Research Article

Cancer Prevention Research

Adulthood Weight Change and Risk of Colorectal Cancer in the Nurses' Health Study and Health Professionals Follow-up Study

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Abstract

We investigated the association between adulthood weight change and colorectal cancer risk in a prospective study with 24 to 34 years of follow-up among 90,988 women and 46,679 men. The primary exposures included weight change from early adulthood (age = 18 years for women, 21 years for men) to baseline enrollment (median age = 43 years for women, 52 years for men), and from baseline to present. In the secondary analyses, we also assessed 4-year weight change during follow-up, and during premenopausal (from age 18 years to menopause) and postmenopausal (from menopause to present) periods in women. Compared to men maintaining their weight from age 21 to baseline, those who gained 20 kg or more were at a higher risk of colorectal cancer (relative risk [RR], 1.64; 95% confidence interval [CI], 1.15–2.35, $P_{trend} < 0.001$), whereas those who lost 8 kg or more had a lower risk (RR, 0.61; 95% CI, 0.30–1.22, $P_{trend} = 0.003$). Similar but weaker associations were found in women and the corresponding RRs were 1.38 (95% CI, 1.13–1.69, $P_{trend} < 0.001$) and 0.80 (95% CI, 0.58–1.09, $P_{trend} = 0.21$). Weight change from baseline to present was not associated with colorectal cancer risk. Four-year weight change during follow-up was positively associated with colorectal cancer risk in men ($P_{trend} = 0.03$) but not in women ($P_{trend} = 0.42$). In addition, in women, weight change before, but not after, menopause was associated with colorectal cancer risk. Our findings provide further scientific rationale for recommendations to maintain a healthy body weight during adulthood. A potential differential association according to sex and timing of weight change warrants further investigation. *Cancer Prev Res; 8(7); 620–7. ©2015 AACR.*

Introduction

Colorectal cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the world (1). Despite the convincing evidence that overweight and obesity increase colorectal cancer risk (2), the influence of weight change on colorectal cancer incidence remains poorly understood. Compared to studies of attained body mass index (BMI), investigation of weight change may better capture the effect of excess body fat during adulthood, and help recommendations about weight control.

Adulthood weight gain has been associated with a higher risk of colorectal cancer in several previous studies (3–11). However, whether the effects of weight gain vary by gender, timing during the lifespan and tumor subsite remain inconclusive. The obesity–colorectal cancer association is generally stronger in men than in women, and stronger for colon cancer, in particular distal colon cancer, than for rectal cancer (2). Although similar patterns were seen for weight gain in some studies (4, 10, 12–15), findings from others were inconsistent (9, 13). In addition, in most studies body weight data were collected at only two time points to calculate weight change (6–10, 14, 15), and therefore a more precise assessment of the timing of weight gain on colorectal cancer risk could not be determined.

In contrast to weight gain, investigation of weight loss is more challenging and evidence is sparse (16). Studies are often limited by statistical power due to low prevalence of sustained weight loss among middle-aged adults. In previous observational studies, weight loss was typically characterized by a single category and a statistically significant inverse association with colon cancer risk was reported in only one study (17). Thus, detailed dose–response analyses of large prospective studies with repeated weight assessments are needed to elucidate the relationship between weight loss and colorectal cancer.

We investigated the association of adulthood weight change with incidence of colorectal cancer in two large U.S. cohort studies, the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). In an earlier examination in

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the HPFS, we observed a positive association between weight gain and colon cancer (3); however, that analysis was focused on late adulthood weight gain among only men, and did not examine associations with rectal cancer. In this study, we present results that encompass weight change in both early and late adulthood in both men and women over 24 to 34 years of follow-up.

Materials and Methods

Study population

The NHS included 121,701 U.S. registered female nurses who were ages 30 to 55 years in 1976. The HPFS included 51,529 U.S. male health professionals who were ages 40 to 75 years in 1986. Details of the two cohorts have been described elsewhere (18, 19). Briefly, follow-up questionnaires were administered at baseline enrollment and every 2 years thereafter to collect lifestyle and medical information (Supplementary Materials). The follow-up proportions were 95.4% in the NHS and 95.9% in the HPFS among participants who were alive up to 2010. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital and the Harvard School of Public Health.

