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ORIGINAL REPORT

Prospective Investigation of Body Mass Index, Colorectal Adenoma, and Colorectal Cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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ABSTRACT

Purpose
Obesity has consistently been linked to an increased risk of colorectal cancer, particularly among men. Whether body mass index (BMI) differentially influences the risk across the stages of colorectal cancer development remains unclear. We evaluated the associations of BMI with colorectal adenoma incidence, adenoma recurrence, and cancer in the context of a large screening trial, in which cases and controls had an equal chance for disease detection.

Methods
We prospectively evaluated the association between baseline BMI and the risk of incident distal adenoma (1,213 cases), recurrent adenoma (752 cases), and incident colorectal cancer (966 cases) among men and women, ages 55 to 74 years, randomly assigned to receive flexible sigmoidoscopy screening as part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. We calculated odds ratios (ORs) and 95% CIs for adenoma incidence and recurrence, and hazard ratios (HRs) and 95% CIs for colorectal cancer incidence, using multivariable-adjusted models.

Results
Compared with normal-weight men (18.5 to 24.9 kg/m^2), obese men (≥ 30 kg/m^2) had significantly higher risk of incident adenoma (OR, 1.32; 95% CI, 1.06 to 1.65) and colorectal cancer (HR, 1.48; 95% CI, 1.16 to 1.89) and a borderline increased risk of recurrent adenoma (OR, 1.50; 95% CI, 0.98 to 2.30). No associations were observed for either adenoma or cancer in women.

Conclusion
Data from this large prospective study suggest that obesity is important throughout the natural history of colorectal cancer, at least in men, and colorectal cancer prevention efforts should encourage the achievement and maintenance of a healthy body weight in addition to regular screenings.

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INTRODUCTION

Colorectal cancer is the fourth most common malignancy diagnosed in the United States after breast, prostate, and lung cancer.[1-2] A substantial fraction of colorectal cancer incidence is thought to be attributable to modifiable risk factors, such as obesity, physical inactivity, cigarette smoking, and diet.[3-5] Colorectal cancer develops through an accumulation of genetic alterations during which normal epithelial tissue progresses to adenoma and then into cancer.[6] Regular screening is shown to be effective in preventing the development of colorectal cancer by removing adenomas.[7-9] Some colorectal cancer risk factors, including nonsteroidal anti-inflammatory drug use and red meat intake, show similar associations with colorectal adenoma,[10-11] but conflicting patterns have been observed for others (eg, smoking and folic acid supplementation).[12-13] The same exposure may have different effects across the stages of cancer development depending, in part, on whether the colorectal tissue is normal, preneoplastic, or neoplastic at the time of exposure.[14] A greater understanding of the relative impact of environmental exposures at the various stages of colorectal cancer development may contribute to more effective prevention and screening recommendations.

Obesity has consistently been linked with an increased risk of colorectal cancer[15-16] in men and colorectal adenoma[17] in both men and women, although more weakly for postmenopausal than premenopausal women. The few studies that have examined obesity in relation to adenoma recurrence suggest a positive association but only in men.[18-19] No previous study,

to our knowledge, has examined body mass index (BMI) in relation to all three outcomes.

In this prospective study with a relatively long period of follow-up, we evaluated and compared the associations between BMI and adenoma incidence, adenoma recurrence, and colorectal cancer for the first time in the context of a colorectal screening trial in which men and women randomly assigned to the intervention arm underwent sigmoidoscopy screening, and cases had an equal chance for disease detection as did controls.

METHODS

Overview

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is a multicenter, randomized controlled trial designed to evaluate the efficacy of screening methods for these four cancers.[20] From 1993 to 2001, 154,952 participants ages 55 to 74 years were recruited at one of 10 US centers (University of Colorado, Georgetown University/Lombardi Cancer Center, Pacific Health Research and Education Institute, Henry Ford Health System, University of Minnesota, Washington University School of Medicine, University of Pittsburgh, University of Utah, Marshfield Clinic Research Foundation, and University of Alabama at Birmingham) and were randomly assigned to the screened or nonscreened trial arm. Individuals were ineligible if they had a previous history of prostate, lung, colorectal, or ovarian cancer, had surgical removal of the prostate, colon, or one lung, were currently being treated for cancer (other than nonmelanoma skin cancer), were current participants in another cancer screening or primary prevention trial, had taken finasteride in the previous 6 months, or, for individuals randomly assigned after mid-1995, if they had a colonoscopy, sigmoidoscopy, barium enema, or more than one prostate-specific antigen (PSA) blood test within the previous 3 years. Screened participants underwent flexible sigmoidoscopy screening at baseline and again during follow-up, either 3 (T3) or 5 (T5) years subsequently (participants randomly assigned before mid-1995 received the second screen at T3, whereas the remaining participants subsequently received it at T5). Participants with abnormal findings were referred to their health care providers for diagnostic endoscopy. Trained personnel abstracted medical records for all diagnostic follow-up visits. At baseline, participants in the screening arm completed a self-administered questionnaire (BQ) with questions on demographic characteristics, medical history, family history of cancer, use of tobacco, selected drugs and hormones, and height and weight as well as a 137-item food frequency questionnaire ascertaining food and beverage intake during the previous 12 months and frequency of vigorous exercise.[21] Overall, 97% and 89% of participants completed the BQ and dietary questionnaire, respectively, before or on the day of baseline sigmoidoscopy. The institutional review boards at the National Cancer Institute and the 10 study centers approved the study. All participants provided written informed consent.

