Research Article

Cancer Epidemiology, Biomarkers & Prevention

Weight Fluctuation and Cancer Risk in Postmenopausal Women: The Women's Health Initiative

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Abstract

Background: Weight cycling, defined by an intentional weight loss and subsequent regain, commonly occurs in overweight and obese women and is associated with some negative health outcomes. We examined the role of various weight-change patterns during early to mid-adulthood and associated risk of highly prevalent, obesity-related cancers (breast, endometrial, and colorectal) in postmenopausal women.

Methods: A total of 80,943 postmenopausal women (age, 63.4 ± 7.4 years) in the Women's Health Initiative Observational Study were categorized by self-reported weight change (weight stable; weight gain; lost weight; weight cycled [1–3, 4–6, 7–10, >10 times]) during early to mid-adulthood (18–50 years). Three site-specific associations were investigated using Cox proportional hazard models [age, race/ethnicity, income, education, smoking, alcohol, physical activity, hormone therapy, diet, and body mass index (BMI)].

Results: A total of 7,464 (breast = 5,564; endometrial = 788; and colorectal = 1,290) incident cancer cases were identified between September 1994 and August 2014. Compared with weight stability, weight gain was significantly associated with risk of breast cancer [hazard ratio (HR), 1.11; 1.03–1.20] after adjustment for BMI. Similarly, weight cycling was significantly associated with risk of endometrial cancer (HR = 1.23; 1.01–1.49). Weight cycling "4 to 6 times" was most consistently associated with cancer risk, showing a 38% increased risk for endometrial cancer [95% confidence interval (CI), 1.08–1.76] compared with weight stable women.

Conclusions: Weight gain and weight cycling were positively associated with risk of breast and endometrial cancer, respectively.

Impact: These data suggest weight cycling and weight gain increase risk of prevalent cancers in postmenopausal women. Adopting ideal body-weight maintenance practices before and after weight loss should be encouraged to reduce risk of incident breast and endometrial cancers. *Cancer Epidemiol Biomarkers Prev; 26(5); 779–86. ©2017 AACR.*

Introduction

Cancer is the second leading cause of death in the United States and most commonly develops in older adults (1). Breast, endometrial, and colorectal cancers are highly prevalent among postmenopausal women and represent nearly half of all newly diagnosed cancer cases in women each year (2). In addition to age, many conventional risk factors also contribute to cancer onset and progression, including obesity. Indeed, one in eight (13%) cases of breast, endometrial, and colorectal cancers are directly attributable to obesity (3), a problem that is augmented in older women due to the pervasiveness of the condition (4).

Approximately two thirds of postmenopausal women report attempting weight loss at any given time (5). Given the futility of long-term weight loss maintenance (6), weight cycling, defined as an intentional weight loss followed by weight regain, is a common occurrence (7). Weight cycling has previously been associated with negative changes in body composition (8) and health outcomes (9, 10), and recent research has begun exploring associations between weight cycling and cancer incidence. Currently, 11 observational studies have been conducted with some (11–18), but not all (19–21), suggesting a positive association between weight cycling and cancer risk—as much as a 3-fold increase for renal cell carcinoma (11, 12) and endometrial cancer (13, 16). However, in many cases, modest findings are attenuated after adjustment for current weight/body mass index (BMI; refs. 15–18). In addition, robust evidence from longitudinal cohort studies is limited and disparate (11, 18, 20, 22), with few studies reporting on breast (18, 20, 21) and colon/colorectal (18, 20) cancer outcomes.

Utilizing data available in the well-characterized Women's Health Initiative Observational Study (WHI OS; ref. 23), we will add to the current body of literature by clarifying the role of various weight-change patterns throughout adulthood on the risk of developing three highly prevalent cancers in postmenopausal women. We hypothesize that adult weight cyclers and weight gainers will be at increased risk of developing breast, endometrial, and/or colorectal cancers compared with postmenopausal women who were weight stable in early and

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mid-adulthood, independent of baseline BMI. Secondarily, we hypothesize that the frequency of weight cycling in early and mid-adulthood will be linearly associated with postmenopausal onset of breast, endometrial, and/or colorectal cancers compared with women who maintain their weight.