Exposure assessment

We asked participants their current weight in biennial questionnaires. Recalled weight at age 18 years was inquired in 1980 in the NHS, and weight at age 21 years was inquired in 1986 in the HPFS. In our primary analysis, we assessed weight change in two periods: from early adulthood (age 18 years for women and age 21 years for men) to baseline enrollment, and from baseline to present (updated weight in each questionnaire cycle). These two exposures represent early and late adulthood weight change, respectively. To evaluate more recent effect of weight change, in the secondary analysis we also assessed 4-year weight change during follow-up, which was calculated and updated using repeated weight assessments 4 years apart, except that in the HPFS the first cycle of weight change was approximated by utilizing the recalled weight change 5 years before baseline (i.e., change in 1981–1986). To capture the influence of sustained weight change during follow-up, we performed a sensitivity analysis by restricting participants to those who remained in the same category of 4-year weight change (i.e., loss $\geq$2 kg, loss or gain <2 kg, or gain $\geq$2 kg) for at least two consecutive questionnaire cycles over 6 years (20). In women, we additionally assessed premenopausal and postmenopausal weight changes, which were defined as the weight change from age 18 years to menopause and from menopause up to date, respectively.

In a validation study, we compared self-reported weight to the average of two weight measurements taken by technicians approximately 6 months apart among a sample of 140 women and 123 men drawn from the two cohorts. Self-reported and measured weights were highly correlated ($r = 0.97$; ref. 21). Recalled weight at age 18 years has also been validated in the parallel NHS II cohort, with a correlation coefficient of 0.87 between recalled weight and weight recorded on college or nursing school records at age 18 years (22). Although not validated in the HPFS, recalled weight during early adulthood in men has also been shown to be accurate ($r = 0.80$) in other studies (23).

Outcome assessment

In both cohorts, self-reported colorectal cancer diagnoses were obtained in biennial questionnaires. We then asked participants for permission to acquire their medical records. We identified deaths through the National Death Index. For all colorectal cancer deaths, we requested permission from next-of-kin to review medical records. A study physician reviewed all records to confirm the colorectal cancer diagnosis and to extract relevant information, including anatomic location.

Statistical analysis

To minimize the influence of reverse causation arising from undiagnosed cancer-induced weight loss, we examined the association between weight change and colorectal cancer risk by introducing a lagged follow-up of 2 to 4 years. Therefore, for the analysis of weight change from early adulthood to baseline, person-years were calculated from 4 years after the date of baseline questionnaire return to the date of colorectal cancer diagnosis, death, or the end of the study period (June 1, 2010, for the NHS and January 31, 2010, for the HPFS), whichever came first. For the analysis of weight change from baseline to present, person-time started accumulating in 1980 in the NHS and 1990 in the HPFS. For the analysis of 4-year weight change, follow-up started from 1982 in the NHS and 1988 in the HPFS.

We used Cox proportional hazards regression model with age as the time scale to estimate hazard ratio (as an estimate of relative risk [RR]) and 95% confidence interval (CI). We adjusted for several colorectal cancer risk factors in the multivariable model (see the footnotes of tables). Test for trend was performed using continuous weight change, and test for trend across weight loss categories was restricted to participants who maintained or lost weight, excluding those who gained weight.

We calculated the population attributable risk conferred by weight gain ($\geq$2 and $\geq$5 kg) to estimate the percentage of colorectal cancer cases in our cohort that, theoretically, would have been prevented if participants had maintained or lost weight, assuming a causal relationship between weight gain and colorectal cancer incidence, holding all other risk-factor distributions constant (24).

More details of the statistical analysis are provided in the Supplement Materials. We used SAS 9.3 for all analyses (SAS Institute Inc.). All statistical tests were two sided and $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the basic characteristics of participants according to categories of weight change from early adulthood to baseline. Among participants who returned questionnaires in 1980 in the NHS (120,947 women) and in 1990 in the HPFS (50,384 men), we excluded those who had a history of cancer (except nonmelanoma skin cancer: 5,338 women and 1,263 men) or who did not provide information on body weight at baseline or early adulthood (24,621 women and 2,442 men). A total of 90,988 women and 46,679 men were included in the main analysis. On average, women gained 6.4 kg from age 18 years to baseline (mean age = 43 years) over an average time of 25 years, and men gained 7.9 kg from age 21 to baseline (mean age = 54 years) over an average time of 33 years. Compared to individuals who gained weight, those

Table 1. Age-standardized characteristics of study participants according to weight change from age 18 (women) or 21 (men) years to baseline[a]

