Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Prospective Study of Body Mass Index, Weight Change, and Risk of Cancer in the Proximal and Distal Colon

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Abstract

Background: Body mass index (BMI) is an established risk factor for colon cancer, but risks may differ between genders and colon subsites. Moreover, whether weight change influences risk is not yet clarified. We investigated these issues in a large, Norwegian, population-based cohort study.

Methods: Participants' weight was measured at examinations up to three times between 1974 and 1988. Hazard ratios (HR) and confidence intervals (CI) were estimated using Cox regression.

Results: During follow-up of 38,822 men and 37,357 women, we identified 228 proximal and 174 distal colon cancer cases in men and 237 and 159 cases, respectively, in women. The association between BMI and colon cancer risk differed between subsites in men (P = 0.02) but not in women (P = 0.95). In men, HRs (95% CIs) per 5 kg/m^2 were 1.07 (0.86-1.33) and 1.49 (1.19-1.87) for proximal and distal colon, respectively. In women, corresponding HRs (95% CIs) were 1.15 (0.99-1.34) and 1.25 (1.05-1.49). Among overweight men (BMI ≥25 kg/m^2), weight gain ≥10 kg gave higher colon cancer risk than weight maintenance (HR, 2.09; 95% CI, 1.21-3.63), whereas risks were similar among men with stable weight, weight loss, or gains <10 kg. Weight change was not associated with risk in women.

Conclusions: The influence of BMI on colon cancer risk differed between subsites in men. Weight gains <10 kg did not influence risk.

Impact: Our results support gender differences and the hypothesis of different etiologies for colon subsites. Whether weight loss in the overweight decreases risk of colon cancer warrants further study. *Cancer Epidemiol Biomarkers Prev; 19(6); 1511–22. ©2010 AACR.*

Introduction

The prevalence of obesity, defined as body mass index (BMI) ≥30 kg/m^2, is rising worldwide (1), and in several European countries, more than 25% of the adult population is now obese (2). Excess weight is associated with several hormones, such as insulin and leptin, growth factors, and inflammatory responses, factors that are likewise associated with colon cancer (3-5). Observational studies support that excess weight increases the risk of colon cancer, but the relation between BMI and colon cancer risk seems to be stronger in men than in women (6, 7).

There is evidence supporting etiologic distinctions between cancers in the proximal and distal colon (8-10). Subsite-specific incidence rates vary with age, gender, and geographic region (8). There are embryologic, morphologic, and biochemical differences between the proximal and distal colon (9). In addition, tumors of the proximal and distal colon differ in their genetic nature (10). However, only a handful of studies have examined the association between BMI and cancer risk by subsite of the colon, and the results are inconclusive (7, 11, 12).

Insulin resistance and subsequent hyperinsulinemia may promote cell growth and colon cancer development. Weight loss increases insulin sensitivity among overweight individuals (13), and weight gain increases fasting serum insulin (14, 15). Furthermore, the risk of colon cancer seems to increase steadily throughout the BMI range, at least in men (16, 17), supporting that weight change influences colon cancer risk. However, few studies have investigated the association between weight change and risk of colon cancer (18), and the results are conflicting (19-22). Moreover, existing studies have usually relied on primarily middle-aged subjects' recall of their weight in young adulthood (19, 20, 23, 24).

The main aim was to study the association between BMI, weight change, and the risk of proximal and distal colon cancer in both men and women. We also studied whether weight loss in the overweight (BMI ≥25 kg/m^2) is associated with decreased risk. We used data from the Norwegian Counties Study, a large, population-based,

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Norwegian cohort study with high attendance rate (>80%), complete follow-up, and where participant's weight and height were measured at examinations up to three times.

Materials and Methods

Study design and population

The Norwegian Counties Study was initiated in 1974. Three screenings were carried out in the counties Finnmark, Oppland, and Sogn og Fjordane. Between 1974 and 1978, all residents ages 35 to 49 years and a random sample ages 20 to 34 years were invited to screening I, in total 34,115 men and 31,509 women (25). The following screenings were carried out 5 and 10 years or 3 and 13 years after screening I (Fig. 1). The attendance at each screening was 88%, 88%, and 84%. A total of 92,234 persons attended at least once, 60,636 at least twice, and 36,894 three times.

The present study was approved by the Norwegian Data Inspectorate and recommended by the Regional Committee for Medical Research Ethics.

Assessment of exposures

The screenings were organized according to a strict protocol, and procedures were identical at all three screenings (25). The invitees received a questionnaire by mail covering smoking habits and recreational and occupational physical activity during the previous year. The completed questionnaire was checked for inconsistencies at the examination. A team of trained nurses carried out the examinations, which included blood pressure measurements and collection of a blood sample. In addition, height and weight were measured to the nearest centimeter and half kilogram. Women were asked whether menopause had occurred.

A four-page semiquantitative food frequency questionnaire (FFQ) to be filled out at home was handed out to 59% of participants at screening I and all at screenings II and III. The reliability and validity of the FFQ and the calculations of nutrient intakes have been described previously (26). At each screening, daily energy intake was calculated for participants who answered at least 20 questions (93%, 82%, and 84%, respectively, of participants who received the FFQ). We eliminated very high and very low energy intakes, defined as the screening-specific top and bottom 1% of ratio of energy intake to estimated basal metabolic rate (27).

Information on the participants' level of education was obtained from Statistics Norway: Using the unique identification number assigned to all Norwegian citizens, the participants were linked to records of the Censuses of 1970, 1980, 1990, and 2001.

