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ARTICLE

Intentional Weight Loss and Obesity-Related Cancer Risk

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Abstract

Background: Epidemiologic studies regarding weight loss and subsequent cancer risk are sparse. The study aim was to evaluate the association between weight change by intentionality and obesity-related cancer incidence in the Women's Health Initiative Observational Study. Eleven cancers were considered obesity related: breast, ovary, endometrium, colon and rectum, esophagus, kidney, liver, multiple myeloma, pancreas, stomach, and thyroid.
Methods: Postmenopausal women (n = 58 667) aged 50–79 years had body weight and waist circumference (WC) measured at baseline and year 3. Weight or WC change was categorized as stable (change $< \pm 5\%$), loss ($\geq 5\%$), and gain ($\geq 5\%$). Self-report at year 3 characterized weight loss as intentional or unintentional. During the subsequent 12 years (mean) of follow-up, 6033 incident obesity-related cancers were identified. Relationships were evaluated using multivariable Cox proportional hazards regression models.
Results: Compared to women with stable weight, women with intentional weight loss had lower obesity-related cancer risk (hazard ratio [HR] = 0.88, 95% confidence interval [CI] = 0.80 to 0.98). A similar result was observed for intentional WC reduction (HR = 0.88, 95% CI = 0.80 to 0.96). Among all cancers, intentional weight loss was most strongly associated with endometrial cancer (HR = 0.61, 95% CI = 0.42 to 0.88). Intentional WC loss was also associated with lower colorectal cancer risk (HR = 0.79, 95% CI = 0.63 to 0.99). Unintentional weight loss or weight gain was not associated with overall obesity-related cancer risk.
Conclusion: Intentional weight or WC loss in postmenopausal women was associated with lower risk of obesity-related cancer. These findings suggest that postmenopausal women who intentionally lose weight can reduce their obesity-related cancer risk.

Currently, more than 39% of adults in the Unites States are obese (1). A recent reassessment by the International Agency for Research on Cancer based on more than 1000 epidemiologic studies identified 13 cancers that have sufficient evidence to be considered to be obesity-related cancers, including those of the esophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, breast (postmenopausal), corpus uteri, ovary, kidney (renal cell), meningioma, and thyroid, as well as multiple myeloma (2).

The evaluation of body weight and cancer has been predominantly based on risk associated with excess body weight rather than on the risk associated with weight loss (2). A recent update of the US Preventive Services Task Force on weight loss and obesity-related morbidity identified health outcomes data

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associated with weight loss as a high priority for future studies (3). Some evidence exists from follow-up of patients undergoing bariatric surgery that intentional weight loss is related to reduced cancer risk (4,5). Evidence also exists in experimental animals for a cancer-preventive effect of calorie restriction (6,7). However, epidemiologic studies regarding weight loss and subsequent cancer risk are sparse.

The results of previous epidemiological studies that investigated the relationship between weight loss and risk of cancer, mainly limited to breast cancer or colorectal cancer, are conflicting (8–10). These mixed findings preclude a strong public health message that people who are overweight or obese could reduce their cancer risk by losing weight. The lack of a standard definition of the weight loss exposure measure may be contributing to the mixed observational study findings. In addition, unintentional weight loss is highly correlated with increased morbidity and mortality and may contribute to reverse causality in observational studies that do not account for intentionality (11–13). Finally, most previous prospective studies used recalled information on past weight rather than direct measures of weight. Given the worldwide obesity epidemic and the established link between obesity and increased risk of many cancers, studies examining whether weight loss is associated with a reduction in cancer risk are needed to provide critical evidence for cancer-preventive interventions. This is particularly important for those people with obesity, because a relevant question for them is whether losing weight will reduce their risk of cancer.

The Women's Health Initiative (WHI) Observational Study (OS) provided a unique opportunity to evaluate the association between weight loss by intentionality and obesity-related cancer risk. In the WHI-OS, weight was measured at baseline and at year 3. In addition, weight loss intentionality was specifically assessed by self-report at year 3. In the present study, we examined the association of weight loss by intentionality with 11 of the 13 cancers judged by the International Agency for Research on Cancer to have sufficient evidence to be considered obesity-related (2). Gallbladder and meningioma were excluded because WHI does not have individual-level data for these two cancers. The primary analysis focused on all 11 obesity-related cancer types combined into one analysis with exploratory analyses examining associations with individual cancers. Further, we explored whether the associations between weight loss and obesity-related cancer risk are modified by covariates, such as race and ethnicity, smoking, baseline body mass index (BMI), and hormone therapy use. The goal was to test the hypothesis that intentional weight loss is associated with subsequent reductions in the risk of obesity-related cancer.

Methods

Women's Health Initiative

The WHI was designed to address major causes of morbidity and mortality in postmenopausal women (14) and included both a set of clinical trials and an OS. Details of the design and implementation of the WHI program have been published elsewhere (15–19). Briefly, a total of 161 808 women ages 50 to 79 years with anticipated survival greater than 3 years were recruited at 40 clinical centers throughout the United States between September 1, 1993, and December 31, 1998. Participants in the OS included 93 676 women who were ineligible or uninterested in participating in the clinical trials or were directly invited to participate in the OS. The study was approved by institutional review boards at the clinical centers, and participants provided written informed consent.