	Women ($n = 79,294$)			Men ($n = 36,180$)		
Variable	**Loss ≥8.0 kg**	**Loss or gain <2.0 kg**	**Gain ≥20.0 kg**	**Loss ≥8.0 kg**	**Loss or gain <2.0 kg**	**Gain ≥20.0 kg**
Participants, *n* %	3,177 (4.0)	12,977 (16.4)	6,725 (8.5)	922 (2.6)	3,723 (10.3)	3,213 (8.9)
Age, year	41.7 (7.1)	41.0 (7.1)	45.0 (6.6)	52.0 (10.0)	51.2 (9.5)	56.2 (9.1)
Weight change, kg[b]	−13.4 (5.8)	0.17 (1.0)	27.6 (7.8)	−13.3 (6.7)	0.27 (1.0)	26.1 (6.5)
Height, in.	64.7 (2.5)	64.2 (2.4)	64.9 (2.4)	70.5 (2.8)	69.9 (2.7)	70.9 (2.7)
BMI at early adulthood, kg/m^2[b]	27.1 (4.0)	21.3 (2.3)	21.7 (3.4)	28.2 (4.0)	23.5 (2.6)	21.9 (3.5)
BMI at baseline, kg/m^2[c]	22.1 (3.2)	21.4 (2.3)	31.9 (4.8)	24.1 (3.4)	23.6 (2.5)	30.0 (4.2)
Physical activity[d]	1.4 (2.1)	1.4 (2.1)	1.0 (1.9)	29.6 (35.3)	30.1 (39.3)	12.2 (18.4)
Pack-years of smoking before age 30	4.9 (5.2)	3.1 (4.3)	2.0 (3.9)	6.0 (7.7)	4.1 (6.4)	6.6 (8.3)
Current smoking, %	64	42	24	9	9	8
Family history of colorectal cancer, %[e]	16	16	16	14	13	13
Current multivitamin use, %	22	24	19	47	46	35
Regular use of aspirin/NSAIDs, %[f,g]	38	35	42	31	28	36
History of endoscopy, %[f]	11	10	9	29	28	25
Postmenopausal, %	35	31	31	—	—	—
Current use of hormones, %[h]	26	29	20	—	—	—
Dietary intake[i]						
Alcohol, g/day	7.2 (12.0)	7.1 (10.9)	3.4 (8.5)	10.0 (13.9)	10.9 (14.6)	11.3 (17.0)
Folate, μg/day	359 (264)	370 (285)	356 (304)	533 (329)	522 (303)	431 (258)
Vitamin D, IU/day	323 (292)	328 (298)	335 (323)	459 (357)	440 (342)	360 (278)
Calcium, mg/day	748 (319)	735 (312)	726 (348)	957 (503)	941 (446)	844 (394)
Total fiber, g/day	14.3 (6.3)	14.1 (6.1)	13.5 (6.0)	24.1 (9.2)	22.7 (7.9)	19.3 (6.0)
Processed red meat, g/day	9.2 (10.2)	9.3 (10.3)	12.0 (11.8)	7.2 (11.9)	7.5 (10.0)	12.4 (13.0)
DASH diet score	24.2 (4.6)	24.0 (4.6)	23.0 (4.7)	26.1 (5.8)	25.6 (5.6)	22.3 (5.2)
AHEI diet score	43.2 (10.0)	42.5 (9.9)	38.9 (9.3)	44.6 (11.6)	43.4 (10.9)	37.5 (9.4)

Abbreviations: AHEI, alternative healthy eating index; BMI, body mass index; DASH, dietary approaches to stop hypertension; NSAID, nonsteroidal anti-inflammatory drug.

[a]All variables were assessed in 1976 in women (NHS) and in 1986 in men (Health Professionals Follow-up Study) unless otherwise specified. Mean (standard deviation) is presented for continuous variables. All variables are age-standardized except age.

[b]Early adulthood represents age of 18 years in women and age of 21 years in men.

[c]BMI in 1976 in women and 1986 in men.

[d]Physical activity represents the frequency of regular activity per week in 1980 in women, and the metabolic equivalent of task (MET)-hours/week in 1986 in men.

[e]Defined as having a diagnosis of colorectal cancer among parents or siblings.

[f]These variables were assessed in 1980 in women.

[g]Regular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥2 tablets of NSAIDs per week.

[h]Proportion of current postmenopausal hormone use is calculated among postmenopausal women only.

[i]Dietary intake was assessed in 1980 in women and in 1986 in men.

who lost or maintained their weight were less likely to take aspirin or nonsteroidal anti-inflammatory drugs, and more likely to smoke, take multivitamins, undergo endoscopy, exercise regularly, and tended to have a high BMI at early adulthood and low BMI at baseline. They also consumed more folate, calcium, and fiber, and less processed red meat, thus overall having a higher score on the healthy eating indices.

