JNCI Cancer Spectrum (2022) 6(1): pkab098

https://doi.org/10.1093/jncics/pkab098
Article

Weight Change and Incident Distal Colorectal Adenoma Risk in the PLCO Cancer Screening Trial

Shisi He, MS [1], Sonja I. Berndt, PharmD, PhD [2], Andrew T. Kunzmann, PhD [3], Cari M. Kitahara, PhD, MHS [4], Wen-Yi Huang, PhD, MSPH [5], Kathryn Hughes Barry, PhD, MPH [1,6,*]

[1]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA; [2]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; [3]Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK; [4]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; [5]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA and [6]Program in Oncology, University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA

*Correspondence to: Kathryn Hughes Barry, PhD, MPH, Department of Epidemiology and Public Health, University of Maryland School of Medicine, 660 W. Redwood St, Howard Hall 100E, Baltimore, MD 21201, USA (e-mail: kbarry@som.umaryland.edu).

Abstract

Background: Although obesity is a known risk factor, the impact of weight change on colorectal adenoma risk is less clear and could have important implications in disease prevention. We prospectively evaluated weight change in adulthood and incident colorectal adenoma. **Methods:** We assessed weight change during early-late (age 20 years to baseline, ie, ages 55-74 years), early-middle (20-50 years), and middle-late (50 years-baseline) adulthood using self-reported weight data in relation to incident distal adenoma in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (cases = 1053; controls = 16 576). For each period, we defined stable weight as greater than −0.5 kg to less than or equal to 1 kg/5 years, weight loss as less than or equal to −0.5 kg/5 years, and weight gain as greater than 1-2, greater than 2-3, or greater than 3 kg/5 years. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression; all tests were 2-sided. **Results:** Compared with stable weight, weight loss during early-late adulthood was associated with reduced adenoma risk (OR = 0.54, 95% CI = 0.34 to 0.86), particularly among those who were overweight or obese at age 20 years (OR = 0.39, 95% CI = 0.18 to 0.84). Results were similar for early-middle adulthood but less pronounced for middle-late adulthood. Weight gain greater than 3 kg/5 years during early-late adulthood was associated with increased risk (OR = 1.30, 95% CI = 1.07 to 1.58, $P_{trend} < .001$). Findings appeared stronger among men (OR for >3 kg/5 years = 1.41, 95% CI = 1.11 to 1.80) than women (OR = 1.09, 95% CI = 0.79 to 1.50, $P_{interaction} = .21$). **Conclusions:** Weight loss in adulthood was associated with reduced adenoma risk, particularly for those who were overweight or obese, whereas weight gain greater than 3 kg/5 years increased risk. Findings underscore the importance of healthy weight maintenance throughout adulthood in preventing colorectal adenoma.

Over the past 30 years, the prevalence of obesity has risen in the United States and worldwide (1-3), leading to increased rates of many chronic diseases. Obesity is an established risk factor for colorectal carcinogenesis (4), with increased risks for both colorectal adenoma, a precursor to colorectal cancer, and colorectal cancer (5-7). A meta-analysis of 23 studies identified a positive dose-response association between obesity and colorectal adenoma (8). Although studies of colorectal cancer have suggested stronger associations with body mass index (BMI) among men than women (7), the evidence is less consistent for adenoma (5,9-12).

To date, most studies have only investigated colorectal adenoma risk in relation to obesity or BMI assessed at one point in time (8), with fewer studies evaluating the role of weight change and most only assessing weight gain. Weight loss is commonly recommended for overweight and obese individuals; in 2016, 49% of US overweight adults reported trying to lose weight in the past year (13). Although weight loss has many beneficial health effects, whether weight loss can reduce adenoma risk among overweight and obese individuals remains an important question. Few studies have evaluated weight loss and colorectal adenoma, yielding mixed results (12,14,15). With regard to weight gain, a recent meta-analysis of 9 studies, of which only 4 were prospective, reported a positive association between weight gain and adenoma risk (16). Although greater cumulative

Received: September 19, 2021; **Revised:** October 21, 2021; **Accepted:** October 22, 2021

lifetime exposure to excess weight could conceivably increase adenoma risk, previous studies have not evaluated the potential modifying role of starting BMI or the timing of weight change throughout adulthood. There may also be critical time periods when weight gain and obesity may have a greater impact on colorectal carcinogenesis.

We prospectively assessed the associations between weight change, including both weight loss and gain, over different periods of adulthood and the risk of incident colorectal adenoma. We also evaluated potential differences in these associations by sex and starting BMI. Our study is unique in its conduct in the screening arm of a large colorectal cancer screening trial that involved screening at both baseline and follow-up, allowing for adenoma detection without regard to clinical indication. This study design had several key advantages, including the ability to prospectively ascertain incident adenoma cases, ensuring that the weight change preceded disease, and a reduced likelihood of screening bias because of equal opportunity of screening in the study population.

