American Journal of Epidemiology

Vol. 152, No. 9
Printed in U.S.A.

Body Mass Index and Colon Cancer Mortality in a Large Prospective Study

Terrell K. Murphy, Eugenia E. Calle, Carmen Rodriguez, Henry S. Kahn, and Michael J. Thun

Obesity has been reported to increase the risk of colon cancer, especially in men. The authors examined this relation in the American Cancer Society's Cancer Prevention Study II, a nationwide mortality study of US adults. After 12 years of follow-up, 1,616 deaths from colon cancer in women and 1,792 in men were observed among 496,239 women and 379,167 men who were cancer free at enrollment in 1982. The authors used Cox proportional hazards analyses to control for effects of age, race, education, smoking, exercise, alcohol, parental history of colon cancer, fat intake, vegetable and grain intake, aspirin use and, in women, estrogen replacement therapy. In men, death rates from colon cancer increased across the entire range of body mass index (BMI). The rate ratio was highest for men with BMI ≥32.5 (rate ratio (RR) = 1.90, 95% confidence interval (CI): 1.46, 2.47) compared with men with BMI between 22.00 and 23.49. In women, a weaker association was seen in the three BMI categories of 27.5–29.9 (RR = 1.26, 95% CI: 1.03, 1.53), 30.0–32.4 (RR = 1.37, 95% CI: 1.09, 1.72), and ≥32.5 (RR = 1.23, 95% CI: 0.96, 1.59). These prospective data support the hypothesis that obesity increases the risk of colon cancer death and that the relation is stronger and more linear in men than in women. *Am J Epidemiol* 2000;152:847–54.

body mass index; cohort studies; colonic neoplasms; obesity

Colon cancer is the third leading cause of cancer mortality in the United States in both men and women (1). Evidence that factors that increase the risk of colon cancer are more common to Westernized cultures comes from international comparisons, from temporal increases in colon cancer within countries coincident with industrialization, and from observations of rate increases in populations as they migrate from low- to high-risk regions (2, 3). Nutritional factors, obesity, and physical activity have been the primary focus of etiologic research.

Several epidemiologic studies have examined the association between obesity, measured by body mass index (weight (kg)/height $(m)^2$) (BMI), and colon cancer risk. Results from these case-control and cohort studies in men consistently indicate positive associations (4–21), whereas results of studies in women suggest either no association or weak positive associations (4, 8, 10, 12, 14, 16–26). At present, there is no clear explanation for these apparent gender-related differences.

In this study we extended follow-up of a large prospective American Cancer Society study of US adults (18) and further examined the association between BMI and colon cancer mortality in both men and women. We also investigated whether other established colon cancer risk factors modify this association in men or women.

MATERIALS AND METHODS

Men and women for this study were selected from the 1,184,659 participants of Cancer Prevention Study II, a prospective mortality study of American men and women begun by the American Cancer Society in 1982 (27, 28). Participants were friends and acquaintances of over 77,000 American Cancer Society volunteers in all 50 states, the District of Columbia, and Puerto Rico. To be eligible for enrollment through this volunteer network, individuals had to be 30 years of age or older and to reside in a household in which at least one person was 45 years of age or older. The median age at cohort entry in 1982 was 57 years for men and 56 years for women. Participants completed a confidential self-administered questionnaire in 1982 that included personal identifiers; demographic characteristics; personal and family history of cancer and other diseases; and various behavioral, occupational, environmental, and dietary exposures.

During the first 6 years of follow-up, the vital status of the participants was ascertained every 2 years through personal inquiries by the volunteers who enrolled the study participants. Since 1988, automated linkage using the National Death Index was used to extend follow-up through December 31, 1994, and to identify deaths among 21,704 (1.8 percent) individuals lost to follow-up between 1982 and 1988 (29). At completion of mortality follow-up in December 1994, 988,145 participants (83.4 percent) were still living, 193,622 (16.3 percent) had died, and 2,892 (0.2

Received for publication June 24, 1999, and accepted for publication February 4, 2000.

Abbreviations: BMI, body mass index; CI, confidence interval; RR, rate ratio.

From the Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA.

Reprint requests to Dr. Eugenia E. Calle, Department of Epidemiology and Surveillance Research, American Cancer Society, 1599 Clifton Road, N.E., Atlanta, GA 30329-4251 (e-mail: jcalle@cancer.org).

percent) had follow-up truncated on September 1, 1988, because of insufficient data for the National Death Index linkage. Death certificates or multiple cause of death codes were obtained for 98.3 percent of all participants known to have died.

