Body Size and Risk of Colon and Rectal Cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC)

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Background: **Body weight and body mass index (BMI) are positively related to risk of colon cancer in men, whereas weak or no associations exist in women. This discrepancy may be related to differences in fat distribution between sexes or to the use of hormone replacement therapy (HRT) in women.** ***Methods:*** **We used multivariable adjusted Cox proportional hazards models to examine the association between anthropometric measures and risks of colon and rectal cancer among 368 277 men and women who were free of cancer at baseline from nine countries of the European Prospective Investigation Into Cancer and Nutrition. All statistical tests were two-sided.** ***Results:*** **During 6.1 years of follow-up, we identified 984 and 586 patients with colon and rectal cancer, respectively. Body weight and BMI were statistically significantly associated with colon cancer risk in men (highest versus lowest quintile of BMI, relative risk [RR] = 1.55, 95% confidence interval [CI] = 1.12 to 2.15; P_{trend} = .006) but not in women. In contrast, comparisons of the highest to the lowest quintile showed that several anthropometric measures, including waist circumference (men, RR = 1.39, 95% CI = 1.01 to 1.93; P_{trend} = .001; women, RR = 1.48, 95% CI = 1.08 to 2.03; P_{trend} = .008), waist-to-hip ratio (WHR; men, RR = 1.51, 95% CI = 1.06 to 2.15; P_{trend} = .006; women, RR = 1.52, 95% CI = 1.12 to 2.05; P_{trend} = .002), and height (men, RR = 1.40, 95% CI = 0.99 to 1.98; P_{trend} = .04; women, RR = 1.79, 95% CI = 1.30 to 2.46; P_{trend}<.001) were related to colon cancer risk in both sexes. The estimated absolute risk of developing colon cancer within 5 years was 203 and 131 cases per 100 000 men and 129 and 86 cases per 100 000 women in the highest and lowest quintiles of WHR, respectively. Upon further stratification, no association of waist circumference and WHR with risk of colon cancer was observed among postmenopausal women who used HRT. None of the anthropometric measures was statistically significantly related to rectal cancer.** ***Conclusions:*** **Waist circumference and WHR, indicators of abdominal obesity, were strongly associated with colon cancer risk in men and women in this population. The association of abdominal obesity with colon cancer risk may vary depending on HRT use in postmenopausal women; however, these findings require confirmation in future studies. [J Natl Cancer Inst 2006;98:920–31]**

A possible association between body size and risk of colorectal cancer has been examined in many epidemiologic studies *(1–30)*. In general, body weight and body mass index (BMI) have been found to be positively related to risk of colon cancer in men, whereas weaker or no associations have been reported for women *(1–30)*. Among the smaller number of studies that examined associations with rectal cancer, most found no association with

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body weight or BMI *(2–5,12,17,27,30)*. The reasons for the apparent discrepancy in the association of body weight with colon cancer risk between men and women are unclear.

One potential reason for the discrepancy is that men and women have different body compositions. Fat makes up a lower percentage of the body mass of men (approximately 20%) than of women (approximately 30%). The relationship of body weight to fat distribution also differs between men and women. Higher body weight is more closely related to abdominal obesity than lower body obesity in men and more closely related to gluteofemoral obesity than to abdominal obesity in women. Furthermore, upper-body fat has been shown to be more strongly associated with metabolic abnormalities than lower-body obesity *(31,32)*. However, only a few prospective studies have examined the association of body fat distribution—as reflected by waist and hip circumference—and colon cancer risk *(11,13,14,19,21)*. Also, in most of these studies *(11,13,14)*, waist and hip circumference were self-reported rather than measured.

Other reasons for sex differences in the association between adiposity and colon cancer risk may be related to use of hormone replacement therapy (HRT) in postmenopausal women. Postmenopausal HRT use has been associated with reduced risk of colon cancer in observational and intervention studies *(33–36)* and has been shown to affect the association between body weight and postmenopausal breast cancer *(37)*; however, little is known about associations with colon cancer *(20)*.

The aim of this study was to examine the association between anthropometric measures, including waist and hip circumference, and risk of colon and rectal cancer in participants of the European Prospective Investigation Into Cancer and Nutrition (EPIC), a large European cohort study. In particular, we examined whether body fat distribution is related to risk of colon and rectal cancer. Furthermore, we aimed to examine whether the associations differ among postmenopausal women who were HRT users and those who were not.