Study Population

The study considered only WHI-OS participants. The following participants were excluded for this analysis: women who had a history of cancer (except nonmelanoma skin cancer) (n = 10, 197) at baseline; women who were enrolled in the WHI but provided no follow-up information (n = 421); women with a missing value of weight or waist circumference (WC) at baseline (n = 671); women with missing value of weight or WC at year 3 (n = 14 306); women with missing data on whether weight change was intentional or unintentional (n = 4198); women with BMI less than 18.5 kg/m^2 (underweight) or missing (n = 1168); women with missing information on other covariates (including education, smoking pack-years, and alcohol intake) (n = 2676); or women who were diagnosed with any of the cancers of interest, died, or were lost to follow-up between baseline and year 3 visit (n = 1372). After exclusions, 58 667 women remained for further analysis. We compared baseline characteristics and incidence of obesity-related cancer between the remaining sample and women who were excluded because of missing values (n = 21 116). Compared with the remaining sample, women who were excluded because of missing values were more likely to be African American and have slightly lower incidence of obesity-related cancer, lower physical activity, and higher baseline BMI and higher WC (Supplementary Table 1, available online).

Exposures

Weight and height were measured in the WHI-OS at clinic visits by trained staff with a balance-beam scale and stadiometer using a standardized protocol at baseline and year 3. Weight and height were used to calculate BMI (weight [kg]/height [m^2]). Hip and WC were also measured at baseline and year 3. WC was measured at the natural waist or narrowest part of the torso to the nearest 0.5 cm.

Weight Change Between Baseline and Year 3. We calculated the weight change between baseline and year 3 and assigned each participant's change in body weight to one of three categories: stable weight, weight loss, or weight gain. The three categories were defined based on percentage change in body weight: stable weight (change of less than 5% from baseline weight), weight loss (decrease of 5% or more from baseline), and weight gain (increase of 5% or more from baseline). A cut point of 5% was used because weight-related comorbidities improve with this amount of weight loss (20).

WC Change Between Baseline and Year 3. Similarly, in the WHI-OS, WC change between baseline and year 3 was also calculated and categorized as follows: stable (<5% change from baseline), loss (decrease of 5% or more since baseline), and gain (increase of 5% or more since baseline). In addition, at year 3 follow-up in the WHI-OS, women were asked, "In the past two years, did you lose five or more pounds not on purpose at any time?" The information was used to categorize weight loss between baseline and year 3 as "intentional" or "unintentional."

Covariates

Information on covariates of interest came from baseline and was collected using self-administered questionnaires. Information on menopausal hormone therapy use was collected

during interviews with review of medication containers. Race and/or ethnicity was self-reported. We considered the following potential confounders at baseline: age (<55, 55–59, 60–64, 65–69, 70–74, >75 years); race and/or ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black, Hispanic or Latino, non-Hispanic white, and other); level of education (high school or less, some college or technical training, college or some post-college, and master or higher); pack-years of smoking (never, <10, 10–<20, 20–<30, 30–<40, ≥40 pack-years); alcohol intake (nondrinker, past drinker, current and <7 drinks per week, current and ≥7 drinks per week); recreational physical activity (total metabolic equivalent tasks hours per week: <5, 5–<10, 10–<20, 20–<30, >30); history of hormone therapy use (none, estrogen alone, estrogen and progestin, mixed); family history of cancer (no, yes); and BMI and WC at baseline.

Outcome

All obesity-related incident cancer cases were considered as outcomes, including cancers of the breast, ovary, endometrium, colon and rectum, esophagus (adenocarcinoma), kidney, liver, pancreas, gastric cardia, and thyroid, as well as multiple myeloma. Our primary objective was to analyze the 11 cancers combined as the major outcome. Each individual cancer was examined as a secondary objective. As of March 31, 2018, in the analytic sample of 58 667 women, a total of 6033 incident obesity-related cancers had been ascertained, including 3355 invasive breast cancers, 574 endometrial cancers, 410 ovarian cancers, 921 colorectal cancers, 374 pancreatic cancers, 225 kidney cancers, 167 thyroid cancers, 202 cases of multiple myeloma, and 139 at the remaining sites (13 esophageal adenocarcinoma, 103 liver cancers, and 23 gastric cardia cancers).

Statistical Analysis

Cox proportional hazards regression models were used to evaluate the relationship (hazard ratios [HRs] and 95% confidence intervals [CIs]) between weight or WC change and obesity-related cancer incidence. The assumptions of proportionality were satisfied for all exposure variables of interest and potential confounding variables. In the multivariable-adjusted models, potential confounders included the variables listed in the Covariates section above. Tests for multiplicative interaction by race and/or ethnicity, BMI at baseline, smoking, and hormone therapy use were performed. In addition, cancer-specific confounders were considered. For breast cancer, we additionally adjusted for family history of breast cancer, history of hormone therapy use, age at menopause, parity, and Gail risk score.

To minimize possible reverse causation, we performed a sensitivity analysis after excluding the first 2 years of follow-up. We also performed another sensitivity analysis after excluding women who were 70 years or older at baseline, because as a group, women at this age lose weight and intentionality is more difficult to assess given changes in life circumstances (11). We conducted a sensitivity analysis for endometrial and ovarian cancer by excluding women with hysterectomy and oophorectomy, respectively. Finally, a restricted cubic spline analysis (21) was performed to investigate possible nonlinear effects of weight loss.

Results

Among 58 667 women, 67.2% had stable weight, 19.5% had weight gain, 7.9% had intentional weight loss, and 5.4% had unintentional weight loss between baseline and year 3. Table 1 shows baseline characteristics of participants by weight change category. Compared to women with stable weight, women with intentional weight loss were more likely to be younger, non-Hispanic white, have some college education, be past smokers and past alcohol drinkers, have fewer children, be never hormone users, be physically inactive, and have higher BMI and higher WC (Table 1).

As shown in Table 2, compared with women with stable weight, women with intentional weight loss (≥5% from baseline weight) had lower obesity-related cancer risk (HR = 0.88, 95% CI = 0.80 to 0.98). We did not observe statistically significant associations between either unintentional weight loss (HR = 0.99, 95% CI = 0.88 to 1.12) or weight gain (HR = 1.04, 95% CI = 0.98 to 1.11) and risk of obesity-related cancer risk.

