identify modifiable risk factors for this disease.

Objective.—To examine body mass index (BMI) at the age of 18 years and at midlife and adult weight change in relation to breast cancer incidence and mortality.

Design.—Cohort study.

Setting.—A cohort of 95 256 US female nurses aged 30 to 55 years who were followed up for 16 years.

Main Outcome Measure.—Incident and fatal breast cancer.

Results.—During 1 203 498 person-years, 2517 incident breast cancers (60% postmenopausal) were documented. Higher current BMI was associated with lower breast cancer incidence before menopause and was minimally associated with incidence after menopause. However, a stronger positive relationship was seen among postmenopausal women who never used hormone replacement (relative risk=1.59 for BMI >31 kg/m^2 vs ≤20 kg/m^2; 95% confidence interval, 1.09-2.32; *P* for trend <.001). Higher BMI at the age of 18 years was associated with lower breast cancer incidence both before and after menopause. Weight gain after the age of 18 years was unrelated to breast cancer incidence before menopause, but was positively associated with incidence after menopause. This increased risk with weight gain was limited to women who never used postmenopausal hormones; among these women, the relative risk was 1.99 (95% confidence interval, 1.43-2.76) for weight gain of more than 20 kg vs unchanged weight (*P* for trend <.001). Current BMI and weight gain were even more strongly associated with fatal postmenopausal breast cancer. In this population, the percentage of postmenopausal breast cancer accounted for by weight gain alone was approximately 16% and by hormone replacement therapy alone was 5%, but when the interaction between these variables was considered, together they accounted for about one third of postmenopausal breast cancers.

Conclusions.—Avoiding adult weight gain may contribute importantly to the prevention of breast cancer after menopause, particularly among women who do not use postmenopausal hormones.

JAMA. 1997;278:1407-1411

From the Departments of Nutrition (Drs Huang, Stampfer, and Willett), Epidemiology (Drs Hankinson, Colditz, Stampfer, Hunter, Manson, Hennekens, and Willett), and Biostatistics (Dr Rosner), Harvard School of Public Health; and the Channing Laboratory (Drs Hankinson, Colditz, Stampfer, Hunter, Manson, Rosner, Speizer, and Willett), Division of Preventive Medicine, Department of Medicine (Drs Manson and Hennekens), and Department of Ambulatory Care and Prevention (Dr Hennekens), Harvard Medical School and Brigham and Women's Hospital, Boston, Mass.

Reprints: Walter C. Willett, MD, DrPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115.

THE RELATION OF body weight to breast cancer is complex. An inverse association between relative weight and breast cancer risk has been found among premenopausal women in most case-control and prospective studies.[1,2] A similar inverse association has been observed between relative weight at the age of 18 years and risk of premenopausal breast cancer.[3] The relation between body weight and postmenopausal breast cancer is less clear. In many case-control studies, body mass index (BMI) has been positively associated with postmenopausal breast cancer.[1,4,5] However, prospective studies have generally suggested only a weak, if any, positive association.[3,6,7] The lack of a clear and consistent positive association between body weight and breast cancer has been perplexing because among postmenopausal women endogenous estrogen levels, which are believed to increase breast cancer incidence, are 50% to 100% higher among heavy women compared with lean women.[8,9] This has suggested that some beneficial aspect of adiposity may counterbalance an adverse effect due to higher endogenous estrogen levels. It is also possible that the use of estrogen preparations after menopause, which appears to increase breast cancer incidence,[10] could obscure any relation of adiposity to breast cancer risk that was due to higher endogenous estrogen levels.

For editorial comment see p 1448.

Few studies have examined weight change in relation to breast cancer risk. Adult weight gain, which largely reflects an increase in body fat, may be a better variable to assess adiposity and its metabolic consequences than body weight itself, which reflects both lean and fat mass.[11,12] Further, greater adiposity is associated with larger tumor size and nodal involvement at diagnosis of breast cancer,[2,3] as well as a poorer survival,[13] which suggests that obesity may relate differently to breast cancer incidence and mortality.

The objectives of this study were to examine prospectively BMI at the age of

18 years and at midlife as well as adult weight change in relation to subsequent risks of premenopausal and postmenopausal breast cancer incidence and mortality among a large cohort of US female nurses. In earlier reports from this cohort, BMI at midlife and at the age of 18 years was inversely related to premenopausal breast cancer incidence.[2,3] However, because of shorter follow-up and the younger age of this cohort, the previous analyses had limited power to evaluate associations among postmenopausal women. The current analysis was based on 16 years of follow-up and included 1439 more cases of breast cancer. The additional power also allowed evaluation of interactions between postmenopausal hormone use and adiposity.

