

Association of Gain and Loss of Weight before and after Menopause with Risk of Postmenopausal Breast Cancer in the Iowa Women's Health Study

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Abstract

Obesity and adult weight gain are well-established risk factors for postmenopausal breast cancer. Although there are a few studies demonstrating the contribution of adult weight gain to breast cancer risk, whether weight gain during a critical time period is specifically associated with risk, or whether subsequent weight loss among women who have gained weight will reduce the excess risk, is not firmly established. We investigated the association of changes in weight (loss or gain in excess of 5% of body weight) using two risk factor models: (a) age 18 to 30 years and age 30 years to menopause and (b) age 30 years to menopause and after the menopause to the baseline study in 1986 on risk of postmenopausal breast cancer in a prospective cohort of 33,660 postmenopausal women in Iowa. Over 15 years of follow-up, 1,987 cases of breast cancer occurred. Data were analyzed using proportional hazards regression models adjusted for established breast cancer risk factors. The most frequently observed pattern of body weight over time was a consistent increase; these women were observed to have the highest rates of breast cancer and served as the reference category for all comparisons. The lowest-risk groups were (a) women who maintained or lost weight from age 18 to 30

years and then lost weight from age 30 years to menopause [risk ratio (RR), 0.36; 95% confidence interval (95% CI), 0.22-0.60] and (b) women who maintained or lost weight from age 30 years to menopause and then lost weight after the menopause (RR, 0.48; 95% CI, 0.22-0.65). Women who gained weight from age 30 years to menopause but then lost weight after the menopause experienced risk reductions (RR, 0.77; 95% CI, 0.64-0.92) although perhaps slightly smaller in magnitude than women who maintained their weight in both time intervals (RR, 0.63; 95% CI, 0.55-0.73). Women who gained weight from age 18 to 30 years and then lost weight from age 30 years to menopause had comparable risk reductions (RR, 0.61; 95% CI, 0.46-0.8) with women who maintained their weight in both time intervals (RR, 0.73; 95% CI, 0.64-0.84). Women who gained weight during the period from age 30 years to menopause but who had stable weight after menopause had rates similar to the reference group. These data suggest prevention of weight gain between age 18 years and menopause or weight loss and maintenance during these years reduces risk of postmenopausal breast cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(3):656-61)

Introduction

Despite advances in the early detection and treatment of breast carcinoma, the morbidity and mortality from this disease remains unacceptably high. Thus, the most promising approach to cancer control is a global commitment to prevention. Excess body weight and obesity are well-established and increasingly important risk factors for postmenopausal breast cancer (1). Given that there is an epidemic of overweight women in the United States (66%; ref. 2), the United Kingdom (56%; ref. 3), and other industrialized countries, this would seem to be a viable intervention target. Evidence that weight loss reduces risk of breast cancer could provide additional motivation for women to lose excess body weight.

Several studies suggest that adult weight gain may be a better predictor of postmenopausal breast cancer than weight or body mass index (BMI) measured at a single point in time (4-6). However, this observation is not entirely consistent, as greater weight in the earlier premenopausal years (up to age 25 years) has been linked to a reduced risk of postmenopausal breast cancer (5, 7, 8). Whether the association between adult

weight gain and risk of postmenopausal breast cancer is evident throughout the premenopausal and postmenopausal years or only at critical time periods of adult life is not known. We therefore investigated the association of changes in weight (loss or gain in excess of 5% of initial body weight) in the time intervals of age 18 to 30 years, age 30 years to menopause, and after the menopause on subsequent risk of postmenopausal breast cancer in a large prospective cohort of postmenopausal women (9).

Materials and Methods

Definition of Cohort. Detailed methods of the Iowa Women's Health Study have been published elsewhere (10). Briefly, in January 1986, we mailed a baseline 16-page questionnaire to 98,029 eligible women age 55 to 69 years who resided in Iowa. These women were randomly selected from the State of Iowa's Drivers' license list, and the 41,836 respondents (42.7% response rate) form the cohort under study. Rates of breast cancer among responders and non-responders were virtually identical (10).

