## Original Contribution

# Body Mass and Colorectal Cancer Risk in the NIH–AARP Cohort

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In most studies, body mass index (BMI) has been associated with increased risk of colorectal or colon cancer in men, but the relation is weaker and less consistent for women, possibly because of interactions with age or hormone replacement therapy. The authors examined the relation between BMI and colorectal cancer incidence in a large, prospective US cohort of 307,708 men and 209,436 women from the NIH–AARP Diet and Health Study. During follow-up of the cohort from 1995 to 2000, 2,314 cases of colorectal cancer were observed in men and 1,029 in women. BMI was related to increased risk of incident colon cancer, but not rectal cancer, for both men and women. For men, relative risks of colon cancer for a BMI of 18.5–<23, 23–<25, 25–<27.5, 27.5–<30, 30–<32.5, 32.5–<35, 35–<40, and ≥40 kg/m$^2$ were 1.0 (referent), 1.11, 1.22, 1.44, 1.53, 1.57, 1.71, and 2.39, respectively (95% confidence interval: 1.59, 3.58; $p$-trend < 0.0005). Corresponding relative risks for women were 1.0, 1.20, 1.29, 1.31, 1.28, 1.13, 1.46, and 1.49 (95% confidence interval: 0.98, 2.25; $p$-trend = 0.02). BMI was related to colon cancer risk for younger (aged 50–66 years) but not older (aged 67–71 years) women. The association was not modified by hormone replacement therapy in women or physical activity in men or women.

body mass index; colonic neoplasms; colorectal neoplasms; humans; obesity; overweight; rectal neoplasms

Colorectal cancer is the second most common cancer in the United States (1). Average body mass of the US population has increased over recent decades, with 34 percent of adults currently estimated as overweight (body mass index (BMI; weight (kg)/height (m$^2$)) 25–<30 kg/m$^2$) and an additional 30.5 percent considered obese (BMI ≥30 kg/m$^2$) (2). For men, a BMI greater than 29 or 30 kg/m$^2$ is associated with increased risk of colon cancer in the majority of studies (3–13). For women, the associations are weaker and less consistently positive (3, 5, 6, 8, 11, 12, 14–19), with recent studies reporting that colorectal cancer is related to BMI in only relatively young (e.g., aged <55 years) (16, 20), premenopausal (17, 21), or, among postmenopausal women, those using hormone replacement therapy (HRT) (21–23). This apparent effect modification may explain why many studies report weak or null associations for women (23).

Data are inconclusive on whether being merely overweight is associated with colorectal cancer. Few studies (12, 24–27) have demonstrated a statistically significant elevated risk associated with overweight BMI categories, which could be due to insufficient statistical power rather than a lack of relation.

Information is also limited on dose response in the obese categories because most studies combine all obese participants into a single group (e.g., BMI ≥30 kg/m$^2$). The Cancer Prevention Study II (26) evaluated risk of colorectal

cancer mortality, but not incidence, for BMI categories as high as $\geq 35$ kg/m$^2$ in men and $\geq 40$ kg/m$^2$ in women. We are aware of no other data on colon cancer risk associated with morbid obesity (BMI $\geq 40$ kg/m$^2$).

The relation with BMI is more often positive for colon cancer than for rectal cancer. Whether rectal cancer is associated with BMI remains unresolved (3, 5, 12, 13, 16, 17, 19, 28–31).

The possibility that physical activity may ameliorate the relation between BMI and colon cancer is attractive, given the difficulty of maintaining a healthy weight through adulthood. Evidence in support of this idea is limited, however (32, 33).

The NIH–AARP Diet and Health Study is a collaboration between the National Institutes of Health (NIH) and AARP (formerly the American Association of Retired Persons). This large cohort consists of over 500,000 men and women, a high proportion of whom are overweight or obese, and among whom more than 3,300 colorectal cancers have developed since 1995. We were able to evaluate whether being merely overweight, but not obese, confers increased risk of colon cancer and to characterize risk at a very high BMI (including morbid obesity, BMI $\geq 40$ kg/m$^2$). In addition, the large study size permitted relatively stable estimation of effect modification, for men and women separately, within subgroups of age and physical activity level, and subgroups of HRT for women. These interactions were evaluated over a wide BMI range, including an upper BMI category of $\geq 35$ kg/m$^2$.

## MATERIALS AND METHODS

### Participants/study population

The NIH–AARP Diet and Health Study comprises a large, prospective cohort of AARP members established in 1995–1996 (34). A self-administered questionnaire was mailed to 3.5 million AARP members, men and women aged 50–71 years living in California; Florida; Pennsylvania; New Jersey; North Carolina; Louisiana; and the Atlanta, Georgia, or Detroit, Michigan, metropolitan areas. A total of 567,169 questionnaires with satisfactory dietary data were returned. We excluded records from 179 persons with duplicate questionnaires, from 261 persons who died before their questionnaire was processed, from 321 persons who moved from the study area before returning the questionnaire, from one person who withdrew, for 15,760 questionnaires completed by surrogates, for 5,236 persons with a previous colorectal cancer diagnosis, and for 13,286 persons for whom information on height or weight was missing. We also excluded 184 cases for whom we had only mortality information, that is, without colorectal cancer incidence data. We further excluded persons with extreme values (more than three interquartile ranges outside the 75th and 25th percentiles, respectively) for weight ($n = 913$) or height ($n = 1,708$). We calculated BMI and excluded 4,295 persons with a BMI of $<18.5$ kg/m$^2$. To remove data for persons with implausible values, we further excluded those persons reporting energy intake ($n = 4,603$) greater than two interquartile ranges outside the 25th and 75th percentiles or red meat intake ($n = 1,223$) or alcohol consumption ($n = 2,055$) greater than two interquar-

tile ranges above the 75th percentile. The analytical cohort consisted of 517,144 participants ($n = 307,708$ men and $n = 209,436$ women). A second questionnaire with more detailed physical activity questions was completed by a subcohort of participants approximately 6 months after the baseline questionnaire ($n = 301,515$ after exclusions). We did not exclude participants reporting previous cancer at baseline, other than colorectal cancer, or persons diagnosed with colorectal cancer early in follow-up. Follow-up began immediately upon our receipt of the questionnaire.