METHODS

In 1976, a health questionnaire was mailed to female registered nurses aged 30 to 55 years who lived in 1 of 11 US states. A total of 121 700 nurses responded to the questionnaire and comprise the Nurses' Health Study cohort. Follow-up questionnaires have been mailed to participants every 2 years to identify newly diagnosed breast cancer cases and to update information on risk factors. Further details have been reported elsewhere.[14] Up to June 1, 1992, the follow-up rate was 95% of potential person-years and did not vary by weight status.

For the present study, we excluded women with any cancer other than nonmelanoma skin cancer and with incomplete information on risk factors at baseline. The analytic cohort included 95 256 women.

Measurement of Exposures

Information was obtained from the baseline questionnaire on age, current weight, height, parity, age at first birth, family history of breast cancer, personal history of benign breast diseases, age at menarche, menopausal status (premenopausal, postmenopausal, or uncertain, as previously defined[3]), age at menopause, and postmenopausal hormone (primarily estrogen and/or progesterone) use, as well as other variables. Updated information was collected by biennial follow-up questionnaires. In 1980, weight at 18 years of age and information regarding alcohol consumption were obtained. Detailed information on physical activity was obtained starting from 1986.

Body mass index, a measure of obesity, was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Women were categorized into 10 groups by using whole-number cut points of current BMI and by deciles of BMI at age 18 years. They were collapsed into 5 groups in the mortality analysis because of a smaller number of end points. Adult weight change from age 18 years to the beginning of each 2-year follow-up interval (8 categories) also was calculated. These categories were collapsed into 5 for the analyses of interactions and mortality.

For women who were premenopausal in 1976 and became postmenopausal during a follow-up interval, weight at menopause was defined as the weight at the beginning of the 2-year interval during which she became postmenopausal. Weight change since menopause was computed and updated as current weight minus weight at menopause.

In a subsample of 184 participants living in the Boston, Mass, area, self-reported weights were highly correlated with actually measured weights (correlation coefficient=0.96, mean difference=1.5 kg). In another sample of 118 younger nurses aged 25 to 42 years, recalled weight at age 18 years was highly correlated with weights at ages 17 to 21 years that were recorded on nursing school physical examination forms (correlation coefficient=0.87, mean difference=1.4 kg).

Ascertainment of Cases

On biennial follow-up questionnaires, we inquired whether breast cancer had been diagnosed during the previous 2 years. We searched the National Death Index for nonrespondents to identify fatal breast cancers. For all cases identified, we requested permission to obtain hospital records. Records were obtained for 96% of women who reported breast cancer, and self-reported cancers were confirmed in 99.4% of records obtained. We excluded the 0.6% of records that failed to confirm breast cancer. Because the degree of accuracy of self-reports was high among those for whom hospital records were obtained, we included self-reported cases for whom records could not be obtained. In situ breast cancers were excluded.

Statistical Analysis

Follow-up began in 1976 when the baseline questionnaire was returned. Follow-up time was accrued up to the date of diagnosis for both incident and fatal breast cancer cases, or date of diagnosis of any cancer other than nonmelanoma skin cancer, or the date of death, or June 1, 1992, whichever came first. Women were not included during the intervals when their current weight at the beginning of a 2-year follow-up interval was missing or their menopausal status was uncertain, but they reentered the analyses when the information became available.

Relative risk (RR) was used as the measure of association. Proportional hazards analyses were used to compute age-adjusted and multivariate-adjusted RRs with 95% confidence intervals (CIs). In tests for trend, BMI and weight change were used as continuous variables. Among postmenopausal women, the population attributable risk percentage due to weight gain (compared with women whose weight changed ≤2 kg), due to ever use of hormones (compared with never users), and due to weight gain and/or ever use of hormones (compared with those who never used hormones and changed weight ≤2 kg) was calculated.[15,16] Confidence intervals for population attributable risk percentages were calculated using the 95% CIs of the RRs used to estimate the attributable risk.

RESULTS

By 1992, 2517 incident invasive breast cancers (1000 premenopausal and 1517 postmenopausal) were identified during 1 203 498 person-years of follow-up. Among premenopausal women, age-adjusted relative risks of incident breast cancer were close to 1.00 for current BMI up to 26 kg/m^2 but declined with greater adiposity (Table 1). Among postmenopausal women, there was a small but nonsignificant positive association between current BMI and breast cancer incidence. After simultaneously controlling for multiple risk factors, RRs did not change materially.