Methods

Study Design

We evaluated weight change and incident colorectal adenoma within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. The PLCO trial was a large, multicenter, randomized controlled trial in the United States that enrolled 154 942 men and women aged 55-74 years from 1993 to 2001 to evaluate the effectiveness of different screening regimens on mortality from prostate, lung, colorectal, and ovarian cancers as described previously (17). Participants in the screening arm underwent flexible sigmoidoscopy screening (FSG) for colorectal cancer at baseline and again during follow-up either 3 or 5 years later, T3 or T5 (18). The study was approved by the human subjects review boards at the National Cancer Institute and at the 10 study centers (National Institutes of Health Institutional Review Board #OH97CN041). Written informed consent was given by all participants.

The cohort of eligible participants (N = 18 588) for the present analysis comprised screening arm participants who completed the baseline general and dietary questionnaires, who had adequate baseline and follow-up trial FSG screenings (insertion ≥50 cm with ≥90% of mucosa visible or suspicious lesion found) with no polyps or abnormal or suspicious findings in the distal colon or rectum at baseline (ie, negative baseline screen), and who had no prior history of colorectal cancer before the follow-up trial screening. The participants also had no personal history of any cancer (except non-melanoma skin) before randomization. We excluded participants who had a self-reported colon-related comorbidity (ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis) or a self-reported history of colorectal polyps (n = 959).

Incident colorectal adenoma cases were those who had a negative baseline trial FSG screen and a positive follow-up trial FSG screen with distal adenoma subsequently histologically confirmed during diagnostic follow-up (n = 1053). We refer to the cases as incident distal adenomas because of FSG coverage of the distal colon and rectum but not the proximal colon. Advanced adenoma was defined as adenoma at least 1 cm in size or containing high-grade dysplasia or villous components. Controls were those who had a negative baseline trial FSG and a negative follow-up trial FSG (n = 16 576).

Weight Change

In the baseline questionnaire, participants self-reported their weight at age 20 years, 50 years, and baseline (age 55-74 years) as well as their height. We defined "early-late adulthood weight change" as the difference in weight between age 20 years and baseline. Similarly, we defined "early-middle adulthood weight change" based on the period from age 20 to 50 years and "middle-late adulthood weight change" based on age 50 years to baseline. To compute a standardized rate of weight change per 5 years, we divided the difference in weight by the number of years between the ages and multiplied by 5, so that $weight\ \Delta(B-A) = \frac{weight_B - weight_A}{AgeB - AgeA} \times 5$. We chose to evaluate weight change per 5 years because 5 years was the shortest possible time period from age 50 years to baseline and using a standardized rate allowed for comparison of results across different periods of adulthood.

We categorized the rate of weight change into 5 groups based on the distribution and used integer cutpoints to aid in interpretability. We defined the stable weight group (referent) as weight loss less than 0.5 kg/5 years or weight gain less than or equal to 1 kg/5 years. We defined the weight loss group as those who lost at least 0.5 kg/5 years to help maximize the sample size in this group because relatively few participants lost weight. We defined 3 weight gain groups: little weight gain ($1 < \Delta \leq 2$ kg/5 years), moderate gain ($2 < \Delta \leq 3$ kg/5 years), and highest gain ($\Delta > 3$ kg/5 years). Supporting the choice of our categories, Sedjo et al. (12) found a statistically significant association with prevalent adenoma for weight gain greater than 1.8 kg/5 years.

Statistical Analysis

We applied multivariable-adjusted logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs) for weight change and incident adenoma. We computed P values for trend by a Wald test for a pseudo-continuous variable using the median values for each weight change category determined in the control group. All tests to determine statistical significance were 2-sided, with $\alpha = 0.05$.

All models adjusted for age (≤59 years, 60-64 years, 65-69 years, ≥70 years), sex, race (non-Hispanic Black, non-Hispanic White, other), starting BMI at age 20 or 50 years (as appropriate for the weight change period, kg/m^2, continuous), total energy intake (kcal/d, continuous), fiber intake (g/1000 kcal, continuous), total red meat intake (g/1000 kcal, continuous), study year of second trial FSG screen (T3 or T5), and smoking (never smoker, former cigarette smoker quit >23 years ago [ie, median among former smokers in control group], former cigarette smoker quit ≤23 years ago, current cigarette smoker with pack-years ≤45 [ie, median among current smokers in control group], current cigarette smoker with pack-years >45, and pipe or cigar smoker only). For models among women only, we additionally adjusted for hormone replacement therapy. We used simple imputation based on the most common category in our total study population to impute missing values (<1%) for smoking, race, and hormone replacement therapy. Additional adjustment for alcohol, other dietary variables, health conditions including diabetes, use of nonsteroidal anti-inflammatory drugs, physical activity, family history of colorectal cancer, study center, and randomization year did not appreciably affect results, and these variables were excluded from the final model.