### Ascertainment of cases

Incident colorectal cancer cases were identified through state cancer registries, linked by name, address, sex, date of birth, and, if available, Social Security number. We estimated that approximately 90 percent of cancer cases were validly identified (35). Incident cases of colorectal carcinoma were defined as being assigned *International Classification of Diseases for Oncology* codes C180–C189, C199, or C209 and having histology codes consistent with colorectal carcinoma. The right colon was defined as extending from cecum to transverse colon, and the left colon from splenic flexure to sigmoid colon.

### Exposure assessment

Study variables were based on participant responses to questions included with a food frequency questionnaire. We created BMI categories nested within World Health Organization classifications (36): 18.5–$<23$ kg/m$^2$ (referent), 23–$<25$ kg/m$^2$, 25–$<27.5$, 27.5–$<30$ kg/m$^2$, 30–$<35$ kg/m$^2$, 35–$<40$ kg/m$^2$, and $\geq 40$ kg/m$^2$.

For analyses stratified on age, we divided the cohort into age tertiles based on number of cases: 50–62 years, 63–66 years, and 67–71 years. HRT was classified as current, former, and never. A three-level physical activity index was created based on two questions addressing sports- and non-sports-related activity. The index was designed to assign to the most active group persons who were highly active in either sports or nonsports activities and to the least active group those who were relatively inactive regarding both types of activities. From the subcohort questionnaire, we evaluated two additional measures—moderate to vigorous physical activity and time spent sitting (i.e., inactivity)—after first confirming that BMI–colorectal cancer associations in the subcohort were similar to those in the baseline cohort.

For statistical adjustment, we categorized cigarette smoking according to 17 levels combining status (never smoked, currently smoking or quit for $<1$ year, quit smoking 1–9 years ago, or quit smoking $\geq 10$ years ago) and dose (1–10, 11–20, 21–30, 31–40, or $\geq 40$ cigarettes/day) to create a never-smoking category, five dose levels each for the two former smoking and the current smoking category, and a missing category. We assigned missing values for physical activity, smoking, and HRT to categories rather than excluding these participants. Supplemental calcium intake from single supplements and multivitamins was categorized as none, $<162$ g/day, 163–$<500$ g/day, 500–$\leq 1,000$ g/day, and $>1,000$ g/day. Alcohol consumption was modeled as

a categorical, four-level variable: none, <5 g/day, 5–<15 g/day, and ≥15 g/day. Other nutrient intakes were adjusted for energy intake by using the residual method (37).

### Data analysis

Age-adjusted incidence rates within BMI categories were calculated by direct standardization using 5-year age categories (38). Rates for men in each age stratum were standardized to the rates for all men in the cohort, and rates for women in each age stratum were standardized to the rates for all women. Relative risks were estimated from Cox regression analysis (39), using age as the underlying time variable, with entry on the date the questionnaire was processed (scanned), shortly after receipt. Participants who did not develop an incident colorectal carcinoma were censored when they died (ascertained by the National Death Index or Social Security Administration Master Death File), when they moved to an area not included by one of the state cancer registries, or at the end of follow-up, December 31, 2000. All statistical tests were two sided, with $\alpha = 0.05$ considered statistically significant. Trends were evaluated as grouped linear variables by using BMI category medians. Statistical interactions were evaluated by treating BMI as a grouped linear variable, using the likelihood ratio test, comparing models with and without interaction terms.

Potential confounders were defined a priori and tested in groups of four. The purpose of testing small groups of covariates in the exposure-disease model rather than introducing variables individually is that variables that may be confounders individually may no longer confound if other covariates are included, because of joint correlations. On the other hand, including large numbers of covariates could change the statistical properties of estimated relative risks in an unknown way. The first group included the four risk factors we considered most strongly associated with colorectal cancer in the literature and associated with BMI in our data set: red meat, supplemental calcium, smoking, and alcohol. We found that these covariates altered beta coefficients by more than 10 percent and thus retained them in the model. We next entered a second group of four covariates—saturated fat, processed meat, fiber, and family history—that we considered slightly less associated with colorectal cancer and with BMI; this set did not further alter beta coefficients by 10 percent, so the group was not included in the model. We repeated this process for a third set of covariates—height, dietary calcium, supplemental folate, and dietary folate—which also did not alter beta coefficients by 10 percent and so were not included in the model. We further tested a broad array of other potential dietary confounders individually and verified that none caused meaningful confounding. Ultimately, we included family history of colorectal cancer in the model, although not actually confounding, because of its importance as a clinical variable.

In separate analyses, relative risk on a continuous scale was analyzed by using natural cubic splines, placing knots at the 2nd, 25th, 75th, and 98th percentiles of BMI with distributions evaluated separately for men and women, BMI centered at 21 kg/m² and adjusted for covariates.

### Sensitivity analysis

We conducted several sensitivity analyses to determine whether alternative assumptions or procedures affected results. First, instead of excluding energy intake, height, weight, and consumption outliers based on distribution percentiles, we removed data for men reporting less than 800 or more than 4,200 calories per day, women reporting less than 600 or more than 3,500 calories per day, and men and women whose BMI was >60 kg/m², and we did not exclude meat or alcohol consumption outliers. Second, we restricted the data set to a first primary colorectal cancer data set in which we excluded all participants with previous cancer at baseline, and we censored participants upon diagnosis of a cancer other than colorectal cancer. In the third sensitivity analysis, we evaluated the effect of excluding the first year of follow-up, a strategy to remove participants who may have lost weight prior to colorectal cancer diagnosis. In the fourth analysis, we tested the effect of creating an indicator variable for missing responses (for smoking, HRT use, and physical activity), rather than excluding participants with missing values, by weighting participants' data based on likelihood of missing values using the Horvitz-Thompson method (40).