Postmenopausal women were stratified by status of hormone use. A stronger positive association was found between current BMI and breast cancer incidence in women who never used postmenopausal hormones (multivariate RR for top vs bottom category=1.59, 95% CI, 1.09-2.32, P for trend <.001). However, little association was observed among current and past hormone users. The interaction between current BMI and postmenopausal hormone use was statistically significant ($P<.001$, 2 df).

The BMI at age 18 years was inversely associated with risk of breast cancer in premenopausal and postmenopausal women after adjustment for weight change from age 18 years and other covariates. The RR for a BMI higher than 25 kg/m^2 vs BMI of 18.2 kg/m^2 or lower was 0.61 (95% CI, 0.45-0.83, P for trend <.001) before menopause and 0.72 (95% CI, 0.56-0.91, P for trend <.001) after menopause.

Weight gain from age 18 years was not significantly associated with breast cancer risk before menopause (Table 2), but was positively associated with the risk after menopause (P for trend=.006).

Compared with women who gained or lost 2 kg or less, those who gained 20 to 25 kg had a multivariate RR of 1.40 (95% CI, 1.10-1.78), and those who gained more than 25 kg had an RR of 1.41 (95% CI, 1.12-1.78). Because few women lost weight after age 18 years, we had limited power to examine weight loss in relation to breast cancer.

A much stronger positive association was found between weight gain and breast cancer incidence in postmenopausal women who never used hormones (Figure). Among never users, the multivariate RRs were 1.61 (95% CI, 1.16-2.22) for weight gain of 10 to 20 kg, and 1.99 (95% CI, 1.43-2.76) for weight gain of more than 20 kg, compared with women with minimal weight change. However, among current and past hormone users, women with greater weight gain did not experience an elevated risk of breast cancer. The interaction between weight change and postmenopausal hormone use was statistically significant ($P<.001$, 2 *df*).

Among postmenopausal women who never used hormones, we further stratified the data by tertiles of BMI at age 18 years. Adult weight gain was somewhat more strongly linked to breast cancer risk within the first tertile of BMI at age 18 years, although the interaction was not significant.

To examine whether the associations of BMI and weight gain with breast cancer incidence would become stronger with increasing time after menopause, we stratified the data by years since menopause (0-4, 5-9, ≥10 years) among all postmenopausal women and among never users of postmenopausal hormones. There was no clear indication that these associations varied with increasing time since menopause. We also stratified all postmenopausal women by age (<50, 50-54, 55-59, ≥60 years) and found little variation in the relations of current BMI or weight gain to risk of breast cancer.

To assess further the timing of weight gain in relation to breast cancer incidence, we examined weight change since menopause among women premenopausal in 1976 who became postmenopausal during follow-up. The risk of breast cancer increased with weight gain after menopause while adjusting for years since menopause and other covariates, but the association was not statistically significant. A similar result was obtained when we reexamined the relation among never users of postmenopausal hormones.

To assess whether the observed associations might be affected by preclinical weight change due to preclinical disease, we conducted another analysis using the weight 4 years before the diagnosis of breast cancer instead of the current weight. This did not appreciably change the associations of obesity and weight gain with breast cancer risk in either premenopausal or postmenopausal women. Similarly, adjustment for alcohol intake (1980-1992 follow-up) and physical activity (1986-1992 follow-up) did not materially influence the associations with BMI or weight change.

Table 1.—Relative Risk of Breast Cancer Incidence According to Current Body Mass Index in a Cohort of US Female Registered Nurses Aged 30 to 55 Years in 1976 and Followed Up for 16 Years

