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Obesity, Weight Gain, Large Weight Changes, and Adenomatous Polyps of the Left Colon and Rectum

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Epidemiologic studies of colorectal neoplasia have usually examined body mass index as a risk factor, but not other aspects of obesity. During 1991–1993, the authors obtained weight histories and comprehensive covariate data from men and women aged 50–75 years who underwent sigmoidoscopy at a health maintenance organization in southern California. Using 483 cases with adenomas and 483 controls, measures of obesity (body mass index), positive energy balance (net weight gain in the past 10 years), and weight variability (large weight changes) were each independently related to adenoma prevalence. Compared with subjects in the lowest quartile of body mass index, multivariate-adjusted odds ratios for subjects in increasingly higher quartiles were 2.1 (95% confidence interval (CI) 1.4–2.3), 1.8 (1.1–2.9), and 1.7 (1.0–2.8), respectively. Compared with subjects who reported a net weight loss during the 10 years before sigmoidoscopy, subjects with net weight gains of 1.5–4.5 kg or ≥4.5 kg had adjusted odds ratios (95% CI) of 2.5 (1.2–5.6) and 1.8 (0.7–4.4), respectively. Compared with subjects who had no large weight changes during adulthood, subjects with 1–2, 3, or ≥4 changes had adjusted odds ratios (95% CI) of 2.0 (1.0–3.9), 2.5 (1.2–5.5), and 1.5 (0.6–3.6), respectively. Obesity, weight gain, and unstable adult weight may be independently associated with colorectal carcinogenesis. *Am J Epidemiol* 1998;147:670–80.

adenomatous polyps; body mass index; colorectal neoplasms; obesity; weight gain; weight loss

Body mass index (BMI) and its components, reported weight and height, have usually been the sole exposures examined in epidemiologic studies of the relation between obesity and colorectal neoplasia. BMI has been rather consistently associated with colon cancer in men, but not consistently with colon cancer in women or with rectal cancer in men and women (1, 2). Studies of adenomatous polyps, precancerous colorectal lesions, have usually reported positive associations between BMI and adenomatous polyps (3–10), although three small studies did not find a positive association (11–13). Evidence is insufficient to determine whether the association with adenomas differs by sex or by anatomic site. However, polyp studies have frequently found that BMI is associated mainly with polyps of large size (4, 5, 7, 9, 10).

One hypothesis about the sex difference in the association of BMI with colon cancer is that excess fat stored in the upper body, a largely masculine tendency with well-documented metabolic consequences, determines risk (1, 14). However, to our knowledge, previous studies of obesity and colorectal neoplasia have not evaluated other potentially important aspects of obesity. Weight variability has been associated with all-cause mortality, cardiovascular disease, and renal cancer (15, 16); and positive energy balance has a clear association with carcinogenicity in rodents (17, 18).

The relation between obesity and colorectal cancer is complicated by the fact that obesity is a joint result of genetics and several dynamic environmental exposures, including highly processed, energy dense diets, and minimal physical activity (19). These exposures often vary by sex and are risk factors for colorectal cancer that may act by mechanisms unrelated to body fat. Because researchers may also not measure these covariates of obesity adequately, it is not clear whether excess body fat per se increases the risk of colorectal cancer. Ironically, obesity in mostly overweight older Americans partially reflects nonsmoking status and the absence of severe alcohol/drug abuse or wasting disease (19–21). Negative confounding is therefore possible. Healthy survivor bias due to nonrecruitment of

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Abbreviation: BMI, body mass index.

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diseased, obese subjects is also possible (22). Confounding may be minimized by examining a variety of covariates. Studies of adenomatous polyps may minimize potential analytic biases resulting from cancer-induced alterations in weight, diet, or recall. In 966 sigmoidoscopy clinic outpatients, we compared adult weight histories of cases with adenomas with those of controls judged free of any kind of polyp. We examined the associations of adenomas with body mass indices over time, as well as with the magnitude and secular occurrence of weight changes, taking into account an unusual number of covariates, including several biochemical markers.

MATERIALS AND METHODS

Subjects were eligible for the study if they underwent screening by flexible sigmoidoscopy at either of two Southern California Kaiser Permanente medical centers from January 1, 1991 through August 25, 1993. Eligible men and women were 50–75 years old; were free of invasive cancer, inflammatory bowel disease, and familial polyposis; were fluent in English; had no previous bowel surgery or history of polyps; were residents of Los Angeles or Orange County; and had no physical or mental disability that precluded an interview. Subjects who had symptoms suggestive of organic intestinal disease were excluded. Cases were subjects diagnosed for the first time with one or more histologically confirmed adenomatous polyps. Controls had no adenomas or polyps of any other type discovered at sigmoidoscopy and were individually matched to cases by sex, age (within 5-year categories), date of sigmoidoscopy (within 3-month periods), and Kaiser center. The average depth of sigmoidoscopic examination was 55 cm (standard deviation (SD), 11 cm) for cases and 59 cm (SD, 5 cm) for controls. This was a case-control study of polyps with regard to the rectosigmoid region only because controls did not undergo colonoscopy.

Details of subject recruitment and data collection have been provided elsewhere (23–26). Briefly, polyp data were obtained from Kaiser pathology reports. Dietary intakes from food and supplements were assessed with a mailed, semiquantitative food frequency questionnaire (24, 27). Serum triglycerides and other blood analytes were assayed using fasting blood samples that were drawn an average of 6 months after sigmoidoscopy (24–26).