Study Population and Outcome Ascertainment

All analyses were restricted to participants randomly assigned to the screening arm of the trial (n = 77,445).

Incident distal colorectal adenoma study. The study population (described previously[22]) comprises participants who had an adequate baseline flexible sigmoidoscopy (insertion ≥ 50 cm with ≥ 90% of mucosa visible or suspicious lesion found) with no polyps or abnormal/suspicious findings in the descending or sigmoid colon (hereafter referred to as the distal colon) or rectum, an adequate follow-up sigmoidoscopy at T3/T5, and no prior history of colorectal cancer before the T3/T5 screening (n = 26,766). Incident colorectal adenoma cases were defined as individuals with a positive follow-up sigmoidoscopy, which was subsequently confirmed during diagnostic endoscopy outside of the study. Participants with positive findings at follow-up sigmoidoscopy that were not subsequently confirmed by diagnostic endoscopy, either because no adenoma was found at diagnostic endoscopy (n = 3,370), diagnostic endoscopy was not performed (n = 418), or information regarding diagnostic follow-up could not be obtained (n = 460), were excluded. We further excluded participants with a self-reported history of colorectal polyps, Crohn's disease, ulcerative colitis, familial polyposis, or Gardner's syndrome at baseline (n = 1,435), as well as participants who had an incomplete BQ (n = 21) or missing or extreme BMI values (< 15 or > 50 kg/m^2; n = 239). Advanced adenoma was defined as adenomas ≥ 1 cm in size, containing high-grade dysplasia, or villous components. Controls were participants without any polyps or abnormal suspicious lesions on the T3/T5 follow-up sigmoidoscopy. After exclusions, there were 1,213 incident distal colorectal adenoma cases (802 men; 411 women) and 19,610 controls (10,672 men; 8,938 women).

Recurrent colorectal adenoma study. The Study of Colonoscopy Utilization (SCU) is an ancillary study nested within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Participants with a positive baseline sigmoidoscopy screen and diagnostic endoscopy no more than 6 months from baseline with no cancer findings were invited to complete the telephone-administered SCU questionnaire, which asked questions about all known colonoscopies performed since random assignment (n = 5,013).[23] These colonoscopies, including details of all identified polyps, were verified through medical record abstraction. We further restricted to participants who were diagnosed with adenoma at baseline endoscopy (verified by medical record abstraction), received a subsequent endoscopy between 6 months and 10 years after baseline endoscopy (hereafter referred to as the surveillance endoscopy), and completed the BQ (n = 1,905). We excluded from this population participants with a history of Crohn's disease, ulcerative colitis, familial polyposis, Gardner's syndrome, or colorectal polyps (n = 210). We also excluded participants with missing or extreme BMI values (< 15 or > 50; n = 19), yielding 1,064 men and 612 women. Individuals who received a diagnosis of adenoma at any surveillance endoscopy were defined as recurrent adenoma cases (n = 752; men, 526; women, 226), and all others were defined as controls (n = 924; men, 538; women, 386). First occurrence of adenoma occurred at a median of 4 years (interquartile range, 2 to 5 years) after baseline endoscopy.

Incident colorectal cancer study. Of the 75,534 participants who completed the BQ, we excluded those with missing (n = 921) or extreme BMI values (< 15 or > 50; n = 139), yielding 36,912 men and 37,562 women for the analysis. Colorectal cancers were ascertained through self-reported annual questionnaires and linkage to the National Death Index (for completeness) and were histologically confirmed through medical record review. In total, 966 colorectal cancer diagnoses (549 men, 417 women) were confirmed during follow-up (median, 11.9 years).