Weight change from early adulthood to baseline was associated with colorectal cancer risk ($P_{trend} < 0.001$ in both women and men, Table 2), and the association appeared to be stronger in men than in women ($P_{interaction} = 0.05$ by gender). Compared with individuals who maintained weight, those who gained 20 kg or more were at a higher risk (multivariable RR, 1.38; 95% CI, 1.13–1.69 in women; 1.64, 95% CI, 1.15–2.35 in men), whereas those who lost 8 kg or more had 20% and 39% lower risk of colorectal cancer in women and men, respectively. We estimated that 13% (95% CI, 5.7%–20.6%) and 20% (95% CI, 4.1%–35.0%) of colorectal cancer cases in our population might be attributable to weight gain of 2 kg or more since early adulthood in women and men, respectively. The corresponding figure for weight gain of 5 kg or more was 6.8% (95% CI, 1.4%–12.1%) in women and 9.7% (95% CI, −0.8%–20.0%) in men.

The association of weight change with colorectal cancer did not appear to differ according to early adulthood BMI, age at baseline, or anatomical locations of tumors, although a somewhat stronger association was found among leaner and older individuals than among heavy or young individuals, and for distal colon cancer than for proximal colon or rectal cancers (Supplementary Tables S1–S3). When stratified by early adulthood BMI, women with initial BMI of ≥21 kg/m^2 who lost weight of at least 8 kg had an RR for colorectal cancer of 0.75 (95% CI, 0.54–1.05) compared to those who maintained their weight, and the corresponding RR among men with BMI of ≥23 kg/m^2 was 0.59 (0.28–1.25). In addition, we stratified by aspirin use and observed a somewhat stronger association between weight change and colorectal cancer risk among users than among nonusers of aspirin (Supplementary Table S4), although the interaction test achieved statistical significance only in women ($P_{interaction} = 0.05$ in women, 0.36 in men). In women, the RR of colorectal cancer associated with 10-kg weight gain was 1.19 (95% CI, 1.09–1.29) among regular users of aspirin, and 1.06 (95% CI, 1.00–1.14) among nonusers.

Table 3 presents the association of weight change from baseline to current time with risk of colorectal cancer. No statistically significant association was detected in either sex ($P_{trend} = 0.60$ in women, 0.21 in men). When stratified by age (Supplementary Table S5), a positive association was found between weight gain and colorectal cancer risk among individuals younger than 70 years, but not among older individuals, although the difference between age strata was only statistically significant in women ($P_{interaction} = 0.03$ in women, 0.93 in men).

Table 2. Relative risk of colorectal cancer according to weight change from age 18 (women) or 21 (men) years to baseline

Weight change, kg	Median, kg	Cases, *n*	Person-years	Age-adjusted RR (95% CI)[a]	Multivariable-adjusted RR (95% CI)[b]
Women					
Loss ≥8.0	−11.3	58	83,615	0.83 (0.61–1.13)	0.80 (0.58–1.09)
Loss 4.0–7.9	−5.4	84	125,438	0.99 (0.76–1.27)	0.96 (0.74–1.24)
Loss 2.0–3.9	−2.7	75	115,144	1.06 (0.82–1.39)	1.05 (0.81–1.37)
Loss or gain <2.0	0	208	358,314	1 (referent)	1 (referent)
Gain 2.0–5.9	4.1	342	505,356	1.12 (0.95–1.34)	1.14 (0.96–1.35)
Gain 6.0–9.9	8.2	300	381,793	1.20 (1.00–1.43)	1.22 (1.02–1.45)
Gain 10.0–19.9	13.6	341	410,171	1.16 (0.98–1.38)	1.18 (0.99–1.41)
Gain ≥20.0	24.9	177	173,694	1.34 (1.09–1.63)	1.38 (1.13–1.69)
P_{trend}				<0.001	<0.001
P for weight loss trend[c]				0.22	0.21
Per 5.0 kg gain per 10 years				1.11 (1.04–1.18)	1.13 (1.06–1.20)
Men					
Loss ≥8.0	−11.3	10	15,858	0.63 (0.32–1.27)	0.61 (0.30–1.22)
Loss 4.0–7.9	−5.0	18	27,090	0.75 (0.43–1.28)	0.73 (0.43–1.26)
Loss 2.0–3.9	−2.3	15	22,820	0.79 (0.44–1.40)	0.78 (0.44–1.39)
Loss or gain <2.0	0	52	67,217	1 (referent)	1 (referent)
Gain 2.0–5.9	4.5	128	160,644	1.02 (0.74–1.40)	1.02 (0.74–1.41)
Gain 6.0–9.9	8.2	119	133,685	1.06 (0.77–1.48)	1.06 (0.77–1.47)
Gain 10.0–19.9	13.6	153	157,842	1.10 (0.80–1.50)	1.09 (0.80–1.51)
Gain ≥20.0	24.5	79	52,841	1.62 (1.14–2.31)	1.64 (1.15–2.35)
P_{trend}				<0.001	<0.001
P for weight loss trend[c]				0.004	0.003
Per 5.0 kg gain per 10 years				1.33 (1.15–1.54)	1.35 (1.16–1.57)

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Adjusted for age, and body weight at age 18 years for women or at age 21 years for men.