Among individual cancers, endometrial cancer had the strongest association with intentional weight loss and lower risk (HR = 0.61, 95% CI = 0.42 to 0.88). The HR for ovarian cancer was similar to endometrial cancer but not statistically significant (HR = 0.69, 95% CI = 0.45 to 1.07). Lower risk of breast cancer was associated with weight loss regardless of intentionality (HR = 0.88, 95% CI = 0.79 to 0.98). We also observed that unintentional weight loss was associated with risk for liver cancer (HR = 2.54, 95% CI = 1.33 to 4.86). Other associations were not statistically significant (Table 2).

A similar lower obesity-related cancer risk was observed for intentional WC reduction compared with women with stable WC (HR = 0.88, 95% CI = 0.80 to 0.96). Endometrial cancer again had the largest reduction in risk associated with intentional WC loss (HR = 0.67, 95% CI = 0.50 to 0.92). Further, we observed lower risk of colorectal cancer associated with intentional WC reduction (HR = 0.79, 95% CI = 0.63 to 0.99). Similarly, unintentional WC reduction was associated with an increased risk for liver cancer. All other associations were not statistically significant (Table 3).

An analysis stratified by baseline BMI showed that the lower risk of obesity-related cancer associated with intentional weight loss was present only among women with obesity (HR = 0.83, 95% CI = 0.71 to 0.99), although the interaction between weight change and obesity status was not statistically significant. The relationship between intentional weight loss and the risk of obesity-related cancer was not substantially modified by race and/or ethnicity, smoking status, or hormone use (Table 4).

Supplementary Tables 2–3 (available online) provide the number of cases for each outcome corresponding to those shown in Tables 2–4.

A sensitivity analysis after excluding the first 2 years of follow-up revealed similar results to those presented above (results not shown). Another sensitivity analysis after excluding women who were at least 70 years old at baseline showed a slightly greater risk reduction for obesity-related cancer associated with intentional weight loss (HR = 0.85, 95% CI = 0.75 to 0.95). We also performed an analysis by categorizing weight change into stable weight (change within ±4.5 kg), weight loss (≥4.5 kg from baseline weight), and weight gain (≥4.5 kg from baseline weight) based on actual change in body weight. We observed that there was a statistically significant increased risk for obesity-related cancer among women with weight gain of 4.5 kg or more relative to women with stable weight (HR = 1.08, 95% CI = 1.01 to 1.17). We performed a sensitivity analysis for endometrial cancer by excluding women with hysterectomy and for ovarian cancer by excluding women with oophorectomy, and results were similar. Finally, the restricted cubic spline analysis revealed a *P* value for the test for

Table 1. Baseline characteristics of participants by weight change between baseline and year 3*

Variable	Stable weight N = 39 424 (mean = 0.4%, range = within ±5%)	Weight gain N = 11 440 (mean = 9.3%, range = 5.0% to 44.6%)	Unintentional weight loss N = 3174 (mean = −9.6%, range = −38.6% to −5.0%)	Intentional weight loss N = 4629 (mean = −9.4%, range = −41.7% to −5.0%)
Age, mean (SD), y	63.7 (7.2)	61.5 (7.1)	66.1 (7.3)	63.3 (7.3)
Race/ethnicity (%)				
American Indian	130 (0.3)	56 (0.5)	15 (0.5)	22 (0.5)
Asian/Pacific Islander	1300 (3.3)	290 (2.5)	86 (2.7)	95 (2.1)
African American/black	2491 (6.3)	861 (7.5)	265 (8.3)	325 (7.0)
Hispanic	1245 (3.2)	386 (3.4)	109 (3.4)	134 (2.9)
Non-Hispanic white	33 728 (85.6)	9697 (84.8)	2660 (83.8)	4006 (86.5)
Education (%)				
High school diploma	7737 (19.6)	2246 (19.6)	748 (23.6)	919 (19.9)
Some college/technical training	13 820 (35.1)	4298 (37.6)	1191 (37.5)	1780 (38.5)
College degree	9909 (25.1)	2679 (23.4)	730 (23.0)	1043 (22.5)
Master or higher	7958 (20.2)	2217 (19.4)	505 (15.9)	887 (19.2)
Smoking (%)				
Never	21 301 (54.3)	5695 (50.0)	1695 (53.7)	2351 (51.1)
Past	16 081 (41.0)	4835 (42.5)	1195 (37.9)	2032 (44.1)
Current	1877 (4.8)	858 (7.5)	265 (8.4)	222 (4.8)
Alcohol use (%)				
Nondrinker	4134 (10.5)	1181 (10.3)	431 (13.6)	519 (11.2)
Past drinker	6455 (16.4)	2187 (19.1)	652 (20.5)	878 (19.0)
<1 drink per month	4361 (11.1)	1455 (12.7)	389 (12.3)	589 (12.7)
<1 drink per week	8079 (20.5)	2442 (21.3)	595 (18.7)	878 (19.0)
1–<7 drinks per week	10 957 (27.8)	2913 (25.5)	709 (22.3)	1191 (25.7)
≥7 drinks per week	5438 (13.8)	1262 (11.0)	398 (12.5)	574 (12.4)
Number of live births (%)				
Never pregnant	3847 (9.8)	1153 (10.1)	336 (10.7)	496 (10.8)
Never had term pregnancy	985 (2.5)	328 (2.9)	85 (2.7)	116 (2.5)
1	3334 (8.5)	1050 (9.2)	290 (9.2)	430 (9.3)
2	10 352 (26.4)	3161 (27.8)	777 (24.7)	1169 (25.4)
3	9837 (25.1)	2712 (23.8)	714 (22.7)	1125 (24.4)
4	5754 (14.7)	1629 (14.3)	464 (14.8)	685 (14.9)
≥5	5114 (13.0)	1356 (11.9)	479 (15.2)	589 (12.8)
Prior hormone use (%)				
No use	14 899 (37.8)	3956 (34.6)	1343 (42.3)	1852 (40.0)
E alone use	12 211 (31.0)	3595 (31.4)	1078 (34.0)	1417 (30.6)
E + P use	9670 (24.5)	3122 (27.3)	583 (18.4)	1071 (23.1)
Mixed use	2644 (6.7)	767 (6.7)	170 (5.4)	289 (6.2)
Family history of cancer	25 196 (66.4)	7255 (66.2)	2036 (67.1)	3048 (68.4)
Physical activity, mean (SD), MET-hours per week	14.5 (14.4)	14.1 (14.4)	11.5 (13.0)	13.3 (14.1)
BMI, mean (SD), kg/m^2	26.6 (5.2)	26.7 (5.2)	27.9 (6.6)	29.9 (7.3)
Waist circumference, mean (SD), cm	83.4 (12.6)	83.6 (12.6)	86.1 (13.9)	88.7 (14.2)