Statistical Analysis

BMI categories were based on World Health Organization cut points for underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (≥ 30 kg/m^2).[24] Odds ratios (ORs) and 95% CIs for incident distal adenoma and recurrent adenoma were calculated from unconditional logistic regression models. Hazard ratios (HRs) and 95% CIs for colorectal cancer were calculated from Cox proportional hazards regression models, with follow-up from the BQ completion date to the date of colorectal cancer diagnosis, loss to follow-up, death, or December 31, 2009, whichever occurred first. Overall and sex-stratified models were conducted using normal weight as the referent category. Base models were adjusted for age, sex, race/ethnicity, study center, study year of screening (for incident adenoma), surveillance time interval and number of surveillance endoscopies (for recurrent adenoma), and screening adequacy and results before colorectal cancer diagnosis (for colorectal cancer). We examined the influence of additional factors, including education, exercise, smoking status, family history of colorectal cancer, regular use of nonsteroidal anti-inflammatory drugs, menopausal hormone therapy use, and intakes of alcohol, total energy, total calcium (diet sources plus supplements), fiber, and red meat, in the base model with BMI modeled continuously (per 5 kg/m^2). Factors that changed the beta coefficient for BMI by 10% or more in the incident adenoma, recurrent adenoma, or colorectal cancer analyses were retained in fully adjusted models. Trend tests were conducted by modeling categorical variables as continuous and evaluating the statistical significance of the Wald test. We chose a priori to further stratify models in women by menopausal hormone therapy use to evaluate effect modification. Tests for multiplicative interactions by sex,

menopausal hormone use, and other factors were performed using the likelihood ratio test, comparing models including cross-product terms to models without. Tests for differences across disease subtypes were conducted using polytomous logistic regression analysis for adenoma subtypes and the Mantel-Haenszel test for heterogeneity for cancer subtypes. *P* values were two-sided, and analyses were conducted using Stata/SE (version 11.0).

RESULTS

Characteristics of the Cohort

The mean BMI was 27.5 kg/m^2 (standard deviation, 4.1 kg/m^2) in men and 27.1 kg/m^2 (standard deviation, 5.3 kg/m^2) in women. Approximately 73.4% of men and 59.6% of women were overweight, and 23.5% of men and 24.9% of women were obese. Compared with normal-weight participants, on average, overweight or obese participants were slightly younger, less likely to be Asian and more likely to be non-Hispanic black, less likely to have a college education, more likely to be former smokers, used both aspirin and ibuprofen regularly, used menopausal hormone therapy formerly, exercised less, and had greater intakes of total energy and red meat and lower intakes of total calcium and total fiber (Table 1).

Within the incident adenoma study population, cases had slightly higher BMI values, were more likely to be male, exercised less, were more likely to be former or current smokers or never-users of menopausal hormone therapy, and consumed less calcium and fiber and more total energy, alcohol, and red meat (Table 2). Similarly, among SCU participants, recurrent adenoma cases had slightly higher BMI values, were more likely to be male, and consumed less total calcium and more total energy, alcohol, and red meat than controls (Table 2).

Incident Distal Colorectal Adenoma

Overall, we observed a nonsignificant positive association between BMI and distal colorectal adenoma risk (Table 3), but in sex-stratified analyses, we observed a significantly increased risk of adenoma for obese men compared with normal-weight men (OR, 1.32; 95% CI, 1.06 to 1.65; *P* trend = .01). In men, no significant differences were observed according to adenoma location or advanced histology (Table 3). Though we found a stronger association for large (≥ 1 cm) adenomas (OR, 1.85; 95% CI, 1.03 to 3.33) versus small adenomas in men (OR, 1.03; 95% CI, 0.78 to 1.36), this difference was not significant (*P* heterogeneity = .20).

No associations were observed between BMI and adenoma among women; however, we observed no evidence of multiplicative interactions by sex (Table 3). A slight, nonsignificant positive association was observed among women who were never-users of menopausal hormone therapy (OR for obese *v* normal-weight, 1.19, 95% CI, 0.77 to 1.83; *P* trend = .45), whereas a nonsignificant inverse association was observed among ever-users (OR, 0.81; 95% CI, 0.56 to 1.18; *P* trend = .30; *P* interaction = .11).

Recurrent Adenoma

Similar to incident adenoma, BMI was associated with a borderline-significant increased risk of recurrent adenoma overall and among men (Table 4), with obese men displaying an increased risk of recurrence compared with normal-weight men (OR, 1.50; 95% CI, 0.98 to 2.30; *P* trend = .07). In men, no significant differences were observed according to adenoma location or advanced versus nonadvanced histology (Table 4). We also did not observe differences according to size of the adenoma (data not shown).