[b]Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1–10, and >10), current smoking status (yes or no), multivitamin use (yes or no), and regular use of aspirin/NSAIDs (yes or no, in men only). In women, postmenopausal status and hormone use were additionally adjusted.

[c]Calculated among participants who lost weight of ≥2.0 kg, or lost or gained weight of <2.0 kg.

Table 4 shows the association between 4-year weight change during follow-up and risk of colorectal cancer. Weight change was associated with colorectal cancer in men ($P_{trend} = 0.03$) but not in women ($P_{trend} = 0.42$; $P_{interaction} = 0.10$ by gender). Among men with sustained change, weight gain of ≥8 kg was associated with 89% higher risk (95% CI, 16%–208%) and weight loss of ≥7 kg associated with 30% lower risk. We did not detect any statistically significant effect modification by age (Supplementary Table S6). To examine whether the weaker association for 4-year weight change in women was due to limited duration of the time interval over which weight change was assessed, we evaluated weight change per 10 years and the results were similar (data not shown).

We further investigated whether the association of the timing of weight change in women was related to menopause. As shown in Table 5, weight change before, but not after menopause, was associated with risk of colorectal cancer ($P_{trend} = 0.04$ and 0.60, respectively). We also stratified by hormone use among postmenopausal women, and the association of weight change with colorectal cancer did not differ according to hormone use ($P_{interaction} = 0.45$; Supplementary Table S7).

Discussion

In the two large prospective cohorts, we found that weight gain from early adulthood to baseline enrollment was associated with a higher risk of colorectal cancer, whereas weight loss was associated with lower risk. The associations appeared stronger in men than in women. Weight change during late adulthood was not associated with colorectal cancer risk. For weight change in the recent 4 years, a statistically significant association was observed in men, but not in women. In women, weight gain before, but not after, menopause was associated with colorectal cancer risk.

Substantial evidence from randomized controlled trials indicates that weight loss due to dietary modification and/or exercise is associated with improved profiles of inflammatory markers, insulin sensitivity, adipokines, and sex hormones (25–29), all of which have been suggested to mediate the relationship between obesity and increased risk of colorectal cancer (30, 31). However, direct epidemiologic evidence on the association of weight loss with colorectal cancer has been sparse and inconsistent. Although surgical weight loss has been inversely associated with the risk of colorectal cancer in a few studies (12, 13, 16, 32), the small sample sizes precluded a detailed dose–response analysis. Similarly, the influence of nonsurgical weight loss on colorectal cancer remains inconclusive in prospective cohort studies, in which weight loss was typically considered only in a single category due to the small number of cases (4, 6–10, 15, 17). To our knowledge, our findings provide the first population-based evidence that weight loss during adulthood may be associated with lower risk of colorectal cancer.

For weight gain since early adulthood, consistent with previous studies (4, 6–8, 10, 11, 15), we found a positive association with colorectal cancer risk and the association was stronger in men than in women. Although it is possible that the older ages of men compared to women at cohort enrollment contribute to the larger elevation of colorectal cancer risk associated with weight gain, we did not find strong evidence that the association between weight change and colorectal cancer risk varied by age at baseline in either men or women (Supplementary Table S2). However, our findings

Table 3. Relative risk of colorectal cancer according to weight change from baseline to present