*Values expressed as *n*(%) for categorical variables, mean (SD) for continuous variables. BMI = body mass index; E = estrogen; HR = hazard ratio; MET = metabolic equivalent tasks; P = progestin.

nonlinearity of 0.2, indicating that the association was consistent with a linear relationship of weight change with obesity-related cancer risk. The linear relationship between weight change and cancer risk was statistically significant (P = .03). A similar linear trend was also observed for WC change in relation to risk (Figure 1).

Discussion

In this large prospective study among postmenopausal women, we observed that intentional weight loss was associated with lower overall risk of obesity-related cancers. There was a linear trend between weight or WC change in relation to the overall risk. Among individual cancers, endometrial cancer had the largest reduction in risk associated with intentional weight loss. Similar results were observed for intentional WC reduction. We observed lower risk of breast cancer associated with weight loss regardless of intentionality and lower risk of colorectal cancer associated with WC reduction. These relationships were not modified by race and/or ethnicity, baseline BMI, smoking status, or prior hormone use.

Previous findings from epidemiological studies regarding the relationship between weight loss and cancer risk are limited and conflicting (8,9,22–26). These inconsistent findings may be due to a lack of standard definition of the weight loss exposure

Table 2. Association (HR, 95% CI) between weight change category from baseline to year 3 and obesity-related cancer risk*

Cancer type	Stable weight	Weight gain HR (95% CI)	Weight loss†		
			Overall HR (95% CI)	Intentional HR (95% CI)	Unintentional HR (95% CI)
Overall obesity-related cancer	—	1.04 (0.98 to 1.11)	0.92 (0.85 to 1.00)	0.88 (0.80 to 0.98)	0.99 (0.88 to 1.12)
Breast‡	Referent	1.03 (0.94 to 1.12)	0.88 (0.79 to 0.98)	0.90 (0.79 to 1.03)	0.84 (0.71 to 1.01)
Colon/rectum	Referent	1.08 (0.91 to 1.27)	0.95 (0.77 to 1.15)	0.88 (0.68 to 1.14)	1.06 (0.80 to 1.41)
Endometrium	Referent	1.16 (0.95 to 1.42)	0.72 (0.54 to 0.96)	0.61 (0.42 to 0.88)	0.94 (0.63 to 1.41)
Ovary	Referent	0.99 (0.77 to 1.26)	0.84 (0.61 to 1.16)	0.69 (0.45 to 1.07)	1.08 (0.69 to 1.71)
Pancreas	Referent	0.97 (0.74 to 1.28)	1.16 (0.86 to 1.57)	1.04 (0.70 to 1.53)	1.38 (0.90 to 2.10)
Kidney	Referent	1.14 (0.82 to 1.59)	1.05 (0.71 to 1.55)	1.04 (0.65 to 1.67)	1.08 (0.60 to 1.95)
Thyroid	Referent	0.70 (0.45 to 1.08)	1.11 (0.71 to 1.74)	1.11 (0.64 to 1.92)	1.13 (0.55 to 2.31)
Multiple myeloma	Referent	1.25 (0.88 to 1.76)	1.23 (0.81 to 1.85)	1.29 (0.78 to 2.13)	1.14 (0.60 to 2.17)
Liver	Referent	1.41 (0.86 to 2.31)	1.42 (0.86 to 2.32)	1.45 (0.73 to 2.86)	2.54 (1.33 to 4.86)

*In the multivariable-adjusted models, we adjusted for age at enrollment (<55, 55–59, 60–64, 65–69, 70–74, >75 years); ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African-American, Hispanic/Latino, non-Hispanic white, and other); education (high school or less, some college/technical training, college or higher); pack-years of smoking (0, 0–<10, 10–<20, 20–<30, 30–<40, ≥40); body mass index (continuous); waist circumference (continuous); recreational physical activity (<5, 5–<10, 10–<20, 20–<30, ≥30 metabolic equivalent per week); alcohol intake (nondrinker, past drinker, <1 drink per month, and current drinker including frequency: <1 drink per month, 1 drink per month to <1 drink per wk, 1–<7 drinks per wk, >7 drinks per wk); family history of cancer (yes, no); and prior hormone use (never use, estrogen-alone use, estrogen plus progestin use, mixed). CI = confidence interval; HR = hazard ratio.
†Hazard ratios for overall, intentional, and unintentional weight loss were from two different models. Results for overall weight loss were from a model with three exposure categories (stable, gain, and loss), and results for intentional and unintentional weight loss were from a model with four exposure categories (stable, gain, intentional, and unintentional).
‡For breast cancer, we replaced family history of cancer with family history of breast cancer and additionally adjusted for parity and Gail risk score.