### RESULTS

We identified 2,314 incident cases of colorectal cancer in men and 1,029 in women. Overweight and obese men were more likely than normal-weight men to be former smokers, whereas proportionally more normal-weight men were never and current smokers (table 1). Normal-weight women were more likely than heavier women to be current smokers. Men and women with a high BMI consumed less alcohol and more red meat than those with a lower BMI.

Colorectal cancer risk for men increased with successively higher BMI categories, with moderately elevated multivariate relative risks for overweight men (BMI 25–<27.5 kg/m² and 27.5–<30 kg/m²) and doubled risks for the morbidly obese (table 2).

With respect to colorectal subsites, BMI was associated with increased colon cancer risk for both men and women (table 2). Among overweight men (BMI 25–<27.5 kg/m² or 27.5–<30 kg/m²), colon cancer risks were 20–40 percent higher than for those whose BMI was <23 kg/m². Risk increased further across the obese range: the relative risk of colon cancer in morbidly obese men was 2.39. Analysis of BMI on a continuous basis using cubic splines showed the dose response in men to be nearly linear on the relative risk scale (figure 1). Among women, relative risk was about 30 percent higher in the overweight categories than in the baseline category, although risk did not rise as steeply in the obese range as it did for men (table 2). Continuous analysis demonstrated that relative risk for women increased quite sharply over the normal range (BMI 18.5–<25 kg/m²), reached a plateau and remained elevated until a BMI of approximately 35 kg/m², and then increased further (figure 2). Adjustment for physical activity changed categorical colon cancer risk estimates only slightly, and only for men (data

TABLE 1.   NIH–AARP study participant characteristics,* by body mass index category, United States, 1995–2000

| | Body mass index category (weight (kg)/height (m)²) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 18.5–<23 | 23–<25 | 25–<27.5 | 27.5–<30 | 30–<32.5 | 32.5–<35 | 35–<40 | ≥40 |
| **Men** | | | | | | | | |
| Participants (no.) | 33,027 | 56,192 | 92,982 | 60,125 | 34,076 | 16,947 | 11,088 | 3,271 |
| Age (years) at entry | 62.8 (5.3) | 62.7 (5.3) | 62.5 (5.3) | 62.2 (5.3) | 61.9 (5.3) | 61.5 (5.4) | 61.1 (5.3) | 60.3 (5.3) |
| Weight (kg) | 69 (6) | 76 (6) | 83 (6) | 91 (7) | 99 (8) | 107 (9) | 117 (10) | 137 (15) |
| Height (cm) | 178 (8) | 178 (7) | 178 (7) | 178 (7) | 178 (7) | 178 (7) | 178 (7) | 177 (8) |
| Alcohol consumption (g/day) | 15 (31) | 16 (300) | 16 (30) | 16 (32) | 15 (31) | 14 (31) | 13 (31) | 9 (25) |
| Red meat intake (g/day) | 64 (54) | 67 (52) | 73 (55) | 82 (58) | 88 (62) | 94 (65) | 101 (69) | 113 (76) |
| Family history of colon cancer (%)† | 8.5 | 8.4 | 8.4 | 8.3 | 8.3 | 8.6 | 8.3 | 8.2 |
| Race/ethnicity (% White) | 91.7 | 92.8 | 92.9 | 93.2 | 92.9 | 92.6 | 92.6 | 91.0 |
| Smoking (%)‡ | | | | | | | | |
| Never | 34.2 | 32.6 | 29.8 | 27.0 | 26.2 | 25.8 | 25.4 | 26.9 |
| Former | 48.3 | 54.3 | 58.8 | 62.5 | 63.5 | 64.2 | 65.0 | 63.5 |
| Current | 15.7 | 11.4 | 9.7 | 8.8 | 8.6 | 8.4 | 7.6 | 7.9 |
| Physical activity level (%)‡ | | | | | | | | |
| Low | 20.5 | 18.8 | 21.0 | 24.8 | 30.0 | 34.3 | 40.9 | 53.2 |
| Medium | 35.3 | 38.4 | 39.8 | 39.9 | 38.9 | 37.0 | 35.0 | 28.9 |
| High | 42.4 | 41.1 | 37.5 | 33.5 | 29.1 | 26.5 | 21.8 | 15.3 |
| Supplemental calcium use (%)§ | 53.6 | 52.6 | 50.9 | 48.9 | 47.0 | 46.4 | 45.1 | 44.7 |
| **Women** | | | | | | | | |
| Participants (no.) | 52,046 | 39,010 | 43,254 | 25,857 | 19,185 | 11,898 | 11,737 | 6,449 |
| Age (years) at entry | 61.8 (5.5) | 62.1 (5.4) | 62.1 (5.3) | 62.1 (5.3) | 61.9 (5.4) | 61.7 (5.3) | 61.1 (5.3) | 60.6 (5.3) |
| Weight (kg) | 57 (5) | 64 (5) | 70 (6) | 76 (6) | 82 (7) | 89 (7) | 98 (9) | 117 (15) |
| Height (cm) | 164 (6.5) | 163 (6.2) | 163 (6.5) | 163 (6.5) | 163 (6.5) | 163 (6.5) | 163 (6.8) | 162 (7.2) |
| Alcohol consumption (g/day) | 7 (12) | 6 (12) | 5 (11) | 4 (10) | 4 (9) | 3 (9) | 3 (8) | 2 (7) |
| Red meat intake (g/day) | 39 (34) | 43 (35) | 46 (36) | 49 (38) | 52 (40) | 55 (41) | 59 (44) | 66 (47) |
| Family history of colon cancer (%)† | 9.7 | 9.6 | 9.7 | 9.8 | 9.5 | 9.7 | 9.9 | 8.7 |
| Race/ethnicity (% White) | 93.1 | 91.6 | 89.6 | 88.6 | 87.4 | 87.3 | 85.8 | 85.1 |
| Smoking (%)‡ | | | | | | | | |
| Never | 42.4 | 43.5 | 43.9 | 45.3 | 46.2 | 46.1 | 46.3 | 45.2 |
| Former | 37.8 | 40.1 | 41.1 | 41.3 | 41.4 | 42.4 | 43.3 | 45.6 |
| Current | 18.2 | 14.8 | 13.4 | 11.8 | 10.8 | 9.8 | 8.7 | 7.6 |
| Physical activity level (%)‡ | | | | | | | | |
| Low | 23.8 | 25.8 | 29.2 | 34.5 | 39.1 | 42.8 | 49.6 | 59.8 |
| Medium | 36.4 | 37.7 | 37.4 | 35.8 | 33.8 | 33.1 | 29.5 | 24.8 |
| High | 37.4 | 33.8 | 30.4 | 26.7 | 23.6 | 20.7 | 17.4 | 11.8 |
| Supplemental calcium use (%)§ | 74.7 | 72.2 | 69.5 | 67.2 | 65.1 | 62.6 | 60.6 | 57.0 |
| Hormone replacement therapy use (%)‡,¶ | | | | | | | | |
| Never | 39.9 | 41.8 | 45.6 | 48.3 | 51.4 | 54.5 | 57.8 | 65.2 |
| Former | 9.9 | 9.8 | 10.4 | 11.1 | 11.1 | 10.9 | 9.9 | 9.7 |
| Current | 49.9 | 47.7 | 43.7 | 40.3 | 37.3 | 34.3 | 32.0 | 24.9 |