Colon cancer deaths were defined as those individuals who died through December 31, 1994, with colon cancer (*International Classification of Diseases*, Ninth Revision, codes 153.0–153.9) as the underlying cause. We excluded from the analysis 20,453 women and 15,313 men with unknown or extreme (≤0.15th percentile or ≥99.85th percentile) height, weight, or calculated BMI values and 22,278 women and 15,529 men who reported weight loss of more than 20 lb (9.07 kg) within the year prior to entry (table 1). We excluded 62,847 women and 43,682 men who gave a positive response to the question "Are you sick now?" and 26,887 women and 27,542 men who had a history of colonic or rectal polyps. We also excluded 41,048 women and 16,322 men who reported prevalent cancer (except nonmelanoma skin cancer) at study entry. To minimize confounding by undiagnosed disease, we excluded the first 3 years of follow-up time and 6,554 women and 10,798 men who died within the first 3 years. After 12 years of follow-up, 1,616 eligible cases among 496,239 women and 1,792 eligible cases among 379,167 men were observed.

In the baseline questionnaire, weight in pounds and height in feet and inches were written by participants on blank lines after the words "Current weight with indoor clothing," "Weight 1 year ago," and "Height (without shoes)." BMI (kg/m^2) was calculated from the reported values. For 0.1 percent of men and 0.3 percent of women, "Current weight with indoor clothing" was missing, and the nonmissing value for "Weight 1 year ago" was substituted. In our analyses, BMI categories for women were defined as follows: <18.5, 18.5–20.49, 20.5–21.99, 22.0–23.49, 23.5–24.99, 25.0–27.49, 27.5–29.99, 30.0–32.49, and ≥32.5. Since the distribution of BMI differed in men and women, we used the following categorization for men: <20.5, 20.5–21.99, 22.0–23.49, 23.5–24.99, 25.0–25.99, 26.0–27.49, 27.5–29.99, 30.0–32.49, and ≥32.5. The BMI category 22.00–23.49 served as the referent group for analyses of both men and women. These categories were chosen to maximize category overlap between men and women and to enable a detailed examination of the association of BMI and colon cancer mortality across a wide range of BMI. In addition, the above categorization included the cutpoints proposed by the World Health Organization (30) for the underweight (BMI < 18.50), normal range (BMI = 18.50–24.99), grade 1 overweight (BMI = 25.00–29.99), grade 2 overweight (BMI = 30.00–39.99), and grade 3 overweight (BMI ≥ 40.00). When World Health Organization-recommended categories were used, we collapsed BMI < 18.50 with BMI = 18.50–24.99 and BMI = 30.00–39.99 with BMI ≥ 40.00 categories because of insufficient numbers in the underweight and grade 3 overweight categories. When World Health Organization-recommended categories were used, BMI < 25.00 was used as the referent group for analyses in both men and women.

We used Cox proportional hazards modeling to compute rate ratios and to adjust for other potential risk factors. All Cox models were stratified on age at entry (1-year strata). Multivariate Cox models also included the following potential cancer risk factors: race (White, Black, other), physical activity (none, light exercise, moderate exercise, heavy exercise, unknown), alcohol use (none, three drinks per week or less, one drink per day, two or more drinks per day, unknown), smoking status (never, current, former, ever smoker but unknown if current, pipe/cigar in men, unknown), educational level (less than high school graduate, high school graduate, some college, college graduate, unknown), parental history of colon cancer (yes, no), fat intake (estimated grams per week for 20 food items divided into tertiles (18)), vegetable and grain intake (the frequency per week of consuming nine vegetable and grain food items, divided into tertiles (18)), aspirin use (none, occasional, 1–15 per month, 16 or more per month, aspirin use but fre-

TABLE 1. Exclusion criteria and eligible cohort for analysis, Cancer Prevention Study II (CPS-II), United States, 1982–1994

Exclusion	CPS-II men (n = 508,353)		CPS-II women (n = 676,306)	
	Men (no.)	Colon cancer deaths (no.)	Women (no.)	Colon cancer deaths (no.)
Unknown body mass index	11,233	78	15,589	96
Extreme body mass index*	4,080	36	4,864	31
Weight loss >20 lb†	15,529	155	22,278	119
Presently sick‡	43,682	371	62,847	376
Colon and rectal polyps	27,542	301	26,887	223
Prevalent colon cancer	1,442	140	1,674	124
Prevalent other cancer§	14,880	150	39,374	247
First 3 years of follow-up time	10,798	272	6,554	266
Final analytical cohort	379,167	1,792	496,239	1,616

* Participants with body mass index, height, or weight less than the 0.15th percentile value or greater than the 99.85th percentile value.