No associations were observed between BMI and recurrent adenoma among women; however, we observed no evidence of multiplicative interactions by sex (Table 4). A nonsignificant positive association between BMI and recurrent adenoma was observed among never-users of menopausal hormone therapy (OR for obese *v* normal-weight, 1.60; 95% CI, 0.63 to 4.04; *P* trend = .31), whereas a nonsignificant decreased risk was observed among ever-users (OR, 0.76; 95% CI, 0.35 to 1.64; *P* trend = .68); however, this difference was not significant (*P* interaction = .68). No differences were observed after excluding participants whose recurrence occurred less than 1 year after the initial diagnosis.

Colorectal Cancer Incidence

We observed an increased risk for colorectal cancer among obese versus normal-weight participants overall (HR, 1.24; 95% CI, 1.04 to 1.47; *P* trend = .02) and after restricting to men (HR, 1.48; 95% CI, 1.16 to 1.89; *P* trend = .002; Table 5). No differential risk patterns were observed by cancer location or between advanced tumors (stage III/IV) versus nonadvanced tumors (stage I/II; Table 5). Slightly stronger associations for obesity were observed in men after excluding the first year of follow-up (HR, 1.71; 95% CI, 1.28 to 2.28; *P* trend < .001).

Among women, no associations were observed between BMI and colorectal cancer; however, we observed no evidence of multiplicative interactions by sex (Table 5). Unlike what we observed for adenoma, a nonsignificant inverse association was observed among never-users of menopausal hormone therapy (HR for obese *v* normal-weight, 0.74; 95% CI, 0.49 to 1.11; *P* trend = .54), whereas a slight positive association was observed for ever-users (HR, 1.29; 95% CI, 0.93 to 1.79; *P* trend = .11; *P* interaction = .02). Results did not differ after excluding the first year of follow-up.

DISCUSSION

In this large, cancer-screening trial, we observed a consistent pattern of increased risk between obesity and colorectal neoplasia among men throughout the colorectal adenoma-cancer progression. In men, the associations were similar across the three outcomes, though slightly stronger for colorectal cancer and adenoma recurrence (albeit limited by power) compared with adenoma incidence.

Our study is consistent with previous studies in having shown stronger positive associations for BMI and colorectal cancer incidence[25-32] and adenoma recurrence,[18-19] in men compared with women. Studies of colorectal adenoma incidence have shown more equivocal results by sex,[33-35] though a meta-analysis of studies suggested that the association is weaker for postmenopausal women compared with premenopausal women.[17] In this study, we observed no associations for colorectal cancer or adenoma incidence or recurrence in women, most of whom were postmenopausal at enrollment. Because adipose tissue becomes the main source of circulating estrogen after menopause,[36] and estrogen levels have been inversely associated with both colorectal adenoma and cancer,[37] obesity may represent opposing effects on colorectal adenoma and cancer development among women after menopause while mainly representing adverse

Table 1. Baseline Characteristics of Study Participants in the Intervention Arm of the PLCO Cancer Screening Trial by BMI (kg/m^2)

Characteristic	BMI Category			
	< 18.5 (n = 569)	18.5-24.9 (n = 24,402)	25.0-29.9 (n = 31,480)	≥ 30 (n= 18,023)
BMI				
Mean	17.5	22.8	27.2	33.9
SD	0.8	1.5	1.4	3.7
Male, % of participants	25	40	59	48
Age, years				
Mean	63.8	63.0	62.8	61.9
SD	5.6	5.5	5.3	5.2
Race/ethnicity, % of participants				
White, non-Hispanic	80	88	89	88
Black, non-Hispanic	5	3	5	8
Asian	12	6	3	1
Other	3	2	3	3
Education, % of participants				
≤ 12 years of high school	29	27	30	35
Post-high school training/some college	33	33	34	37
College graduate or postgraduate	37	40	36	28
Hours of exercise per week				
Mean	2.8	3.1	2.7	2.1
SD	1.9	1.7	1.8	1.7
Smoking status, % of participants				
Never	45	46	40	41
Former	27	38	45	47
Current	27	13	10	8
Pipe or cigar smoker only	2	3	5	4
Alcohol intake, g/d				
Mean	9.6	10.9	11.7	9.3
SD	24.3	22.1	23.7	23.2
Family history of colorectal cancer, % of participants	13	10	10	10
NSAID use, % of participants				
Neither taken regularly	43	42	38	35
Aspirin only	29	31	33	31
Ibuprofen only	13	12	12	14
Both taken regularly	14	15	17	19
Total energy intake, kcal/d				
Mean	1,844	1,917	2,088	2,130
SD	736	728	805	847
Menopausal hormone therapy use (women only), % of participants				
Never	36	29	33	40
Former	15	15	17	19
Current	48	55	49	40
Total calcium intake*				
Mean	745	705	621	608
SD	402	358	308	294
Red meat intake†				
Mean	27.5	30.0	37.3	42.6
SD	18.5	19.9	21.6	23.6
Total fiber intake†				
Mean	12.7	12.4	11.5	11.1
SD	4.3	3.8	3.5	3.4