Weight change, kg	Median, kg	Cases, *n*	Person-years	Age-adjusted RR (95% CI)[a]	Multivariable-adjusted RR (95% CI)[b]
Women					
Loss ≥5.0	−8.2	126	135,680	0.98 (0.71–1.36)	0.97 (0.70–1.34)
Loss 2.0–4.9	−3.2	200	219,230	1.15 (0.85–1.56)	1.15 (0.85–1.56)
Loss 1.0–1.9	−1.4	61	78,634	0.87 (0.65–1.16)	0.89 (0.67–1.19)
Loss or gain <1.0	0	332	602,816	1 (referent)	1 (referent)
Gain 1.0–5.9	3.2	600	951,912	0.94 (0.71–1.24)	0.94 (0.71–1.25)
Gain 6.0–11.9	9.1	485	663,412	1.02 (0.77–1.35)	1.00 (0.75–1.33)
Gain ≥12.0	17.2	406	553,194	1.07 (0.80–1.43)	1.03 (0.77–1.37)
P_{trend}				0.16	0.60
P for weight loss trend[c]				0.10	0.36
Per 5.0 kg gain per 10 years				1.00 (0.99–1.02)	1.00 (0.99–1.01)
Men					
Loss ≥5.0	−7.7	37	32,308	0.94 (0.64–1.36)	0.94 (0.65–1.37)
Loss 2.0–4.9	−3.2	78	75,146	0.93 (0.71–1.23)	0.93 (0.71–1.23)
Loss 1.0–1.9	−1.4	36	31,104	1.06 (0.73–1.52)	1.07 (0.75–1.55)
Loss or gain <1.0	0	174	163,328	1 (referent)	1 (referent)
Gain 1.0–2.9	2.3	106	113,278	0.97 (0.76–1.24)	0.97 (0.76–1.24)
Gain 3.0–7.9	4.5	126	144,458	1.03 (0.81–1.31)	1.01 (0.80–1.29)
Gain ≥8.0	11.3	59	66,786	1.18 (0.86–1.63)	1.15 (0.83–1.58)
P_{trend}				0.15	0.21
P for weight loss trend[c]				0.20	0.27
Per 5.0 kg gain per 10 years				1.01 (0.99–1.03)	1.01 (0.99–1.03)

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Adjusted for age, and body weight at baseline.

[b]Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0–20, 21–40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5–16.7, 16.8–30.1, 30.2–53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0–4.9, 5.0–9.9, 10.0–14.9, 15–29.9, ≥30.0 g/day), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles, and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past, or current users) were additionally adjusted.

[c]Calculated among participants who lost weight of ≥1.0 kg, or lost or gained weight of <1.0 kg.

are indeed consistent with the notion that obesity has a more marked influence on colorectal cancer incidence in men than in women (2). Although the exact mechanisms remain to be elucidated, sex hormones have been suggested to explain the difference between men and women (33, 34). In women, ovarian hormone production declines after menopause and adipose tissue becomes the primary organ for estrogen secretion, resulting in a 2-fold or greater level of circulating estrogen in women with high BMI than those with normal weight (35, 36). Estrogen protects against colorectal cancer development, possibly through regulation of gene transcription and modulation of cellular processes involved in cell proliferation, apoptosis, and angiogenesis (37). However, obese men are characterized by a progressive decrease of testosterone with increasing body weight (38). Low testosterone has been associated with higher risk of colorectal cancer in men, but not in women (39). Therefore, it is possible that the increased level of circulating estrogen mitigates the detrimental effect of adiposity in postmenopausal women (31, 33), whereas the lower testosterone in men elevates the metabolic risk of colorectal cancer associated with obesity. These hormonal alterations might collectively contribute to a weaker association of obesity with colorectal cancer in women than in women.

Consistent with this hypothesis, we observed that weight gain before, but not after, menopause was associated with higher risk of colorectal cancer. Alternatively, it is possible that this differential association by menopause may reflect the observation that weight gain during early and middle adulthood seems to be more important than weight gain during late adulthood, as shown in this study. In agreement with our results, several prior studies also reported a stronger association of weight gain (9) or high BMI (40) with colorectal cancer among premenopausal women than among postmenopausal women, although the evidence remains inconclusive (5, 6, 41). Further investigation is needed to elucidate the potential role of hormonal factors in the observed sex difference of the adiposity–colorectal cancer relationship.

Furthermore, the human large intestine consists of several compartments characterized with different embryologic origins, genetic background, and biochemical environment (42–46). A growing body of evidence suggests that risk factors of colorectal cancer vary by tumor subsites (47). In this study, we observed that weight change was more strongly associated with risk of distal colon cancer than that of proximal colon or rectal cancer. This aligns with previous evidence that obesity is more consistently associated with colon cancer, in particular distal colon cancer, than with rectal cancer (48, 49), and a stronger association between weight gain and distal colon cancer has been reported in several studies (5–7).