Weight, height, and weight history

Subjects were asked about their weight history, height, and about a variety of nondietary risk factors during a script-standardized, in-person interview, administered on average 5 months after sigmoidoscopy. For the weight history, an interviewer began by asking the subject's weight at age 18 years. He then asked, "Until what age did you continue to weigh between plus and minus 10 pounds of [the last weight given]?" The interviewer recorded the new weight attained. This was repeated until the subject's age/weight at sigmoidoscopy was reached. However, because subjects found it difficult to exclude weight changes <10 lbs (<4.5 kg), interviewers were instructed to record any weight change that was recalled. Subjects were asked to exclude weight changes associated with pregnancy.

Statistical analysis

Of 628 cases and 689 controls identified as eligible potential subjects, interview data were obtained from 529 cases and 563 controls. Twenty subjects with missing dietary questionnaires were dropped from the dataset; five subjects were dropped who lacked weight, height, or weight at age 18 years; and 33 cases and 66 controls were dropped because they were no longer part of a case-control pair. The resulting dataset contained 483 matched pairs.

Body mass index was used to measure body fatness at specific points in the adult weight history (28). "Current BMI" refers to BMI at sigmoidoscopy. BMI values were calculated from reported weight and height and assigned to quartiles. Quartiles of BMI and of height were defined within gender because gender differentially influences body composition (19).

As a measure of positive energy balance, or excess energy flow, over a prolonged period, net weight gained during the 5 years and 10 years prior to sigmoidoscopy was determined by subtracting the weight for 5 and 10 years previously from the weight at sigmoidoscopy. In most instances, the subject had not reported a weight for exactly 5 or 10 years before sigmoidoscopy. Weights 5 or 10 years earlier were then estimated by interpolation between the last reported weight prior to 5 or 10 years before sigmoidoscopy and the weight at sigmoidoscopy. Sixty-two percent of cases and 58 percent of controls required only minimal interpolation to estimate weight 5 years ago; 56 percent of cases and 58 percent of controls required only minimal interpolation to estimate weight 10 years ago. Minimal interpolation was defined as having a last reported body weight within 5 years before the desired weight or having stable weight (no large adult weight changes, net adult gain <4.5 kg). We assumed that interpolation from weights >5 years distant was valid for the remaining subjects because, unless they failed to report the weight changes we asked about, any weight changes they had must have

been small or occurred gradually over a long period. We did not calculate weight gained during periods prior to 10 years before sigmoidoscopy because reported weight changes were sparse between ages 25 and 40 years. However, we calculated the net weight gained between age 18 years and the date of sigmoidoscopy. We did not ask the reasons for weight changes.

Net weight gains for 5 years before and 10 years before sigmoidoscopy and as an adult (from age 18 years to sigmoidoscopy) were divided into categories determined a priori. These three variables were treated as crude measures of rates of weight gain. Median weight gain divided by time was similar in categories across the three variables. We did not define weight gain categories within sex because we expected adult weight gain in most Americans to consist primarily of body fat. Because we hypothesized that periods of negative energy balance inhibit proliferation of neoplastic cells, the reference category (Q1) for 5 and 10 years before examination consisted of subjects who had lost weight. The next category (Q2) consisted of subjects who had not had an appreciable net change in weight. The Q3 and Q4 categories consisted of subjects who had gained weight at increasingly larger rates. For the net weight gained as an adult, the reference category consisted of subjects who gained no more than 4.5 kg (10 lbs) because virtually all subjects had gained some weight since age 18 years.

As measures of weight variability, we divided the number of large weight changes (gains or losses) into categories, with the reference category consisting of subjects who reported zero changes of ≥4.5 kg (≥10 lbs). We divided into categories a second version of this variable in which all adult weight changes, including those <4.5 kg, were counted. We also formed categorical variables for the number of large weight gains (compared with no large weight gains), the number of large weight losses (compared with no large weight losses), the number of rapid large weight changes (change that occurred in ≤5 years), and the number of weight cycles (compared with no weight cycles). A weight cycle was defined as each occurrence, ≤5 years apart, of a large gain followed by a large loss (or vice versa).

Conditional logistic regression (n = 483 pairs) was used to estimate matched odds ratios (29). As a test for trend in effect across categories, we used the two-sided p value associated with a coefficient fitted to the ordinal value of the category.

RESULTS

This largely urban study population consisted of 162 female case-control pairs and 321 male pairs; 54 percent of all subjects were white, 19 percent Latino, 16 percent black, and 11 percent Asian/Pacific Islanders. Ethnicity did not vary appreciably between cases and controls (data not shown). Results obtained from cases and controls for major covariates have been presented elsewhere (23, 25, 26, 30).

Table 1 shows means and ranges of body size and weight history variables. Also, the median (range) for the number of weight cycles was zero (0–11); for the number of rapid weight changes, zero (0–11); and for the number of large weight losses, zero (0–6). This did not differ by sex or polyp status (data not shown) other than slight variations in ranges. There were no clear differences in mean BMI or in the means/medians of other weight history variables in cases compared with controls. However, using a BMI of 25 as the cut-off (19, 31), about 75 percent of all subjects were overweight or obese. Most had gained substantial weight from age 18 years to mean age 62 years. When subjects in the upper three quartiles of BMI were compared with those in the lowest quartile, an association of current BMI with adenoma risk appeared (table 2). BMIs at 5 and 10 years before sigmoidoscopy were not associated with adenoma risk as strongly or consistently as was the current BMI, and all three BMIs were highly correlated (in controls, for current BMI and 10 years previously: Pearson r = 0.89, p = 0.0001). We retained only current BMI in further analyses. Neither height nor BMI at age 18 years was associated with adenomas.