† Metric equivalent: 20 lb = 9.07 kg.

‡ Participants were asked on entry questionnaire if they were "sick at the present time."

§ Except nonmelanoma skin cancer.

quency unknown, aspirin use but duration unknown) and, in women, estrogen replacement therapy (never, current, former). Rate ratios reported in the text are those obtained from multivariate analyses.

We assessed whether other risk factors for colon cancer modified the association between BMI and colon cancer mortality by including multiplicative interaction terms between BMI (<25, 25–29.99, ≥30) and each of the above risk factors in separate multivariate models. To assess whether age modified the association, we categorized attained age into four strata (<60 years, 60–<70 years, 70–<80 years, and ≥80 years). Statistical significance of the interaction terms was assessed at the $p = 0.05$ level using the likelihood ratio test.

RESULTS

Table 2 shows the age-adjusted percent distribution of BMI categories across levels of other risk factors for colon cancer. At baseline, men and women in the highest BMI categories (BMI ≥ 30 or World Health Organization grade 2 or grade 3 overweight) were more likely to be Black, never drinkers, less educated, and less physically active. They also were more likely to report high fat intake, low consumption of vegetables and grains, and more use of aspirin. Men in the BMI ≥ 30 category were likely to be former smokers, whereas women were likely to be never smokers. Women with a BMI of ≥30 were likely to report no estrogen replacement therapy use. Rate ratios from age-adjusted and multivariate survival analyses at each BMI level for men and women are summarized in tables 3 and 4, respectively.

Men

The relation between BMI and colon cancer death rates was stronger in men (table 3) than in women (table 4). In men, the increase in mortality appeared linear across all BMI levels. After controlling for other risk factors, we found significant, positive associations for all levels of BMI greater than 25.0. The strongest association was for the highest category (BMI ≥ 32.5) (rate ratio (RR) = 1.90, 95 percent confidence interval (CI): 1.46, 2.47). The linear association continued below the referent BMI level, implying an increase in risk of death with increasing BMI across the entire BMI range examined. When World Health Organization categories were used, the increased risk was observed at BMI 25–29.99 (RR = 1.34, 95 percent CI: 1.21, 1.48) and BMI ≥30 (RR = 1.75, 95 percent CI: 1.49, 2.05).

The association between BMI and colon cancer death rates in men varied significantly (p for interaction = 0.01) by educational level. No increased risk of death was associated with higher BMI levels in men with less than a high school education. The increased risk observed among more educated men appeared to increase slightly with increasing education (among college graduates, RR = 1.53, 95 percent CI: 1.26, 1.84 for BMI 25.0–29.9; RR = 2.33, 95 percent CI: 1.73, 3.14 for BMI ≥30). There was no significant effect modification by attained age or any other covariate.

Women

Among women, after adjusting for all other risk factors, we found higher death rates from colon cancer in the three highest categories of BMI (BMI 27.5–29.9, RR = 1.26, 95 percent CI: 1.03, 1.53; BMI 30.0–32.4, RR = 1.37, 95 percent CI: 1.09, 1.72; and BMI ≥32.5, RR = 1.23, 95 percent CI: 0.96, 1.59) (table 4). When we used World Health Organization-recommended BMI categories, women in the highest category (BMI ≥ 30) had a significantly increased risk of colon cancer mortality (RR = 1.25, 95 percent CI: 1.06, 1.46).

Alcohol intake significantly modified (p for interaction = 0.01) the association between BMI and colon cancer mortality in women. Among women reporting one drink per day and women reporting two or more drinks per day, high BMI of ≥30 was associated with a greater than twofold increased risk (RR = 2.49, 95 percent CI: 1.53, 4.03 and RR = 2.28, 95 percent CI: 1.48, 3.52, respectively), whereas no significant increase was noted in heavy women who did not drink or drank less than daily. There was no significant effect modification by attained age or any other covariate.