In contrast to weight change from early to middle adulthood, weight change during late adulthood, as reflected by change from baseline to present, was not associated with colorectal cancer risk in this study. It has been shown that body weight tends to increase, peaking at about 65 to 70 years, and then decrease with further aging (50). In addition, body composition changes with aging, with an increase in fat mass and a decrease in muscle mass (51, 52). These aging-related anthropometric changes pose challenge for investigation of body size change during late adulthood and complicate the interpretation of findings, particularly for weight change as it does not distinguish lean and fat mass (53). Indeed, we found some evidence that age may modify the relationship between weight change during late adulthood and colorectal cancer risk. Weight

Table 4. Relative risk of colorectal cancer according to 4-year weight change during follow-up

		Overall				Among sustained change[c]	
Weight change, kg	Median, kg	Cases, *n*	Person-years	Age-adjusted RR (95% CI)[a]	Multivariable-adjusted RR (95% CI)[b]	No. of cases	Multivariable-adjusted RR (95% CI)[b]
Women							
Loss ≥7.0	−10.0	93	94,404	1.01 (0.74–1.37)	0.99 (0.73–1.35)	54	1.15 (0.72–1.84)
Loss 2.0–6.9	−3.6	275	328,248	0.92 (0.72–1.18)	0.91 (0.71–1.17)	125	1.09 (0.73–1.64)
Loss 1.0–1.9	−1.4	89	100,280	0.98 (0.77–1.24)	0.97 (0.77–1.23)	37	1.16 (0.79–1.70)
Loss or gain <1.0	0	459	634,414	1 (referent)	1 (referent)	228	1 (referent)
Gain 1.0–2.9	2.3	248	394,774	0.87 (0.67–1.11)	0.87 (0.68–1.12)	111	1.04 (0.69–1.57)
Gain 3.0–7.9	4.5	331	457,124	1.04 (0.82–1.33)	1.04 (0.81–1.32)	161	1.14 (0.77–1.69)
Gain ≥8.0	10.4	99	150,272	1.01 (0.75–1.36)	0.98 (0.73–1.32)	56	1.22 (0.77–1.92)
P_{trend}				0.44	0.42		0.71
P for weight loss trend[d]				0.76	0.57		0.74
Men							
Loss ≥7.0	−9.1	24	24,840	0.86 (0.55–1.34)	0.84 (0.54–1.32)	15	0.70 (0.39–1.24)
Loss 2.0–6.9	−3.2	92	97,148	0.91 (0.70–1.17)	0.91 (0.70–1.18)	55	0.91 (0.65–1.28)
Loss 1.0–1.9	−1.4	28	34,026	0.81 (0.54–1.22)	0.82 (0.55–1.22)	17	0.93 (0.55–1.58)
Loss or gain <1.0	0	190	192,200	1 (referent)	1 (referent)	120	1 (referent)
Gain 1.0–2.9	1.8	97	110,914	0.92 (0.72–1.18)	0.92 (0.72–1.18)	50	0.91 (0.64–1.27)
Gain 3.0–7.9	4.5	120	126,606	1.11 (0.87–1.40)	1.09 (0.86–1.39)	68	1.05 (0.77–1.44)
Gain ≥8.0	11.3	26	21,618	1.42 (0.93–2.16)	1.40 (0.91–2.13)	22	1.89 (1.16–3.08)
P_{trend}				0.02	0.03		0.005
P for weight loss trend[d]				0.15	0.09		0.02

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Adjusted for age, and body weight at the start of each time period (continuous).

[b]Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0–20, 21–40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5–16.7, 16.8–30.1, 30.2–53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0–4.9, 5.0–9.9, 10.0–14.9, 15–29.9, ≥30.0 g/day), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles), and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past or current users) were additionally adjusted.

[c]Among participants who remained in the same category of weight change (defined as gain ≥2.0 kg, gain or loss <2.0 kg, or loss ≥2.0 kg) for at least two consecutive questionnaire cycles.

[d]Calculated among participants who lost weight of ≥1.0 kg, or lost or gained weight of <1.0 kg.

gain was suggestively associated with a higher risk of colorectal cancer among participants younger, but not older, than 70 years.

Although adiposity has been generally regarded as a tumor promoter, the critical period during which excess fatness increases colorectal cancer risk has yet to be determined. Our results suggest a sex-specific manner of action in which timing of exposure modifies the association of weight gain with colorectal cancer. In men, both remote and recent weight gain poses risk for colorectal cancer, whereas in women weight gain from early to middle adulthood, but not in recent years, appeared to be critical for colorectal cancer development. Consistent with our findings, in the NIH-AARP cohort, weight changes from 18 to 35 years and from 50 years to baseline (approximately 60 years) were both associated with colorectal cancer risk in men, whereas only weight change from 18 to 35 years was associated with the risk in women (4). In the Norwegian Counties Study, a stronger association between BMI and colon cancer was reported in women with follow-up of ≥10 years than <10 years, whereas no difference by duration of follow-up was detected in men (6). As an analogy to pack-years of smoking, "overweight years" as a measure of cumulative exposure to excess body size has been associated with colorectal cancer risk in women (5). Collectively, these results suggest a longer induction period for the tumorigenic effect of obesity in women than in men. This might be related to the beneficial effect of adipocytes-derived estrogen on obesity-induced carcinogenesis as discussed above (54). However, given the sparse evidence, further research is warranted to better understand the role of adiposity across the life course on colorectal cancer risk.