In control subjects, the BMI and weight history variables were nearly all associated with each other (table 3) and with previously identified risk factors for colorectal polyps. Current BMI was only moderately associated with BMI at age 18 years (Spearman r = 0.35, p = 0.0001), but current BMI was strongly associated with total weight gained during adulthood (Spearman r = 0.68, p = 0.0001). Current BMI was also more consistently and more strongly associated with several dietary variables, exercise, and with blood nutrient concentrations than were the weight history variables (not shown). For example, the Spearman correlation between BMI and the whole blood ascorbate concentration was −0.17 (p = 0.001, n = 383 controls), whereas it was zero for other weight history variables versus ascorbate.

In univariate models adjusted for matching variables (table 4), weight gain during the 10 years before sigmoidoscopy was positively associated with adenomas (referent group: subjects who lost weight). Polyp risk was less consistently associated with weight gain during the 5 years before sigmoidoscopy. A very weak polyp risk may have been associated with one, but not more than one, large weight loss (table 4). For this

TABLE 1. **Means and ranges of variables describing body habitus at or preceding the sigmoidoscopic examination of Kaiser Permanente outpatients, Los Angeles, California, 1991–1993***

Variable	Females		Males	
	Cases (n = 162)	Controls (n = 162)	Cases (n = 321)	Controls (n = 321)
Body mass index (kg/m²) at sigmoidoscopy				
Mean	27.6	27.0	27.4	27.0
Range	18.3–43.4	16.6–44.7	15.9–51.0	19.6–43.7
Weight (kg) at sigmoidoscopy				
Mean	72	71	85	83
Range	42–123	39–127	53–166	52–132
Height (m)				
Mean	1.61	1.62	1.75	1.75
Range	1.42–1.80	1.45–1.83	1.55–1.93	1.52–1.98
Weight (kg) at age 18 years				
Mean	54	55	68	67
Range	34–91	39–82	40–127	36–136
No. of large weight changes†				
Median	2	2	2	2
Range	0–13	0–12	0–12	0–13
Net weight gain (kg) over last 5 years‡				
Mean	2.1	1.7	1.6	1.3
Range	−22 to 20	−18 to 33	−14 to 22	−15 to 22
Net weight gain (kg) over last 10 years§				
Mean	4.3	3.8	3.2	2.6
Range	−11 to 34	−25 to 55	−38 to 34	−21 to 28
Net weight gain (kg) as an adult¶				
Mean	18	16	17	16
Range	−16 to 50	−9 to 59	−34 to 82	−32 to 69

* Values are mean (range) for n = 966 subjects (i.e., 483 case-control pairs) unless otherwise stated. Using the paired t test to compare cases and controls within gender, there were no significant differences ($p < 0.10$) for any of the variables shown.

† Median number of weight changes of ≥4.5 kg (≥10 lbs) reported for the period between age 18 years and the date of sigmoidoscopy, excluding weight changes associated with pregnancy.

‡ Reported weight (kg) at sigmoidoscopy minus weight 5 years previously, with the latter reported by the subject or interpolated from the weights in the weight history that preceded and followed the point 5 years before examination. Because a value for one subject could not be interpolated due to a weight change of unknown magnitude, he was treated as missing; thus, total n = 965.

§ Reported weight (kg) at sigmoidoscopy minus weight 10 years previously, with the latter reported by the subject or interpolated as in the previous footnote. Because values for two subjects could not be interpolated due to weight changes of unknown magnitude, they were treated as missing; thus, total n = 964.

¶ Reported weight (kg) at sigmoidoscopy minus reported weight at age 18 years (no interpolations required).

reason, we investigated the possibility that a single large weight loss might have occurred in some subjects shortly before sigmoidoscopy. We included in multivariate analyses (see below) a dichotomous variable: whether or not there was a large weight loss ≤5 years before sigmoidoscopy. Net weight gain during adulthood was weakly associated with polyp risk. Subjects who reported one or more large weight changes were more likely to have an adenoma than subjects who had never had a large weight change (gain or loss), whereas there was no risk associated with such small weight changes as were reported (latter not shown). Odds ratios for the number of large weight gains (not shown) compared with zero large weight gains were very similar to those obtained for the number of large weight changes compared with zero large weight changes, and the two variables were highly correlated (Spearman $r = 0.93$, $p = 0.0001$, in controls). However, the number of large weight changes was also determined by the number of large weight losses (Spearman $r = 0.48$, $p = 0.0001$, in controls), possibly because of weight cycling (Spearman $r = 0.51$, $p = 0.0001$, for number of large weight changes vs. weight cycles in controls; $r = 0.78$, $p = 0.0001$ for number of large weight changes vs. rapid large weight changes). We pursued only the number of large weight changes, not gains, in further analyses. The numbers of rapid weight changes (table 4) and weight cycles (not shown) were not clearly associated with polyps.