Risk Factor Assessment. The questionnaire solicited information on factors known or suspected to be relevant to breast cancer risk, including family history of breast cancer, pregnancy history, menstrual history, physical activity, and smoking history. We used the 127-item Willett semiquantitative food frequency questionnaire to assess baseline alcohol

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and energy consumption in 1986; its use for this cohort has been shown (11). Average daily alcohol intake over the previous year was calculated from summing across all alcoholic beverages the product of the frequency of consumption of each of red wine, white wine, beer, and liquor by the nutrient content of each item's serving size. Women reported current height and weight at baseline as well as weight at age 18, 30, 40, and 50 years. From this list of weights, we defined weight at menopause as a woman's weight at the age closest to her reported age at menopause. A paper tape measure and written instructions were enclosed so that a friend could measure the circumference of the waist (1 inch above the umbilicus) and hips (maximal protrusion) according to a validated protocol (12). Anthropometric measures were used to derive the BMI [weight (kg)/height (m)²] and the ratio of the waist circumference to that of the hips (waist-to-hip ratio).

Follow-up. We mailed follow-up questionnaires in 1987, 1989, 1992, and 1997 to establish vital status and change of address. Through linkage with the National Death Index, we identified nonrespondents who were deceased. We ascertained additional deaths and cancer incidence through the State Health Registry of Iowa, a part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program (13). Annually, we matched by computer a list of cohort members and the records of Iowans with incident cancer in the Health Registry using combinations of first, last, and maiden name; zip code; birth date; and Social Security number.

Exclusion Criteria. For the analyses presented here, we excluded women at baseline if they were not postmenopausal ($n = 569$), had had a mastectomy or partial breast removal ($n = 1,870$), had any cancer other than skin cancer at baseline ($n = 2,292$), or were missing weight information ($n = 1,871$). We also excluded an additional 1,574 women with onset of menopause at age <35 years, because we were studying weight change between age 30 years and menopause in both analyses. These exclusions left a total of 33,660 women eligible for analysis.

Analytic Methods. The length of follow-up for each individual in the study was calculated as the time from completion of the baseline questionnaire to the date of breast cancer diagnosis, date of move from Iowa, or date of death. If none of these events applied, the woman was assumed to be cancer free and living in Iowa through December 31, 2000. Women continued to be followed and contributed additional person-years if diagnosed with a cancer other than breast cancer.

Risk ratios (RR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression analysis. Survival was modeled as a function of age, because age is a better predictor of breast cancer risk in this cohort than length of follow-up time (14). We defined two primary risk factor models: (a) combinations of weight change from the time intervals age 18 to 30 years and from age 30 years to menopause and (b) combinations of weight change from the time intervals age 30 years to menopause and from menopause to baseline. Weight change was categorized as weight gain (increase of at least 5% body weight from beginning to end of interval), weight loss (decrease of at least 5% body weight), or no change (change in body weight of <5%). This cut point was selected based on the distribution of weight change variables before any analyses of breast cancer. To avoid groups with sparse cells, the initial weight change categories combined the no change and weight loss groups. In all analyses, women who gained weight during both the first and the second time intervals within each risk factor model were defined as the reference group, as this was the most common category and provided the most stable baseline rates on which to show comparison. Two sets of regression models were fitted: one adjusting only for age and one adjusting for both age and

potential confounding variables associated with the development of breast cancer: BMI at age 18 years, age at menopause, education, age at menarche, oral contraceptive use, use of hormone replacement therapy (HRT), number of live births, age at first live birth, smoking status, and alcohol consumption. All statistical tests were two sided and all analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) and Splus (Insightful, Inc., Seattle, WA) software systems.

Results

Through December 31, 2000 after 15 years and >440,000 person-years of follow-up, 1,987 incident breast cancers were identified in the cohort at risk. On average, women gained weight over time (Fig. 1). Mean weight at age 18 years was 122 pounds, at age 30 years was 132 pounds, at age 50 years was 146 pounds, and at baseline (age 55-69 years) was 153 pounds. Gaining weight consistently throughout adult life was the most common pattern of weight change in this population; 30% of women gained weight both from age 30 years to menopause and after the menopause to the 1986 baseline, whereas 39% of women gained weight both from age 18 to 30 years and from age 30 years to menopause. Baseline measurements of BMI and waist and hip circumferences of the women within each of the patterns of weight change categories are given in Table 1. Predictably, women who gained weight in both time intervals in each risk factor model were markedly heavier compared with women who gained in one interval and lost or maintained in the other interval, whereas those women who either did not change or lost weight in both intervals were markedly lighter. The timing of weight change was not associated with body size at baseline. There were no differences in baseline BMI and waist or hip measurements between women who gained then lost weight, who gained then maintained, or who were weight steady then gained weight in either of the models.