NOTE. Missing values are not shown.
Abbreviations: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SD, standard deviation.
*Energy adjusted using the density method (mg/1,000 kcal).
†Energy adjusted using the density method (gm/1,000 kcal).

effects among men and premenopausal women.[38] The stronger associations for BMI in men compared with women may also be explained by a greater tendency of men to deposit fat around their abdomen[39]; excess abdominal fat has been linked with metabolic abnormalities, including a higher risk of diabetes and cardiovascular disease.[40-42] One large prospective study showed an increased risk for colon cancer among women with higher waist circumference and waist-to-hip ratio but not BMI.[43] Thus, studies with measures of body fat distribution

Table 2. Baseline Characteristics of Study Participants in the Colorectal Adenoma Incidence and Recurrence Analyses by Case and Control Status

Characteristic	Incidence		Recurrence	
	Cases (n = 1,213)	Controls (n = 19,610)	Cases (n = 752)	Controls (n = 924)
BMI, kg/m^2				
Mean	27.6	27.0	27.7	27.4
SD	4.5	4.5	4.3	4.5
Male, % of participants	66	54	70	58
Age at diagnosis/pseudodiagnosis, years				
Mean	66.7	66.7	66.9	68.0
SD	5.0	4.9	5.4	5.4
Race/ethnicity, % of participants				
White, non-Hispanic	90	88	92	95
Black, non-Hispanic	4	3	2	3
Asian	4	6	3	1
Other	2	3	3	1
Education, % of participants				
≤ 12 years of high school	29	27	30	33
Post-high school training/some college	33	33	35	32
College graduate or postgraduate	38	40	36	34
Hours of exercise per week, % of participants				
< 1	32	25	30	31
1-2	25	25	26	25
≥ 3	32	38	36	38
Smoking status, % of participants				
Never	39	49	28	35
Former	46	41	51	47
Current	11	5	14	15
Pipe or cigar smoker only	4	5	6	3
Alcohol intake, g/d				
Mean	14.8	10.2	17.6	14.4
SD	29.6	21.7	30.4	30.9
Family history of colorectal cancer, % of participants	10	9	13	12
Personal history of diabetes, % of participants	7	6	6	7
NSAID use, % of participants				
Neither taken regularly	40	40	43	42
Aspirin only	34	32	33	31
Ibuprofen only	10	12	10	13
Both taken regularly	15	16	14	14
Total energy intake, kcal/d				
Mean	2,197	2,075	2,221	2,082
SD	837	795	976	884
Menopausal hormone therapy use (women only), % of participants				
Never	40	32	43	40
Former	14	16	13	17
Current	46	52	44	43
Total calcium intake*				
Mean	575	642	538	606
SD	273	318	243	307
Red meat intake†				
Mean	40	36	41	38
SD	23	22	22	21
Total fiber intake†				
Mean	11.2	12.0	11.1	11.3
SD	3.5	3.6	3.4	3.5

NOTE. Missing values are not shown.
Abbreviations: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
*Energy adjusted using the density method (mg/1,000 kcal).
†Energy adjusted using the density method (gm/1,000 kcal).