TABLE 2. Odds ratios (OR) and 95 percent confidence intervals (CI) for the association of quartiles of body mass index (BMI) (kg/m²) and height with colorectal polyps, Los Angeles, California, 1991–1993 (n = 966)*

Variable	Quartile of BMI				p trend
	Q1	Q2	Q3	Q4	
BMI at exam†					
Adjusted OR	1.0	1.8	1.8	1.6	0.02
95% CI		1.2–2.5	1.3–2.6	1.1–2.2	
BMI 5 years before‡					
Adjusted OR	1.0	1.4	1.6	1.3	0.10
95% CI		1.0–2.0	1.1–2.3	0.9–1.9	
BMI 10 years before§					
Adjusted OR	1.0	1.1	1.5	1.3	0.06
95% CI		0.8–1.6	1.1–2.2	0.9–1.8	
BMI at age 18 years¶					
Adjusted OR	1.0	0.9	1.1	1.1	0.45
95% CI		0.6–1.3	0.8–1.6	0.8–1.6	
Height#					
Adjusted OR	1.0	1.0	0.8	1.0	0.91
95% CI		0.7–1.5	0.6–1.2	0.7–1.4	

* Conditional logistic regression models fitted to quartiles of BMI or height that were defined within gender using all 966 subjects (i.e., 483 case-control pairs). All models adjusted for the following matching variables: sex, age (within 5-year categories), date of sigmoidoscopy (within 3-month categories), and Kaiser center.

† Quartiles for BMI at sigmoidoscopy were: for women, Q1 = 16.6 to <23.461, Q2 = 23.461 to <26.51, Q3 = 26.51 to <30.2, Q4 = 30.2 to 44.7; for men, Q1 = 15.9 to <24.41, Q2 = 24.41 to <26.63 to 29.2, Q4 = 29.2 to 51.0.

‡ Quartiles for BMI 5 years before sigmoidoscopy were: for women, Q1 = 16.3 to <23.828, Q2 = 23.928 to <26.111, Q3 = 26.111 to <28.97, Q4 = 28.97 to 45.9; for men, Q1 = 16.5 to <24.14, Q2 = 24.14 to <26.21, Q3 = 26.21 to <28.792, Q4 = 28.792 to 52.8. One subject with a missing BMI was assigned to Q2.

§ Quartiles for BMI 10 years before sigmoidoscopy were: for women, Q1 = 17.0 to <22.68, Q2 = 22.68 to <25.15, Q3 = 25.15 to <28.1; Q4 = 28.1 to 47.6; for men, Q1 = 18.5 to <23.82, Q2 = 23.82 to <25.782, Q3 = 25.782 to <28.04, Q4 =28.04 to 41.1. Two subjects with missing data were assigned to Q2.

¶ Quartiles for BMI at age 18 years were: for women, Q1 = 13.7 to <18.7, Q2 = 18.7 to <20.55, Q3 = 20.55 to <22.5, Q4 = 22.5 to 36.7; for men, Q1 = 12.4 to <19.56, Q2 = 19.56 to <21.45, Q3 = 21.45 to <23.67, Q4 = 23.67 to 43.1.

Quartiles for height (m) were: for women, Q1 = 1.42 to <1.57, Q2 = 1.57 to <1.60, Q3 = 1.60 to <1.68, Q4 = 1.68 to 1.83; for men, Q1 = 1.52 to <1.70, Q2 = 1.70 to <1.75, Q3 = 1.75 to <1.80, Q4 = 1.80 to 1.98.

TABLE 3. Spearman correlation coefficients for body mass index (BMI) (kg/m²) and weight history variables in controls, Los Angeles, California, 1991–1993 (n = 483)*

	BMI	BMI18†	#LWC†	WG10†,‡	WG5†,‡	#WL†	#RWC†	#WCyc†	AdWG†
BMI	–	0.35	0.50	0.52	0.49	–0.01^{NS}	0.39	0.15	0.68
BMI18	–	–	–0.04^{NS}†	–0.11	–0.03^{NS}	0.23	0.02^{NS}	0.19	–0.35
#LWC	–	–	–	0.28	0.21	0.48	0.78	0.51	0.54
WG10‡	–	–	–	–	0.82	–0.23	0.13	–0.11	0.60
WG5‡	–	–	–	–	–	–0.24	0.11	–0.09	0.50
#WL	–	–	–	–	–	–	0.45	0.78	–0.18
#RWC	–	–	–	–	–	–	–	0.56	0.38
#WCyc	–	–	–	–	–	–	–	–	–0.01^{NS}
AdWG	–	–	–	–	–	–	–	–	–
#WG	0.58	–0.13	0.93	0.40	0.34	0.17	0.70	0.31	0.69

* For all correlations, $p < 0.05$ unless otherwise indicated.

† BMI18, BMI at age 18 years; #LWC, no. of large weight changes (≥4.5 kg); WG10, net weight gain during the 10 years before sigmoidoscopy; WG5, net weight gain during the 5 years before sigmoidoscopy; #WL, no. of large weight losses during adulthood; #RWC, no. of rapid weight changes (≥4.5 kg); #WCyc, no. of weight cycles; AdWG, net weight gain during adulthood; #WG, no. of large weight gains (≥4.5 kg); NS, not significant.

‡ For WG10 and WG5, n = 482.