To evaluate whether the association between weight change and adenoma differed by sex or starting BMI (overweight or

obese vs underweight or normal weight), we conducted stratified analyses. We computed global *P* values for interaction using likelihood ratio tests comparing nested models with and without the interaction terms using an ordinal weight change variable. We estimated the *P* value for heterogeneity for a specific category of interest between strata using a Wald test. We applied polytomous logistic regression to compute *P* values for heterogeneity by advanced adenoma status (advanced, nonadvanced) or anatomic site (rectum only, distal colon only).

Results

The average age at trial entry in both the incident colorectal adenoma and control groups was approximately 62 years (Table 1). Controls tended to consume more fiber, fewer calories, and less red meat than cases. A higher proportion of cases (67.1%) than controls (55.3%) was male. Also, cases had a statistically significantly higher BMI at age 50 years than controls ($P = .001$), but we did not observe a statistically significant case-control difference for BMI at age 20 years ($P = .08$). Cases had a higher percentage of current smokers than controls. When we compared cases and controls included in our study with those who were excluded, we observed similar characteristics (data not shown).

Compared with stable weight, weight loss from early-late adulthood was associated with a reduced colorectal adenoma risk (OR = 0.54, 95% CI = 0.34 to 0.86) (Figure 1). This corresponded to an absolute risk decrease from 5.6% to 3.5%. The results were similar for weight loss from early-middle adulthood (OR = 0.57, 95% CI = 0.37 to 0.88) but less pronounced for middle-late adulthood (OR = 0.85, 95% CI = 0.69 to 1.05) (Figure 1).

Weight gain from early-late adulthood was associated with an increased adenoma risk ($P_{trend} < .001$), with participants in

Table 1. Participant characteristics by incident distal colorectal adenoma status in the PLCO Cancer Screening Trial[a]

Covariates	Case (n = 1053)	Control (n = 16 576)	*P*
Age, mean (SD)	61.9 (5.2)	62.1 (5.2)	.22[b]
≤59 y, No. (%)	405 (38.5)	5844 (35.3)	.15[c]
60-64 y, No. (%)	316 (30.0)	5428 (32.8)	
65-69 y, No. (%)	217 (20.6)	3513 (21.2)	
≥70 y, No. (%)	115 (10.9)	1791 (10.8)	
Diet, mean (SD)			
Energy, kcal/d	2187.4 (822.4)	2082.2 (759.6)	<.001[b]
Fiber, g/1000 kcal[d]	11.2 (3.5)	11.9 (3.6)	<.001[b]
Total red meat, g/1000 kcal[d]	39.7 (22.9)	35.7 (21.9)	<.001[b]
Sex, No. (%)			<.001[c]
Male	707 (67.1)	9172 (55.3)	
Female	346 (32.9)	7404 (44.7)	
BMI at age 20 y, mean (SD), kg/m^2	22.4 (3.0)	22.2 (3.0)	.08[b]
BMI ≥ 25 kg/m^2, No. (%)	177 (16.8)	2689 (16.2)	.62[c]
BMI < 25 kg/m^2, No. (%)	876 (83.2)	13 887 (83.8)	
BMI at age 50 y, mean (SD), kg/m^2	26.3 (4.2)	25.9 (4.1)	.001[b]
BMI ≥ 25 kg/m^2, No. (%)	628 (59.6)	9021 (54.4)	.001[c]
BMI < 25 kg/m^2, No. (%)	425 (40.4)	7555 (45.6)	
Race, No. (%)			.006[c]
Non-Hispanic Black	37 (3.5)	470 (2.8)	
Non-Hispanic White	958 (91.0)	14 768 (89.1)	
Other	58 (5.5)	1338 (8.1)	
Hormone replacement therapy (women only), No. (%)			.02[c]
Never	134 (38.7)	2340 (31.6)	
Former	47 (13.6)	1094 (14.8)	
Current	165 (47.7)	3970 (53.6)	
Smoking[e], No. (%)			<.001[c]
Never	406 (38.6)	8101 (48.9)	
Former (>23 y cigarette cessation)	196 (18.6)	3280 (19.8)	
Former (≤23 y cigarette cessation)	303 (28.8)	3519 (21.2)	
Current (≤45 pack-years)	47 (4.5)	464 (2.8)	
Current (>45 pack-years)	58 (5.5)	400 (2.4)	
Pipe or cigar only	43 (4.1)	812 (4.9)	
Study year of second FSG screen, No. (%)			<.001[c]
T3	210 (19.9)	4746 (28.6)	
T5	843 (80.1)	11 830 (71.4)	

[a]Percentages presented in the table are based on the data in the respective column. BMI = body mass index; FSG = flexible sigmoidoscopy; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.
[b]*P* value was calculated by a *t* test. All tests were 2-sided.
[c]*P* value was calculated by a χ^2 test. All tests were 2-sided.
[d]Variables were standardized to total energy intake (per 1000 kcal).
[e]We divided former cigarette smokers by the median number of years since cessation among former smokers in the control group (23 years). We divided current cigarette smokers by the median pack-years (packs smoked per day x years smoked) among current smokers in the control group (45 pack-years).