The distribution of weight gain from age 30 years to menopause by potential confounding variables is shown in Table 2. Women who gained weight in each of the intervals studied (age 18-30 years, age 30 years to menopause, and from the menopause to baseline) were more likely to have a low BMI at age 18 years, increased parity, and low physical activity. Women who gained weight from age 30 years to menopause were also more likely to have a later menopause, to not use HRT, to be older at first birth, to be former or never smokers, and to consume more calories and less alcohol.

Rates of breast cancer in the different weight change categories are shown in Table 3. The highest rates of breast cancer were observed among women who gained weight in both time intervals for each risk factor model. The RR of

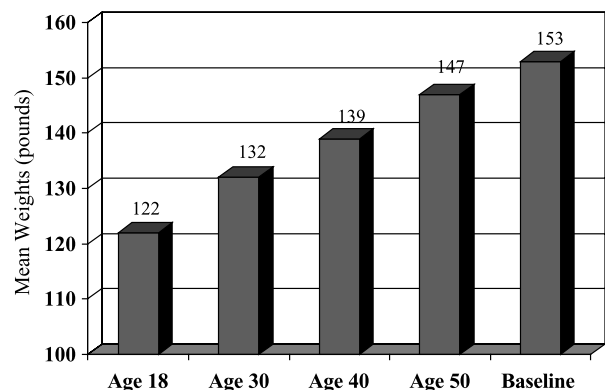


Figure 1. Mean weights of women over time.

Table 1. Distribution of baseline anthropometric variables across categories of weight change

Risk factor model	Initial interval	Subsequent interval	Initial weight change	Subsequent weight change	% of Cohort with pattern of change	Baseline BMI (kg/m ²)	Baseline waist circumference (in)	Baseline waist-to-hip ratio
1	Age 30 y to menopause	Menopause to baseline	Gain	Gain	30	30.1 (5.0)	37.7 (5.2)	0.863 (0.083)
				No change	23	26.7 (4.4)	34.4 (4.9)	0.839 (0.084)
				Loss	8	26.3 (4.9)	34.3 (5.4)	0.841 (0.087)
				No change/loss	17	27.1 (4.4)	34.6 (5.0)	0.837 (0.085)
				No change	18	23.3 (3.2)	30.7 (4.0)	0.798 (0.079)
2	Age 18-30 y	Age 30 y to menopause	Gain	Gain	39	22.6 (4.1)	30.6 (4.7)	0.811 (0.079)
				No change	15	29.2 (5.2)	36.9 (5.5)	0.860 (0.085)
				Loss	4	26.0 (4.5)	33.6 (5.0)	0.830 (0.084)
				No change/loss	4	26.7 (5.2)	34.4 (5.8)	0.838 (0.095)
				Gain	23	26.8 (4.4)	34.4 (4.9)	0.834 (0.081)
				No change	17	23.6 (3.4)	30.9 (4.1)	0.801 (0.078)
				Loss	2	23.4 (4.6)	30.8 (5.1)	0.802 (0.075)

NOTE: Values are means (SD).

breast cancer associated with weight gain from age 30 years to menopause following an interval of no weight change (model 1) or before a period of no weight change after the menopause (model 2) were not significantly lower than the reference category of women who gained weight in both intervals; women who lost or maintained weight from age 18 to 30 years and who gained weight between age 30 years and menopause had a RR (95% CI) of 0.91 (0.81-1.03; model 1), whereas women who had gained weight from age 30 years to menopause only and maintained weight after the menopause had a RR (95% CI) of 0.93 (0.82-1.04).