Table 3. ORs and 95% CIs for Incident Distal Colorectal Adenoma by BMI (kg/m^2)

		Any Distal Colorectal Adenoma			Distal Colon			Rectal			Advanced			Nonadvanced		
BMI Category*	Nonparticipants	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†
All																
18.5-24.9	6,652	346	1.00	Ref	268	1.00	Ref	94	1.00	Ref	70	1.00	Ref	182	1.00	Ref
25.0-29.9	8,601	546	1.06	0.92 to 1.22	422	1.05	0.90 to 1.24	144	1.04	0.79 to 1.36	138	1.34	0.99 to 1.80	267	0.99	0.81 to 1.20
≥ 30	4,237	312	1.17	0.99 to 1.38	240	1.15	0.95 to 1.39	74	1.05	0.76 to 1.46	72	1.37	0.96 to 1.95	154	1.14	0.90 to 1.44
P, trend‡			.08			.16			.79			.08			.30	
Men																
18.5-24.9	2,947	188	1.00	Ref	147	1.00	Ref	51	1.00	Ref	38	1.00	Ref	105	1.00	Ref
25.0-29.9	5,455	403	1.13	0.94 to 1.36	312	1.12	0.91 to 1.38	101	1.06	0.74 to 1.50	105	1.47	1.00 to 2.16	205	1.05	0.82 to 1.35
≥ 30	2,241	208	1.32	1.06 to 1.65	155	1.26	0.98 to 1.61	54	1.30	0.86 to 1.97	48	1.49	0.95 to 2.35	105	1.24	0.92 to 1.67
P, trend‡			.01			.07			.23			.09			.17	
Women																
18.5-24.9	3,705	158	1.00	Ref	121	1.00	Ref	43	1.00	Ref	32	1.00	Ref	77	1.00	Ref
25.0-29.9	3,146	143	0.97	0.76 to 1.23	110	0.96	0.73 to 1.26	43	1.07	0.69 to 1.66	33	1.14	0.69 to 1.89	62	0.89	0.63 to 1.26
≥ 30	1,996	104	0.96	0.73 to 1.26	85	1.00	0.74 to 1.36	20	0.69	0.39 to 1.22	24	1.18	0.66 to 2.10	49	1.00	0.67 to 1.47
P, trend‡			.75			.97			.26			.60			.91	
P, interaction by sex§			.22			.32			.58			.78			.35	

Abbreviations: BMI, body mass index; OR, odds ratio; Ref, reference.

*Results for BMI < 18.5 not shown owing to small numbers of cases.

† Adjusted for age at screening (T3 or T5; < 64, 64-67, 68-71, ≥ 72 years), sex (if applicable), study center, year of screening (T3/T5), race/ethnicity (white non-Hispanic, black non-Hispanic, Asian, other, missing), exercise (< 1 hr/wk, 1-2 hr/wk, ≥ 3 hr/wk, missing), smoking status (never smoked tobacco, former cigarette smoker, current cigarette smoker, never smoked cigarettes but ever smoked a pipe or cigar, missing), menopausal hormone therapy use (never, former, current, missing), and sex-specific quartiles of intakes of total energy, total calcium, and red meat.

‡Calculated by modeling BMI categories as continuous and evaluating statistical significance of Wald test; excludes BMI < 18.5.

§Calculated by comparing the fit of a model including a cross-product term between BMI (continuous variable) and sex to a model without this term using the likelihood ratio test; models exclude BMI < 18.5.

Table 4. ORs and 95% CIs for Colorectal Adenoma Recurrence by BMI (kg/m^2)

		Any Recurrent Adenoma			Proximal Colon			Distal Colon			Rectum			Advanced			Nonadvanced		
BMI Category*	Nonparticipants	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†	Cases	OR	95% CI†
All																			
18.5-24.9	290	195	1.00	Ref	91	1.00	Ref	64	1.00	Ref	21	1.00	Ref	46	1.00	Ref	149	1.00	Ref
25.0-29.9	405	358	1.25	0.95 to 1.66	156	1.12	0.78 to 1.61	130	1.39	0.92 to 2.10	35	1.08	0.56 to 2.11	84	1.35	0.81 to 2.24	274	1.22	0.90 to 1.65
≥ 30	224	199	1.31	0.94 to 1.82	108	1.44	0.95 to 2.19	61	1.22	0.74 to 1.99	16	0.90	0.41 to 1.99	58	1.36	0.76 to 2.44	141	1.29	0.90 to 1.84
P, trend‡			.10			.08			.41			.80			.31			.16	
Men																			
18.5-24.9	141	110	1.00	Ref	51	1.00	Ref	38	1.00	Ref	11	1.00	Ref	25	1.00	Ref	85	1.00	Ref
25.0-29.9	268	272	1.34	0.93 to 1.93	119	1.14	0.72 to 1.82	100	1.65	0.97 to 2.80	22	0.70	0.29 to 1.70	59	1.22	0.62 to 2.41	213	1.34	0.91 to 1.98
≥ 30	128	144	1.50	0.98 to 2.30	77	1.50	0.88 to 2.56	48	1.69	0.90 to 3.16	7	0.47	0.15 to 1.47	42	1.51	0.69 to 3.29	102	1.46	0.92 to 2.31
P, trend‡			.07			.13			.11			.19			.30			.11	
Women																			
18.5-24.9	149	85	1.00	Ref	40	1.00	Ref	26	1.00	Ref	10	1.00	Ref	21	1.00	Ref	64	1.00	Ref
25.0-29.9	137	86	1.27	0.79 to 2.04	37	1.27	0.67 to 2.39	30	1.25	0.59 to 2.65	13	2.00	0.59 to 6.82	25	2.16	0.91 to 5.12	61	1.14	0.68 to 1.93
≥ 30	96	55	1.15	0.66 to 2.01	31	1.54	0.73 to 3.23	13	0.72	0.28 to 1.85	9	1.54	0.41 to 5.76	16	1.44	0.52 to 4.02	39	1.10	0.59 to 2.03
P, trend‡			.54			.25			.62			.54			.34			.72	
P, interaction by sex§			.94			.67			.28			.26			.48			.65	