Adjusting the univariate models for BMI eliminated the weak association of polyp risk with net weight gain during adulthood (table 4). However, BMI adjustment of the other weight gain and weight change variables either did not appreciably change results or caused appreciable but incomplete attenuation that appeared to be easily explainable. The attenuation proved to be more than reversible after further adjustment for either smoking (number of large weight changes) or for having had a large weight loss ≤5 years before sig-

TABLE 4. Univariate odds ratios (OR) and 95 percent confidence intervals (CI) for the association of categories of weight changes during adulthood and the prevalence of colorectal polyps, Los Angeles, California, 1991–1993 (n = 966)*

Variable	Quartile				p trend
	Q1	Q2	Q3	Q4	
Net weight gain vs. weight loss over last 5 years†					
Model 1					
OR	1.0	1.2	0.9	1.5	0.12
95% CI		0.8–1.9	0.6–1.4	1.0–2.4	
Model 2					
OR	1.0	1.1	0.7	1.3	0.66
95% CI		0.7–1.8	0.4–1.2	0.8–2.1	
Net weight gain vs. weight loss over last 10 years†					
Model 1					
OR	1.0	1.3	1.5	1.7	0.03
95% CI		0.8–2.2	0.9–2.5	1.1–2.9	
Model 2					
OR	1.0	1.3	1.2	1.4	0.29
95% CI		0.7–2.1	0.7–2.1	0.8–2.4	
Net weight gain as an adult‡					
Model 1					
OR	1.0	1.2	1.4	1.4	0.07
95% CI		0.8–1.7	1.0–2.1	0.9–2.1	
Model 2					
OR	1.0	1.0	1.1	1.1	0.59
95% CI		0.7–1.5	0.7–1.7	0.7–1.8	
No. of large weight changes (±≥4.5 kg)§					
Model 1					
OR	1.0	1.8	1.9	1.8	0.18
95% CI		1.0–3.0	1.1–3.4	1.1–3.1	
Model 2					
OR	1.0	1.6	1.6	1.4	0.79
95% CI		0.9–2.8	0.9–2.9	0.8–2.6	
No. of large weight losses (≥4.5 kg) as an adult¶					
Model 1					
OR	1.0	1.3	1.0		0.64
95% CI		0.9–1.8	0.6–1.4		
Model 2					
OR	1.0	1.4	1.0		0.39
95% CI		1.0–1.9	0.7–1.5		
No. of rapid large weight changes#					
Model 1					
OR	1.0	0.8	1.2	1.1	0.34
95% CI		0.6–1.2	0.8–1.8	0.8–1.7	
Model 2					
OR	1.0	0.8	1.1	1.0	0.71
95% CI		0.6–1.1	0.7–1.7	0.7–1.5	

* Conditional logistic regression models fitted to categories of weight change variables that were defined using all 966 subjects (i.e., 483 case-control pairs). Models 1 and 2 adjusted for the matching variables: sex, age (within 5-year categories), date of sigmoidoscopy (within 3-month categories), and Kaiser center. Model 2 was also adjusted for body mass index (BMI) (kg/m²).

† Categories of net weight gained (kg) during the 5 years before sigmoidoscopy were: Q1 = −21.8 to −0.7, Q2 = >−0.7 to 0.7, Q3 = >0.7 to 2.3, Q4 = >2.3 to 33.3. One subject with missing data was assigned to Q2. Categories for net weight gained (kg) during the 10 years before sigmoidoscopy were: Q1 = −38.1 to −1.4, Q2 = >−1.4 to 1.4, Q3 = >1.4 to 4.5, Q4 = >4.5 to 54.6. Two subjects with missing data were assigned to Q2. Categories were defined to yield rates of weight change that were roughly comparable for both the 5- and 10-year periods before sigmoidoscopy. The reference category Q1 comprised subjects who lost weight during the period in question.

‡ Categories of the net total weight gained (kg) from age 18 years to the date of sigmoidoscopy were: Q1 = −34.1 to 4.5, Q2 = >4.5 to 13.6, Q3 = >13.6 to 22.7, Q4 = >22.7 to 81.8. Using the mean no. of years elapsed from age 18 years to sigmoidoscopy for all subjects, categories were defined to yield rates of weight gain roughly comparable to those defined for weight gained during the 5 and 10 years before sigmoidoscopy. However, the reference category included subjects with small net weight gains up to 4.5 kg because subjects rarely had a net weight loss during adulthood.

§ Categories of the number of large weight changes of ≥4.5 kg during adulthood (18 years to date of sigmoidoscopy) were: Q1 = 0 changes, Q2 = 1–2 changes, Q3 = 3 changes, Q4 = ≥4 changes.

¶ Categories of the no. of large weight losses of ≥4.5 kg during adulthood were: Q1 = 0 changes, Q2 = 1 loss, Q3 = ≥2 losses.

\# Categories of the no. of rapid weight changes (gain or loss of ≥4.5 kg that occurred over a time span of ≤5 years) were: Q1 = 0, Q2 = 1, Q3 = 2, Q4 = ≥3 changes.

moidoscopy (amount of weight gain over the last 5 years, 10 years) (table 5). The attenuation of the 10-year weight gain results was also reversible simply by adjusting it for the 5-year gain. Because smokers who quit smoking usually have a single large weight change (gain) shortly after quitting, the low polyp risk of ex-smokers (23) may have biased toward the null the positive association of polyps with the number of

TABLE 5. Multivariate adjusted odds ratios (OR) and 95 percent confidence intervals (CI) for the categories of body size and weight history variables that may have been independently associated with colorectal polyps in the Kaiser Permanente sigmoidoscopy population, Los Angeles, California, 1991–1993 (n = 966)*