Table 3. Association (HR, 95% CI) between waist circumference (WC) change category from baseline to year 3 and obesity-related cancer risk*

Cancer type	Stable WC (mean = 0.2, range within ±5)	WC gain HR (95% CI) (mean = 9.6, range = 5–32.9)	WC loss†		
			Overall HR (95% CI) (mean = −8.9, range = −31.0 to −5)	Intentional HR (95% CI) (mean = −8.8, range = −31 to −5)	Unintentional HR (95% CI) (mean = −9.1, range = −30.1 to −5)
Overall obesity-related cancer	Referent	1.00 (0.94 to 1.06)	0.91 (0.85 to 0.98)	0.88 (0.80 to 0.96)	1.00 (0.89 to 1.13)
Breast‡	Referent	0.99 (0.91 to 1.07)	0.93 (0.84 to 1.03)	0.90 (0.80 to 1.01)	1.00 (0.85 to 1.18)
Colon/rectum	Referent	1.01 (0.86 to 1.18)	0.90 (0.75 to 1.08)	0.79 (0.63 to 0.99)	1.15 (0.87 to 1.51)
Endometrium	Referent	1.05 (0.87 to 1.27)	0.73 (0.56 to 0.95)	0.67 (0.50 to 0.92)	0.88 (0.57 to 1.34)
Ovary	Referent	1.11 (0.88 to 1.39)	1.06 (0.80 to 1.40)	1.08 (0.79 to 1.48)	1.01 (0.63 to 1.64)
Pancreas	Referent	0.94 (0.73 to 1.20)	0.88 (0.65 to 1.19)	0.88 (0.62 to 1.26)	0.88 (0.53 to 1.46)
Kidney	Referent	1.10 (0.81 to 1.49)	0.75 (0.50 to 1.12)	0.62 (0.38 to 1.03)	1.06 (0.59 to 1.88)
Thyroid	Referent	0.86 (0.59 to 1.25)	1.17 (0.77 to 1.77)	1.40 (0.90 to 2.17)	0.56 (0.21 to 1.53)
Multiple myeloma	Referent	0.89 (0.64 to 1.25)	0.69 (0.44 to 1.07)	0.83 (0.51 to 1.33)	0.38 (0.14 to 1.03)
Liver	Referent	1.41 (0.91 to 2.21)	1.12 (0.65 to 1.94)	0.72 (0.34 to 1.54)	2.00 (1.00 to 3.97)

*In the multivariable-adjusted models, we adjusted for age at enrollment (<55, 55–59, 60–64, 65–69, 70–74, >75); ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African-American, Hispanic/Latino, non-Hispanic white, and other); education (high school or less, some college/technical training, college or higher); pack-years of smoking (0, 0<–<10, 10–<20, 20–<30, 30–<40, ≥440), body mass index (continuous); waist circumference (continuous); recreational physical activity (<5, 5–<10, 10–<20, 20–<30, ≥30 metabolic equivalent per week); alcohol intake (nondrinker, past drinker, <1 drink per month, and current drinker including frequency: <1 drink per month, 1 drink per month to <1 drink per wk, 1 to <7 drinks per wk, >7 drinks per wk); family history of cancer (yes, no); and prior hormone use (never use, estrogen-alone use, estrogen plus progestin use, mixed). CI = confidence interval; HR = hazard ratio.
†Hazard ratios for overall, intentional, and unintentional weight loss were from two different models. Results for overall weight loss were from a model with three exposure categories (stable, gain, and loss), and results for intentional and unintentional weight loss were from a model with four exposure categories (stable, gain, intentional, and unintentional).
‡For breast cancer, we replaced family history of cancer with family history of breast cancer and additionally adjusted for parity and Gail risk score.

measure and/or failure to distinguish whether weight loss was intentional. Our recent analyses in the WHI revealed lower endometrial cancer risk associated with intentional weight loss, but not with unintentional weight loss (27), and lower breast cancer risk associated with weight loss regardless of intentionality (28). The Iowa Women's Health Study (24) used recalled weight change over a 35-year period and observed that women with intentional weight loss no less than 9.1 kg had a 19% lower breast cancer risk (risk ratio = 0.81, 95% CI = 0.66 to 1.00), whereas unintentional weight loss was not associated with lower breast cancer risk (24). A recent meta-analysis reported a pooled relative risk of 0.82 (95% CI = 0.70 to 0.96) for breast cancer associated with weight loss (29). We observed reduced risk of breast cancer associated with weight loss, although results

Table 4. Association (HR 95% CI) between weight change category from baseline to year 3 and obesity-related cancer risk by potential effect modifiers*