Follow-up and case identification

We defined a subject's baseline screening as the first screening where weight was measured, age ≥18 years, the questions about smoking and physical activity were answered, and our requirements about daily energy intake were fulfilled. With BMI as the main exposure, follow-up started at the baseline screening. With weight change as the main exposure, follow-up started at the last weight measurement. The subjects were followed until the date of diagnosis of cancer (any site), death, emigration, or December 31, 2005, whichever came first.

Information on cancer incidence and death or emigration was obtained through linkage with the Cancer Registry of Norway and Statistics Norway using the unique identification number. Cancers coded as 153 according to the International Classification of Diseases, Seventh Edition were included as colon cancers. Cancers occurring in the ascending colon, including the cecum and appendix (153.0, 153.6), or transverse colon (153.1, includes the hepatic and splenic flexures) were classified as proximal, whereas cancers occurring in the descending colon or sigmoid colon were classified as distal (153.2-153.3). Cases occurring in the rectosigmoid area (153.4) or with unspecified subsite (153.9) were not included as events in subsite analyses.

Study sample

A total of 46,640 men and 45,176 women had their weight measured at least once (Fig. 1). The analyses were restricted to subjects assigned a baseline screening (see above). We also required at least one height measurement and information on education. In the analyses of weight change, we furthermore required at least one weight measurement after baseline. We excluded subjects with BMI <18.5 kg/m^2, subjects who were diagnosed with cancer (any site) before start of follow-up, and subjects who died, emigrated, or were diagnosed with cancer within the first year of follow-up. A total of 38,822 men and 37,357 women were included in the analyses of BMI, and 21,687 men and 21,539 women were also included in the analyses of weight change.

Statistical analysis

We calculated BMI (weight/height^2) at each screening using the mean of a subject's height measurements. BMI was analyzed as a continuous variable and categorized according to WHO guidelines using the additional cutoff points in the reference range and for the preobese (18.50-22.99, 23.00-24.99, 25.00-27.49, 27.50-29.99, and ≥30.00 kg/m^2; ref. 28).

We calculated absolute weight change, an individual's weight at the last measurement minus weight at baseline (categorized as ≤−2, −1.9 to 1.9, 2.0-4.9, 5.0-9.9, and ≥10.0 kg). We also calculated change in BMI per year, the slope in a linear regression model fitting an individual's BMI measurements from baseline and later against time, which we categorized as ≤−0.050, −0.050 to 0.049, 0.050 to 0.099, 0.100 to 0.299, and ≥0.300 kg/m^2 per year.

At each screening, we classified the participants as sedentary, moderately active, or active by combining the categories of recreational and occupational physical activity (29) and as current, former, and never smokers. Participants were classified as former instead of never smokers at a screening if they had been classified as former or daily

smokers at a previous screening. Each participant was classified as having primary schooling, secondary, or higher education using the most recent information available from the Censuses.

To examine the relationship between BMI, weight change (absolute weight change and change in BMI per year), and the risk of colon cancer, we used Cox regression and estimated hazard ratios (HR) and 95% confidence intervals (CI) separately for men and women. All models were adjusted for age by using attained age as the time variable and by controlling for year of birth (<1930, 1930-1934, 1935-1939, 1940-1944, ≥1945) in a stratified Cox model. Multivariable models were additionally adjusted for physical activity, smoking, height (sex-specific quintiles), energy intake (sex-specific quintiles), education, and county of residence. Models including