Materials and Methods

Women's Health Initiative

The Women's Health Initiative (WHI) is a large, multicenter clinical trial (CT) and observational study (OS) examining the leading causes of morbidity and mortality in postmenopausal women (ages 50–79 years old). Women (161,808) were recruited from 40 U.S. clinic centers from 1993 to 1998. Of those, 93,676 women joined the OS and are being followed through 2020 (23). Study protocols and procedures were approved by the institutional review boards at all 40 clinical centers and are overseen by the coordinating center, as well as a study-wide data and safety monitoring board (24). All participants signed informed consent forms. Women were excluded if they had medical conditions with a predicted survival of <3 years, if they had adherence or retention issues (alcohol or drug dependency, mental illness, and dementia), or if they were currently involved in another clinical trial. Full details can be found in the published recruitment and methods (25) and design (23) articles.

Current study sample

The current study sample includes only women from the WHI OS who completed relevant interviews, self-administered questionnaires (personal habits and food frequency), and physical measurements at baseline. Characteristics of OS participants at baseline are listed in detail elsewhere (23, 25, 26). Women were censored during follow-up if they died or were lost to follow-up or were not diagnosed with either breast, endometrial, or colorectal cancer. Figure 1 shows the study flow of how we obtained our final sample for analysis. Women were excluded from the final sample analysis if they were missing information on weight-change pattern category ($n = 818$); missing pertinent baseline covariates of interest (listed below; $n = 4{,}852$); or reported history of breast, endometrial, or colorectal cancer at baseline ($n = 7{,}103$). For analyses of endometrial cancer, women were also excluded if they reported hysterectomy at baseline ($n = 33{,}046$). Women who reported hysterectomy during follow-up were censored from endometrial cancer analyses at the date of reported hysterectomy. Thus, the final analysis sample for this study was 80,943 women, with the exception of endometrial cancer analyses, in which the analysis sample was 47,897 women.

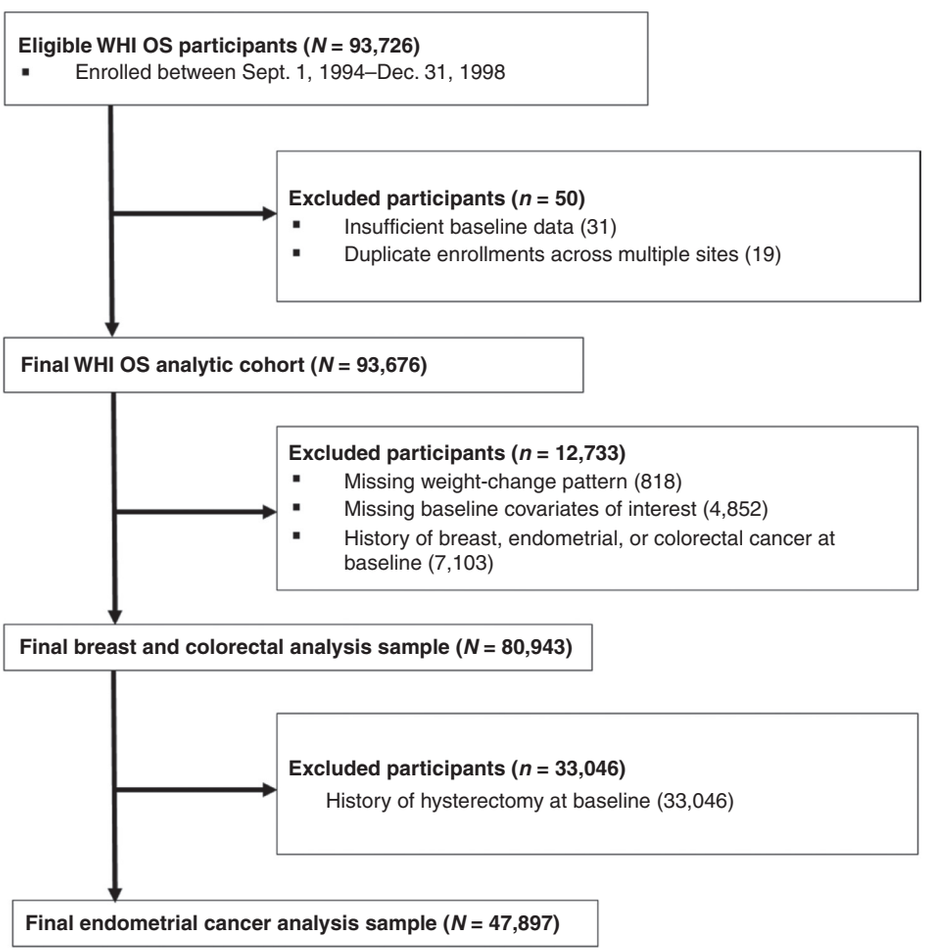

Figure 1.
Study sample flow diagram.