Lowest rates of breast cancer were observed among women who maintained or lost weight in the initial interval with additional loss in the subsequent interval regardless of the risk factor model considered. Compared with women who gained weight in both intervals, women who lost or maintained weight from age 18 to 30 years and who lost weight from age 30 years to menopause had a RR (95% CI) of 0.35 (0.21-0.59; model 2) and women who lost or maintained weight from age 30 years to menopause and who lost weight after the menopause had a RR (95% CI) of 0.46 (0.34-0.64; model 1).

Compared with the reference category of women who gained weight in both intervals in the first risk factor model, weight gain from age 18 to 30 years was not associated with an increased risk of breast cancer when subsequent weight from age 30 years to menopause was either unchanged (RR, 0.76; 95% CI, 0.66-0.88) or decreased (RR, 0.62; 95% CI, 0.47-0.82). These relative risks were similar to that among women whose weight remained stable in both time intervals (RR, 0.71; 95% CI, 0.61-0.82). Likewise, compared with the reference category of women who gained weight in both intervals in the second risk factor model, weight gain from age 30 years to menopause was not associated with increased risk of breast cancer if subsequent weight decreased after the menopause (RR, 0.78; 95% CI, 0.65-0.94). This relative risk was slightly higher than that for women whose weight remained stable in both time intervals (RR, 0.62; 95% CI, 0.54-0.72).

Although we were interested in whether weight gain at different times of adult life was associated with different magnitudes of subsequent breast cancer risk, a complicating factor was that the average weight gain between age 30 years and menopause (15 pounds) was greater than the average weight gain between age 18 to 30 years (10 pounds) and after the menopause (6 pounds). Thus, we did additional analyses in which combinations of weight change were treated as continuous rather than categorical variables. For a given combination, models were fit that simultaneously included weight change in the first interval, weight change in the second interval, and the corresponding interaction as well as the same

potential confounding variables mentioned previously. The resulting relative risk functions are shown in Fig. 2. Results seem to suggest that weight gain between age 30 years and menopause was associated with greater risk than weight gain between age 18 and 30 years.

We did additional analyses to explore whether the association between weight change and breast cancer risk was modified by family history, level of physical activity, occupational status, calorie intake, or type of alcohol consumed (i.e., beer/red wine/white wine/liquor). No material differences were observed (data not shown). Analyses excluding the first 2 years of follow-up also did not alter the results (data not shown). For 2,015 women, age at menopause was closer to baseline age than it was to age 50 years. A sensitivity analysis excluding these women from the analyses did not affect the results. We examined whether the relationship between weight change and breast cancer risk was modified by the use of HRT by stratifying the analyses according to never and ever users of HRT. There was no difference, suggesting that HRT did not modify the relationship between weight change over adult life and risk of breast cancer (data not shown).

Discussion

The current study has several important findings. First, the highest rates of postmenopausal breast cancer were observed among women who progressively gained weight throughout adulthood. Second, loss of weight, regardless of when it was initially gained during adulthood, was associated with a lower risk of postmenopausal breast cancer compared with the typical pattern observed in this cohort of continued weight gain. For example, weight loss from age 30 years to menopause among women who had gained weight between age 18 and 30 years resulted in incidence rates similar to those of women who did not initially gain weight. This observation should serve as motivation and reinforcement to women that loss of weight may be an effective breast cancer risk reduction strategy. Third, although somewhat speculative, is the impression that weight gain after age 30 years was more deleterious than weight gain between age 18 and 30 years. This inference was based primarily on the observation that the incidence rates of breast cancer for women who gained weight before age 30 years but not subsequently was 400 per 100,000 per year, whereas women who gained weight from age 30 years to menopause but not subsequently had incidence rates of 488 per 100,000 per year. It is important to note that these rates are statistically indistinguishable from each other and further follow-up of this cohort is needed to resolve whether this

apparent pattern is real. Moreover, women who gained weight before age 30 years but not subsequently still had higher rates of breast cancer than women who maintained weight throughout their adult life.