Variable	Quartile				p trend
	Q1	Q2	Q3	Q4	
BMI at exam†					
OR	1.0	2.1	1.8	1.7	0.13
95% CI		1.4–2.3	1.1–2.9	1.0–2.8	
Net weight gain vs. weight loss over last 10 years‡					
OR	1.0	1.1	2.5	1.8	0.09
95% CI		0.5–2.6	1.1–5.6	0.7–4.4	
No. of large weight changes (±≥4.5 kg)§					
OR	1.0	2.0	2.5	1.5	0.86
95% CI		1.0–3.9	1.2–5.5	0.6–3.6	
No. of rapid large weight changes¶					
OR	1.0	0.6	1.0	0.9	0.99
95% CI		0.4–0.9	0.6–1.8	0.5–1.7	
Large weight loss ≤5 years before exam#					
OR	1.0	3.2			–
95% CI		1.8–5.8			
Net weight gain vs. weight loss over last 5 years**					
OR	1.0	2.5	0.8	1.9	0.98
95% CI		1.0–5.9	0.3–1.8	0.8–4.9	

* Conditional logistic regression models fitted to categories of body mass index (BMI) (kg/m²) and weight history variables for n = 966 subjects (i.e., 483 case-control pairs). All models adjusted for the matching variables (see table 2), the BMI/weight history variables listed above, and these covariates: smoking (present, past, never smoker), race, regular use of nonsteroidal anti-inflammatory drugs (yes/no), vigorous leisure-time exercise ≥3 times per week (yes/no), caloric intake, and dietary fiber.

† Quartiles for BMI at sigmoidoscopy were: for women, Q1 = 16.6 to <23.461, Q2 = 23.461 to <26.51, Q3 = 26.51 to <30.2, Q4 = 30.2 to 44.7; for men, Q1 = 15.9 to <24.41, Q2 = 24.41 to <26.63 to 29.2, Q4 = 29.2 to 51.0.

‡ Categories for net weight gained (kg) during the 10 years before sigmoidoscopy were: Q1 = −38.1 to −1.4, Q3 = >−1.4 to 1.4, Q3 = >1.4 to 4.5, Q4 = >4.5 to 54.6. Two subjects with missing data were assigned to Q2. The reference category Q1 comprised subjects who lost weight during the period in question.

§ Categories of the number of large weight changes of ≥4.5 kg during adulthood (18 years to date of sigmoidoscopy) were: Q1 = 0 changes, Q2 = 1–2 changes, Q3 = 3 changes, Q4 = ≥4 changes.

¶ Categories of the number of rapid weight changes (gain or loss of ≥4.5 kg that occurred over a time span of ≤5 years) were: Q1 = 0, Q2 = 1, Q3 = 2, Q4 = ≥3 changes.

Dichotomous variable, where Q2 = subjects who had at least one large weight loss (≥4.5 kg) that ended during the period ≤5 years before sigmoidoscopy. Q1 = subjects who did not.

** Categories of net weight gained (kg) during the 5 years before sigmoidoscopy were: Q1 = −21.8 to −0.7, Q2 = >−0.7 to 0.7, Q3 = >0.7 to 2.3, Q4 = >2.3 to 33.3. One subject with missing data was assigned to Q2. Categories for net weight gained (kg) during the 10 years before sigmoidoscopy were: Q1 = −38.1 to −1.4, Q2 = >−1.4 to 1.4, Q3 = >1.4 to 4.5, Q4 = >4.5 to 54.6. Two subjects with missing data were assigned to Q2. Categories were defined to yield rates of weight change that were roughly comparable for both the 5- and 10-year periods before sigmoidoscopy. The reference category Q1 comprised subjects who lost weight during the period in question.

large weight changes. Polyp risk was associated with having had a large weight loss ≤5 years before sigmoidoscopy (table 5); this must therefore have biased the polyp-weight gain associations (for the 5 or 10 years before examination) toward the null.

As seen, current BMI was a relatively strong predictor of diet, blood nutrients, exercise, and weight history variables. Nevertheless, in multivariate analyses, net weight gain during the past 10 years, the number of large weight changes during adulthood, and current BMI were clearly associated with adenoma risk independently of each other (table 5). Adjusting the number of large weight changes for smoking and adjusting the 10-year weight gain for either the 5-year gain or for pre-examination weight loss strengthened the results for these variables; the other weight variables and covariates in the model are presented because they are of interest, but did not substantively alter the results. BMI, 10-year gain, and large weight changes were also more strongly associated with large polyps (≥1 cm) than with small polyps (table 6), although confidence intervals were wide for the num-

TABLE 6. Multivariate adjusted odds ratios (OR) and 95 percent confidence intervals (CI) for the categories of body size and weight history variables when stratified according to the size of the largest adenomatous polyp, Los Angeles, California, 1991–1993*

Variable	Quartile				p trend
	Q1	Q2	Q3	Q4	
BMI at exam†					
Large polyps (n = 139 cases)					
OR	1.0	2.9	2.1	2.5	0.04
95% CI		1.2–6.7	0.9–4.6	1.1–5.4	
Small polyps (n = 339 cases)					
OR	1.0	1.6	1.8	1.6	0.09
95% CI		1.0–2.6	1.1–2.9	0.9–2.6	
Net weight gain vs. weight loss over last 10 years‡					
Large polyps (n = 139 cases)					
OR	1.0	2.0	2.0	2.9	0.14
95% CI		0.6–7.4	0.6–6.7	0.8–10.3	
Small polyps (n = 339 cases)					
OR	1.0	1.2	1.4	1.5	0.15
95% CI		0.6–2.3	0.7–2.7	0.8–2.9	
No. of large weight changes (=≥4.5 kg)§					
Large polyps (n = 139 cases)					
OR	1.0	7.0	8.3	4.4	0.70
95% CI		1.7–29.3	2.0–34.9	1.1–18.5	
Small polyps (n = 339 cases)					
OR	1.0	1.2	1.4	1.6	0.12
95% CI		0.6–2.4	0.7–3.1	0.8–3.3	