* Values are expressed as mean (standard deviation) unless other specified.
† First-degree relative diagnosed with colorectal cancer, by self-report.
‡ Values do not add to 100% because of missing information.
§ Combined multivitamin and single supplement use.
¶ Proportions among postmenopausal women.

**TABLE 2.   Colorectal, colon, and rectal cancer incidence and risk in relation to body mass index among participants in the NIH–AARP study, United States, 1995–2000**

| | Body mass index category (weight (kg)/height (m)$^2$) | | | | | | | | *p*-trend |
|---|---|---|---|---|---|---|---|---|---|
| | 18.5–<23 | 23–<25 | 25–<27.5 | 27.5–<30 | 30–<32.5 | 32.5–<35 | 35–<40 | ≥40 | |
| **Colorectal cancer** | | | | | | | | | |
|   Men | | | | | | | | | |
|     No. of cases | 207 | 356 | 683 | 495 | 289 | 150 | 95 | 39 | |
|     Age-adjusted rate* | 13.9 | 13.9 | 16.3 | 18.7 | 19.7 | 20.9 | 21.5 | 31.1 | |
|     Age-adjusted HR†,‡ | 1.0 | 1.01 | 1.18 | 1.36 | 1.43 | 1.54 | 1.55 | 2.27 | <0.0005 |
|     95% CI† | Ref† | 0.85, 1.20 | 1.01, 1.38 | 1.15, 1.60 | 1.20, 1.71 | 1.25, 1.90 | 1.21, 1.97 | 1.61, 3.21 | |
|     MV† HR§ | 1.0 | 1.00 | 1.14 | 1.27 | 1.32 | 1.40 | 1.40 | 2.05 | <0.0005 |
|     95% CI | Ref | 0.84, 1.18 | 0.98, 1.33 | 1.08, 1.50 | 1.10, 1.58 | 1.13, 1.74 | 1.09, 1.79 | 1.45, 2.91 | |
|   Women | | | | | | | | | |
|     No. of cases | 210 | 187 | 228 | 140 | 102 | 54 | 74 | 34 | |
|     Age-adjusted rate* | 9.1 | 10.5 | 11.6 | 11.9 | 11.8 | 10.3 | 14.7 | 13.4 | |
|     Age-adjusted HR‡ | 1.0 | 1.16 | 1.27 | 1.31 | 1.30 | 1.13 | 1.65 | 1.48 | <0.0005 |
|     95% CI | Ref | 0.95, 1.41 | 1.05, 1.53 | 1.05, 1.62 | 1.03, 1.65 | 0.84, 1.53 | 1.26, 2.15 | 1.03, 2.12 | |
|     MV HR§ | 1.0 | 1.14 | 1.23 | 1.25 | 1.22 | 1.04 | 1.49 | 1.28 | 0.03 |
|     95% CI | Ref | 0.94, 1.39 | 1.02, 1.48 | 1.00, 1.54 | 0.96, 1.55 | 0.77, 1.42 | 1.13, 1.95 | 0.88, 1.85 | |
| **Colon cancer** | | | | | | | | | |
|   Men | | | | | | | | | |
|     No. of cases | 136 | 260 | 479 | 367 | 219 | 110 | 76 | 29 | |
|     Age-adjusted rate* | 9.1 | 10.2 | 11.4 | 13.7 | 14.9 | 15.5 | 17.3 | 23.4 | |
|     Age-adjusted HR‡ | 1.0 | 1.12 | 1.27 | 1.53 | 1.66 | 1.73 | 1.90 | 2.66 | <0.0005 |
|     95% CI | Ref | 0.91, 1.38 | 1.05, 1.53 | 1.26, 1.87 | 1.34, 2.05 | 1.34, 2.22 | 1.43, 2.51 | 1.78, 3.98 | |
|     MV HR§ | 1.0 | 1.11 | 1.22 | 1.44 | 1.53 | 1.57 | 1.71 | 2.39 | <0.0005 |
|     95% CI | Ref | 0.90, 1.37 | 1.01, 1.48 | 1.18, 1.76 | 1.23, 1.90 | 1.22, 2.03 | 1.29, 2.27 | 1.59, 3.58 | |
|   Women | | | | | | | | | |
|     No. of cases | 151 | 141 | 172 | 106 | 77 | 42 | 52 | 28 | |
|     Age-adjusted rate* | 6.5 | 7.9 | 8.7 | 9.0 | 8.9 | 8.0 | 10.4 | 11.1 | |
|     Age-adjusted HR‡ | 1.0 | 1.21 | 1.33 | 1.37 | 1.37 | 1.23 | 1.62 | 1.71 | <0.0005 |
|     95% CI | Ref | 0.96, 1.52 | 1.07, 1.66 | 1.07, 1.76 | 1.04, 1.80 | 0.87, 1.73 | 1.18, 2.22 | 1.15, 2.57 | |
|     MV HR§ | 1.0 | 1.20 | 1.29 | 1.31 | 1.28 | 1.13 | 1.46 | 1.49 | 0.02 |
|     95% CI | Ref | 0.95, 1.51 | 1.03, 1.60 | 1.01, 1.68 | 0.97, 1.69 | 0.80, 1.60 | 1.06, 2.02 | 0.98, 2.25 | |