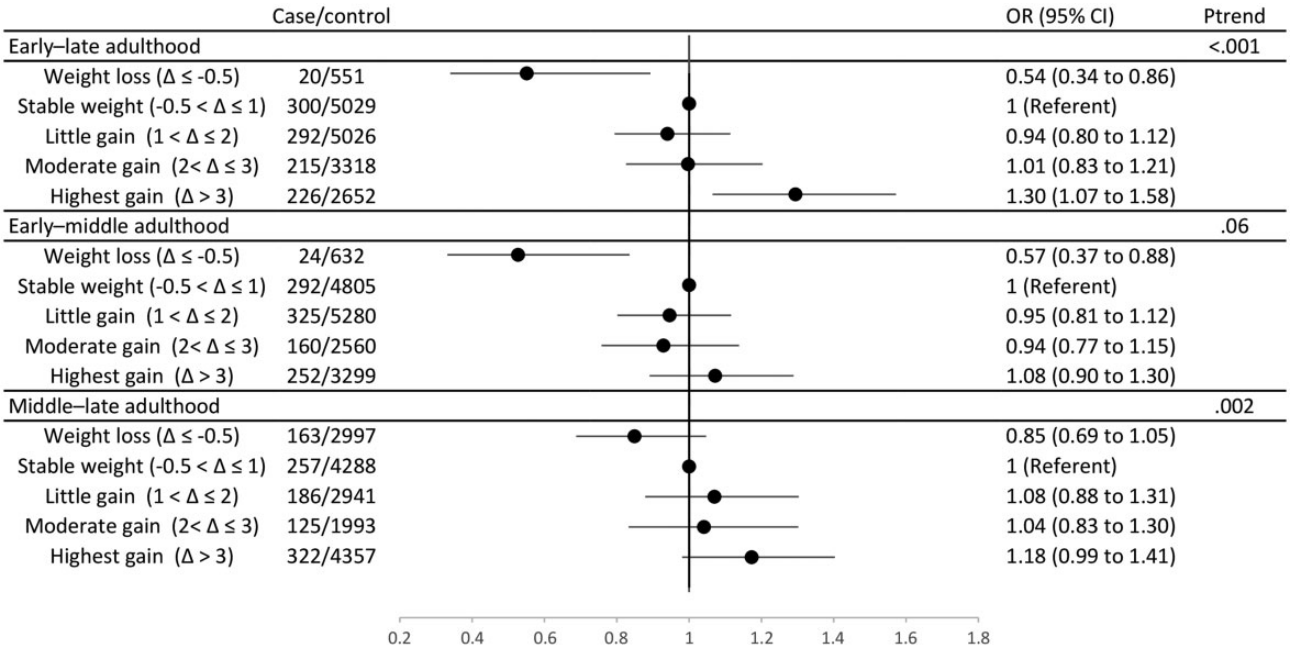

Figure 1. Weight change in adulthood (kg/5 years) and incident distal colorectal adenoma in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression adjusting for race, age group, sex, total red meat, fiber, total energy intake, body mass index (BMI) at age 20 years for early-late adulthood and early-middle adulthood or BMI at age 50 years for middle-late adulthood (continuous), smoking status, and study year of second trial sigmoidoscopy screen. We computed P_{trend} based on a pseudo-continuous variable of median values for each weight change category in the control group using a 2-sided Wald test in the multivariable-adjusted logistic regression model. The error bars represent the 95% CIs.

the highest gain group (>3 kg/5 years) having 1.30 (95% CI = 1.07 to 1.58) times greater risk of developing adenoma compared with those with stable weight (Figure 1). This corresponded to an absolute risk increase from 5.6% to 7.9%. We also observed positive associations for weight gain from early-middle adulthood (OR = 1.08, 95% CI = 0.90 to 1.30, P_{trend} = .06) and middle-late adulthood (OR = 1.18, 95% CI = 0.99 to 1.41, P_{trend} = .002) (Figure 1). All models were adjusted for starting BMI (ie, BMI at age 20 or 50 years), suggesting that adenoma risk associated with weight change was not due to starting BMI. Starting BMI was not independently associated with adenoma risk in the adjusted models ($P > .05$).

When we stratified by starting BMI (Table 2), weight loss from early-late adulthood was statistically significantly associated with a reduced risk of colorectal adenoma only among those who were overweight or obese initially (ie, at age 20 years) (OR = 0.39, 95% CI = 0.18 to 0.84); no association was observed for those with a starting BMI less than 25 kg/m^2 (OR = 0.79, 95% CI = 0.43 to 1.45, $P_{heterogeneity}$ = .16). Associations for weight gain and colorectal adenoma were similar regardless of starting BMI, except for middle-late adulthood. Here, there was a statistically significant positive trend with adenoma risk ($P_{trend} < .001$) for those who were overweight or obese at age 50 years, but not for those with a BMI less than 25 kg/m^2 at age 50 years (P_{trend} = .88, $P_{interaction}$ = .03). The other P values for heterogeneity by starting BMI were all greater than .20 (data not shown).