* Conditional logistic regression models fitted to categories of body mass index (BMI) (kg/m²) or weight history variables and stratified on polyp diameter (large polyp = ≥1 cm) for 478 case-control pairs; 5 pairs excluded due to missing data on polyp size. All models adjusted for the matching variables (see table 2) and these covariates: smoking (present, past, never smoker), race, regular use of nonsteroidal anti-inflammatory drugs (yes/no), vigorous leisure-time exercise ≥3 times per week (yes/no), caloric intake, and dietary fiber.

† Quartiles for BMI at sigmoidoscopy: for women, Q1 = 16.6 to <23.461, Q2 = 23.461 to <26.51, Q3 = 26.5 to <30.2, Q4 = 30.2 to 44.7; for men, Q1 = 15.9 to <24.41, Q2 = 24.41 to <26.63, Q3 = 26.63 to <29.2, Q4 = 29.2 to 51.0.

‡ Categories for net weight gained (kg) during the 10 years before sigmoidoscopy were: Q1 = −38.1 to −1.4, Q2 = >−1.4 to 1.4, Q3 = >1.4 to 4.5, Q4 = >4.5 to 54.6. Two subjects with missing data were assigned to Q2. The reference category Q1 comprised subjects who lost weight during the period in question.

§ Categories of the number of large weight changes of ≥4.5 kg during adulthood (18 years to date of sigmoidoscopy) were: Q1 = 0 changes, Q2 = 1–2 changes, Q3 = 3 changes, Q4 = ≥4 changes.

ber of large weight changes, because of a relatively small sample in the referent category of zero changes. Results did not clearly differ when stratified according to the location (rectal, left colon) of the subject's largest polyp (not shown). Including the following variables in at least some multivariate models did not appreciably change the results: family history of colorectal cancer, smoking dose (pack-years), education, the number of meals or snacks eaten per day, serum triglycerides, serum high density lipoprotein, red cell folate, whole blood ascorbate, plasma β-carotene, plasma ferritin, the plasma α- to γ-tocopherol ratio (a measure of α-tocopherol status), and intakes of saturated fat, red meat, ethanol, iron, or total daily servings of fruits and vegetables. Stratifying on whether subjects did (n = 208) or did not report changing diet after sigmoidoscopy did not appreciably affect results.

The variables shown in the last three lines in table 5 were not associated with polyps in a hypothesized manner. Clearly, the number of rapid, large weight changes was not positively associated with polyps. Although not included in table 5, the number of weight cycles, as defined in this study, was another measure of weight variability and was not associated with adenomas. Polyp risk was strongly associated with having at least one large weight loss if it occurred ≤5

years before examination (table 5). However, when we stratified this variable on polyp size, weight loss ≤5 years before examination was primarily a risk factor for small polyps <1 cm (odds ratio (OR) = 3.5, 95 percent confidence interval (CI) 1.7–7.1), especially small polyps in men (odds ratio (OR) = 7.3, 95 percent CI 7.3, 2.7–19.5). With regard to the 5-year weight gain (table 5, last line), the association with polyp risk was inconsistent. However, large weight losses ≤5 years before sigmoidoscopy appeared to exert negative confounding on the 5-year weight gain variable: 5-year weight gain was more strongly associated with polyps in the multivariate compared with the univariate model (table 5 vs. table 4) because of adjustment for pre-examination weight loss. Apparently, the reference group contained both low risk subjects who lost weight gradually and high risk subjects who had a large weight loss episode.

DISCUSSION

Current body mass index, the net amount of weight gained during the 10 years before sigmoidoscopy, and the number of large weight changes during adulthood were the three obesity-related variables clearly and independently associated with colorectal adenomas in this study. After multivariate adjustment, subjects in the upper three quartiles of BMI were about twice as likely to have a colorectal adenoma as those in the lowest quartile. In the same model, subjects who gained weight (Q3, Q4) during the 10 years before sigmoidoscopy were roughly twice as likely to have an adenoma as those who lost weight or maintained weight. Finally, subjects who had one or more large weight changes during adulthood were about twice as likely to have polyps as those who never had a large weight change. All three variables appeared to be associated more strongly with large adenomas than with small ones, suggesting that these variables may be indicators of cancer promotion activity.

In sedentary populations, differences in BMI primarily reflect differential accumulation of body fat (19). Excess visceral fat, in particular, appears to cause changes in hepatic function and associated blood indicators that may be carcinogenic. One such potentially carcinogenic metabolic change is hyperinsulinemia (1). Another is hypertriglyceridemia, which has been associated with adenomas in this and other studies (14, 26). Though we presently lack data on adipose distribution or insulin exposure, adjusting BMI for serum triglyceride concentration did not alter BMI odds ratios. Also, the BMI association with polyps did not appear to be stronger in men than in women, although men tend to carry adipose centrally. Our study population was unusually ethnically diverse. Because the distribution and effects of body fat may be genetically influenced (19, 32, 33), we will assess potential effect modification by sex and race when we have accrued more subjects.