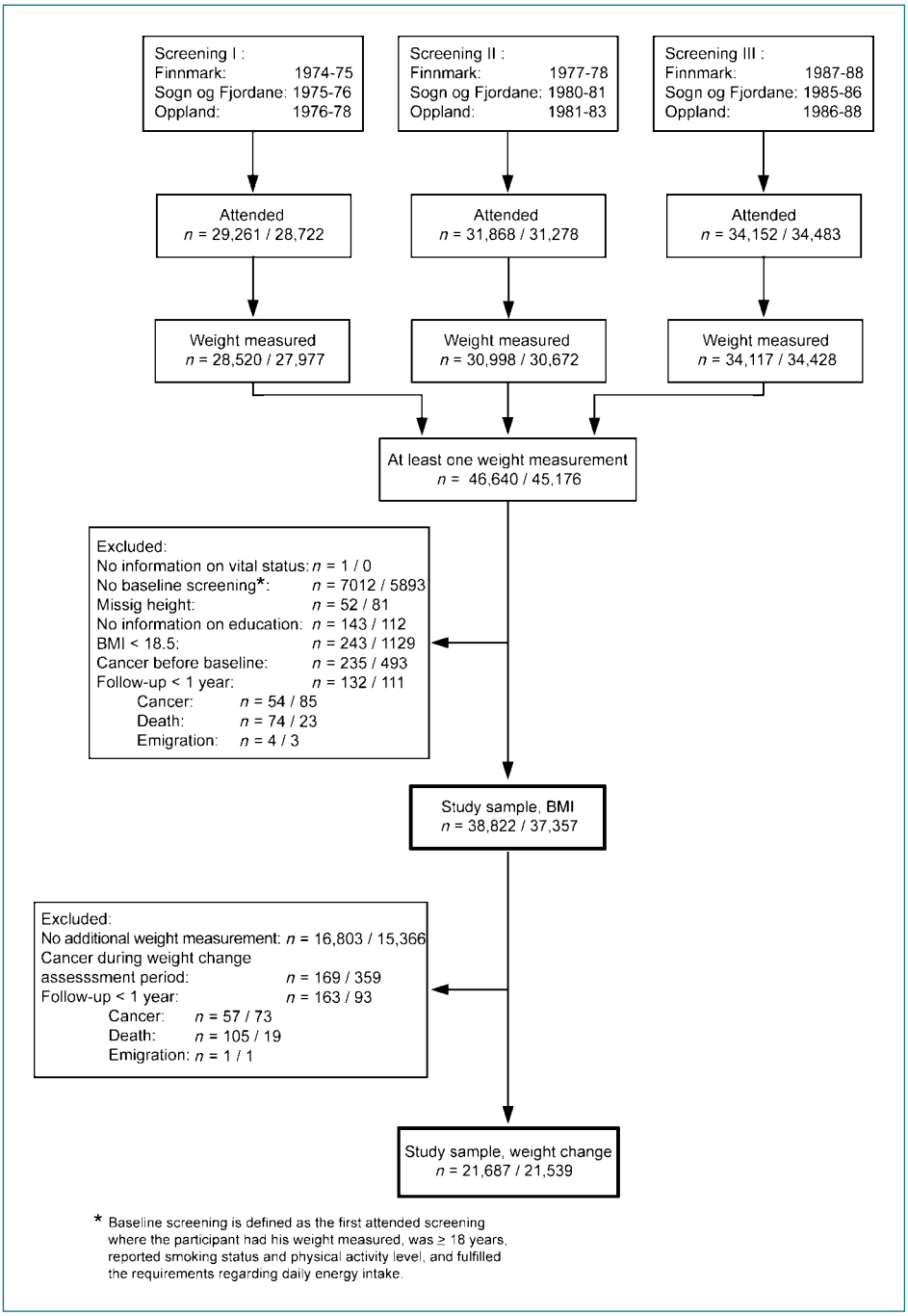

Figure 1. Flow chart illustrating how study samples were obtained (*n* = men/women).

Table 1. Characteristics of study sample by BMI at baseline

	BMI (kg/m^2) at baseline				
	18.50-22.99	23.00-24.99	25.00-27.49	27.50-29.99	≥30.00
Men (*n* = 38,822)					
No. participants	9,408	10,820	10,942	5,130	2,522
Years of follow-up, mean (SD)	23.3 (6.3)	23.3 (6.3)	22.8 (6.3)	22.1 (6.5)	21.0 (6.8)
Baseline screening (%)					
Screening I	40.6	40.4	39.0	37.0	33.0
Screening II	31.2	30.0	28.6	28.0	28.0
Screening III	28.2	29.6	32.5	35.0	39.0
Age (y), mean (SD)*	39.3 (8.4)	40.9 (7.4)	42.2 (6.8)	43.0 (6.4)	43.7 (6.6)
Weight (kg), mean (SD)*	68.0 (6.0)	74.8 (5.8)	81.0 (6.4)	88.3 (7.1)	98.7 (10.1)
Height (cm), mean (SD)	177.1 (6.7)	176.3 (6.6)	175.9 (6.5)	175.7 (6.7)	175.2 (6.9)
Energy intake (kJ/d), mean (SD)*	8,889 (2,232)	8,573 (2,277)	8,210 (2,319)	7,847 (2,285)	7,488 (2,242)
Physical activity level (%)*					
Sedentary	22.4	21.7	23.5	26.4	32.5
Moderately active	45.0	46.3	45.1	42.6	39.7
Active	32.6	31.9	31.5	31.1	27.8
Smoking status (%)*					
Never smoker	25.8	27.9	26.5	24.5	22.8
Former smoker	16.9	24.5	29.7	33.2	33.2
Current smoker	57.3	47.6	43.9	42.3	44.0
Education (%)					
Primary schooling	34.2	34.6	39.1	45.1	48.4
Secondary education	48.1	49.5	48.2	45.3	44.1
Higher education	17.8	15.9	12.6	9.6	7.5
Women (*n* = 37,357)					
No. participants	15,388	8,663	6,452	3,392	3,462
Years of follow-up, mean (SD)	23.6 (6.0)	23.8 (6.1)	23.5 (6.2)	23.4 (6.3)	22.9 (6.3)
Baseline screening (%)					
Screening I	38.8	41.9	40.9	39.9	38.6
Screening II	29.0	28.0	27.8	28.9	28.8
Screening III	32.2	30.1	31.3	31.2	32.6
Age (y), mean (SD)*	39.2 (7.7)	41.6 (7.0)	42.7 (6.7)	43.8 (6.6)	44.4 (6.6)
Weight (kg), mean (SD)*	57.4 (5.0)	64.1 (4.8)	69.4 (5.5)	75.3 (5.9)	87.3 (11.0)
Height (cm), mean (SD)	164.1 (5.9)	163.5 (5.9)	162.9 (6.1)	162.1 (6.1)	161.3 (6.4)
Energy intake (kJ/d), mean (SD)*	5,828 (1,641)	5,543 (1,558)	5,404 (1,531)	5,301 (1,526)	5,267 (1,534)
Physical activity level (%)*					
Sedentary	27.4	24.7	24.8	24.4	28.3
Moderately active	66.3	67.6	66.0	66.3	62.9
Active	6.4	7.8	9.2	9.2	8.8
Smoking status (%)*					
Never smoker	41.6	45.9	50.1	53.5	55.3
Former smoker	15.0	17.5	17.3	16.6	16.6
Current smoker	43.3	36.6	32.6	30.0	28.1
Education (%)					
Primary schooling	33.7	39.4	44.5	50.2	56.7
Secondary education	49.9	48.3	45.4	42.1	37.1
Higher education	16.5	12.2	10.1	7.7	6.2

*At baseline.

weight change were also adjusted for BMI. Due to lack of detailed information, other potential confounders, such as alcohol and fiber intake, were not explored. Values of BMI, physical activity, smoking, and energy intake were updated at each attended screening, where information on all these covariates was available. With weight change as the main exposure, baseline values were used throughout the follow-up period because new values were not registered