When we stratified by sex (Table 3), we observed a more pronounced association between weight change and incident adenoma in men than women, although the $P_{interaction}$ was not statistically significant at the 0.05 level ($P_{interaction}$ = .21). Among men, those who lost weight from early-late adulthood had a reduced adenoma risk (OR = 0.50, 95% CI = 0.28 to 0.90), whereas the association for women was weaker (OR = 0.65, 95% CI = 0.29 to 1.44). Men who gained more than 3 kg/5 years from early-late adulthood had 1.41 times (95% CI = 1.11 to 1.80) greater risk compared with those with stable weight. In contrast, the OR for women was 1.09 (95% CI = 0.79 to 1.50).

Risks were similar for advanced and nonadvanced adenoma (Supplementary Table 1, available online), except weight loss from middle-late adulthood was associated with a stronger reduced risk for advanced adenoma (OR = 0.50, 95% CI = 0.32 to 0.79) than nonadvanced adenoma (OR = 0.90, 95% CI = 0.68 to 1.21, $P_{heterogeneity}$ = .03). We did not find evidence of a difference in the results by anatomic site for any of the 3 time periods (Supplementary Table 2, available online).

Discussion

Our study is among the first to prospectively examine the association between weight loss in adulthood and incident colorectal adenoma. We found that weight loss from early-late adulthood, particularly among those who were initially overweight or obese, was associated with a statistically significantly reduced adenoma risk. Previous observational studies did not observe an association between weight loss and adenoma risk (12,14,15). However, our findings are consistent with a study that observed a lower likelihood of adenoma following bariatric surgery (19), suggesting a beneficial effect of weight loss on adenoma risk in an initially obese population.

We observed a positive association between weight gain in early-late adulthood and incident adenoma, which is consistent with previous studies. Meta-analyzing 6 retrospective and 4 prospective studies, Schlesinger et al. (16) found that adults with high weight gain (median weight gain = 17.4 kg during adulthood) had an increased adenoma risk (OR = 1.39, 95% CI = 1.17 to 1.65) compared with those who had no or minimal weight gain. This odds ratio was similar to the odds ratio for our highest weight gain group (OR = 1.30, 95% CI = 1.07 to 1.58), which

Table 2. Weight change in adulthood and incident distal colorectal adenoma stratified by starting BMI[a] in the PLCO Cancer Screening Trial

	BMI $\geq$ 25 kg/m^2		BMI $<$ 25 kg/m^2	
Weight change (kg/5 y)	Case/control	OR (95% CI)[b]	Case/control	OR (95% CI)[b]
Early-late adulthood				
Weight loss ($\Delta \leq -0.5$)	8/321	0.39 (0.18 to 0.84)	12/230	0.79 (0.43 to 1.45)
Stable weight ($-0.5 < \Delta \leq 1$)	56/892	1 (Referent)	244/4137	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	45/656	1.12 (0.74 to 1.70)	247/4370	0.91 (0.76 to 1.10)
Moderate gain ($2 < \Delta \leq 3$)	32/427	1.19 (0.75 to 1.89)	183/2891	0.98 (0.80 to 1.20)
Highest gain ($\Delta > 3$)	36/393	1.59 (0.99 to 2.57)	190/2259	1.27 (1.03 to 1.57)
P_{trend}[c]		.001		.02
Early-middle adulthood				
Weight loss ($\Delta \leq -0.5$)	13/363	0.55 (0.29 to 1.05)	11/269	0.64 (0.35 to 1.20)
Stable weight ($-0.5 < \Delta \leq 1$)	50/777	1 (Referent)	242/4028	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	56/677	1.24 (0.83 to 1.85)	269/4603	0.91 (0.76 to 1.09)
Moderate gain ($2 < \Delta \leq 3$)	18/313	0.82 (0.47 to 1.44)	142/2247	0.96 (0.77 to 1.19)
Highest gain ($\Delta > 3$)	40/559	1.10 (0.70 to 1.72)	212/2740	1.10 (0.90 to 1.35)
P_{trend}[c]		.15		.13
Middle-late adulthood				
Weight loss ($\Delta \leq -0.5$)	119/2114	0.88 (0.67 to 1.16)	44/883	0.89 (0.63 to 1.26)
Stable weight ($-0.5 < \Delta \leq 1$)	116/1824	1 (Referent)	141/2464	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	92/1361	1.11 (0.84 to 1.48)	94/1580	1.06 (0.81 to 1.40)
Moderate gain ($2 < \Delta \leq 3$)	74/1029	1.17 (0.86 to 1.58)	51/964	0.94 (0.67 to 1.32)
Highest gain ($\Delta > 3$)	227/2693	1.36 (1.07 to 1.73)	95/1664	0.97 (0.73 to 1.29)
P_{trend}[c]		$<$.001		.88

[a]For early-middle and early-late adulthood, we stratified by BMI at age 20 years; for middle-late adulthood, we stratified by BMI at age 50 years. BMI = body mass index; CI = confidence interval; OR = odds ratio; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

[b]Odds ratios and 95% confidence intervals were calculated by logistic regression within each stratum. Within each stratum, we adjusted for race, age group, sex, total red meat, fiber, total energy intake, BMI at age 20 years for early-late adulthood and early-middle adulthood or BMI at age 50 years for middle-late adulthood (continuous), smoking status, and study year of second trial sigmoidoscopy screen.