| | 18.5–<23 | 23–<25 | 25–<27.5 | 27.5–<30 | 30–<32.5 | 32.5–<35 | ≥35 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Rectal cancer** | | | | | | | | | |
|   Men | | | | | | | | | |
|     No. of cases | 74 | 101 | 218 | 135 | 74 | 42 | 33 | | |
|     Age-adjusted rate* | 5.0 | 4.0 | 5.2 | 5.1 | 5.0 | 5.6 | 5.5 | | |
|     Age-adjusted HR‡ | 1.0 | 0.80 | 1.05 | 1.03 | 1.01 | 1.19 | 1.12 | | 0.10 |
|     95% CI | Ref | 0.59, 1.08 | 0.81, 1.37 | 0.77, 1.36 | 0.73, 1.40 | 0.81, 1.74 | 0.74, 1.70 | | |
|     MV HR§ | 1.0 | 0.78 | 1.01 | 0.96 | 0.94 | 1.10 | 1.0 | | 0.31 |
|     95% CI | Ref | 0.58, 1.06 | 0.77, 1.31 | 0.72, 1.28 | 0.68, 1.30 | 0.75, 1.61 | 0.68, 1.58 | | |
|   Women | | | | | | | | | |
|     No. of cases | 60 | 49 | 60 | 37 | 26 | 14 | 32 | | |
|     Age-adjusted rate* | 2.6 | 2.8 | 3.0 | 3.2 | 3.0 | 2.7 | 4.1 | | |
|     Age-adjusted HR‡ | 1.0 | 1.06 | 1.18 | 1.21 | 1.16 | 1.02 | 1.61 | | 0.06 |
|     95% CI | Ref | 0.73, 1.55 | 0.82, 1.68 | 0.80, 1.82 | 0.73, 1.84 | 0.57, 1.83 | 1.05, 2.48 | | |
|     MV HR§ | 1.0 | 1.05 | 1.13 | 1.16 | 1.09 | 0.95 | 1.44 | | 0.20 |
|     95% CI | Ref | 0.72, 1.53 | 0.79, 1.63 | 0.76, 1.76 | 0.68, 1.75 | 0.52, 1.71 | 0.92, 2.25 | | |

  * Incidence rate: cases per 10,000 person-years, adjusted for age by 5-year intervals using the direct standardization method.

  † HR, hazard ratio; CI, confidence interval; Ref, referent category; MV, multivariate.

  ‡ In the age-adjusted model, age is the underlying time metric and was adjusted for by incorporation into the baseline hazard.

  § Multivariate model was adjusted for age (by incorporation into the baseline hazard), alcohol, smoking (status and dose), supplemental calcium, and red meat consumption (and hormone replacement therapy use in women).
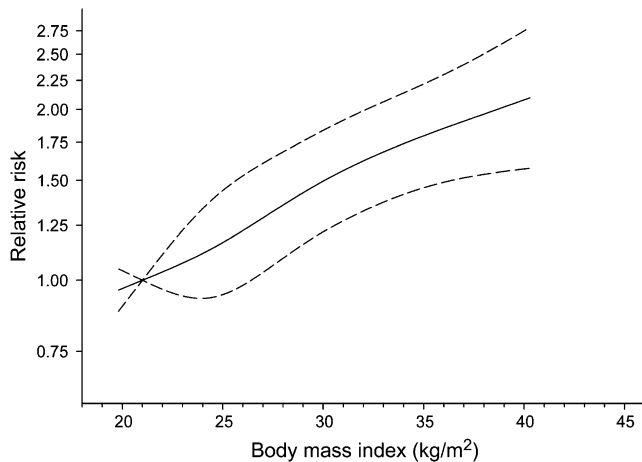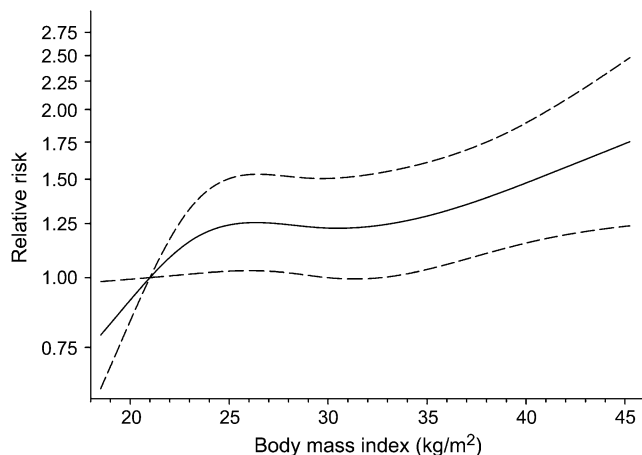
**FIGURE 1.** Relative risk of colon cancer in relation to body mass index in men, NIH–AARP Diet and Health Study, United States, 1995–2000. Relative risks are modeled on a continuous basis by using natural cubic splines. The graph is linear on the beta-coefficient scale; relative risks are exponentiated coefficients. Relative risks are indicated by the solid line and 95% confidence intervals by dashed lines. The reference point is a body mass index of 21 kg/m$^2$, with knots placed at the 2nd, 25th, 75th, and 98th percentiles of the distribution of men's body mass index. The graphic display is truncated at 1% and 99% of men's body mass index. All models were adjusted for age, alcohol consumption, red meat intake, supplemental calcium, family history, and smoking.