Table 2. HRs and 95% CIs of subsite-specific colon cancer according to BMI

	BMI (kg/m^2)					Per 5 kg/m^2	P_{trend}*
	18.50-22.99	23.00-24.99	25.00-27.49	27.50-29.99	≥30.00		
Men (n = 38,822)							
Person-years	192,585	239,739	260,619	130,423	63,736		
Total colon							
No. cases†	69	112	140	75	54		
Age-adjusted HR (95% CI)‡	1 (reference)	1.15 (0.85-1.55)	1.20 (0.90-1.60)	1.21 (0.87-1.67)	1.79 (1.25-2.56)	1.25 (1.08-1.44)	0.003
Multivariable HR (95% CI)§	1 (reference)	1.16 (0.86-1.56)	1.19 (0.89-1.60)	1.20 (0.86-1.68)	1.80 (1.25-2.59)	1.25 (1.08-1.45)	0.004
Proximal colon							
No. cases†	44	58	68	38	20		
Age-adjusted HR (95% CI)‡	1 (reference)	0.94 (0.63-1.39)	0.92 (0.63-1.34)	0.96 (0.62-1.49)	1.05 (0.62-1.78)	1.02 (0.82-1.26)	0.88
Multivariable HR (95% CI)§	1 (reference)	0.97 (0.66-1.44)	0.96 (0.65-1.42)	1.03 (0.66-1.61)	1.17 (0.68-2.00)	1.07 (0.86-1.33)	0.56
Distal colon							
No. cases†	18	42	57	27	30		
Age-adjusted HR (95% CI)‡	1 (reference)	1.65 (0.95-2.87)	1.86 (1.10-3.17)	1.66 (0.91-3.01)	3.78 (2.10-6.78)	1.58 (1.28-1.96)	<0.0001
Multivariable HR (95% CI)§	1 (reference)	1.55 (0.89-2.70)	1.67 (0.98-2.87)	1.44 (0.79-2.65)	3.26 (1.79-5.95)	1.49 (1.19-1.87)	<0.01
Women (n = 37,357)							
Person-years	321,014	206,934	166,709	90,266	94,556		
Total colon							
No. cases†	115	95	81	57	71		
Age-adjusted HR (95% CI)‡	1 (reference)	1.01 (0.77-1.32)	0.96 (0.72-1.28)	1.15 (0.84-1.59)	1.32 (0.98-1.78)	1.12 (1.00-1.25)	0.06
Multivariable HR (95% CI)§	1 (reference)	1.05 (0.80-1.38)	1.03 (0.77-1.38)	1.27 (0.92-1.76)	1.48 (1.09-2.02)	1.17 (1.04-1.31)	0.01
Proximal colon							
No. cases†	65	55	49	31	37		
Age-adjusted HR (95% CI)‡	1 (reference)	1.03 (0.72-1.48)	1.04 (0.71-1.51)	1.11 (0.72-1.72)	1.22 (0.81-1.84)	1.08 (0.93-1.26)	0.31
Multivariable HR (95% CI)§	1 (reference)	1.09 (0.76-1.56)	1.13 (0.77-1.65)	1.27 (0.82-1.97)	1.43 (0.94-2.19)	1.15 (0.99-1.34)	0.07
Distal colon							
No. cases†	42	34	28	25	30		
Age-adjusted HR (95% CI)‡	1 (reference)	0.99 (0.63-1.56)	0.92 (0.57-1.48)	1.40 (0.85-2.31)	1.54 (0.96-2.48)	1.22 (1.03-1.45)	0.03
Multivariable HR (95% CI)§	1 (reference)	1.03 (0.65-1.62)	0.97 (0.60-1.58)	1.50 (0.90-2.50)	1.65 (1.01-2.70)	1.25 (1.05-1.49)	0.01

*To test for linear trend, BMI was modeled as a continuous variable.

†Classified according to last measurement of BMI.

‡Age-adjusted HRs based on a stratified Cox model (year of birth: <1930, 1930-1934, 1935-1939, 1940-1944, ≥1945) using attained age as the time variable.

§Multivariable HRs are based on the age-adjusted model, additionally adjusted for level of physical activity, height, energy intake, smoking, education, and county of residence.