[c]P_{trend} was calculated by a Wald test for a pseudo-continuous variable using the median values for each weight change category in the control group. All tests were 2-sided.

Table 3. Weight change in adulthood and incident distal colorectal adenoma stratified by sex in the PLCO Cancer Screening Trial

	Men		Women	
Weight change (kg/5 y)	Case/control	OR (95% CI)[a]	Case/control	OR (95% CI)[a]
Early-late adulthood				
Weight loss ($\Delta \leq -0.5$)	13/343	0.50 (0.28 to 0.90)	7/208	0.65 (0.29 to 1.44)
Stable weight ($-0.5 < \Delta \leq 1$)	197/2806	1 (Referent)	103/2223	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	199/2834	0.99 (0.80 to 1.21)	93/2192	0.86 (0.64 to 1.15)
Moderate gain ($2 < \Delta \leq 3$)	149/1835	1.09 (0.86 to 1.37)	66/1483	0.85 (0.62 to 1.18)
Highest gain ($\Delta > 3$)	149/1354	1.41 (1.11 to 1.80)	77/1298	1.09 (0.79 to 1.50)
P_{trend}[b]		$<$.001		.43
Early-middle adulthood				
Weight loss ($\Delta \leq -0.5$)	14/340	0.48 (0.27 to 0.85)	10/292	0.76 (0.38 to 1.50)
Stable weight ($-0.5 < \Delta \leq 1$)	190/2384	1 (Referent)	102/2421	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	214/2935	0.88 (0.72 to 1.08)	111/2345	1.07 (0.81 to 1.41)
Moderate gain ($2 < \Delta \leq 3$)	106/1493	0.84 (0.65 to 1.08)	54/1067	1.11 (0.79 to 1.57)
Highest gain ($\Delta > 3$)	183/2020	1.02 (0.81 to 1.27)	69/1279	1.16 (0.84 to 1.61)
P_{trend}[b]		.23		.21
Middle-late adulthood				
Weight loss ($\Delta \leq -0.5$)	114/1918	0.83 (0.64 to 1.06)	49/1079	0.92 (0.63 to 1.34)
Stable weight ($-0.5 < \Delta \leq 1$)	179/2606	1 (Referent)	78/1682	1 (Referent)
Little gain ($1 < \Delta \leq 2$)	136/1589	1.23 (0.98 to 1.56)	50/1352	0.78 (0.55 to 1.13)
Moderate gain ($2 < \Delta \leq 3$)	85/1049	1.14 (0.87 to 1.50)	40/944	0.84 (0.57 to 1.25)
Highest gain ($\Delta > 3$)	193/2010	1.24 (0.99 to 1.55)	129/2347	1.04 (0.77 to 1.41)
P_{trend}[b]		.001		.49

[a]Odds ratios and 95% confidence intervals were calculated by logistic regression within each stratum adjusting for race, age group, total red meat, fiber, total energy intake, BMI at age 20 years for early-late adulthood and early-middle adulthood or BMI at age 50 years for middle-late adulthood (continuous), smoking status, and study year of second trial sigmoidoscopy screen. For models among women only, we removed the pipe or cigar only category from the smoking variable due to small sample size and also adjusted for hormone replacement therapy. BMI = body mass index; CI = confidence interval; OR = odds ratio; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

[b]P_{trend} was calculated in each stratum by a Wald test for a pseudo-continuous variable using the median values for each weight change category in the control group. All tests were 2-sided.

had a median gain of 31.8 kg from age 20 years to baseline. Among the 4 prospective studies in this meta-analysis, 2 of them (20,21) evaluated early-late adulthood weight change. Consistent with our study, Wise et al. (20) found a statistically significantly increased risk of colorectal adenoma in the weight gain group (≥30 kg since age 18 years) compared with the stable weight group. Botma et al. (21), however, who studied a cohort of mismatch repair gene mutation carriers, did not detect a statistically significant association between weight gain and adenoma risk.

An advantage of our study was the ability to examine weight change during several different periods of adulthood. We observed some evidence of a stronger effect of weight loss in early-middle adulthood than middle-late adulthood. Our findings may be in part because weight loss at younger ages is more likely to be intentional (eg, because of diet and/or exercise). In contrast, weight loss at older ages may be more likely unintentional (eg, because of illness) (22). However, we were unable to investigate this further because we did not have data on intentionality of weight loss in our study. With regard to weight gain, we observed positive associations with colorectal adenoma in all 3 time periods, suggesting the importance of weight gain throughout adulthood in adenoma risk. The mechanism by which increased weight and obesity increases adenoma risk is unknown, but insulin resistance and subsequent hyperinsulinemia leading to increased insulin-like growth factor 1 (IGF1) signaling may promote colorectal neoplasia through increased cell proliferation and reduced apoptosis (23).