Some limitations of our study should be noted. First, weight information was self-reported or recalled and thus subject to measurement error. However, robust validity has been established in previous validation studies within the two cohorts (21–23). Second, although the homogeneity of the study population is a potential limitation, this reduces the likelihood of uncontrolled confounding, and it is unlikely that the observed relationship between weight change and colorectal cancer differs substantially from the general population. However, our findings should be confirmed in other populations.

This study also has several strengths, including the two large well-established cohorts, long-term follow-up, and detailed analysis on weight loss. Furthermore, repeated assessments of body weight across adulthood provided us a unique opportunity to examine the potential modification by timing of exposure, and by menopausal status in women.

In conclusion, our results indicate that weight gain from early to middle adulthood is associated with a higher risk of colorectal cancer, whereas weight loss during this period is associated with lower risk. The associations appear stronger in men than in women. We do not find strong evidence that weight change during late adulthood affects colorectal cancer risk. A potential differential association according to timing of weight change and menopausal status warrants further investigation. Our findings provide further scientific rationale for recommendations for adults to maintain a healthy body weight, especially during early/middle adulthood.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Table 5. Relative risk of colorectal cancer according to premenopausal and postmenopausal weight change[a]

Weight change, kg	Median, kg	Cases, *n*	Person-years	Age-adjusted RR (95% CI)[b]	Multivariable-adjusted RR (95% CI)[c]
Premenopausal					
Loss ≥8.0	−11.3	61	69,456	1.06 (0.78–1.45)	1.03 (0.75–1.40)
Loss 4.0–7.9	−5.4	69	94,056	1.10 (0.82–1.47)	1.09 (0.81–1.45)
Loss 2.0–3.9	−2.7	44	83,726	0.86 (0.61–1.21)	0.85 (0.60–1.19)
Loss or gain <2.0	0	146	254,822	1 (referent)	1 (referent)
Gain 2.0–5.9	4.1	261	418,654	1.11 (0.90–1.36)	1.10 (0.90–1.35)
Gain 6.0–9.9	8.2	297	422,150	1.17 (0.95–1.42)	1.15 (0.94–1.41)
Gain 10.0–19.9	14.1	539	689,926	1.19 (0.99–1.43)	1.16 (0.96–1.40)
Gain ≥20.0	27.2	432	511,662	1.23 (1.02–1.49)	1.20 (0.99–1.45)
P_{trend}				0.01	0.04
P for weight loss trend[d]				0.95	0.87
Postmenopausal					
Loss ≥8.0	−11.3	90	67,964	1.17 (0.92–1.49)	1.16 (0.91–1.47)
Loss 4.0–7.9	−5.0	120	113,008	1.07 (0.87–1.31)	1.05 (0.86–1.29)
Loss 2.0–3.9	−2.7	137	115,010	1.28 (1.05–1.55)	1.25 (1.03–1.52)
Loss or gain <2.0	0	462	538,248	1 (referent)	1 referent)
Gain 2.0–5.9	3.6	398	463,230	0.96 (0.84–1.10)	0.96 (0.83–1.10)
Gain 6.0–9.9	7.7	240	240,400	1.04 (0.89–1.22)	1.04 (0.88–1.22)
Gain ≥10.0	13.6	235	220,330	1.09 (0.92–1.28)	1.08 (0.92–1.28)
P_{trend}				0.58	0.60
P for weight loss trend[d]				0.40	0.55

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Premenopausal weight change was calculated by the weight change from age 18 years up to menopause, and postmenopausal weight change was the weight change from menopause up to date.

[b]Adjusted for age, and body weight at age 18 years (for premenopausal weight change) or at menopause (for postmenopausal weight change).

[c]Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1–10, and >10), current smoking status (yes or no), multivitamin use (yes or no), regular use of aspirin/NSAIDs (yes or no), endoscopic screening (yes or no), postmenopausal hormone use (current, past, and never users), physical activity (<6.5, 6.5–16.7, 16.8–30.1, 30.2–53.3, ≥53.4 MET-hours/week), alcohol consumption (0–4.9, 5.0–9.9, 10.0–14.9, 15–29.9, ≥30.0 g/d), and intake of folate (in quartiles), calcium (in quartiles), vitamin D (in quartiles) and processed red meat (in quartiles).

[d]Calculated among women who lost weight of ≥2.0 kg, or lost or gained weight of <2.0 kg.

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