Table 3. Characteristics of study sample by absolute weight change

	Weight change (kg)*				
	≤−2	−1.9 to 1.9	2.0-4.9	5.0-9.9	≥10.0
Men (n = 21,687)					
No. participants	3,661	6,636	5,723	4,305	1,362
Years of follow-up, mean (SD)	16.8 (5.4)	17.8 (5.1)	17.9 (4.7)	17.4 (4.7)	17.1 (4.4)
Age (y), mean (SD)†	42.1 (6.3)	41.8 (6.4)	40.7 (6.8)	39.4 (7.3)	38.1 (7.8)
Weight (kg), mean (SD)†	80.7 (11.2)	76.4 (9.7)	76.2 (9.5)	77.2 (10.2)	79.6 (11.9)
Height (cm), mean (SD)	175.6 (6.5)	175.4 (6.5)	175.6 (6.5)	176.2 (6.6)	177.2 (6.6)
BMI (kg/m^2)†	26.1 (3.2)	24.8 (2.7)	24.7 (2.7)	24.8 (2.9)	25.3 (3.4)
Weight change (kg), mean (SD)*	−4.5 (3.1)	0.1 (0.9)	3.1 (0.9)	6.7 (1.4)	13.1 (3.8)
Time interval (y), mean (SD)‡	8.3 (2.6)	8.0 (2.7)	8.3 (2.6)	9.0 (2.3)	9.6 (1.9)
Energy intake (kJ/d), mean (SD)†	8,672 (2,310)	8,859 (2,278)	8,771 (2,243)	8,699 (2,387)	8,560 (2,456)
Physical activity level (%)†					
Sedentary	22.9	19.3	19.4	19.6	23.8
Moderately active	43.1	44.8	45.4	45.4	42.1
Active	34.0	35.8	35.1	35.1	34.1
Smoking status (%)†					
Never smoker	20.5	26.7	27.7	26.7	20.7
Former smoker	27.6	25.5	25.5	24.8	21.9
Current smoker	51.9	47.8	46.7	48.5	57.4
Education (%)					
Primary schooling	49.7	43.1	40.5	41.1	42.8
Secondary education	42.6	45.9	47.0	47.4	48.6
Higher education	7.7	11.0	12.5	11.5	8.6
No. weight measurements (%)§					
Two	57.2	60.9	57.8	51.3	47.1
Three	42.8	39.1	42.2	48.7	52.9
Women (n = 21,539)					
No. participants	3,539	5,839	5,552	4,695	1,914
Years of follow-up, mean (SD)	18.2 (4.9)	18.7 (4.5)	18.5 (4.3)	18.1 (3.9)	17.7 (3.9)
Age (y), mean (SD)†	42.0 (6.9)	41.7 (6.6)	40.8 (6.8)	39.8 (6.9)	38.8 (7.3)
Weight (kg), mean (SD)†	70.0 (12.4)	63.6 (9.5)	63.2 (9.5)	64.1 (9.9)	67.4 (11.4)
Height (cm), mean (SD)	162.5 (6.1)	162.9 (5.9)	162.8 (6.0)	162.7 (6.0)	163.1 (6.0)
BMI (kg/m^2)†	26.5 (4.6)	24.0 (3.5)	23.9 (3.5)	24.2 (3.6)	25.3 (4.1)
Weight change (kg), mean (SD)*	−5.1 (4.1)	0.2 (0.9)	3.1 (0.8)	6.7 (1.4)	13.8 (4.1)
Time interval (y), mean (SD)‡	8.1 (2.6)	7.9 (2.6)	8.4 (2.5)	9.0 (2.3)	9.5 (2.0)
Energy intake (kJ/d), mean (SD)†	5,721 (1,625)	5,831 (1,591)	5,883 (1,636)	5,781 (1,639)	5,463 (1,614)
Physical activity level(%)†					
Sedentary	24.2	22.4	22.5	23.7	28.3
Moderately active	67.4	69.0	69.9	68.6	64.7
Active	8.4	8.7	7.6	7.6	7.0
Smoking status (%)†					
Never smoker	43.6	49.2	50.7	49.6	45.2
Former smoker	16.3	14.9	14.8	15.3	15.0
Current smoker	40.1	35.9	34.5	35.0	39.8
Education (%)					
Primary schooling	53.0	45.4	43.9	45.4	47.8
Secondary education	40.1	44.5	45.4	45.6	44.5

(*Continued on the following page*)

Table 3. Characteristics of study sample by absolute weight change (Cont'd)

	Weight change (kg)*				
	≤−2	−1.9 to 1.9	2.0-4.9	5.0-9.9	≥10.0
Higher education	7.0	10.1	10.6	9.0	7.7
No. weight measurements (%)§					
Two	57.1	58.9	56.4	52.9	49.1
Three	42.9	41.1	43.6	47.1	50.9

*Weight at baseline subtracted from weight at last measurement.
†At baseline.
‡Time between baseline and last measurement.
§Number of measurements including baseline and later.

again after start of follow-up. For total colon cancer, we examined whether gender modified the effect of BMI and weight change and whether BMI at baseline (<25, ≥25 kg/m^2) modified the effect of weight change.

To test for linear trends, the exposure was modeled as a continuous variable. For weight change, these tests were restricted to subjects who gained or maintained weight. We used the Wald statistic to test for heterogeneity of the estimated multivariable HRs for distal and proximal colon cancers. To test the proportional hazards assumption for weight change, we included interaction terms between weight change and attained age in the multivariable model. Trend tests, effect modifications, and the proportional hazards assumption were evaluated with the likelihood ratio test.

We studied the associations between BMI, weight change, and total colon cancer risk before menopause in analyses where women were followed until menopause, defined as the first screening where they reported being postmenopausal or age 55 if menopause had not occurred at the last attended screening. We also studied the associations after menopause by following women from the first screening where they reported being postmenopausal. For both genders, we did separate analyses including person-years corresponding to follow-up time <10 and ≥10 years.

Tests of statistical significance were two-sided and $P < 0.05$ was considered statistically significant. All analyses were done using SAS 9.1.3 (SAS Institute).

Results

Body mass index

During a mean follow-up of 23.2 years, we identified 450 cases of colon cancer in men and 419 in women. Mean age at diagnosis was 62.9 years. In men, 228 cases occurred in the proximal colon, 174 in the distal colon, and 34 in the rectosigmoid area, and 14 cases were coded with unspecified subsite. In women, the corresponding numbers were 237, 159, 12, and 11. Mean BMI at baseline was 25.2 kg/m^2 (range, 18.5-47.4) for men and 24.5 (range, 18.5-56.5) for women. Age was positively related to BMI, whereas energy intake and education were inversely related to BMI (Table 1). In men, level of physical activity was also inversely related to BMI. The highest proportion of current smokers was found in the lowest BMI category for both genders. The distribution of education and age, BMI, smoking, physical activity level, and systolic blood pressure at inclusion was similar among subjects with at least one weight measurement and subjects in the BMI study sample.