We observed a stronger association for weight change and adenoma among men; findings were attenuated and did not reach statistical significance in women. Geer et al. (24) found that men had greater amounts of visceral and hepatic adipose tissues than women at the same BMI, which may contribute to differing findings by sex. Another possible mechanism could be due to the modifying effect of estrogen. Studies have found that obesity is positively associated with estrogen production in women (25), and estrogens have a protective effect against colorectal carcinogenesis (26). Although Botma et al. (21) did not observe statistically significant associations for weight change regardless of sex, similar to our study Jung et al. (27) found statistically significant associations in men but not in women. However, there was no formal test of effect modification by sex.

Similar to the meta-analysis by Schlesinger (16), we did not observe evidence of differences in the association between weight change and adenoma risk by anatomic site. We also did not observe differences by advanced adenoma status, except for weight loss in middle-late adulthood, which was statistically significantly associated with advanced, but not nonadvanced, adenoma. Sedjo et al. (12) found a statistically significant association between weight gain and advanced adenoma but not nonadvanced adenoma; however, there was no formal test for heterogeneity. Our findings are similar to those of Morois et al. (15), who did not observe statistically significant differences by advanced adenoma status.

Our study had several limitations. Because participants were screened with sigmoidoscopy, our study was limited to distal colorectal adenoma; we were unable to assess risk for proximal adenoma. It is also possible that some controls in our study had undetected proximal adenoma, which may have attenuated our findings for weight change. Our study population largely comprised non-Hispanic White individuals, and therefore additional research is needed in more diverse populations. We used weight information from self-administered questionnaires, and there may be errors in the participants' ability to accurately recall their weight. However, because all weight information was acquired before sigmoidoscopy, any misreporting likely did not vary by disease status. In our analyses by starting BMI, we were unable to separately evaluate associations for the overweight and obese categories because of small numbers, particularly for weight loss.

Our study also had several strengths. This is one of the few prospective studies that evaluated incident adenoma in relation to weight change, including weight loss and gain, in different time periods in adulthood. Further, in drawing our population from the screening arm of the PLCO trial, we were able to restrict our population to those who had a negative baseline trial screen, allowing us to identify incident adenomas based on the follow-up trial screen 3-5 years later. Most studies are limited to prevalent adenoma, which could have been present for many years before detection, making the assessment of weight change before adenoma development difficult and increasing the potential for reverse causation to occur. Reverse causation is a major problem in studies of weight loss and cancer, but based on our prospective study design we do not expect this to have influenced our findings. Within the PLCO screening arm, all patients had an equal opportunity to be screened, minimizing potential selection bias because of unequal access to care. In addition, we were able to adjust for a variety of potential confounders.

In conclusion, although the sample size for the weight loss group was relatively small, we found that weight loss in adulthood was associated with a statistically significant 46% reduced risk of incident distal colorectal adenoma. When we stratified by starting BMI, the weight loss finding was more pronounced and achieved statistical significance only among those who were overweight or obese in early adulthood. Our findings are consistent with other studies in demonstrating a positive association for adulthood weight gain and incident adenoma. Although additional studies are needed to replicate these findings, our study highlights the importance of healthy weight maintenance and avoidance of weight gain throughout adulthood in preventing colorectal adenoma. Given the rise in obesity among adults (2), our findings suggest weight loss may help prevent adenoma in addition to other known health benefits.

Funding

This work was supported by the National Cancer Institute, National Institutes of Health (K07 CA230182 to K.H.B.; support from the National Cancer Institute Intramural Research Program to S.I.B., C.M.K., and W.Y.H.) and Queen's University Belfast (Patrick G. Johnston Fellowship to A.T.K.). This work was also supported by funds through the Maryland Department of Health's Cigarette Restitution Fund Program (salary support for K.H.B.). The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute and by contracts from the Division of Cancer Prevention, National Cancer Institute.

Notes

Role of the funders: The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the

manuscript; or the decision to submit the manuscript for publication.

Disclosures: The authors have no conflicts of interest to disclose.

Author contributions: Shisi He: Conceptualization, Formal analysis, Methodology, Visualization, Writing—Original Draft, Writing—Review & Editing. Sonja I. Berndt: Conceptualization, Methodology, Writing—Review & Editing. Andrew T. Kunzmann: Methodology, Writing—Review & Editing. Cari M. Kitahara: Methodology, Writing—Review & Editing. Wen-Yi Huang: Conceptualization, Methodology, Writing—Review & Editing. Kathryn Hughes Barry: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing—Review & Editing.

Acknowledgements: The authors thank the National Cancer Institute for access to data collected by the PLCO Cancer Screening Trial. The authors also thank Mr Thomas Riley, Mr Patrick Wright, Mr Jerome Mabie and Mr Tom Hickey at Information Management Services, Inc. for their contributions to this study. The results reported here and the conclusions derived are the sole responsibility of the authors.