Weight-change pattern classifications

Weight changes were obtained through participants' responses to two questions on the self-reported baseline personal habits questionnaire. The first question asked women to mark the one answer that best described their weight changes during their adult life, excluding times when pregnant or sick. Possible responses were as follows: [1] weight has stayed about the same (within 10 pounds), [2] steady gain in weight, [3] lost weight as an adult and kept it off, or [4] weight has gone up and down again by more than 10 pounds.

If [4] was marked, a subquestion was asked about how many times weight went up and down again by more than 10 pounds (1 to 3 times, 4 to 6 times, 7 to 10 times, 11 to 15 times, or more than 15 times). A weight cycle for the purposes of this evaluation was defined by a participant marking response [4], targeting intentional weight loss and subsequent regain, and further classification by the number of weight cycles reported, using definitions previously employed in the WHI (11).

Ascertainment of cancer cases

Women were queried annually about new cancer diagnoses on annual mailed questionnaires during follow-up (23). The question asked on the medical history update questionnaire was as follows: "Has a doctor told you for the first time that you have a new cancer, malignant growth, or tumor?" If the participant marked "yes" to this question, a subquestion was asked to determine the type of cancer or malignancy. All cancer cases were verified by medical record review and pathology reports by physician adjudicators at the clinical centers using standardized criteria in accordance with the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding guidelines. Information was obtained on outcomes and cause of death in participants who were lost to follow-up and/or known to be deceased by routinely searching the National Death Index. All cases were the first diagnosed cancer at that site for that individual and first diagnosis for any of the three cancer sites of interest. For endometrial cancer cases, only non-hysterectomized women at baseline were considered at risk, and women who reported hysterectomy during follow-up prior to endometrial cancer diagnosis were censored at the time of hysterectomy. Our analyses focused on identifying mutually exclusive categories of incident breast, endometrial, and colorectal cancers, as well as a composite of the three cancers.

Baseline covariates of interest

The following variables, collected at baseline, represent potential confounders between exposure and outcome, and are included in our subsequent statistical modeling. All demographic, personal and family medical history, and personal habits and risk exposure data were captured by self-administered questionnaire and interview at baseline. Following a standardized written protocol, certified and trained staff additionally measured height, weight, and waist/hip circumference during the baseline clinic visit (23).

The confounders included in multivariable analyses include age at enrollment; race/ethnicity (Caucasian, African American, Hispanic/Latina); family income (less than $50,000/year, $50,000/year or more); education (less than a college degree, college degree or more); smoking status (never, former, current); alcohol intake (<1 drink/week, ≥1 drink/week); physical activity level (metabolic equivalent tasks [MET]/week) (27); hormone therapy use (never, ever); Healthy Eating Index (HEI-2005 score, 0–100; ref. 28); and BMI (kg/m^2) at baseline.

Statistical analysis

Baseline data were summarized using descriptive statistics, and equivalence of means and proportions across weight-change patterns were compared using ANOVA and Pearson χ^2 tests, respectively. Hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional models (29) were used to estimate the association between weight-change patterns and incident breast cancer, endometrial cancer, colorectal cancer, and the three cancers combined. Each cancer outcome was modeled separately for cancer types (breast, endometrial, and colorectal cancers) and a composite of all three cancer outcomes defined as incidence of any of the three. The relationship between cancer risk and weight-change pattern was adjusted for age, race/ethnicity, education, income, smoking status, alcohol intake, hormone therapy use, physical activity level, healthy eating index score, and baseline BMI, as specified above. P values for trend were estimated by modeling number of weight cycle events as an ordinal predictor. Person-years of follow-up were calculated as the time elapsed from the completion of the baseline questionnaire to the cancer event, last follow-up contact, or date of reported hysterectomy (for endometrial cancer risk only). A formal test for interaction between weight-change pattern category and obesity at baseline (BMI ≥30 vs. BMI <30) was nonsignificant ($P = 0.13$). All statistical analyses were conducted by using SAS v9.4 (SAS Institute) assuming a type I error rate of 0.05 with no adjustment for multiplicity of comparisons due to the hypothesis-generating nature of the study.