We found a significant positive association between BMI and total colon cancer risk in both genders but with a stronger trend in men (Table 2). Gender did not, however, significantly modify the effect of BMI ($P_{interaction} = 0.75$). In men, the association differed by subsite ($P_{heterogeneity} = 0.02$). No association was found between BMI and risk of cancer in the proximal colon, whereas we found a strong positive association in the distal colon. In women, the association with BMI was significant only for the distal colon, but there was no significant difference between subsites ($P_{heterogeneity} = 0.95$). We found no association for premenopausal or perimenopausal women but a positive association for postmenopausal women [multivariable HRs, 0.79 (95% CI, 0.30-2.10) and 1.76 (95% CI, 1.13-2.74), respectively, comparing highest to lowest category of BMI; $P_{interaction} = 0.09$, for BMI and menopausal status]. In men, the association between BMI and colon cancer risk was similar for follow-up <10 and ≥10 years ($P_{interaction} = 0.67$). In women, no association was found for follow-up <10 years. For follow-up ≥10 years, women in the two upper categories of BMI were at significantly increased risk compared with women in the reference category [HRs, 1.50 (95% CI, 1.05-2.14) and 1.69 (95% CI, 1.20-2.37), respectively]. There was, however, no significant interaction between follow-up time and BMI ($P_{interaction} = 0.29$).

Weight change

During a mean follow-up of 18.0 years, 283 cases of colon cancer in men and 270 in women were identified. In men, 141 cases occurred in the proximal colon, 112 in the distal colon, and 20 in the rectosigmoid area, and 10 cases were coded with unspecified subsite. The corresponding

numbers in women were 158, 100, 6, and 6. Mean weight change between baseline and last measurement was 2.3 kg (range, −38.5 to 48) for men and 2.7 kg (range, −57 to 54) for women. Age at baseline was inversely related to weight change (Table 3). There was a weak negative correlation between weight change and BMI at baseline (Pearson correlation coefficient = −0.12 for men and −0.14 for women). Participants who lost weight or gained >10 kg tended to have a higher baseline BMI and were more likely to be sedentary and current smokers at baseline, but less likely to have higher education, than participants in the other categories. The mean time between baseline and the last weight measurement was longest in the two upper categories of weight gain. The proportion with higher education was lower in the weight change study sample than in the BMI study sample (10.8% versus 14.1% for men and 9.3% versus 12.6% for women).

For men, we found no association between weight change and proximal colon cancer risk and a suggested positive association between weight gain and distal colon cancer risk ($P_{heterogeneity}$ = 0.41; Table 4). We found no association between weight change and colon cancer risk for women neither in the proximal nor in the distal colon ($P_{heterogeneity}$ = 0.49). Gender did not modify the effect of weight change ($P_{interaction}$ = 0.44).

We found no association between weight change and colon cancer risk among men with BMI <25 kg/m^2 at baseline (Table 5). Among men with BMI ≥25 kg/m^2, men who gained ≥10 kg had increased risk compared with men who maintained weight, but BMI at baseline

Table 4. HRs and 95% CIs of subsite-specific colon cancer according to absolute weight change

	Weight change (kg)					P_{trend}*
	≤−2	−1.9 to 1.9	2.0-4.9	5.0-9.9	≥10.0	
Men (*n* = 21,687)						
Person-years	61,577	118,217	102,655	74,934	23,334	
Total colon						
No. cases	45	90	78	47	23	
Age-adjusted HR (95% CI)†	0.97 (0.68-1.38)	1 (reference)	1.06 (0.79-1.44)	0.94 (0.66-1.34)	1.62 (1.02-2.56)	0.25
Multivariable HR (95% CI)‡	0.87 (0.60-1.25)	1 (reference)	1.06 (0.78-1.43)	0.92 (0.64-1.31)	1.45 (0.91-2.31)	0.52
Proximal colon						
No. cases	19	45	47	22	8	
Age-adjusted HR (95% CI)†	0.82 (0.48-1.41)	1 (reference)	1.28 (0.85-1.92)	0.88 (0.53-1.47)	1.13 (0.53-2.39)	0.67
Multivariable HR (95% CI)‡	0.76 (0.44-1.31)	1 (reference)	1.26 (0.84-1.90)	0.86 (0.51-1.44)	1.02 (0.47-2.18)	0.45
Distal colon						
No. cases	21	33	24	23	11	
Age-adjusted HR (95% CI)†	1.23 (0.71-2.12)	1 (reference)	0.90 (0.53-1.52)	1.27 (0.75-2.17)	2.12 (1.07-4.22)	0.06
Multivariable HR (95% CI)‡	1.07 (0.61-1.86)	1 (reference)	0.89 (0.53-1.51)	1.22 (0.71-2.08)	1.87 (0.93-3.75)	0.14
Women (*n* = 21,539)						
Person-years	64,460	109,029	102,669	85,112	33,952	
Total colon						
No. cases	57	79	55	52	27	
Age-adjusted HR (95% CI)†	1.19 (0.84-1.67)	1 (reference)	0.77 (0.55-1.09)	0.93 (0.66-1.33)	1.28 (0.82-1.98)	0.46
Multivariable HR (95% CI)‡	1.05 (0.74-1.50)	1 (reference)	0.79 (0.56-1.11)	0.94 (0.66-1.34)	1.20 (0.77-1.88)	0.50
Proximal colon						
No. cases	36	44	34	26	18	
Age-adjusted HR (95% CI)†	1.34 (0.87-2.09)	1 (reference)	0.86 (0.55-1.34)	0.84 (0.52-1.36)	1.53 (0.88-2.65)	0.38
Multivariable HR (95% CI)‡	1.21 (0.77-1.90)	1 (reference)	0.88 (0.56-1.38)	0.85 (0.52-1.38)	1.46 (0.83-2.56)	0.45
Distal colon						
No. cases	18	33	18	22	9	
Age-adjusted HR (95% CI)†	0.90 (0.51-1.60)	1 (reference)	0.61 (0.34-1.08)	0.95 (0.55-1.63)	1.02 (0.49-2.14)	0.85
Multivariable HR (95% CI)‡	0.76 (0.42-1.37)	1 (reference)	0.61 (0.34-1.09)	0.94 (0.54-1.62)	0.91 (0.43-1.94)	0.97

*To test for linear trend, weight change was modeled as a continuous variable. The test was restricted to subjects who gained or maintained weight.