DISCUSSION

These prospective mortality data support the hypothesis that BMI is an independent risk factor for colon cancer death in both sexes but that the relation is stronger and more linear in men than in women. Our findings in men are consistent with those of several other studies (4–21) that have reported an increase in risk from the lowest to highest BMI levels. Other studies have also found a weak association between BMI and colon cancer in women and increased risk only at the highest levels of BMI (4, 10, 12, 14, 16–26). While the reasons for the gender difference seen in these studies are not completely understood, one hypothesis is that the greater tendency for abdominal or central adiposity in men (in contrast to the tendency for peripheral fat deposition in women) may be important. If central adiposity is indeed more important in colon carcinogenesis than generalized or peripheral obesity (4, 9, 24, 26), then BMI may simply be a more accurate indicator of central adiposity in men than in women. Consequently, the weaker effect seen in women may reflect greater misclassification of the relevant exposure.

Recently, Giovannucci (31) outlined a mechanism by which elevated BMI may influence colon cancer risk and suggested that altered glucose-insulin dynamics may be involved. Prolonged elevated insulin levels (hyperinsulinemia) resulting from increased insulin resistance and glycemic load may increase colon cancer risk by acting as a tumor growth promoter or mitogen. Since central obesity is correlated with insulin resistance and hyperinsulinemia, the finding of a stronger association in men in our study, along with the observation that muscle tissue in women is more sensitive to insulin than that in men (32), would support the hyperinsulinemia hypothesis.

Another potential explanation for the weaker association between BMI and colon cancer mortality in women may be the possible protective effects of estrogen. Observational studies report an inverse association between estrogen

TABLE 2. Age-adjusted percent distribution of body mass index (weight (kg)/height (m)^2) (BMI) categories among levels of colon cancer risk factors, Cancer Prevention Study II, United States, 1982–1994

	Men						Women					
	BMI <25		BMI 25–<30		BMI ≥30		BMI <25		BMI 25–<30		BMI ≥30	
	No.*	%†	No.	%	No.	%	No.	%	No.	%	No.	%
Age (years) at entry												
<50	34,835	38.3	45,591	50.1	10,499	11.6	101,589	69.1	31,010	21.1	14,324	9.8
50–59	54,053	36.7	77,674	52.7	15,562	10.6	110,201	63.3	46,172	26.5	17,804	10.2
60–69	42,132	41.3	51,205	50.2	8,673	8.5	70,519	58.8	36,606	30.5	12,775	10.7
70–79	17,233	50.2	15,106	44.0	2,003	5.8	27,861	59.8	14,331	30.8	4,409	9.5
≥80	2,858	62.1	1,580	34.3	163	3.5	5,770	66.8	2,285	26.5	583	6.8
Race												
White	142,300	39.9	180,524	50.6	33,963	9.5	299,350	65.0	118,387	25.7	42,991	9.3
Black	4,797	34.5	6,846	50.1	2,122	15.4	9,371	38.5	8,930	37.7	5,633	23.8
Missing/other race	4,014	47.0	3,786	43.7	815	9.3	7,219	61.6	3,087	27.5	1,271	11.0
Smoking												
Never smoker	41,064	40.7	49,503	49.7	9.623	9.6	158,611	60.4	74,871	28.2	29,874	11.4
Current smoker	35,992	47.5	35,714	44.7	6,519	7.9	71,717	71.9	21,248	21.5	6,721	6.5
Former smoker	39,189	35.9	58,597	53.7	11,272	10.5	66,566	66.2	24,533	24.7	9,283	9.2
Smoker, status unknown	1,981	35.5	2,575	52.0	577	12.5	5,665	64.2	2,319	25.8	892	10.0
Pipe/cigars	28,508	37.7	38,972	51.9	7,660	10.4						
Alcohol												
Never	24,580	40.9	28,992	48.7	6,165	10.4	59,690	59.9	27,337	27.8	12,226	12.3
3 per week	16,734	39.6	21,823	51.0	4,113	9.5	41,137	68.6	14,298	24.3	4,254	7.1
1 per day	18,607	41.2	22,952	50.4	3,820	8.3	36,029	71.9	10,901	22.1	3,016	6.0
>1 per day	45,828	40.5	58,614	50.9	10,106	8.7	54,042	73.7	15,211	21.1	3,814	5.2
Education												
Less than high school	20,032	34.6	27,178	51.4	6,763	14.0	30,015	49.3	20,914	33.1	10,156	17.6
High school graduate	27,340	36.5	39,728	52.5	8,326	11.0	92,126	61.2	42,539	28.1	16,365	10.7
Some college	38,937	38.7	51,749	51.2	10,190	10.0	98,347	66.1	36,882	25.0	13,216	8.8
College graduate	62,676	44.3	70,006	48.3	11,068	7.4	91,076	70.5	27,765	22.3	9,192	7.2
Exercise												
No exercise	1,868	30.5	2,929	49.0	1,219	20.5	4,351	47.6	2,785	31.1	1,848	21.3
Light exercise	25,986	34.0	40,767	52.2	10,963	13.8	64,068	55.9	32,695	29.8	15,923	14.3
Moderate exercise	100,238	40.8	123,450	50.7	20,637	8.6	220,858	66.2	85,220	25.3	28,438	8.5
Heavy exercise	21,301	45.6	22,119	46.8	3,659	7.6	20,874	69.5	6,807	22.6	2,366	7.8
Parental history of colon cancer												
No	146,838	39.8	185,672	50.4	35,849	9.7	305,077	63.6	126,260	26.3	48,526	10.1
Yes	4,273	40.2	5,484	50.3	1,051	9.5	10,863	66.3	4,144	25.4	1,369	8.3