Results

Study sample characteristics

Average age of the study sample ($N = 80{,}943$) was 63.4 ± 7.3 years with a mean BMI of 27.2 ± 5.8 kg/m^2. Nearly half of all women reported obtaining college education or higher (42%), and over one third had an annual family income of at least $50,000 (40%). Compared with women in the WHI OS excluded from the present analysis ($n = 12{,}733$), women in our analyses were significantly younger, were more likely to have at least a college education, and report hormone therapy use (61 vs. 50%; all $P < 0.01$).

At the baseline examination, 37% of women described themselves as adult weight cyclers, 32% as maintaining a stable weight, 28% as steadily gaining weight, and 3% as losing weight and keeping it off. Among weight cyclers, 43% reported weight cycling 1 to 3 times, and the prevalence of weight cycling declined as frequency increased (4–6 times, 32%; 7–10 times, 14%; more than 10 times, 11%). Characteristics of women at baseline, overall and by weight-change pattern, are shown in Table 1.

When comparing baseline demographic characteristics across weight-change pattern categories, in comparison to women in both the lost weight and weight stable groups, women who gained and cycled weight were younger with higher BMI at baseline, and were more likely to be past smokers and have lower physical activity levels. Weight cyclers were more likely to be African American than women who lost weight (9.5% vs. 5.3%) and less likely to report consuming alcohol (34%) versus all other weight-

Table 1. Baseline characteristics of the study sample, overall and by type of weight-change pattern

Baseline characteristic	Overall $N = 80,943$	Stable weight $n = 25,508$	Stable gain $n = 23,021$	Lost weight $n = 2,315$	Weight cycle $n = 30,099$
Age (years)[a]	63.4 ± 7.3	64.6 ± 7.4	62.8 ± 7.2	64.9 ± 7.6	62.8 ± 7.2
Race/ethnicity					
Caucasian	83.6	82.6	84.8	82.8	83.5
African American	8.0	7.3	7.1	5.3	9.5
Hispanic/Latina	3.8	3.8	3.6	5.5	3.9
Education, college or more	42.2	42.9	43.6	46.3	40.1
Income, $50,000/year or more	39.6	40.2	41.4	38.5	37.8
Hormone therapy use, ever	60.9	60.9	61.3	56.3	61.1
Alcohol intake, ≥1 drink/week	38.3	42.6	39.2	39.9	33.8
Smoking status					
Past smoker	42.9	37.6	44.3	37.3	46.6
Current smoker	6.3	7.0	5.2	8.3	6.6
Physical activity level (MET-h/week)[a]	13.7 ± 14.3	15.7 ± 15.3	11.6 ± 12.5	16.9 ± 16.1	13.4 ± 14.3
Health eating index (HEI-2005 score)[a]	69.2 ± 10.5	70.0 ± 10.4	68.2 ± 10.6	71.2 ± 10.3	69.2 ± 10.6
BMI (kg/m^2)[a]	27.2 ± 5.8	23.8 ± 4.1	29.1 ± 5.4	23.1 ± 4.0	29.1 ± 5.9
Underweight (<18.5 kg/m^2)	1.2	2.5	0.1	7.5	0.4
Normal weight (18.5 to <25 kg/m^2)	39.7	71.2	21.6	69.7	24.5
Overweight (25.0 to <30 kg/m^2)	34.0	20.1	44.2	18.3	39.3
Obese (≥30 kg/m^2)	25.0	6.1	34.0	4.6	35.8

NOTE: Values are presented as percentages unless otherwise noted.
Abbreviations: MET, physical activity in metabolic equivalents.
[a]Values are presented as means ± standard deviations.

change pattern groups. Weight gainers were more likely to be white (85%) but least likely to be current smokers compared with all other weight-change pattern groups (all $P < 0.01$). In addition, women in the lost weight group were least likely to report using hormone therapy (56.3%), but most likely to be current smokers, and reported the highest levels of physical activity across all groups (16.9 ± 16.1 MET-h/day).

A total of 7,464 incident cases of cancer (breast cancer, $n =$ 5,564, 72.8%; endometrial cancer, $n = 788$, 10.3%; colorectal cancer, $n = 1,290$, 16.9%) were identified among women who met study criteria between enrollment in September 1994 and August 2014. These women had a similar average BMI compared with the total study sample (27.5 ± 5.9 kg/m^2). Women who reported colorectal cancer were slightly older, more likely to be African American and current smokers, and less likely to report hormone therapy use (52%) and had lower alcohol intake compared with women who were diagnosed with either breast or endometrial cancer (data not shown).