Characteristic	Stable weight	Weight gain HR (95% CI)	Weight loss		$P_{interaction}$
			Intentional HR (95% CI)	Unintentional HR (95% CI)	
Race/ethnicity					0.5
Non-Hispanic white	Referent	1.05 (0.98 to 1.12)	0.89 (0.80 to 0.99)	1.02 (0.90 to 1.16)	
African American/black	Referent	1.01 (0.76 to 1.34)	0.70 (0.43 to 1.14)	0.78 (0.44 to 1.14)	
Hispanic	Referent	0.91 (0.57 to 1.46)	1.53 (0.83 to 2.83)	0.58 (0.21 to 1.62)	
American Indian	Referent	0.90 (0.28 to 2.95)	0.52 (0.08 to 3.27)	3.58 (0.49 to 26.02)	
Asian/Pacific Islander	Referent	0.73 (0.42 to 1.29)	0.56 (0.22 to 1.43)	0.91 (0.39 to 2.13)	
Baseline BMI (kg/m^2)					0.5
Normal weight (BMI <25)	Referent	0.98 (0.89 to 1.08)	0.90 (0.73 to 1.10)	1.04 (0.85 to 1.26)	
Overweight (25–<30)	Referent	1.07 (0.96 to 1.19)	0.96 (0.81 to 1.12)	1.02 (0.83 to 1.25)	
Obesity (≥30)	Referent	1.12 (0.98 to 1.28)	0.83 (0.71 to 0.99)	0.89 (0.70 to 1.13)	
Smoking					0.3
Never	Referent	0.99 (0.90 to 1.09)	0.90 (0.78 to 1.03)	0.97 (0.82 to 1.15)	
Former	Referent	1.03 (0.93 to 1.13)	0.87 (0.75 to 1.00)	1.00 (0.82 to 1.21)	
Current	Referent	1.43 (1.13 to 1.81)*	0.99 (0.62 to 1.60)	1.06 (0.68 to 1.64)	
Hormone use					0.7
No use	Referent	1.01 (0.90 to 1.12)	0.91 (0.78 to 1.06)	1.02 (0.85 to 1.23)	
Estrogen alone	Referent	1.15 (1.02 to 1.30)	0.89 (0.73 to 1.08)	1.01 (0.81 to 1.27)	
Estrogen plus progestin	Referent	0.99 (0.88 to 1.11)	0.90 (0.74 to 1.09)	0.95 (0.73 to 1.23)	
Mixed	Referent	1.02 (0.80 to 1.30)	0.71 (0.46 to 1.08)	0.89 (0.54 to 1.47)	

*In the multivariable-adjusted models, we adjusted for the same confounders as listed in Tables 2 and 3 but the stratified variable for each stratified analysis. BMI = body mass index; CI = confidence interval; HR = hazard ratio.

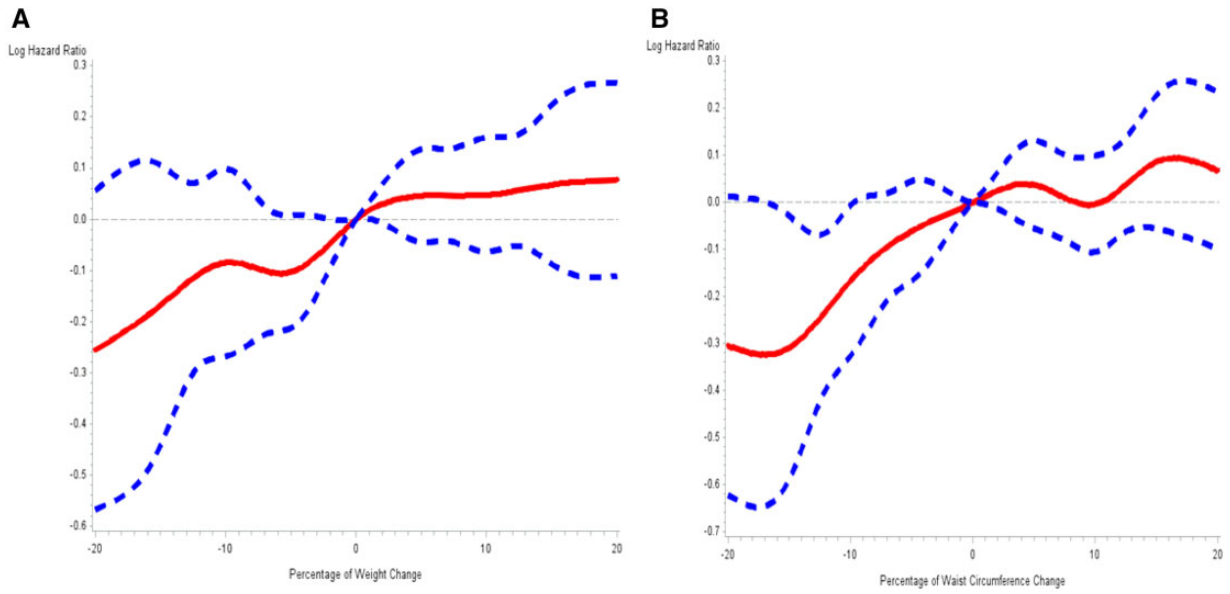

Figure 1. A) Spine analysis for weight loss and obesity-related cancer risk. *P* for non-linear test of percentage of weight change = 0.2. *P* for overall effect of percentage of weight change =0.03. **B)** Spine analysis for waist circumference loss and obesity-related cancer risk. *P* for nonlinear test of percentage of waist circumference change = 0.13. *P* for overall effect of percentage of waist circumference change =0.04. **red solid** = estimated curve; **blue dashed lines** = confidence intervals.

became statistically nonsignificant when splitting the group into intentional and unintentional. This may be due to lower power to detect a modest association after splitting. Our findings line up with most previous studies that do not include intentionality.

Currently, there is little evidence from randomized clinical trials in humans showing effects of weight loss interventions on risk of developing cancers (30). This may be due to lack of sustained weight loss or limited study power. However, studies have shown that moderate weight loss interventions have resulted in improvement in insulin sensitivity and decreased inflammatory markers (31,32). Both insulin sensitivity and inflammatory responses are potential mechanisms linking obesity and cancer risk (33). Several randomized trials have shown that intentional weight loss lowered serum sex hormones or inflammatory markers (34–36), which may decrease risk of postmenopausal breast and endometrial cancer. There is also evidence that short-term interventions may affect

undiagnosed cancer and then affect subsequent health outcomes 5 to 10 years later (37,38). Preclinical studies also support a beneficial effect of calorie restriction and weight loss on both chemically induced and spontaneous tumors (6,39–43). Caloric restriction has been shown to increase the life span of rodents (44,45) and dogs (46) and has extended the life span and delayed cancer development in rhesus monkeys (47). In humans, bariatric surgery studies found 20 kg sustained weight loss was associated with reduced cancer risk (48–50).