**FIGURE 2.** Relative risk of colon cancer in relation to body mass index in women, NIH–AARP Diet and Health Study, United States, 1995–2000. Relative risks are modeled on a continuous basis by using natural cubic splines. The graph is linear on the beta-coefficient scale; relative risks are exponentiated coefficients. Relative risks are indicated by the solid line and 95% confidence intervals by dashed lines. The reference point is a body mass index of 21 kg/m$^2$, with knots placed at the 2nd, 25th, 75th, and 98th percentiles of the distribution of women's body mass index. The graphic display is truncated at 1% and 99% of women's body mass index. All models were adjusted for age, alcohol consumption, red meat intake, supplemental calcium, family history, and smoking.

not shown). Restricting analysis to never smokers did not appreciably affect results for either men or women (data not shown). Within the colon, associations were similar on the left and right sides. Sensitivity analyses indicated that associations were largely unaffected by particular assumptions or procedures. Defining outliers based on biologic plausibility rather than using a statistical approach and not excluding persons with high alcohol or meat intake provided similar results for men, although associations were weakened and no longer statistically significant for women. Multivariate colon cancer risks for women with a BMI of 18.5–<23 kg/m$^2$ (reference category), 23–<25 kg/m$^2$, 25–<27.5 kg/m$^2$, 27.5–<30 kg/m$^2$, 30–<32.5 kg/m$^2$, 32.5–<35 kg/m$^2$, 35–<40 kg/m$^2$, and ≥40 kg/m$^2$ were 1.0, 1.17, 1.26, 1.30, 1.24, 1.05, 1.36, and 1.36, respectively (95 percent confidence interval: 0.88, 2.11; $p$-trend = 0.09). The remaining sensitivity analyses resulted in estimated relative risks very similar to those from the main analysis: analysis of first primary cancers only, exclusion of first year of follow-up, and assigning missing covariates as missing rather than assigning them to categories (data not shown).

Rectal cancer was not associated with BMI in men (table 2). Among women, we observed a borderline significant relation in an age-adjusted ($p = 0.06$) but not multivariate-adjusted ($p = 0.20$) model. In a sensitivity analysis excluding the first year of follow-up, we found marginally significant multivariate relative risks for women for BMI categories of 18.5–<23 kg/m$^2$, 23–<25 kg/m$^2$, 25–<27.5 kg/m$^2$, 27.5–<30 kg/m$^2$, 30–<32.5 kg/m$^2$, 32.5–<35 kg/m$^2$, and ≥35 kg/m$^2$ of 1.0, 1.07, 1.34, 1.29, 1.27, 1.27, and 1.58, respectively (95 percent confidence interval: 0.94, 2.65; $p$-trend = 0.08).

Age did not significantly modify the BMI–colon cancer association for men ($p$-interaction = 0.77, table 3). By contrast, colon cancer was associated with BMI in women aged 50–62 and 63–66 years, but not in those aged 67–71 years. The relation between colon cancer and BMI in the younger two groups was as strong as the BMI–colon cancer association for men. The interaction across the three age groups was not initially statistically significant, but the $p$ value was reduced to 0.05 after combining two younger groups.

HRT did not significantly modify the BMI–colon cancer relation, although we observed a stronger association for current HRT users ($p$-trend = 0.01) than in former users ($p$-trend 0.16) or never users ($p$-trend 0.49; table 4). However, the interaction was not statistically significant ($p$-interaction = 0.28). We additionally stratified on both age (50–66 years at baseline vs. 67–71 years) and HRT use to create six strata. The BMI relation was positive in all three HRT classifications for women in the age group 50–66 years (table 4), whereas, among women in the age group 67–71 years, colon cancer was not associated with BMI in any of the HRT strata (data not shown).

The physical activity index combining sports and non-sports physical activity, time per week spent in moderate to vigorous intensity activity, or time spent sitting per day (inactivity) did not modify the relation between colon cancer and BMI for men or women Alcohol did not modify the colon cancer–BMI association for either men or women, nor did the relation between BMI and colon cancer in women differ by number of years since menopause.