Body Mass Index, kg/m²	No. of Cases	Person-Years of Follow-up	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk* (95% CI)
Premenopausal Women				
≤20.0	100	71 477	1.00 (Reference)	1.00 (Reference)
20.1-21.0	132	79 084	1.13 (0.87-1.47)	1.15 (0.89-1.49)
21.1-22.0	130	90 250	0.93 (0.72-1.21)	0.97 (0.74-1.25)
22.1-23.0	128	75 222	1.05 (0.81-1.36)	1.08 (0.83-1.40)
23.1-24.0	125	68 273	1.09 (0.84-1.42)	1.13 (0.87-1.48)
24.1-25.0	87	58 816	0.86 (0.64-1.14)	0.90 (0.67-1.20)
25.1-26.0	84	45 082	1.05 (0.78-1.40)	1.09 (0.82-1.47)
26.1-28.0	80	55 076	0.81 (0.60-1.08)	0.86 (0.64-1.16)
28.1-31.0	75	54 564	0.75 (0.56-1.02)	0.80 (0.59-1.08)
>31.0	59	55 160	0.58 (0.42-0.80)	0.62 (0.45-0.86)
P for trend				<.001
Postmenopausal Women				
≤20.0	94	38 816	1.00 (Reference)	1.00 (Reference)
20.1-21.0	110	43 666	1.06 (0.80-1.39)	1.05 (0.80-1.38)
21.1-22.0	143	57 122	1.04 (0.80-1.34)	1.03 (0.80-1.34)
22.1-23.0	168	56 168	1.22 (0.95-1.57)	1.22 (0.94-1.56)
23.1-24.0	167	59 859	1.12 (0.87-1.44)	1.13 (0.88-1.46)
24.1-25.0	158	57 596	1.08 (0.84-1.40)	1.10 (0.85-1.42)
25.1-26.0	116	48 856	0.93 (0.71-1.22)	0.94 (0.72-1.23)
26.1-28.0	202	64 414	1.21 (0.94-1.54)	1.26 (0.98-1.61)
28.1-31.0	199	64 625	1.18 (0.92-1.50)	1.24 (0.97-1.59)
>31.0	160	59 372	1.04 (0.80-1.34)	1.13 (0.87-1.46)
P for trend				.53

*Adjusted for age (continuous), height (continuous), history of benign breast diseases (yes or no), family history of breast cancer (yes or no), age at menarche (≤9, 10, 11, 12, 13, 14, >14 years), parity (nulliparous, 1-2, 3-4, ≥5 births), and age at first birth (nulliparous, ≤24, 25-29, ≥30 years). In postmenopausal women, relative risks were adjusted for age at menopause (<45, 45-49, 50-55, >55 years) and postmenopausal hormone use (never, current, or past) in addition to the variables listed above. CI indicates confidence interval.

Among premenopausal women, breast cancer mortality (201 deaths) tended to be positively associated with current BMI and weight gain since age 18 years (for current BMI >28 kg/m² vs ≤21 kg/m², RR=1.22, 95% CI, 0.77-1.92, *P* for trend=.27, and for weight gain of >20 kg vs ≤2-kg change, RR=1.27, 95% CI, 0.71-2.29, *P* for trend=.03). Among postmenopausal women, these associations with breast cancer mortality (279 deaths) were stronger. The multivariate RRs were 1.90 (95% CI, 1.26-2.88) for a current BMI higher than 28 kg/m² compared with a BMI of 21 kg/m² or less (*P* for trend=.09), and 2.44 (95% CI, 1.40-4.25) for weight gain of more than 20 kg compared with weight change of 2 kg or less (*P* for trend=.01). These associations were strongest among never users of postmenopausal hormones (RR=2.17 [95% CI, 1.23-3.82], *P* for trend=.02, for current BMI >28 kg/m², and RR=3.80 [95% CI, 1.61-8.97], *P* for trend=.003, for weight gain >20 kg).

Among postmenopausal women, the population attributable risk of breast cancer for ever use of hormones compared with all never users was 5% (95% CI, 0%-10%) and for weight gain of more than 2 kg after age 18 years compared with women with stable weights was 16% (95% CI, 2%-28%). However, when those who never used hormones and did not change weight were analyzed as the comparison group, 34% (95% CI, 14%-50%) of postmenopausal breast cancer incidence in this population could be attributable to weight gain, hormone use, or both.