To our knowledge, our study is the first study to analyze the relationship between WC change and the risk of cancer. Overall, we observed similar results for weight loss and WC reduction in relation to obesity-related cancer risk. For colorectal cancer, we observed that WC reduction but not weight loss was associated with lower risk of colorectal cancer. Although the association for intentional weight loss was not statistically significant, the pattern of the association was similar. The correlation between weight and WC was high ($r = 0.8$) in our data; however, it is possible that achieved WC reduction may be more beneficial than weight loss. Studies have shown that WC reduction in individuals with obesity resulted in improvements in insulin sensitivity and blood lipid profiles and a reduction in colon tissue Ki-67 expression (an established biomarker of cancer risk) (51,52). Previous studies examining weight loss compared with stable weight showed a statistically nonsignificant lower risk of colorectal cancer or no association (10). Song et al. (53) and Rapp et al. (54) have reported that weight loss over time was associated with reduced colorectal cancer risk among men, but not women. These null associations between weight loss and colorectal cancer risk may be due to a small number of cases for the weight loss group or failure to differentiate between intentional and unintentional weight loss (55) or weight change may be less predictive of colorectal cancer risk in women than WC (56).

We did not observe that weight gain (≥5%) was associated with obesity-related cancer risk, which conflicts with most previous studies that have reported positive associations between weight gain during adulthood and risk for many cancers (57,58). However, most of the studies in these two meta-analyses looked at weight gain from age 18 years to baseline, and not recent weight gain. Our finding may be because 5% weight gain may not be large enough to have resulted in an increase in risk. Of note, there was increased risk for obesity-related cancer among women with weight gain of 4.5 kg or more relative to women with stable weight, although a 10-pound weight gain is not much more than a 5% weight gain in women with baseline obesity.

Strengths of this study include the large prospective design, long-term follow-up, measured body weight and WC at baseline and follow-up, centrally adjudicated cancer cases, and determination of intentional or unintentional weight loss. However, several limitations deserve mention. First, weight or WC changes were based on baseline and year 3 visit and did not consider change beyond 3 years of follow-up. It is possible that a woman who lost weight between baseline and year 3 may subsequently have gained back weight after the 3-year exposure period. This lack of sustained weight loss would lead to an attenuation of the associations. Second, the assessment of intentionality for weight loss was self-reported and did not exactly match with the amount of weight loss used in the study, which may lead to some degree of misclassification. Third, our findings are limited to postmenopausal women and may not generalize to other populations. Fourth, although our study is one of the largest prospective cohort studies to date among postmenopausal women, the study power to analyze cancer risk for rare individual cancer sites was limited.

Our data demonstrate that intentional weight loss or WC reduction among postmenopausal women was associated with lower risk of obesity-related cancers. These findings provide evidence that older women with obesity can reduce their cancer risk through weight loss efforts.

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References

1. Hales C, Carroll M, Fryar C, et al. Prevalence of obesity among adults and youth: United States, 2015–2016. Hyattsville, MD: Centers for Disease Control and Prevention, National Center for Health Statistics; 2017. https://www.cdc.gov/nchs/data/databriefs/db288.pdf. Accessed January 10, 2019.
2. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer–viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794–798.
3. LeBlanc ES, Patnode CD, Webber EM, et al. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320(11):1172–1191.
4. Tee MC, Cao Y, Warnock GL, et al. Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. *Surg Endosc*. 2013;27(12):4449–4456.
5. Ward KK, Roncancio AM, Shah NR, et al. Bariatric surgery decreases the risk of uterine malignancy. *Gynecol Oncol*. 2014;133(1):63–66.
6. Harvie M, Howell A. Energy balance adiposity and breast cancer—energy restriction strategies for breast cancer prevention. *Obes Rev*. 2006;7(1):33–47.