TABLE 3. Associations of body mass index with colon cancer, by age, for participants in the NIH–AARP study, United States, 1995–2000

| | Body mass index category (weight (kg)/height (m)$^2$) | | | | | | | p-trend |
|---|---|---|---|---|---|---|---|---|
| | 18.5–<23 | 23–<25 | 25–<27.5 | 27.5–<30 | 30–<32.5 | 32.5–<35 | ≥35 | |
| **Men, by age (years)*** | | | | | | | | |
| 50–62 | | | | | | | | |
| MV HR† | 1.0 | 0.94 | 0.98 | 1.22 | 1.32 | 1.30 | 1.69 | <0.0005 |
| 95% CI† | Ref† | 0.65, 1.36 | 0.69, 1.38 | 0.86, 1.72 | 0.91, 1.92 | 0.84, 2.00 | 1.11, 2.56 | |
| No. of cases | 44 | 74 | 139 | 121 | 79 | 41 | 49 | |
| 63–66 | | | | | | | | |
| MV HR | 1.0 | 1.26 | 1.42 | 1.53 | 1.67 | 1.73 | 1.80 | 0.002 |
| 95% CI | Ref | 0.87, 1.83 | 1.00, 2.00 | 1.06, 2.19 | 1.13, 2.46 | 1.11, 2.72 | 1.11, 2.91 | |
| No. of cases | 41 | 89 | 167 | 117 | 72 | 36 | 29 | |
| 67–71 | | | | | | | | |
| MV HR | 1.0 | 1.14 | 1.30 | 1.59 | 1.60 | 1.71 | 1.98 | <0.0005 |
| 95% CI | Ref | 0.81, 1.60 | 0.95, 1.77 | 1.14, 2.21 | 1.11, 2.31 | 1.10, 2.67 | 1.24, 3.19 | |
| No. of cases | 51 | 97 | 173 | 129 | 68 | 33 | 27 | |
| Interaction‡ | | | | | | | | 0.77 |
| **Women, by age (years)*** | | | | | | | | |
| 50–62 | | | | | | | | |
| MV HR | 1.0 | 1.16 | 1.24 | 1.43 | 1.26 | 1.17 | 1.76 | 0.03 |
| 95% CI | Ref | 0.76, 1.77 | 0.83, 1.86 | 0.91, 2.25 | 0.76, 2.09 | 0.64, 2.14 | 1.11, 2.78 | |
| No. of cases | 47 | 40 | 49 | 34 | 23 | 14 | 35 | |
| 63–66 | | | | | | | | |
| MV HR | 1.0 | 1.14 | 1.48 | 1.41 | 1.62 | 1.28 | 1.74 | 0.03 |
| 95% CI | Ref | 0.74, 1.77 | 0.99, 2.21 | 0.89, 2.23 | 1.00, 2.63 | 0.69, 2.38 | 1.05, 2.87 | |
| No. of cases | 43 | 39 | 58 | 34 | 29 | 14 | 27 | |
| 67–71 | | | | | | | | |
| MV HR | 1.0 | 1.26 | 1.18 | 1.15 | 1.05 | 0.99 | 0.98 | 0.72 |
| 95% CI | Ref | 0.88, 1.80 | 0.83, 1.69 | 0.76, 1.73 | 0.66, 1.69 | 0.55, 1.79 | 0.57, 1.69 | |
| No. of cases | 61 | 62 | 65 | 38 | 25 | 14 | 18 | |
| Interaction§ | | | | | | | | 0.15 |

* Adjusted for age (by incorporation into the baseline hazard), smoking, supplemental calcium, alcohol, red meat consumption (and hormone replacement therapy use in women).
† MV HR, multivariate hazard ratio; CI, confidence interval; Ref, referent category.
‡ Interaction p-value based on grouped linear interaction terms.
§ p-interaction comparing across three age categories; collapsing age categories to two groups and comparing women aged 50–66 years (grouping 50–62 years and 63–66 years) with those aged 67–71 years, p-interaction = 0.05.

## DISCUSSION

We observed an elevated colorectal cancer risk with higher BMI in both men and women: The increased risk was confined to the colon, whereas rectal cancer risk was unrelated to BMI. Colon cancer risk was clearly elevated for men and women who were merely overweight (i.e., BMI 25–<30 kg/m$^2$). This finding has important public health implications because a substantial proportion of the US population is overweight. Although many studies have been conducted, evidence for a statistically significantly increased colorectal or colon cancer risk for overweight men (12, 24–26) or women (26, 27) is limited, possibly because few studies

to date have had sufficient power to detect such an association. This study included a very large number of overweight participants and enough cases to observe stable, statistically significant increased risks within overweight categories.

Morbidly obese men were at markedly higher risk of colon cancer relative to those less obese (BMI 30–<40 kg/m$^2$). Most previous studies have grouped all participants with a BMI above 29 or 30 kg/m$^2$ into a single category (4, 10–12, 15, 25, 27, 30). We had sufficient numbers of cases with a very high BMI to analyze the three World Health Organization classifications ≥30 kg/m$^2$ defining obesity, including morbid obesity, as distinct and statistically stable categories.

**TABLE 4.  Colon cancer risk in relation to body mass index and HRT\* use† among participants in the NIH–AARP study, United States, 1995–2000**