Fat intake												
Low	47,250	40.4	58,735	50.6	10,259	9.0	93,356	64.3	38,994	26.2	13,991	9.5
Medium	46,886	40.1	59,470	50.5	11,096	9.4	95,690	64.7	37,811	25.7	14,060	9.5
High	45,902	39.5	58,860	49.9	12,728	10.6	93,529	62.8	38,016	26.5	15,849	10.7
Vegetable and grain intake												
Low	43,181	37.7	58,408	51.1	12,926	11.2	86,442	59.9	39,741	28.0	17,235	12.1
Medium	44,877	38.8	60,426	51.6	11,455	9.7	87,034	63.8	35,399	26.4	13,417	9.9
High	51,980	43.4	58,231	48.4	9,702	8.2	109,099	67.5	39,681	24.3	13,248	8.1
Aspirin use												
Nonuser	37,801	41.9	44,260	49.0	8,167	9.1	62,013	65.9	23,278	24.8	8,813	9.4
Occasional	26,779	40.2	34,705	50.8	6,226	8.9	60,816	65.7	22,871	25.4	8,239	8.9
1–15 per month	20,714	39.5	27,381	51.0	5,229	9.5	45,044	64.5	16,897	25.8	6,632	9.7
≥16 per month	9,238	39.3	11,589	50.2	2,298	10.5	17,427	60.6	8,131	27.3	3,521	12.2
Use, duration unknown	26,830	38.7	35,670	51.4	6,957	10.0	71,273	63.2	30,526	26.9	11,148	9.9
Use, frequency unspecified	29,749	38.5	37,551	50.3	8,023	11.2	59,367	60.3	28,701	28.0	11,542	11.7
Estrogen replacement therapy use												
Never user							182,850	62.5	73,796	26.6	30,670	10.9
Current user							30,444	71.5	9,559	22.3	2,687	6.2
Former user							52,414	64.6	22,583	26.3	7,152	9.1
Unknown use							20,233	65.7	8,044	25.6	2,628	8.7

* Columns not summing to total reflect missing data.
† All risk factors except age at interview are age adjusted to the age distribution of the male and female study populations.

TABLE 3. Colon cancer mortality by body mass index level among men, Cancer Prevention Study II, United States, 1982–1994

Body mass index (weight (kg)/ height (m)^2)	No. of deaths (n = 1,792)	Person-years	Minimally adjusted rate ratio*	95% confidence interval	Fully adjusted rate ratio†	95% confidence interval
<20.5	37	83,092	0.78	0.55, 1.11	0.74	0.52, 1.06
20.5–21.9	84	184,398	0.87	0.67, 1.12	0.85	0.66, 1.10
22.0–23.4	207	411,400	1.00		1.00	
23.5–24.9	290	613,885	0.98	0.82, 1.17	0.98	0.82, 1.18
25.0–25.9	329	573,206	1.24	1.04, 1.47	1.23	1.03, 1.46
26.0–27.4	310	564,008	1.21	1.02, 1.45	1.20	1.01, 1.43
27.5–29.9	321	525,346	1.43	1.20, 1.71	1.40	1.18, 1.68
30.0–32.4	134	207,355	1.60	1.29, 1.99	1.55	1.25, 1.94
≥32.5	80	111,780	1.98	1.53, 2.56	1.90	1.46, 2.47
<25.0	618	1,292,776	1.00		1.00	
25.0–29.9	960	1,662,560	1.35	1.22, 1.49	1.34	1.21, 1.48
≥30.0	214	319,135	1.80	1.54, 2.11	1.75	1.49, 2.05