Prior presentations: We presented an e-poster on this project at the 2020 AACR Virtual Annual Meeting II. The abstract is published in Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27-28 and Jun 22-24. Philadelphia (PA): AACR; *Cancer Res* 2020; 80(16 Suppl):Abstract nr LB-158. doi: 10.1158/1538–7445. AM2020-LB-158.

Data Availability

The data underlying this article are available upon request to the PLCO Cancer Data Access System: https://cdas.cancer.gov/plco/.

References

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288(14):1723–1727.
2. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315(21):2284–2291.
3. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. *NCHS Data Brief*. 2020;360:1–8.
4. Comstock SS, Hortos K, Kovan B, McCaskey S, Pathak DR, Fenton JI. Adipokines and obesity are associated with colorectal polyps in adult males: a cross-sectional study. *PLoS One*. 2014;9(1):e85939.
5. Kitahara CM, Berndt SI, De González AB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *J Clin Oncol*. 2013;31(19):2450–2459.
6. Ben Q, An W, Jiang Y, et al. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology*. 2012;142(4):762–772.
7. Abar L, Vieira AR, Aune D, et al. Height and body fatness and colorectal cancer risk: an update of the WCRF–AICR systematic review of published prospective studies. *Eur J Nutr*. 2018;57(5):1701–1720.
8. Okabayashi K, Ashrafian H, Hasegawa H, et al. Body mass index category as a risk factor for colorectal adenomas: a systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(8):1175–1185.
9. Morimoto LM, Newcomb PA, Ulrich CM, Bostick RM, Lais CJ, Potter JD. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev*. 2002;11(10):1012–1018.
10. Jacobs ET, Ahnen DJ, Ashbeck EL, et al. Association between body mass index and colorectal neoplasia at follow-up colonoscopy: a pooling study. *Am J Epidemiol*. 2009;169(6):657–666.
11. Neugut AI, Lee WC, Garbowski GC, et al. Obesity and colorectal adenomatous polyps. *J Natl Cancer Inst*. 1991;83(5):359–361.
12. Sedjo RL, Byers T, Levin TR, et al. Change in body size and the risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):526–531.
13. Martin CB, Herrick K, Sarafrazi N, Ogden C. Attempts to lose weight among adults in the United States, 2013-2016. *NCHS Data Brief*. 2018;313:1–8.
14. Wernli KJ, Newcomb PA, Wang Y, et al. Body size, IGF and growth hormone polymorphisms, and colorectal adenomas and hyperplastic polyps. *Growth Horm IGF Res*. 2010;20(4):305–309.
15. Morois S, Mesrine S, Josset M, Clavel-Chapelon F, Boutron-Ruault M-C. Anthropometric factors in adulthood and risk of colorectal adenomas: the French E3N-EPIC prospective cohort. *Am J Epidemiol*. 2010;172(10):1166–1180.
16. Schlesinger S, Aleksandrova K, Abar L, et al. Adult weight gain and colorectal adenomas—a systematic review and meta-analysis. *Ann Oncol*. 2017;28(6):1217–1229.
17. Prorok PC, Andriole GL, Bresalier RS, et al.; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21(6 Suppl):273S–309S.
18. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med*. 2012;366(25):2345–2357.
19. Kedrin D, Gandhi S-CC, Wolf M, et al. Bariatric surgery prior to index screening colonoscopy is associated with a decreased rate of colorectal adenomas in obese individuals. *Clin Transl Gastroenterol*. 2017;8(2):e73.
20. Wise LA, Rosenberg L, Palmer JR, Adams-Campbell LL. Anthropometric risk factors for colorectal polyps in African-American women. *Obesity*. 2008;16(4):859–868.
21. Botma A, Nagengast FM, Braem M, et al. Body mass index increases risk of colorectal adenomas in men with Lynch syndrome: The GEOLynch Cohort Study. *J Clin Oncol*. 2010;28(28):4346–4353.
22. McMinn J, Steel C, Bowman A. Investigation and management of unintentional weight loss in older adults. *BMJ*. 2011;342:d1732.
23. Jochem C, Leitzmann M. Obesity and colorectal cancer. *Recent Results Cancer Res*. 2016;208:17–41.
24. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. *Gend Med*. 2009;6(Suppl 1):60–75.
25. Cleary MP, Grossmann ME. Minireview: obesity and breast cancer: the estrogen connection. *Endocrinology*. 2009;150(6):2537–2542.
26. Barzi A, Lenz AM, Labonte MJ, Lenz H-J. Molecular pathways: estrogen pathway in colorectal cancer. *Clin Cancer Res*. 2013;19(21):5842–5848.
27. Jung YS, Park JH, Park DI, Sohn CI, Choi K. Weight change and obesity are associated with a risk of adenoma recurrence. *Dig Dis Sci*. 2016;61(9):2694–2703.