Abbreviations: BMI, body mass index; hr/wk, hours per week; OR, odds ratio; Ref, reference.

*Results for BMI < 18.5 not shown owing to small numbers of cases.

†Adjusted for age at recurrence (for participants) or last surveillance colonoscopy (for controls; < 63, 63-67, 68-71, ≥ 72 years), sex (if applicable), study center, surveillance period, No. of surveillance endoscopies, race/ethnicity (white non-Hispanic, black non-Hispanic, Asian, other, missing), exercise (< 1 hr/wk, 1-2 hr/wk, ≥ 3 hr/wk, missing), smoking status (never smoked tobacco, former cigarette smoker, current cigarette smoker, never smoked cigarettes but ever smoked a pipe or cigar, missing), menopausal hormone therapy use (never, former, current, missing), and sex-specific quartiles of intakes of total energy, total calcium, and red meat.

‡Calculated by modeling BMI categories as continuous and evaluating statistical significance of Wald test; excludes BMI < 18.5.

§Calculated by comparing the fit of a model including a cross-product term between BMI (continuous variable) and sex to a model without this term using the likelihood ratio test; models exclude BMI < 18.5.

Table 5. HRs and 95% CIs for Incident Colorectal Cancer by BMI (kg/m^2)

	Any Colorectal Cancer			Proximal Colon			Distal Colon			Rectum			Advanced			Nonadvanced		
BMI Category*	Cases	HR	95% CI†	Cases	HR	95% CI†	Cases	HR	95% CI†	Cases	HR	95% CI†	Cases	HR	95% CI†	Cases	HR	95% CI†
All																		
18.5-24.9	284	1.00	Ref	157	1.00	Ref	65	1.00	Ref	56	1.00	Ref	112	1.00	Ref	157	1.00	Ref
25.0-29.9	424	1.11	0.95 to 1.29	228	1.10	0.89 to 1.35	101	1.13	0.82 to 1.56	92	1.17	0.83-1.64	151	1.03	0.80 to 1.32	256	1.18	0.97 to 1.45
≥ 30	254	1.24	1.04 to 1.47	144	1.32	1.04 to 1.66	53	1.07	0.73 to 1.55	52	1.20	0.81 to 1.78	100	1.27	0.96 to 1.67	141	1.22	0.96 to 1.54
P, trend‡		.02			.02			.70			.35			.10			.09	
Men																		
18.5-24.9	128	1.00	Ref	65	1.00	Ref	31	1.00	Ref	31	1.00	Ref	54	1.00	Ref	68	1.00	Ref
25.0-29.9	270	1.19	0.96 to 1.48	136	1.15	0.85 to 1.55	64	1.19	0.77 to 1.85	68	1.27	0.83 to 1.96	86	0.92	0.65 to 1.29	173	1.41	1.06 to 1.87
≥ 30	148	1.48	1.16 to 1.89	74	1.48	1.05 to 2.09	36	1.48	0.90 to 2.42	35	1.38	0.83 to 2.27	53	1.32	0.89 to 1.95	85	1.53	1.11 to 2.13
P, trend‡		.002			.02			.12			.21			.19			.01	
Women																		
18.5-24.9	156	1.00	Ref	92	1.00	Ref	34	1.00	Ref	25	1.00	Ref	58	1.00	Ref	89	1.00	Ref
25.0-29.9	154	1.07	0.86 to 1.34	92	1.10	0.82 to 1.47	37	1.13	0.70 to 1.81	24	1.04	0.59 to 1.83	65	1.22	0.85 to 1.75	83	1.01	0.74 to 1.36
≥ 30	106	1.03	0.80 to 1.33	70	1.23	0.89 to 1.69	17	0.66	0.36 to 1.21	17	0.95	0.50 to 1.79	47	1.24	0.83 to 1.84	56	0.96	0.68 to 1.36
P, trend‡		.74			.21			.25			.89			.27			.85	
P, interaction by sex§		.12			.41			.27			.39			.90			.17	

Abbreviations: BMI, body mass index; HR, hazard ratio; Ref, reference.