* Matched on age.

† Matched on age and adjusted for race, education, smoking status, exercise, alcohol, parental history of colon cancer, fat intake, vegetable and fiber intake, and aspirin use.

replacement therapy in postmenopausal women and colorectal polyps (33), colon cancer incidence (34), and mortality (35). Conversion of androgens to estrogens by adipose tissue is the primary source of extraglandular estrogen production in postmenopausal women, and circulating estrogen levels increase with age and obesity (36–39). If estrogen production by adipose tissue protects against colon cancer in women, why not in men? Estrogen levels increase with obesity in both sexes (40). Estrogen supplementation in males has been shown to increase insulin resistance rather than improve insulin sensitivity (41), and the estradiol/testosterone ratio is positively associated with plasma glucose and insulin levels (42). Assuming a role of hyperinsulinemia in colon carcinogenesis, elevated estrogen levels as a consequence of obesity in males may lead to a relative estrogen/testosterone imbalance, followed by increased insulin resistance and hyperinsulinemia, and an increase in colon cancer risk. Leptin and insulin-like growth factor-1 are additional hormones that may participate in the pathway between obesity and the incidence or dissemination of colon cancer (43, 44). A specific role for these hormones in colon cancer risk deserves further investigation in populations where hormone levels have been measured.

Interactions between BMI and physical activity in younger women (17) and between BMI and family history in younger men and women (4) have been reported for colon cancer risk. We did not observe significant interaction by these variables in our data. However, we did find significant effect modifi-

TABLE 4. Colon cancer mortality by body mass index level among women, Cancer Prevention Study II, United States, 1982–1994

Body mass index (weight (kg)/ height (m)^2)	No. of deaths (n = 1,616)	Person-years	Minimally adjusted rate ratio*	95% confidence interval	Fully adjusted rate ratio†	95% confidence interval
<18.5	42	99,647	1.18	0.85, 1.64	1.10	0.79, 1.53
18.5–20.4	154	522,629	1.03	0.84, 1.26	1.01	0.82, 1.23
20.5–21.9	265	780,624	1.15	0.97, 1.36	1.15	0.96, 1.36
22.0–23.4	251	777,527	1.00		1.00	
23.5–24.9	230	641,012	1.03	0.86, 1.23	1.03	0.86, 1.23
25.0–27.4	311	793,397	1.08	0.92, 1.28	1.07	0.91, 1.27
27.5–29.9	169	365,713	1.29	1.06, 1.56	1.26	1.03, 1.53
30.0–32.4	112	228,574	1.42	1.14, 1.79	1.37	1.09, 1.72
≥32.5	82	213,061	1.31	1.02, 1.68	1.23	0.96, 1.59
<25.0	942	2,821,437	1.00		1.00	
25.0–29.9	480	1,159,109	1.08	0.97, 1.21	1.08	0.96, 1.20
≥30.0	194	441,635	1.30	1.11, 1.52	1.25	1.06, 1.46

* Matched on age.

† Matched on age and adjusted for race, education, smoking status, exercise, alcohol, parental history of colon cancer, fat intake, vegetable and fiber intake, estrogen replacement therapy, and aspirin use.

cation by alcohol intake of the association between BMI and colon cancer mortality in women. While not significant, this interaction was also suggested in men. High alcohol consumption is a probable independent risk factor for cancers of the colon and rectum (45). Several mechanisms for its action have been advanced, including induction of microsomal enzymes that convert procarcinogens to more active forms (46), inhibition of DNA repair (47), and an indirect effect operating through depletion of several beneficial nutrients, including folate and methionine (48–52). It seems biologically plausible that alcohol consumption also may modify the effect of other exposures on colon cancer.