Several previous studies have examined whether weight gain is a risk factor for breast cancer. Far less is known whether the timing of such weight gain during adult life is important. Greater weight in early adulthood (age 18-20 years; refs. 4, 5, 15) and at first full-term pregnancy (8) seems to decrease subsequent risk of both premenopausal and postmenopausal breast cancer. The apparent greater risk associated with weight gain in the later premenopausal years (i.e., from age 30 years to menopause) in our analysis is consistent with the findings of Trentham-Dietz et al. (16) who associated weight gain after age 30 years with a slightly greater risk of breast cancer [odds ratio (OR), 1.15; 95% CI, 1.08-1.23] than weight gained between age 21 and 30 years (OR, 1.09; 95% CI, 1.05-1.11). Zeigler et al. (7) reported women who had gained ≥ 11 pounds in the fourth decade to have 2.3 times the risk of developing breast cancer in their 50s compared with women in the bottom quintile (RR, 2.6; 95% CI, 1.21-4.21). Two other case-control studies have observed that both excess weight at age 25 years (17) and at age 30 years (18) and that weight gain since age 25 and 30 years, respectively, increased breast cancer risk.

The biological effect of weight gain may in part depend on the influence of other hormone-related variables, such as puberty, pregnancy, lactation, and menopause. For example, weight gain during pubescent years is distributed primarily on the hips and buttocks (gynoid), whereas weight gain during adult years (including during pregnancy and menopause) accumulates preferentially around the waist (android; refs. 3, 19). Several studies have reported that abdominal adiposity (a high waist-to-hip ratio) is a risk factor for postmenopausal breast cancer (4, 20), although the data are not entirely consistent (21).

Given the overwhelming evidence that obesity is a risk factor for breast cancer, it would seem to be important to explore any possible benefit of weight loss. However, there are no direct clinical trial data and few observational data on the subject. Previous reports have linked weight loss after age 35 years (ref. 22; OR, 0.8; 95% CI, 0.69-0.94), between ages 22 and 44 years (OR with >10 kg weight loss, 0.6; 95% CI, 0.3-1.3; ref. 23), and before but not after age 45 years (ref. 16; OR per 5 kg weight loss, 0.9; 95% CI, 0.84-0.98) with reduction in risk of postmenopausal breast cancer. A study among 490 American Asian women in their early 50s provided suggestive evidence that weight loss in the previous decade of life may reduce risk of postmenopausal breast cancer, but the 95% CIs were wide and thus consistent with no effect (RR, 0.69; 95% CI, 0.29-1.66; ref. 7). A further study reported an inverse association between weight loss after age 45 years and risk of postmenopausal breast cancer (OR for weight loss of >10 kg, 0.6; 95% CI, 0.3-1.2; ref. 23), but the 95% CIs included the null value of 1.0.

The benefits of weight loss compared with weight maintenance on breast cancer risk were consistent regardless of the period of initial or subsequent weight gain. That is, the relative risks and incidence rates were always lower for the "loss" category than that for the "no change" category. However, it is important to note that only for model 2 and among women who maintained weight between age 18 and 30 years were the differences statistically significant (RR, 0.36; 95% CI, 0.22-0.60 versus RR, 0.73; 95% CI, 0.64-0.84). Previous studies have also failed to show the benefits of weight loss compared with weight maintenance on breast cancer risk (8, 16, 22, 24-27). Some studies have even reported a weak positive association between weight loss, in comparison with weight maintenance, on breast cancer risk (4, 17).

Loss or gain of weight after the menopause was not associated with a material difference in risk of breast cancer in this analysis compared with the apparent effect of weight loss before menopause. Previous cohort studies have associ-

ated weight gain after the menopause with nonsignificant increases in risk (4). A recent analysis from the Women's Health Initiative (15) found that weight loss after the menopause was associated with lower breast cancer risk compared with the more usual situation of weight gain over this time. However, the association seemed to be restricted to the subset of women who had never taken HRT (15). One possible explanation for this observation is that HRT may obscure a potential relationship between weight change and breast cancer risk by elevating levels of estrogen among both lean and overweight postmenopausal women (28). This did not seem to be the case in the current study, as there was no differential association between weight change after the menopause and breast cancer within strata of HRT use.