†Age-adjusted HRs based on a stratified Cox model (year of birth: <1930, 1930-1934, 1935-1939, 1940-1944, ≥1945) using attained age as the time variable.

‡Multivariable HRs are based on the age-adjusted model, additionally adjusted for baseline BMI, level of physical activity, height, energy intake, smoking, education, and county of residence.

Table 5. HRs and 95% CIs of colon cancer according to absolute weight change and BMI at baseline

	Weight change (kg)					P_{trend}*
	≤−2	−1.9 to 1.9	2.0-4.9	5.0-9.9	≥10.0	
Men ($P_{interaction}$ = 0.16)						
BMI <25†						
No. cases	12	44	44	23	5	
Person-years	25,657	67,390	59,773	43,119	12,302	
Age-adjusted HR (95% CI)‡	0.75 (0.39-1.41)	1 (reference)	1.20 (0.79-1.82)	0.92 (0.56-1.53)	0.80 (0.32-2.02)	0.46
Multivariable HR (95% CI)§	0.73 (0.38-1.38)	1 (reference)	1.19 (0.78-1.80)	0.91 (0.55-1.51)	0.76 (0.30-1.93)	0.40
BMI ≥25†						
No. cases	33	46	34	24	18	
Person-years	36,920	50,828	42,882	31,815	11,032	
Age-adjusted HR (95% CI)‡	1.03 (0.66-1.62)	1 (reference)	0.93 (0.60-1.45)	0.96 (0.59-1.58)	2.20 (1.27-3.81)	0.04
Multivariable HR (95% CI)§	1.01 (0.65-1.58)	1 (reference)	0.93 (0.60-1.45)	0.94 (0.57-1.55)	2.09 (1.21-3.63)	0.07
Women ($P_{interaction}$ = 0.72)						
BMI <25†						
No. cases	15	47	36	29	12	
Person-years	28,597	77,761	73,598	56,962	18,374	
Age-adjusted HR (95% CI)‡	0.90 (0.50-1.61)	1 (reference)	0.85 (0.55-1.31)	0.94 (0.59-1.50)	1.32 (0.70-2.49)	0.71
Multivariable HR (95% CI)§	0.87 (0.49-1.56)	1 (reference)	0.87 (0.56-1.34)	0.98 (0.62-1.57)	1.36 (0.72-2.58)	0.56
BMI ≥25†						
No. cases	42	32	19	23	15	
Person-years	35,863	31,268	29,071	28,149	15,579	
Age-adjusted HR (95% CI)‡	1.18 (0.75-1.87)	1 (reference)	0.66 (0.37-1.16)	0.88 (0.51-1.50)	1.11 (0.60-2.05)	0.71
Multivariable HR (95% CI)§	1.15 (0.72-1.82)	1 (reference)	0.66 (0.38-1.17)	0.89 (0.52-1.52)	1.10 (0.60-2.04)	0.71

*To test for linear trend, weight change was modeled as a continuous variable. The test was restricted to those who gained or maintained weight.

†Value of BMI at baseline.

‡Age-adjusted HRs based on a stratified Cox model (year of birth: <1930, 1930-1934, 1935-1939, 1940-1944, ≥1945) using attained age as the time variable.

§Multivariable HRs are based on the age-adjusted model, additionally adjusted for level of total physical activity, height, energy intake, smoking, education, and county of residence.

did not significantly modify the effect of weight change ($P_{interaction}$ = 0.16). We found no association in either women with BMI <25 kg/m^2 or BMI ≥25 kg/m^2 ($P_{interaction}$ = 0.72).

Results before and after menopause are not presented, as only 20 cases of colon cancer occurred in premenopausal or perimenopausal women. The association between weight change and colon cancer risk was similar for follow-up <10 and ≥10 years ($P_{interaction}$ = 0.86 for men and 0.10 for women).

Analyses with change in BMI per year gave similar results to absolute weight change (results not shown), as the two weight change measures were highly correlated (Pearson correlation coefficient = 0.93).

Excluding subjects with less than 3 years of follow-up gave similar results for both BMI and weight change.

Discussion

In this prospective study, we observed positive associations between BMI and risk of colon cancer, which was somewhat stronger for men than for women. In both genders, a significant association was found in the distal colon only, although a significant difference between subsites was found in men only. In women, the association between BMI and colon cancer risk may be limited to postmenopausal women and follow-up ≥10 years. Weight change was not associated with risk of colon cancer in women. For overweight men, weight gain of ≥10 kg was associated with substantially increased risk, whereas weight loss was not associated with decreased risk.

Compared with the results on BMI and colon cancer risk in recent systematic reviews (6, 7), we have found a similar association for men and a slightly stronger association for women. Harriss et al. (7) did meta-analyses on colon subsites also. No differences between the proximal and distal colon were found [HRs per 5 kg/m^2 increase in BMI, 1.28 (95% CI, 1.18-1.39) and 1.16 (95% CI, 0.99-1.37), respectively, for men and 1.12 (95% CI, 0.97-1.37) and 1.09 (95% CI, 0.95-1.24), respectively, for women], but subsite analyses included few studies. Case-control

studies for men have mainly observed a stronger association between BMI and cancer risk in the distal than in the proximal colon (11, 30-33), although one found positive associations of similar strength for both subsites (12). In women also, case-control studies suggest a stronger association in the distal colon (11, 19, 30, 31, 33), but one study found a stronger association in the proximal colon (12).