Weight-change patterns and incident cancer

In minimally adjusted models (age, race/ethnicity, education, income), self-reported weight cycling and weight gain were significantly associated with an increased risk of all three cancers combined (11% and 22%) and by site (8%–56% and 19%–51%; Table 2), respectively. The one exception lies between weight cycling and colorectal cancer (HR, 1.12; 0.98–1.29). After multivariate adjustment of common risk factors (smoking, alcohol, hormone therapy use, physical activity, and healthy eating index score), there were no significant changes in risk estimates among weight gainers or cyclers. Weight gain remained significantly associated with risk of breast cancer (HR, 1.11; 1.03–1.20) after adjustment for BMI at baseline. Similarly, weight cycling was

Table 2. Risk of incident breast, endometrial, and colorectal cancer by weight-change pattern

	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
Stable weight	1.0	1.0	1.0
All three cancers combined ($N = 7,464$)			
Weight gain	1.22 (1.15–1.29)	1.20 (1.13–1.27)	1.07 (0.91–1.24)
Lost weight	0.92 (0.79–1.07)	0.93 (0.79–1.08)	0.93 (0.79–1.09)
Weight cycle	1.11 (1.05–1.17)	1.10 (1.04–1.17)	1.02 (0.96–1.08)
Breast cancer ($n = 5,564$)			
Weight gain	1.19 (1.11–1.27)	1.17 (1.10–1.26)	1.11 (1.03–1.20)
Lost weight	0.90 (0.75–1.08)	0.91 (0.76–1.09)	0.90 (0.75–1.08)
Weight cycle	1.08 (1.01–1.15)	1.07 (1.00–1.15)	1.02 (0.95–1.21)
Endometrial cancer ($n = 788$)			
Weight gain	1.51 (1.25–1.81)	1.48 (1.22–1.79)	1.16 (0.95–1.42)
Lost weight	0.95 (0.58–1.55)	0.99 (0.60–1.63)	1.02 (0.62–1.68)
Weight cycle	1.56 (1.30–1.87)	1.58 (1.32–1.89)	1.23 (1.01–1.49)
Colorectal cancer ($n = 1,290$)			
Weight gain	1.21 (1.05–1.39)	1.17 (1.01–1.35)	1.07 (0.91–1.24)
Lost weight	0.91 (0.63–1.32)	0.91 (0.60–1.32)	0.94 (0.65–1.36)
Weight cycle	1.12 (0.98–1.29)	1.09 (0.95–1.26)	1.00 (0.86–1.16)

Model 1: Age, race/ethnicity, education, income.
Model 2: model 1 + smoking status, alcohol intake, physical activity, hormone therapy use, health eating index.
Model 3: model 2 + BMI at baseline.

Table 3. Risk of incident breast, endometrial, and colorectal cancer by weight cycling frequency

	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
Stable weight	1.0	1.0	1.0
All three cancers combined			
1–3 times	1.13 (1.05–1.21)	1.13 (1.05–1.21)	1.07 (1.00–1.15)
4–6 times	1.13 (1.04–1.22)	1.12 (1.04–1.22)	1.01 (0.93–1.10)
7–10 times	1.06 (0.95–1.18)	1.06 (0.95–1.19)	0.92 (0.82–1.04)
>10 times	1.02 (0.89–1.16)	1.00 (0.87–1.14)	0.85 (0.74–0.98)
P for trend	0.09	0.05	<0.01
Breast cancer			
1–3 times	1.13 (1.04–1.22)	1.13 (1.04–1.23)	1.09 (1.00–1.18)
4–6 times	1.06 (0.97–1.17)	1.07 (0.97–1.17)	0.98 (0.89–1.09)
7–10 times	1.03 (0.90–1.17)	1.04 (0.91–1.18)	0.94 (0.81–1.08)
>10 times	0.92 (0.79–1.08)	0.92 (0.78–1.08)	0.82 (0.69–0.97)
P for trend	<0.01	<0.01	<0.01
Endometrial cancer			
1–3 times	1.37 (1.10–1.71)	1.42 (1.14–1.78)	1.22 (0.97–1.53)
4–6 times	1.81 (1.44–2.28)	1.84 (1.46–2.33)	1.38 (1.08–1.76)
7–10 times	1.38 (0.97–1.97)	1.44 (1.01–2.05)	0.96 (0.66–1.39)
>10 times	1.70 (1.17–2.48)	1.71 (1.17–2.51)	1.06 (0.70–1.59)
P for trend	0.24	0.36	0.19
Colorectal cancer			
1–3 times	1.07 (0.90–1.27)	1.03 (0.87–1.23)	0.99 (0.83–1.18)
4–6 times	1.19 (0.99–1.43)	1.14 (0.94–1.37)	1.03 (0.84–1.25)
7–10 times	1.19 (0.92–1.55)	1.12 (0.86–1.46)	0.99 (0.75–1.31)
>10 times	1.12 (0.82–1.52)	1.02 (0.74–1.39)	0.85 (0.61–1.19)
P for trend	0.53	0.84	0.75