7. Hursting SD, Smith SM, Lashinger LM, et al. Calories and carcinogenesis: lessons learned from 30 years of calorie restriction research. *Carcinogenesis*. 2010;31(1):83–89.
8. Emaus MJ, van Gils CH, Bakker MF, et al. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. *Int J Cancer*. 2014;135(12):2887–2899.
9. Harvie M, Howell A, Vierkant RA, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):656–661.
10. Karahalios A, English DR, Simpson JA. Weight change and risk of colorectal cancer: a systematic review and meta-analysis. *Am J Epidemiol*. 2015;181(11):832–845.
11. McMinn J, Steel C, Bowman A. Investigation and management of unintentional weight loss in older adults. *BMJ*. 2011;342:d1732.
12. Wijnhoven HA, van Zon SK, Twisk J, et al. Attribution of causes of weight loss and weight gain to 3-year mortality in older adults: results from the Longitudinal Aging Study Amsterdam. *J Gerontol A Biol Sci Med Sci*. 2014;69(10):1236–1243.
13. Williamson DF, Pamuk E, Thun M, et al. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. *Am J Epidemiol*. 1995;141(12):1128–1141.
14. Jin SG. Child mortality patterns in rural areas of Anhui and Henan provinces in China, 1990. *Biomed Environ Sci*. 1998;11(3):264–276.
15. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9):S18–77.
16. Jackson RD, LaCroix AZ, Cauley JA, et al. The Women's Health Initiative Calcium-Vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9):S98–106.
17. Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9):S107–21.
18. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9):S87–97.
19. Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative PostMenopausal Hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9):S78–86.
20. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *Circulation*. 2014;129(25 suppl 2):S102–38.
21. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed*. 1997;54(3):201–208.
22. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the Women's Health Initiative randomized clinical trials. *JAMA Oncol*. 2015;1(5):611–621.
23. Kawai M, Minami Y, Kuriyama S, et al. Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study. *Br J Cancer*. 2010;103(9):1443–1447.
24. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. *Int J Obes*. 2003;27(12):1447–1452.
25. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. *J Natl Cancer Inst*. 2004;96(21):1635–1638.
26. Trentham-Dietz A, Nichols HB, Hampton JM, et al. Weight change and risk of endometrial cancer. *Int J Epidemiol*. 2006;35(1):151–158.
27. Luo J, Chlebowski RT, Hendryx M, et al. Intentional weight loss and endometrial cancer risk. *J Clin Oncol*. 2017;35(11):1189–1193.
28. Chlebowski RT, Luo J, Anderson GL, et al. Weight loss and breast cancer incidence in postmenopausal women. *Cancer*. 2019;125(2):205–212.
29. Hardefeldt PJ, Penninkilampi R, Edirimanne S, et al. Physical activity and weight loss reduce the risk of breast cancer: a meta-analysis of 139 prospective and retrospective studies. *Clin Breast Cancer*. 2018;18(4):e601–e612.
30. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849.
31. Pakiz B, Flatt SW, Bardwell WA, et al. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. *Int J Behav Med*. 2011;18(4):333–341.
32. Ho TP, Zhao X, Courville AB, et al. Effects of a 12-month moderate weight loss intervention on insulin sensitivity and inflammation status in nondiabetic overweight and obese subjects. *Horm Metab Res*. 2015;47(4):289–296.
33. Iyengar NM, Gucalp A, Dannenberg AJ, et al. Obesity and cancer mechanisms: tumor microenvironment and inflammation. *J Clin Oncol*. 2016;34(35):4270–4276.
34. Campbell KL, Foster-Schubert KE, Alfano CM, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. *J Clin Oncol*. 2012;30(19):2314–2326.
35. van Gemert WA, Schuit AJ, van der Palen J, et al. Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. *Breast Cancer Res*. 2015;17(1):120.
36. van Gemert WA, May AM, Schuit AJ, et al. Effect of weight loss with or without exercise on inflammatory markers and adipokines in postmenopausal women: the SHAPE-2 trial, a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev*. 2016;25(5):799–806.
37. Santen RJ, Yue W, Heitjan DF. Occult breast tumor reservoir: biological properties and clinical significance. *Horm Cancer*. 2013;4(4):195–207.
38. Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? *Ann Intern Med*. 1997;127(11):1023–1028.
39. Cleary MP. Impact of obesity on development and progression of mammary tumors in preclinical models of breast cancer. *J Mammary Gland Biol Neoplasia*. 2013;18(3-4):333–343.
40. Kumar SP, Roy SJ, Tokumo K, et al. Effect of different levels of calorie restriction on azoxymethane-induced colon carcinogenesis in male F344 rats. *Cancer Res*. 1990;50(18):5761–5766.
41. Olivo-Marston SE, Hursting SD, Perkins SN, et al. Effects of calorie restriction and diet-induced obesity on murine colon carcinogenesis, growth and inflammatory factors, and microRNA expression. *PLoS One*. 2014;9(4):e94765.
42. Lanza-Jacoby S, Yan G, Radice G, et al. Calorie restriction delays the progression of lesions to pancreatic cancer in the LSL-KrasG12D; Pdx-1/Cre mouse model of pancreatic cancer. *Exp Biol Med (Maywood)*. 2013;238(7):787–797.
43. Yoshida K, Inoue T, Hirabayashi Y, et al. Calorie restriction and spontaneous hepatic tumors in C3H/He mice. *J Nutr Health Aging*. 1999;3(2):121–126.
44. Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. *Ageing Res Rev*. 2012;11(2):254–270.
45. Forster MJ, Morris P, Sohal RS. Genotype and age influence the effect of caloric intake on mortality in mice. *FASEB J*. 2003;17(6):690–692.
46. Kealy RD, Lawler DF, Ballam JM, et al. Effects of diet restriction on life span and age-related changes in dogs. *J Am Vet Med Assoc*. 2002;220(9):1315–1320.
47. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009;325(5937):201–204.
48. Adams TD, Stroup AM, Gress RE, et al. Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)*. 2009;17(4):796–802.
49. Christou NV, Lieberman M, Sampalis F, et al. Bariatric surgery reduces cancer risk in morbidly obese patients. *Surg Obes Relat Dis*. 2008;4(6):691–695.
50. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol*. 2009;10(7):653–662.
51. Beeken RJ, Croker H, Heinrich M, et al. The impact of diet-induced weight loss on biomarkers for colorectal cancer: an exploratory study (INTERCEPT). *Obesity (Silver Spring)*. 2017;25(suppl 2):S95–S101.
52. Andersson DP, Wahrenberg H, Toft E, et al. Waist circumference to assess reversal of insulin resistance following weight reduction after bariatric surgery: cohort and cross-sectional studies. *Int J Obes*. 2014;38(3):438–443.
53. Song M, Hu FB, Spiegelman D, et al. Adulthood weight change and risk of colorectal cancer in the Nurses' Health Study and Health Professionals Follow-up Study. *Cancer Prev Res (Phila)*. 2015;8(7):620–627.
54. Rapp K, Klenk J, Ulmer H, et al. Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. *Ann Oncol*. 2008;19(4):641–648.
55. Hamilton W, Round A, Sharp D, et al. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. *Br J Cancer*. 2005;93(4):399–405.
56. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr*. 2007;86(3):556–565.
57. Chen Q, Wang J, Yang J, et al. Association between adult weight gain and colorectal cancer: a dose-response meta-analysis of observational studies. *Int J Cancer*. 2015;136(12):2880–2889.
58. Vrieling A, Buck K, Kaaks R, et al. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):641–649.