*Results for BMI < 18.5 not shown owing to small numbers of cases.

†Adjusted for age at baseline questionnaire completion (< 58, 58-61, 62-66, ≥ 67 years); sex (if applicable); study center; screening at baseline, T3, or T5 and prior to colorectal cancer diagnosis; screening adequacy and results at baseline, T3, or T5 screen and prior to colorectal cancer diagnosis (negative, positive for adenoma, inadequate/not done); race/ethnicity (white non-Hispanic, black non-Hispanic, Asian, other, missing); smoking status (never smoked tobacco, former cigarette smoker, current cigarette smoker, never smoked cigarettes but ever smoked a pipe or cigar, missing); and menopausal hormone therapy use (never, former, current, missing).

‡Calculated by modeling BMI categories as continuous and evaluating statistical significance of Wald test; excludes BMI < 18.5.

§Calculated by comparing the fit of a model including a cross-product term between BMI (continuous variable) and sex to a model without this term using the likelihood ratio test; models exclude BMI < 18.5.

are needed to provide a more accurate estimation of the risks of colorectal adenoma and cancer associated with excess adiposity in women.

Meta-analyses have suggested that BMI may be more strongly associated with colon versus rectal adenoma[44] and cancer[15-16] incidence. Similarly, a pooled analysis of seven prospective studies found an association with recurrent adenomas in the proximal colon but not distal colon or rectum.[19] Although we did not observe any statistically significant differences in associations by tumor location, we observed a qualitative difference in men in the association between BMI and recurrent adenoma in the rectum (nonsignificantly inverse) compared with the proximal and distal colon (nonsignificantly positive). Consistent with previous studies,[19,45-46] we observed no differences in the associations between BMI and advanced versus nonadvanced colorectal adenoma incidence or recurrence. Likewise, we observed no differences by cancer stage (I/II *v* III/IV). As our study was conducted within a screening trial, the proportion of cancers diagnosed at an earlier stage was larger than in other studies.

Biologic mechanisms by which obesity increases colorectal tumor risks are unclear, which may be in part because of the apparent complexity of this association and could depend on the timing of the exposure.[14] The consistent associations of obesity with incident and recurrent adenoma and cancer in our study suggest that obesity contributes to risk at all disease stages, including adenoma initiation and tumor advancement to adenoma recurrence and cancer development. BMI reflects numerous exposures in addition to adiposity, including various hormones, cytokines, and reactive oxygen species associated with chronic, low-grade systemic inflammation, dietary intake, and overall energy balance.[47] Additional studies are needed to identify the biologic underpinnings of this association.

Our study is unique in that it is conducted within a cancer screening trial, in which cases had an equal chance for disease detection as controls and colorectal cancer screening was less likely to be influenced by BMI or other factors.[48] Although some previous studies had controlled for self-reported history of endoscopic screening,[33-34] adjustment for potential screening-related biases was even more complete with this design. In addition, all participants were randomly assigned to receive screening by a standardized protocol for colorectal neoplasia, further minimizing differences in screening. Participants came from 10 different screening centers representing a broad population distribution in the United States, although they had higher levels of education, were more physically active, and were less likely to be current smokers.[49]

Our study was limited by the exclusive use of sigmoidoscopy in the trial and, thus, we were unable to investigate the association between BMI and incident proximal adenoma. Also, we relied on self-reported height and weight, which may have introduced some measurement error in our exposure assessment; however, such error would have likely biased our results to the null. We lacked information on body fat distribution, which could have provided greater insight into the role of obesity and colorectal neoplasia risk.

In summary, in this large prospective study conducted in the context of a screening trial, we observed increased risks of incident adenoma, recurrent adenoma, and cancer in middle-aged obese men undergoing screening with sigmoidoscopy. These observations suggest that obesity contributes to not only colorectal tumor initiation but also progression, and that regular screenings, detection, and removal of colorectal adenomas do not eliminate the risk of colorectal cancer associated with obesity. Colorectal cancer prevention efforts should encourage the achievement and maintenance of a healthy body weight in addition to regular screenings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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