Model 1: Age, race/ethnicity, education, income.
Model 2: model 1 + smoking status, alcohol intake, physical activity, hormone therapy use, healthy eating index.
Model 3: model 2 + BMI at baseline.

significantly associated with risk of endometrial cancer (HR, 1.23; 1.01–1.49) after BMI adjustment compared with stable weight women. Aside from these findings, BMI adjustment rendered all other previously significant associations nonsignificant. Weight loss was not associated with cancer risk in any of the models. Tests for interaction showed that the association between weight-change pattern categories and cancer risk did not vary substantially across obese and nonobese BMI categories at baseline (P interaction 0.13).

In analyses examining the association between frequency of weight cycling (defined as the number of times weight cycled 10 pounds or more) and cancer incidence, weight cycling 4 to 6 times was most consistently associated with increased risk of any of the three cancer types, increasing endometrial cancer risk by 84% (95% CI, 1.46–2.33) when compared with weight stability in model 2 multivariate-adjusted models (Table 3). After BMI adjustment, this association was only slightly attenuated to 38% (95% CI, 1.08–1.76). All other previously significant associations were attenuated to nonsignificance after BMI adjustment. Weight cycling frequency was not significantly associated with risk of colorectal cancer in any frequency comparisons. Interestingly, P for trend indicated a negative dose–response relationship in the BMI-adjusted model for weight cycling frequency and risk of all three cancers combined and breast cancer alone (all $P < 0.01$).

Discussion

The purpose of our study was to evaluate the role of various weight-change patterns during adulthood and risk of breast, endometrial, and colorectal cancers in the well-characterized WHI OS with 20 years of follow-up (1994–2014). In this large prospective study, we observed that weight gain was associated with increased risk of breast cancer in postmenopausal women. Moreover, prior history of weight cycling increased risk of endometrial cancer. Results underscore the importance of maintaining a healthy body weight throughout the life cycle to reduce risk of negative health outcomes in later life.

Our results, showing a positive association between weight gain and cancer incidence in multivariate-adjusted models, are in general agreement with a larger body of data linking obesity to increased cancer risk (20, 21, 30, 31). Additionally, our weight cycling findings align with some (13, 15, 16), but not all (18, 20–22), prior studies suggesting a positive association between weight cycling and endometrial cancer incidence. For instance, three case–control studies show a 2-fold (15) to 3-fold (13, 16) increase in the odds of weight cycling in women who developed endometrial cancer compared with those who were cancer free. Likewise, two (18, 22) of three (20) prospective cohort studies suggest a positive association between weight cycling and endometrial cancer risk, with hazard ratios ranging from 1.06 (18) to 2.13 (22) compared with non-cyclers, prior to BMI adjustment. All prior studies assessing the association between weight cycling and breast (18, 20, 21) and colorectal (18, 20) risk in postmenopausal women present null findings, which is in agreement with our findings. In most studies, positive results were attenuated to nonsignificance after adjustment for baseline BMI or body weight (15, 16, 18, 22). However, our findings suggest prior weight gain and weight cycling increase breast and endometrial cancer risk, respectively. Therefore, adjustment for BMI is essential to delineate the independent influence of weight cycling and weight gain on cancer risk, yet it is important to note there are limitations in the interpretation of these associations, as these two factors are intricately related.