COMMENT

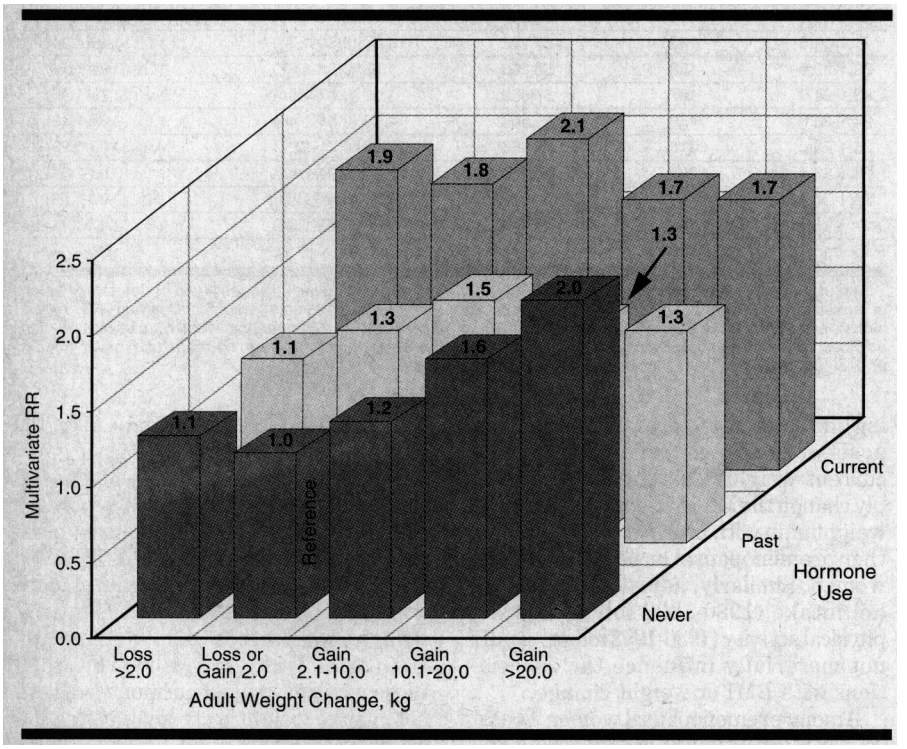
Body mass index at ages 18 or 20 years has generally been inversely associated with incidence of premenopausal breast cancer.[3,17] In the Iowa Women's Health Study,[18] as in this cohort, a higher BMI at age 18 years was also associated with lower risk of postmenopausal breast cancer. Higher current BMI has also been associated with a decreased incidence of premenopausal breast cancer.[19] In a meta-analysis, the RR for a BMI difference of 8 kg/m² was 0.70 (95% CI, 0.54-0.91) for 4 cohort studies and 0.88 (95% CI, 0.76-1.02) for the 19 case-control studies.[20]

Table 2.—Relative Risk of Breast Cancer Incidence According to Weight Change From Age 18 Years to the Beginning of Each Follow-up Interval in a Cohort of US Female Registered Nurses Aged 30 to 55 Years in 1976 and Followed Up for 16 Years

	Premenopausal Women			Postmenopausal Women		
Weight Change, kg	No. of Cases	Person-Years of Follow-up	Multivariate-Adjusted Relative Risk* (95% CI)	No. of Cases	Person-Years of Follow-up	Multivariate-Adjusted Relative Risk† (95% CI)
Loss ≥10.0	12	12843	0.94 (0.51-1.73)	22	10971	1.12 (0.70-1.78)
Loss 2.1-9.9	95	68582	1.06 (0.81-1.39)	103	47194	1.04 (0.80-1.36)
Loss or gain of 2.0	133	92062	1.00 (Reference)	123	55135	1.00 (Reference)
Gain 2.1-5.0	177	119591	0.97 (0.76-1.22)	198	73082	1.20 (0.96-1.51)
Gain 5.1-10.0	222	145493	0.91 (0.74-1.14)	316	115548	1.18 (0.96-1.45)
Gain 10.1-20.0	251	139780	1.01 (0.82-1.25)	441	153099	1.20 (0.98-1.47)
Gain 20.1-25.0	58	34570	0.95 (0.70-1.30)	145	43800	1.40 (1.10-1.78)
Gain >25.0	52	40083	0.74 (0.54-1.03)	169	51665	1.41 (1.12-1.78)
P for trend			.07			.006

*Adjusted for age (continuous), height (continuous), history of benign breast diseases (yes or no), family history of breast cancer (yes or no), age at menarche (≤9, 10, 11, 12, 13, 14, >14 years), parity (nulliparous, 1-2, 3-4, ≥5 births), age at first birth (nulliparous, ≤24, 25-29, ≥30 years), and body mass index at age 18 years (continuous). CI indicates confidence interval.

†Adjusted for age at menopause (<45, 45-49, 50-55, >55 years) and postmenopausal hormone use (never, current, or past) in addition to the variables listed above.



Relative risk (RR) of breast cancer by adult weight change and hormone use among postmenopausal women. Relative risk was adjusted for age, height, history of benign breast diseases, family history of breast cancer, age at menarche, parity, age at first birth, age at menopause, and body mass index at age 18 years.