The finding of significant interaction by educational level in men is hard to explain. This may reflect chance or inadequate control for factors associated with lower education such as increased physical activity. Though we included a physical activity covariate in multivariate analyses, the limited information available may not have provided adequate control.

Strengths of our study include its prospective design, similar analytical methods for men and women, ability to control for a large number of other risk factors, exclusion of latent disease, and large size. Limitations include reliance on mortality rather than incidence data, lack of colon cancer subsite data, lack of anthropometric measurements, lack of screening data, and reliance on single, self-reported measurements for BMI determination.

Because of our reliance on mortality data, our results reflect the potential effect of body mass index on colon cancer incidence, survival, or both. In addition, we have no information on colon cancer screening, a factor that is likely to influence survival. If lean individuals are more likely to get screened, they would be expected to have more diagnosed colon polyps and fewer invasive cancers. However, a recently published study of incident colon polyps in a subgroup of this cohort offers little support for such a screening bias (53). In that study, a modest but positive association was seen between increasing body mass index and risk of self-reported incident colon polyps (53).

Finally, study participants are, on average, more educated and affluent than the US population as a whole, and they are less likely to be of non-White race. While these differences may influence comparisons of absolute rates of disease or exposure between this population and that of the United States, they are unlikely to compromise internal validity.

The findings of our study add to the current literature suggesting that obesity increases the risk of colon cancer mortality and that the effect is considerably greater in men. Future research may focus on the role of sex hormones in explaining the different association seen in men and women, with attention to the effects of estrogen, leptin, and insulin-like growth factors.

REFERENCES

1. Cancer facts and figures. Atlanta, GA: American Cancer Society, 1998.
2. Parkin DM, Muir CS. Cancer incidence in five continents. Comparability and quality of data. IARC Sci Publ 1992;(120): 45–173.
3. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 1968;40:43–68.
4. Caan BJ, Coates AO, Slattery ML, et al. Body size and the risk of colon cancer in a large case-control study. Int J Obes Relat Metab Disord 1998;22:178–84.
5. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. Ann Epidemiol 1996;6:276–82.
6. Garfinkel L. Overweight and cancer. Ann Intern Med 1985; 103:1034–6.
7. Garland C, Shekelle RB, Barrett-Connor E, et al. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet 1985;1:307–9.
8. Gerhardsson de Verdier M, Hagman U, Steineck G, et al. Diet, body mass and colorectal cancer: a case-referent study in Stockholm. Int J Cancer 1990;46:832–8.
9. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
10. Graham S, Marshall J, Haughey B, et al. Dietary epidemiology of cancer of the colon in western New York. Am J Epidemiol 1988;128:490–503.
11. Le Marchand L, Wilkens LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. Cancer Causes Control 1992;3:349–54.
12. Le Marchand L, Wilkens LR, Kolonel LN, et al. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res 1997;57: 4787–94.
13. Lee IM, Paffenbarger RS Jr. Quetelet's index and risk of colon cancer in college alumni. J Natl Cancer Inst 1992;84:1326–31.
14. Must A, Jacques PF, Dallal GE, et al. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992; 327:1350–5.
15. Nomura A, Heilbrun LK, Stemmermann GN. Body mass index as a predictor of cancer in men. J Natl Cancer Inst 1985;74: 319–23.
16. Phillips RL, Snowdon DA. Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. J Natl Cancer Inst 1985;74:307–17.
17. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer—beyond physical activity. Cancer Res 1997;57:75–80.
18. Thun MJ, Calle EE, Namboodiri MM, et al. Risk factors for fatal colon cancer in a large prospective study. J Natl Cancer Inst 1992;84:1491–500.
19. Waaler HT. Height, weight and mortality. The Norwegian experience. Acta Med Scand Suppl 1984;679:1–56.
20. West DW, Slattery ML, Robison LM, et al. Dietary intake and colon cancer: sex- and anatomic site-specific associations. Am J Epidemiol 1989;130:883–94.
21. Wu AH, Paganini-Hill A, Ross RK, et al. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. Br J Cancer 1987;55:687–94.
22. Dietz AT, Newcomb PA, Marcus PM, et al. The association of body size and large bowel cancer risk in Wisconsin (United States) women. Cancer Causes Control 1995;6:30–6.
23. Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer 1990;13:9–17.
24. Martinez ME, Giovannucci E, Spiegelman D, et al. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 1997;89:948–55.
25. Chute CG, Willett WC, Colditz GA, et al. A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women. Cancer Causes Control 1991;2:117–24.
26. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control