Most studies on weight change and colon cancer risk have assessed the influence of weight change since early adulthood (19-21, 24, 34). Three recent studies have looked at weight change over shorter intervals using weight recorded prospectively, but results are inconsistent (22, 35, 36). No association between weight gain and risk of colon cancer was found in a Swedish study of men (35). In an Austrian study (22), there was no association in women, but weight loss was associated with a decreased risk in men. In both studies, weight and height were measured, and weight change was assessed over similar time intervals. The third study, also in men, found a positive trend for weight change and total colon cancer risk (36), but a positive association was found in the proximal colon only. Furthermore, weight change was associated with risk of colon cancer only among men with BMI $\leq$25 kg/m^2, also contrary to our results. This latter study did, however, differ from ours, as the participants were older (40-75 y at inclusion) and weight was self-reported. It has been reported that accuracy and degree of underreporting is related to weight and BMI (37, 38). Moreover, weight change was assessed over shorter intervals than in our study, and weight change was updated such that risk was influenced only by weight change in the prior 2 to 4 years.

Why BMI is more strongly related to colon cancer risk in men than in women is unexplained, but it may be related to hormonal factors. Some studies indicate that estrogen may modify the effect of BMI on colon or colorectal cancer risk (39-41). Contrary to our results, these studies have found a stronger association in premenopausal or estrogen-positive women than in postmenopausal or estrogen-negative women. Other studies have, however, not found the effect of BMI to be modified by use of hormone replacement therapy (HRT) in postmenopausal women (42, 43). We could not study effect modification by HRT. Of the postmenopausal women who attended screening III, the only screening where HRT use was registered, only 376 reported HRT use. We found indication of a stronger association between BMI and colon cancer risk after menopause. A possible explanation is the long induction period relating BMI to colon cancer rather than the modifying effect of estrogen. The women in our study were already middle aged or elderly when the prevalence of obesity started to rise in Norway, and the proportion that has been overweight from an early age is probably low. This may also explain why we found indication of a stronger association with BMI for follow-up $\geq$10 years. A difference between follow-up <10 and $\geq$10 years was not observed for men, but the men may have been overweight from an earlier age than the women (44).

The influence of BMI may be different in the proximal and distal colon. Two forms of genetic instability in colorectal cancer have been described: chromosomal instability and microsatellite instability (10). Sporadic microsatellite instability and chromosomal instability tumors occur mostly in the proximal and distal colon, respectively. An excess of left-sided colon cancers in high-risk compared with low-risk populations have been observed (8). Diet (45-47) seems to be more related to distal than proximal colon cancer risk. Our results agree with these observations, which support that lifestyle-related factors influence distal more than proximal colon cancer risk.

The exact biological mechanism that relates weight and weight change to colon cancer can only be hypothesized using data from epidemiologic studies but may involve insulin, insulin-like growth factors, and leptin (3, 4). Obesity is furthermore associated with a chronic inflammatory response, which is thought to promote carcinogenesis (5). We found site-specific associations, suggesting that slightly different mechanisms may be operational in the proximal and distal colon. Other studies have found similar associations in the proximal and distal colon. The prevalence of certain risk factors, such as use of HRT and nonsteroidal anti-inflammatory medication, which possibly modify the effect of BMI, was very low in our cohort. A higher prevalence of these risk factors in other studies may explain the divergent results (48).

We found no evidence that gains of <10 kg increased risk even in subjects who were initially overweight. Abdominal adiposity might be a more important risk factor than body fatness overall because central body fat is more closely related to metabolic abnormalities than peripheral body fat (49, 50), and measures of central adiposity, such as waist circumference and waist-to-hip ratio, have been associated with risk of colon cancer independently of BMI in other studies (23, 51). Hence, the distribution of fat accumulation might be of greater importance than the weight gain itself. We did not observe any decreased risk for overweight persons who lost weight. Weight loss is difficult to maintain, and we could not distinguish those who maintained their weight loss from those who did not.

Important strengths of our study are the high number of women and men recruited from the general population, the high participation rate, and follow-up done by linkage to high-quality national registries. Reporting of neoplasms to the Cancer Registry of Norway is mandatory, and the estimated completeness for 2001 to 2005 is 99.8% for the colon (52). Moreover, participants' weight and height were measured by trained nurses in a standardized manner. In addition, we have assessment of exposures up to three times. However, we have no exposure measurements since 1988, nor have we other anthropometric measures than weight and height. In addition, real interactions may be undetected because the test for interaction lacks power (53).

In conclusion, our results on BMI and colon cancer overall agree with previous studies but extend these to include weight measured three times, analyses on subsites, weight change, and differences between genders. Although the effects of BMI and weight change were not significantly modified by gender, our results indicate gender differences. For men, the association between BMI and risk of colon cancer differed significantly between the proximal and distal colon, giving support to the hypothesis that the etiology differs for subsites of the colon. Weight loss did not influence the risk of colon cancer, not even in the overweight, but overweight men who gained ≥10 kg were at increased risk. Weight change did not influence colon cancer risk in women. Future studies should examine risk by subsite. Public health recommendations on weight change and colon cancer prevention depend on further studies, preferably with participants' weight and other anthropometric measures recorded at regular intervals during the whole follow-up.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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A Prospective Study of Body Mass Index, Weight Change, and Risk of Cancer in the Proximal and Distal Colon

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