The apparent benefits of weight loss were contingent on maintenance of such weight losses. Weight loss maintenance is notoriously difficult to achieve. A recent survey however reported 25% of successful dieters managed to maintain their

Table 2. Distribution of other risk factors by weight change pattern from age 30 years to menopause

Variable	Weight gain, n (%)	No change, n (%)	Weight loss, n (%)
BMI at age 18 y			
≤18.6	4,656 (70.7)	1,760 (26.7)	168 (2.6)
18.7-20.0	4,786 (63.8)	2,455 (32.7)	264 (3.5)
20.1-21.1	3,438 (60.8)	1,954 (34.6)	259 (4.6)
21.2-22.9	4,135 (57.6)	2,552 (35.5)	493 (6.9)
>22.9	3,576 (53.8)	2,247 (33.8)	830 (12.5)
Age at menopause (y)			
<45	2,951 (42.1)	3,625 (51.7)	431 (6.2)
45-49	6,025 (65.2)	2,622 (28.4)	599 (6.5)
50-54	9,141 (66.8)	3,769 (27.6)	772 (5.6)
≥55	2,527 (67.8)	979 (26.3)	219 (5.9)
Education level			
Less than high school	1,745 (61.0)	912 (31.9)	203 (7.1)
High school	10,768 (61.9)	5,520 (31.8)	1,100 (6.3)
High school or higher	8,087 (60.7)	4,532 (34.0)	713 (5.4)
Age at menarche (y)			
<12	3,194 (61.9)	1,592 (30.8)	377 (7.3)
12	5,516 (61.2)	2,918 (32.4)	586 (6.5)
13	6,027 (60.4)	3,370 (33.8)	578 (5.8)
≥14	5,771 (62.2)	3,050 (32.9)	465 (5.0)
Oral contraceptive use			
Never	16,533 (61.3)	8,856 (32.8)	1,605 (6.0)
Ever	4,043 (61.7)	2,101 (32.1)	407 (6.2)
HRT			
Never	13,330 (63.5)	6,421 (30.6)	1,227 (5.9)
Ever	7,118 (57.6)	4,459 (36.1)	779 (6.3)
No. live births			
0	1,609 (55.9)	1,058 (36.8)	210 (7.3)
1-2	6,220 (58.4)	3,707 (34.8)	717 (6.7)
3-4	8,358 (62.5)	4,275 (31.9)	750 (5.6)
>4	4,356 (66.2)	1,889 (28.7)	331 (5.0)
Age at first live birth (y)			
<20	3,981 (61.4)	2,034 (31.4)	465 (7.2)
20-24	9,361 (61.4)	4,946 (32.5)	928 (6.1)
25-29	4,179 (62.2)	2,235 (33.2)	309 (4.6)
≥30	1,308 (65.6)	598 (30.0)	88 (4.4)
Smoking status			
Current	2,372 (48.3)	2,057 (41.9)	482 (9.8)
Former	3,847 (59.9)	2,156 (33.6)	415 (6.5)
Never	14,130 (64.7)	6,619 (30.3)	1,099 (5.0)
Daily alcohol consumption (g)			
0	11,861 (63.2)	5,751 (30.6)	1,156 (6.2)
≤4	4,918 (61.1)	2,663 (33.1)	470 (5.8)
>4	3,865 (56.5)	2,581 (37.7)	395 (5.8)
Physical activity level			
Low	9,927 (63.8)	4,724 (30.4)	913 (5.9)
Moderate	5,574 (60.8)	3,082 (33.6)	520 (5.7)
High	4,784 (57.3)	3,012 (36.1)	558 (6.7)
Total caloric intake			
<1,375	4,520 (58.6)	2,644 (34.3)	554 (7.2)
1,376-1,275	4,886 (60.8)	2,652 (33.0)	494 (6.2)
1,725-2,125	4,850 (62.2)	2,488 (31.9)	462 (5.9)
>2,125	5,032 (63.9)	2,473 (31.4)	367 (4.7)

Table 3. Association of premenopausal and postmenopausal weight change with breast cancer