1994;5:38–52.
27. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. Natl Cancer Inst Monogr 1985;67:49–52.
28. Stellman SD, Garfinkel L. Smoking habits and tar levels in a new American Cancer Society prospective study of 1.2 million men and women. J Natl Cancer Inst 1986;76:1057–63.
29. Calle EE, Terrell DD. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. Am J Epidemiol 1993;137:235–41.
30. WHO Expert Committee on Physical Status. The use and interpretation of anthropometry. Geneva, Switzerland: World Health Organization, 1995.
31. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.
32. Donahue RP, Prineas RJ, DeCarlo Donahue R, et al. The female 'insulin advantage' in a biracial cohort: results from the Miami Community Health Study. Int J Obes Relat Metab Disord 1996;20:76–82.
33. Potter JD, Bostick RM, Grandits GA, et al. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. Cancer Epidemiol Biomarkers Prev 1996;5:779–84.
34. Kampman E, Bijl AJ, Kok C, et al. Reproductive and hormonal factors in male and female colon cancer. Eur J Cancer Prev 1994;3:329–36.
35. Calle EE, Miracle-McMahill HL, Thun MJ, et al. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. J Natl Cancer Inst 1995;87:517–23.
36. Simpson ER, Bulun SE, Nichols JE, et al. Estrogen biosynthesis in adipose tissue: regulation by paracrine and autocrine mechanisms. J Endocrinol 1996;150(suppl):S51–7.
37. Gordon GG, Olivo J, Rafil F, et al. Conversion of androgens to estrogens in cirrhosis of the liver. J Clin Endocrinol Metab 1975;40:1018–26.
38. Edman CD, MacDonald PC. Effect of obesity on conversion of plasma androstenedione to estrone in ovulatory and anovulator young women. Am J Obstet Gynecol 1978;130:456–61.
39. Hemsell DL, Grodin JM, Brenner PF, et al. Plasma precursors of estrogen. II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. J Clin Endocrinol Metab 1974;38:476–9.
40. Kley HK, Deselaers T, Peerenboom H, et al. Enhanced conversion of androstenedione to estrogens in obese males. J Clin Endocrinol Metab 1980;51:1128–32.
41. Polderman KH, Gooren LJ, Asscheman H, et al. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 1994;79:265–71.
42. Tchernof A, Despres JP, Dupont A, et al. Relation of steroid hormones to glucose tolerance and plasma insulin levels in men. Importance of visceral adipose tissue. Diabetes Care 1995;18:292–9.
43. Akagi Y, Liu W, Zebrowski B, et al. Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I. Cancer Res 1998;58:4008–14.
44. Sierra-Honigmann MR, Nath AK, Murakami C, et al. Biological action of leptin as an angiogenic factor. Science 1998;281:1683–6.
45. World Cancer Research Fund (WCRF) Panel, Potter JD (chair). Diet, nutrition, and the prevention of cancer: a global perspective. Washington, DC: WCRF/American Institute of Cancer Research, 1997.
46. Seitz H, Garro A, Lieber C. Sex-dependent effect of chronic ethanol consumption in rats on hepatic microsome mediated mutagenicity of benzo(a)pyrene. Cancer Lett 1981;13:97–102.
47. Farinati F, Espina N, Lieber C, et al. In vivo inhibition by chronic ethanol exposure of methylguanine transferase activity and DNA repair. Ital J Gastroenterol 1985;17:48–9.
48. Potter JD. Nutrition and colorectal cancer. Cancer Causes Control 1996;7:127–46.
49. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85:875–84.
50. Giovannucci E, Rimm EB, Ascherio A, et al. Alcohol, low-methionine–low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst 1995;87:265–73.
51. Freudenheim JL, Graham S, Marshall JR, et al. Folate intake and carcinogenesis of the colon and rectum. Int J Epidemiol 1991;20:368–74.
52. Slattery ML, Schaffer D, Edwards SL, et al. Are dietary factors involved in DNA methylation associated with colon cancer? Nutr Cancer 1997;28:52–62.
53. Kahn H, Tatham L, Thun M, et al. Risk factors for self-reported colon polyps. J Gen Intern Med 1998;13:303–10.