The association of adenomas with weight gain during the 10 years before sigmoidoscopy may indicate that a sustained positive energy balance was present and carcinogenic. Positive energy balance has long been associated with cancer in animal experiments, although the mechanisms are undetermined (17, 18). In humans, sustained excessive intakes of certain nutrients are associated with high caloric intakes and may possibly promote carcinogenesis, e.g., fat (17). Although we adjusted for several dietary factors, accurate measurement of diet is always difficult and residual confounding by specific dietary factors cannot be ruled out. A positive energy balance "effect" could also be mediated by surges in serum insulin, serum lipids, or other acute postprandial changes triggered by overconsumption (1, 14).

The numbers of weight changes, rapid weight changes, and weight cycles (as defined in this study) were examined as potential obesity-related risk factors for colorectal polyps because repeated episodes of weight loss followed by weight gain have been associated with all-cause mortality and renal cancer in humans (15–16), as well as with increasing hyperinsulinemia in a longterm study of rats (34). Most epidemiologic studies of weight cycling have not asked subjects the reasons for their weight changes, leaving it questionable whether weight changes were due to intentional dieting and rebound weight gain (15). Unfortunately, "intentionality" data were also not collected in the present study. However, the data that were collected were unusually extensive. The results show that a history of large weight changes was associated with an increased risk of colorectal polyps. However, there was little support for the hypothesis that polyp risk is increased by repeated episodes of weight cycling, whether intentional or not. We found that polyp risk did not increase with additional numbers of weight changes. Also, the number of weight cycles was not positively associated with polyps risk, nor were rapid weight gains associated with risk. It is more accurate to say that subjects who had never had a large weight gain or loss were at lower risk than those who had.

Only the number of large weight changes (≥4.5 kg), not small ones, predicted polyp risk. This was despite the fact that some subjects appeared extraordinarily weight conscious, recalling numerous small weight changes throughout adulthood. The number of large weight losses during adulthood was not associated with risk. Therefore, illnesses typified by repeated

episodes of weight loss over time do not appear to explain the association of large weight changes with polyp risk in these data.

It is plausible that a history of large weight changes reflects some cancer-promoting aspect of obesity acting in parallel to BMI. We found that such obesity-related blood indicators as plasma C-peptide (preliminary data) and serum triglycerides were correlated with current BMI even among subjects with a low BMI (<25: data not shown). In addition, animals on the same experimental high fat diet will all gain weight over time, but some will become considerably more obese than others (35). A history of large weight changes may identify a carcinogenic risk due to high fat diets, sedentary life-styles, or other poorly measured life-style factors in some subjects who are genetically resistant to obesity.

The association of small adenomas with large weight losses occurring ≤5 years before sigmoidoscopy was unexpected. Chronic disease is one explanation for the reduced prevalence of overweight in men beginning at age 55 years; the prevalence of overweight in women is not reduced until age 75 years (36). Because recent large weight losses were largely confined to male subjects and because small polyps are unlikely to have caused weight loss, we can only speculate that some chronic disease-associated factor may act as an initiator of adenomas. Adjusting for a large weight loss ≤5 years before sigmoidoscopy did not appreciably alter the results for BMI, large weight changes, or 10-year weight gain. (After multivariate adjustment that included the 5-year weight gain, the 10-year weight gain actually represented weight gain during the 5–10 years before sigmoidoscopy.) Because large weight loss episodes appeared to negatively confound any association of weight gain with polyps during the period immediately before sigmoidoscopy, weight gain may have increased polyp risk or size during the entire 10 years before sigmoidoscopy.

To our knowledge, this is the first study to evaluate the relations, concurrently, between colorectal polyps, BMI, periods of weight gain, and several measures of weight variability. We were also able to adjust for a variety of potential confounders, including several biochemical indicators. In contrast to subjects in many polyp studies, many of our subjects had sigmoidoscopies as part of the routine screening encouraged at Kaiser-Permanente and were asymptomatic (23).

Still, the study had some potential limitations. We studied polyps of the distal colon and rectum only. This does not invalidate the results (24, 26), but results may not be generalizable to proximal neoplasia if etiology differs by polyp location. Data were usually collected several months after sigmoidoscopy. However, results did not differ according to whether subjects reported changing diet after examination, nor have we found evidence of changing blood analyte concentrations over time (25). We cannot be certain whether large weight changes reported by subjects were due to conscious efforts to control body weight, due to life-style changes, or to illness (15). However, we have used a variety of data to identify explanations that appear more or less likely than others. Cross-comparison of the results obtained from different weight history variables is important because results may vary considerably when using different individual variables (36). Because BMI and weight history variables were correlated with each other and possibly measured with error (e.g., recall), spurious findings and residual confounding are possible. Finally, the observed associations may have been attenuated by a kind of healthy survivor bias (22), particularly at high levels of obesity. Many of the Kaiser insurees who were most obese may have been dead or too ill to attend the outpatient clinics from which subjects were recruited. People remaining in the highest quartile of BMI may have had life-style or genetic traits that made them less susceptible to cancer.

In summary, three obesity-related variables were independently associated with colorectal adenomas in this study, BMI, weight gain during the previous 10 years, and a history of large weight changes. Careful comparison of results obtained from several measures of weight variability suggested that a history of even one large weight change may indicate the presence of cancer-promoting metabolic factors or diet/life-style characteristics that are not reflected adequately by changes in body mass index. Rather than concluding that repeated weight cycling increases risk, it may be more accurate to say that life-style factors that happen to facilitate stable weight maintenance are protective.

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