After menopause, a modest elevation in breast cancer incidence with increasing adiposity has been found in many case-control studies.[5] However, prospective studies, as in this analysis, have generally shown no association or only weakly positive overall associations.[3,6,18] Among Swedish women older than 55 years,[19] the RR for breast cancer was 1.13 for a BMI of 28.0 kg/m^2 or higher compared with a BMI of less than 22 kg/m^2. In a large Norwegian cohort, the RR was 1.22 for top vs bottom quintile of BMI in women aged 65 to 69 years.[7] Some have suggested that the lack of a clear positive association in most prospective studies may be due to misclassification because weight was only obtained at baseline and weight changes during the follow-up period were not captured. However, our study avoided this by updating weight every 2 years. Thus, it is more likely that recall or selection biases have affected the findings of case-control studies.

Adult weight gain has been associated with higher incidence of postmenopausal breast cancer in several studies.[18] In our study and others that examined both recent body weight and weight gain, the magnitude of excess risk was greater for adult weight gain than for higher recent body weight.[11,17]

The timing of weight gain may be important in evaluating breast cancer risk. In principle, weight gained near or after menopause might have a more adverse effect on breast cancer risk because this weight would not carry with it any residual protective effect from the premenopausal period. However, when we evaluated the effect of weight gain after menopause, this did not support a stronger association with breast cancer risk. Nevertheless, further examination of the patterns of weight gain and weight cycling at various ages would be desirable.

Increased exposure to estrogen and progesterone is hypothesized to elevate the risk of breast cancer.[21] Among premenopausal women, obesity has been shown to reduce serum estradiol and progesterone levels because of an increased frequency of anovulation.[22] After menopause, plasma estrogen is derived largely from adipose tissue. Thus, estrogen production in postmenopausal women is directly correlated with body weight.[8] In addition, obese women have a higher biologically available estrogen level because of a decrease in plasma sex hormone–binding globulin concentration.[23] As a result, excess weight in postmenopausal women would be expected to be associated with an increased risk of breast cancer. This adverse effect of excess body fat, however, appears to be offset, at least in part, by a protective effect of overweight in early adulthood. These opposing effects may lead to the weak overall association between midlife adiposity and postmenopausal breast cancer incidence seen in this and in other prospective studies.

One limitation of most previous studies is that they did not examine BMI in relation to breast cancer risk among women classified by use of postmenopausal hormones. In our study the lack of a strong overall association between adiposity and postmenopausal breast cancer was partly explained by the use of postmenopausal hormones. Among current users, estrogen levels are elevated by exogenous hormones even

among lean women, which may have obscured an effect of adiposity on breast cancer because the increases in estrogen levels with these pharmacologic doses are generally greater than those due to obesity.[8,24,25] Among past users, who include women with a variety of durations and recency of use, current plasma estrogens may be reduced to the level of never users, but a possible residual effect of postmenopausal hormones on breast tissue may explain why the effect of obesity was not evident. Only among never users, in whom plasma estrogen levels were never influenced by exogenous postmenopausal hormones, was a clear positive association between BMI, weight gain, and risk of breast cancer observed.

Although obesity appears to reduce breast cancer incidence before menopause, it did not reduce premenopausal breast cancer death and did appreciably increase cancer mortality after menopause in this and a large Norwegian study.[7] The high breast cancer mortality in heavier postmenopausal women may be explained by both a greater incidence and a higher case fatality[13,26] related to delayed detection in overweight women[2,7] and more rapid growth of metastatic tissues due to impaired immunity and higher estrogen levels.[27]

In summary, adiposity and weight gain appear to have diverging effects on premenopausal and postmenopausal breast cancer. Before menopause, adiposity appears to reduce breast cancer incidence, but not mortality. After menopause, adult weight gain increases the risk of both breast cancer incidence and mortality. The weak overall association between adiposity and postmenopausal breast cancer incidence appears to be accounted for in part by the opposing effects of early obesity and subsequent weight gain and is also obscured by the use of postmenopausal hormones. The risks associated with obesity and weight gain are much stronger in postmenopausal women who never used hormones. Thus, avoiding weight gain during adult life may contribute importantly to the prevention of breast cancer incidence and mortality after menopause, particularly among women who do not use postmenopausal hormones.

This study was supported by research grant CA 40356 from the National Institutes of Health. Dr Huang was supported by a training grant in Harvard Education Program in Cancer Prevention Control (5-R25-CA57711-04).

We are indebted to the participants in the Nurses' Health Study for their continuing outstanding dedication and commitment and to Mark Shneyder, Karen Corsano, MA, and Barbara Egan for their unfailing assistance.

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