Risk factor model	Initial interval	Subsequent interval	Initial weight change*	Subsequent weight change*	No. cases	Person-years	Incidence [†]	RR (95% CI) [‡]	RR (95% CI) [§]	
1	Age 30 y to menopause	Menopause to baseline	Gain	Gain	710	132,929	530	1.00 (Reference)	1.00 (Reference)	
				No change	494	102,131	488	0.93 (0.83-1.04)	0.93 (0.82-1.04)	
				Loss	148	36,683	404	0.77 (0.64-0.92)	0.78 (0.65-0.94)	
				No change/loss	Gain	325	73,973	437	0.83 (0.72-0.94)	0.82 (0.72-0.94)
					No change	266	79,989	334	0.63 (0.55-0.73)	0.62 (0.54-0.72)
2	Age 18-30 y	Age 30 y to menopause	Gain	Gain	879	171,216	513	1.00 (Reference)	1.00 (Reference)	
				No change	272	67,562	400	0.78 (0.68-0.89)	0.76 (0.66-0.88)	
				Loss	55	17,737	310	0.61 (0.46-0.80)	0.62 (0.47-0.82)	
				No change/loss	Gain	471	99,828	473	0.93 (0.83-1.03)	0.91 (0.81-1.03)
					No change	289	76,825	376	0.73 (0.64-0.84)	0.71 (0.61-0.82)
					Loss	15	8,581	176	0.36 (0.22-0.60)	0.35 (0.21-0.59)

*Weight gain (loss) defined as increase (decrease) of at least 5% of body weight from beginning to end of interval.

[†]Age-adjusted incidence per 100,000 person-years.

[‡]Accounting for age at baseline.

[§]Accounting for age at baseline, BMI at age 18 years, age at menopause, education, age at menarche, oral contraceptive use, HRT, number of live births, age at first live birth, smoking status, and alcohol consumption.

weight loss for at least 5 years (29) and should refute the notion that all attempts at weight loss are ill fated. At worst, attempts to lose weight are known to limit the unremitting trend to gain weight over adult life (30). Weight maintenance over adult life

(from age 18 years to postmenopausal years) has been associated with a 30% to 60% lower risk of postmenopausal breast cancer compared with the largest weight gainers within previous studies (4, 6, 22-25, 27, 31-33).