| | Body mass index category (weight (kg)/height (m)$^2$) | | | | | | p-trend |
|---|---|---|---|---|---|---|---|
| | 18.5–<23 | 23–<25 | 25–<27.5 | 27.5–<30 | 30–<35 | ≥35 | |
| **Women, by HRT use** | | | | | | | |
| Never | | | | | | | |
|   MV HR\* | 1.0 | 1.41 | 1.29 | 1.26 | 1.05 | 1.38 | 0.49 |
|   95% CI\* | Ref\* | 1.04, 1.92 | 0.96, 1.75 | 0.90, 1.77 | 0.75, 1.48 | 0.96, 1.99 | |
|   No. of cases | 76 | 88 | 98 | 61 | 65 | 53 | |
| Former | | | | | | | |
|   MV HR | 1.0 | 0.83 | 0.86 | 0.96 | 1.00 | 1.68 | 0.16 |
|   95% CI | Ref | 0.42, 1.63 | 0.45, 1.62 | 0.47, 1.97 | 0.51, 1.97 | 0.82, 3.58 | |
|   No. of cases | 22 | 14 | 17 | 12 | 15 | 12 | |
| Current | | | | | | | |
|   MV HR | 1.0 | 1.07 | 1.56 | 1.52 | 1.69 | 1.55 | 0.01 |
|   95% CI | Ref | 0.70, 1.63 | 1.06, 2.29 | 0.96, 2.40 | 1.09, 2.64 | 0.85, 2.84 | |
|   No. of cases | 50 | 39 | 57 | 30 | 35 | 14 | |
| Interaction‡ | | | | | | | 0.28 |
| **Women aged 50–66 years at baseline, by HRT use** | | | | | | | |
| Never | | | | | | | |
|   MV HR | 1.0 | 1.21 | 1.23 | 1.17 | 0.94 | 1.54 | 0.22 |
|   95% CI | Ref | 0.79, 1.83 | 0.82, 1.83 | 0.75, 1.84 | 0.60, 1.47 | 0.99, 2.40 | |
|   No. of cases | 45 | 43 | 55 | 34 | 36 | 41 | |
| Former | | | | | | | |
|   MV HR | 1.0 | 0.99 | 1.31 | 1.53 | 1.21 | 2.19 | 0.11 |
|   95% CI | Ref | 0.39, 2.54 | 0.57, 3.02 | 0.63, 3.75 | 0.49, 2.98 | 0.85, 5.61 | |
|   No. of cases | 10 | 8 | 13 | 10 | 10 | 9 | |
| Current | | | | | | | |
|   MV HR | 1.0 | 1.17 | 1.64 | 1.62 | 2.18 | 1.88 | 0.003 |
|   95% CI | Ref | 0.71, 1.95 | 1.02, 2.61 | 0.93, 2.83 | 1.31, 3.63 | 0.95, 3.71 | |
|   No. of cases | 33 | 28 | 39 | 21 | 30 | 12 | |
| Interaction‡ | | | | | | | 0.33 |

\* HRT, hormone replacement therapy; MV HR, multivariate hazard ratio; CI, confidence interval; Ref, referent category.

† Adjusted for age (by incorporation into the baseline hazard), smoking, supplemental calcium, alcohol, and red meat consumption; among postmenopausal women.

‡ Interaction p-value based on grouped linear interaction terms.

Among women, much of the increased colon cancer risk occurred at a relatively low BMI (23–<25 kg/m$^2$ and 25–<27.5 kg/m$^2$ in categorical analysis, within the normal range in continuous analysis), and risk was modified by age. We had sufficient power to analyze age interaction across relatively narrow age groups. Among women aged 50–62 and 63–66 years at baseline, the BMI relation with colon cancer was as strong for women as it was for men, whereas, among women aged 67–71 years, we observed no relation. Our results support the hypothesis (23) that the BMI–colon cancer relation is modified by age in women, but they contradict findings that BMI is related to colon cancer in only those women who are premenopausal or of premenopausal

age (16, 17, 22). We found that overweight and obese women were at increased risk many years beyond menopause. Our results also contrast with the previous report that, among postmenopausal women, BMI is related to colon cancer in HRT users only (21).

We did not find an association between BMI and rectal cancer in men, and only an equivocal relation for women. The previous literature is conflicting (3, 5, 9, 12, 14, 16, 17, 24, 28–31), suggesting that the relation between BMI and rectal cancer, if it exists, is weak.

Our results suggest that physical activity does not diminish the relation between obesity and colon cancer, at least in older age groups. The mechanisms of action hypothesized

for obesity and physical activity overlap considerably (41), so an interaction is plausible. Although others have reported that physical activity attenuated (33) or eliminated (32) the relation between BMI and colon cancer, we found no such evidence. In addition to being an independent protective factor for colon cancer risk, physical activity may help keep body weight in check, which our study suggests would be beneficial. However, we did not find that being "heavy but physically active" conferred protection from colon cancer.

Possible modes of action by which obesity could increase colorectal cancer risk include insulin resistance (20, 42), chronic inflammation (43, 44), and increased colorectal epithelial proliferation (45, 46). Because this study found elevated risks well beyond the age of menopause and did not find convincing effect modification by HRT status, it does not support previously proposed hypotheses related to an interaction of estrogen and insulin (21, 23). However, measures of adiposity other than BMI may be more closely related to insulin, may better predict colon cancer in women, and so may be better able to demonstrate such an interaction.

The NIH–AARP cohort of more than 500,000 people has accumulated over 3,300 colorectal cancer cases. Large sample size permitted stable, relatively precise estimates across a wide BMI range, including analysis of key subgroups. Importantly, the very contemporary nature of the cohort reflects the experience of the generation currently at elevated colon cancer risk in the United States and abroad. A limitation of our study is the relatively short follow-up of participants (average, 4.5 years), although it is likely that long-term BMI ranking of study participants is reflected in the baseline BMI distribution. Self-reported height and weight are unlikely to be limiting because correlations between self-reported and measured weight are quite good (37), as is recalled weight (47). In addition, we demonstrated a strong relation between BMI and total mortality in this cohort (48), lending some validity to our capture of relative weight.

In conclusion, this study demonstrates that colon cancer risk increases with BMI in a nearly linear manner for men, and it increases through the normal and overweight range for women. Even men and women who were only overweight, which is a high proportion of US adults in the age range 50–70 years, were at higher risk than those who were leaner. Although the literature suggests that BMI is only weakly associated with colon cancer in women or that the association is restricted to those who are premenopausal, we found that excess weight was a risk factor for women at least through age 66 years and that, in this age group, associations were as strong as they were for men. Physical activity did not dampen the association between colon cancer and excess weight, indicating the importance of weight control as a prevention strategy for this very common malignancy.

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