Many plausible hypotheses exist connecting weight regain and cycling to cancer via biological mechanisms similar to those for

obesity. This makes biological sense, as prior observational studies demonstrate weight loss has been associated with loss of lean muscle mass and weight regain with increased adiposity (8, 32–37). If fat mass replaces fat free mass as a consequence of weight cycling, then weight cycling may lend to a more sarcopenic obese phenotype (8, 32, 38). Sarcopenia alone is associated with cardiovascular disease markers, such as insulin resistance (39), and when accompanied by obesity, evidence suggests that worse cardiometabolic (40, 41) and cancer survival (42) outcomes exist. However, it is unknown if sarcopenic obesity leads to increased cancer incidence.

Both low muscle mass and increased adiposity due to weight cycling may be metabolically linked to cancer via altered metabolic (43) and endocrine (44) pathways, as well as enhanced inflammatory responses (45–47) and immune changes (48–50). Increases in insulin-like growth factor-1 (IGF-1; refs. 51, 52) interact with and contribute to synthesis of bioavailable estrogens (43), increasing cell proliferation and survival (43, 53–55). Evidence suggests an upregulation of cytokines from increased fat mass may have a negative effect on muscle mass (56), promoting a cyclical trend toward a more sarcopenic obese phenotype. Another possibility is that weight cycling may be associated with an altered immune response by inducing changes in natural killer cells (48, 49).

This is the first study to comprehensively assess the role of various weight-change patterns and risk of breast, endometrial, and colorectal cancers in postmenopausal women independent of BMI, in addition to analyzing dose–response information on the frequency of weight cycling across all three cancers. The most important strength of this study is its large study population and the prospective nature of the WHI OS assuring temporal sequence between exposure and outcome variables. Other strengths include a large number of weight cyclers, intentionality of weight loss, and number of weight cycles, which permitted a dose–response analysis for weight cycling frequency. In addition, endometrial cancer analyses omit women with prior hysterectomy at baseline and censor at the date of hysterectomy reported during follow-up. This is important because women with a hysterectomy would no longer be at risk for endometrial cancer; thus, the inclusion of women with hysterectomy could bias the estimates for risk of endometrial cancer. Lastly, reported cancers were adjudicated locally and centrally for accuracy, and only independent, first-time breast, endometrial, and colorectal cancer diagnoses were assessed to ensure that previous cancer diagnoses at any of the three sites of interest did not affect future cancer outcomes.

However, there are some limitations to this study to consider. Weight-change data were self-reported and recalled, and changes in body composition were not evaluated in this data set. Correlations between recalled weight and objectively measured weight gradually decrease over time (57) and may be underestimated more so among women (58) and heavier individuals (59). Despite this, many similar studies (11–16, 18, 20–22) use self-reported recall data to report weight cycling exposure. The quality of weight-change data was somewhat limited in that specific magnitude and rate of weight loss and regain, as well as timing of weight cycles throughout adulthood, were not evaluated. Despite an attempt to put our findings in context of the larger body of literature, a single, uniform definition of weight cycling does not exist and differs significantly across studies—from 5% and 10% (20) to 10- (refs. 11, 12, 18, 22; in the present study) and 20-pound change (13, 15, 16, 21)—making cross-study comparisons difficult. Although we present dose–response information, these comparisons are limited by small sample sizes, particularly among high weight cycling–frequency categories. Whether BMI is a result of, or contributes to, weight cycling behavior throughout adulthood remains elusive, and residual confounding should be considered. Finally, results for our composite cancer outcome are heavily influenced by the large number of breast cancer cases reported (73% of total). Future studies should consider incorporating longitudinal, objective measures of weight and body composition changes, as well as data on magnitude, duration, and timing of weight cycles, to better characterize weight-change patterns and risk of future health outcomes.

In summary, the results of our study suggest that weight gain and weight cycling, independent of BMI, are associated with risk of breast and endometrial cancers, respectively, in postmenopausal women. Together, these data emphasize the importance of adopting effective ideal body weight maintenance practices during adulthood to maximize health benefit. Further investigation is needed to understand the independent effects of weight cycling and BMI on cancer risk and to clarify the biological mechanisms relating weight cycling, and particularly sarcopenia, to cancer incidence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H. Sangi-Haghpeykar, M.Z. Vitolins
Development of methodology: L.M. Welti, D.P. Beavers, H. Sangi-Haghpeykar
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.J. Caan, M.Z. Vitolins
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.P. Beavers, H. Sangi-Haghpeykar
Writing, review, and/or revision of the manuscript: L.M. Welti, D.P. Beavers, B.J. Caan, H. Sangi-Haghpeykar, M.Z. Vitolins, K.M. Beavers
Study supervision: L.M. Welti

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