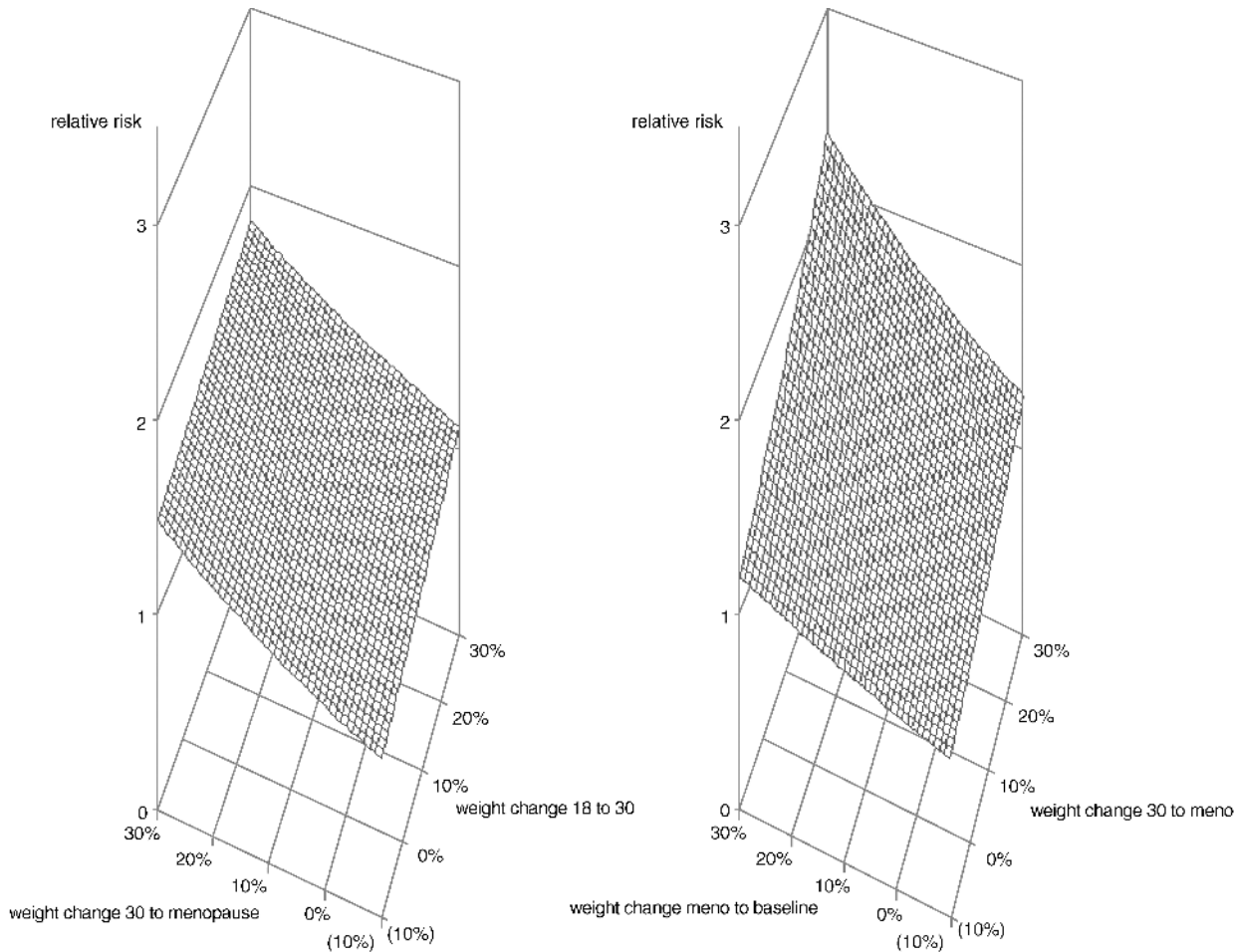


Figure 2. Predicted relative risk of postmenopausal breast cancer based on models with different combinations of continuously distributed weight change variables. Models were fit using Cox proportional hazards regression, fitting simultaneously weight change in the first interval, weight change in the second interval, and the corresponding interaction. RRs are adjusted for age at baseline, BMI at age 18 years, age at menopause, education, age at menarche, oral contraceptive use, HRT, number of live births, age at first live birth, smoking status, and alcohol consumption.

The current study has several notable strengths. The large sample size and extensive data collection at baseline allowed for adjustment for many potential confounders. The data on recalled weight permitted systematic assessment of weight change in different periods of adult life. Validation studies have shown good correlations between self-reported and actual measurements of current weight within this cohort (12). Others have reported good conciliation between recall and existing records of weight at age 20 years (correlation of 0.87; ref. 34). The potential to underreport weight and weight change among overweight subjects (35) would, if anything, have weakened the associations shown here.

Despite these strengths, several limitations should be considered when interpreting these results. Although we were interested in whether weight gain at different times of adult life was associated with different magnitudes of subsequent breast cancer risk, adult weight gain is *also* associated with changes in the distribution of body fat, with some evidence that peripheral obesity is particularly increased (36). Because central fat seems to be a risk factor for breast cancer, it might have been more important to examine changes in fat distribution. Unfortunately, the design of the study precluded the ability to do so. Weight at menopause was not ascertained from direct questioning but was defined as one of the self-reported weights at either age 30, 40 or 50 years, which was closest to her age at menopause. This may mean that any changes in weight occurring around the time of the menopause may not necessarily be accounted for in our analysis. Finally, the issue of generalizability must be considered. The Iowa population is primarily Caucasian; thus, the findings in this study may not be generalizable to other racial ethnic groups. However, the observed patterns of weight gain over the premenopausal and postmenopausal years in this cohort are representative of those seen among the general population in the United States (2).

The major public health message is that avoiding adult weight gain, or arresting the unremitting weight gain over adult life, should be encouraged. For women who have gained weight, successful weight loss may lower breast cancer risk. A 5% weight loss represents a realistic goal that has been associated with significant reductions in cardiovascular disease (37) and type II diabetes (38). Given the increasing prevalence of overweight among women in western societies, prevention of weight gain and successful weight loss programs could bring about significant reductions in breast cancer rates.

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