Subjects and Methods

Study Population

The EPIC is an ongoing multicenter prospective cohort study designed primarily to investigate the relationship between nutrition and cancer. The EPIC study consists of subcohorts recruited in 23 administrative centers in 10 European countries—Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom. The 519 978 eligible male and female participants were aged between 25 and 70 years at enrollment (1992–2000) and were recruited from the general population residing in a given geographic area (i.e., town or province). Exceptions were the French cohort (based on female members of a health insurance plan for school employees), the Utrecht cohort in The Netherlands (based on women attending breast cancer screening), the Ragusa cohort in Italy (based on blood donors and their spouses), and the Oxford cohort in the United Kingdom (including mainly vegetarian volunteers and healthy eaters). Eligible subjects were invited to participate in the study, and those who accepted gave written informed consent and completed questionnaires on their diet, lifestyle, and medical history. Subjects were then invited to a center to provide a blood sample and to have anthropometric measurements taken. The methods have been reported in full by Riboli et al. *(38,39)*. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local institutions where subjects had been recruited for the EPIC study.

This study is based on 495 417 participants without prevalent cancer at any site at baseline, as reported on the lifestyle questionnaire or based on information from the cancer registries. We excluded the Umea, Sweden, cohort (n = 24 811) because participants did not provide information on leisure time physical activity that was compatible with the other EPIC questionnaires. We also excluded subjects without measured body height or weight and thus excluded the cohorts from Norway (n = 35 956), 48 960 participants from the French cohorts, and 7903 participants from the other cohorts. For the "health-conscious" group based in Oxford (UK), linear regression models were used to predict sex- and age-specific values from subjects with both measured and self-reported body measures, as previously described *(40,41)*. We further excluded 2166 participants with missing questionnaire data or with missing dates of diagnosis or follow-up and, to reduce the impact on the analysis of implausible extreme values, the 7344 participants who were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement that was calculated from body weight, height, and age *(42)*. Therefore, the study included a total of 368 277 participants.

Assessment of Endpoints

Incident colorectal cancer case patients were identified by population cancer registries (Denmark, Italy, The Netherlands, Spain, Sweden, the United Kingdom) or by active follow-up (France, Germany, Greece), depending on the follow-up system in each of the participating centers. Active follow-up used a combination of methods, including health insurance records, cancer and pathology registries, and direct contact with participants or next of kin. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Follow-up began at the date of enrollment and ended at either the date of diagnosis of colorectal cancer, death, or last complete follow-up. By April 30, 2004, for the centers using record linkage with cancer registry data, complete follow-up was available through December 31, 1999 (Turin, Italy); June 30, 2000 (Bilthoven, The Netherlands); December 31, 2000 (Asturias and Murcia, Spain; Cambridge, UK); December 31, 2001 (Oxford, UK; Malmö, Sweden; Florence, Naples, Ragusa, and Varese, Italy); December 31, 2002 (Granada, Navarra, and San Sebastian, Spain; Aarhus and Copenhagen, Denmark); and June 30, 2003 (Utrecht, The Netherlands). For the centers using active follow-up, the last contact dates were June 30, 2002 (France); November 19, 2002 (Greece); December 16, 2003 (Heidelberg, Germany); and March 11, 2004 (Postdam, Germany). Mortality data were coded following the rules of the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), and cancer incidence data were coded according to the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). We included all patients with colon (C18) and rectal (C19, C20) cancer.

Assessment of Anthropometric Data, Diet, and Lifestyle Factors

Weight and height were measured with subjects wearing no shoes to the nearest 0.1 kg, and—depending on study center—to

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the nearest 0.1, 0.5, or 1.0 cm, respectively *(40)*. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured either at the narrowest torso circumference (France; Italy; Utrecht, The Netherlands; Denmark) or at the midpoint between the lower ribs and iliac crest (Bilthoven, The Netherlands; Potsdam, Germany; Malmö, Sweden; Oxford, UK, general population). In Spain; Greece; Heidelberg, Germany; and Cambridge, UK, a combination of methods was used, although most participants were measured at the narrowest torso circumference. Hip circumference was measured at the widest circumference (France; Italy; Spain; Bilthoven, The Netherlands; Greece; Malmö, Sweden) or over the buttocks (the United Kingdom; Utrecht, The Netherlands; Germany; Denmark). Results of the present analyses for waist and hip circumference were similar for the different assessment methods. Waist and hip circumference measurements were missing for 3869 (1.05%) and 6399 (1.74%) participants, respectively, who were excluded for analyses on these variables. For this study, body weight and waist and hip circumference were corrected, as described in detail elsewhere *(40)*, to reduce heterogeneity due to protocol differences in clothing worn during measurement.

Diet during the 12 months before enrollment was measured by country-specific validated questionnaires *(43)*. Most centers adopted a self-administered dietary questionnaire covering 88–266 food items. In Greece, Spain, and Ragusa, Italy, the questionnaire was administered at a personal interview. In Malmö, Sweden, a questionnaire combined with a food record was used. Country-specific food composition tables were used to calculate nutrient intakes *(44)*.

Recreational and household activity was computed as average metabolic equivalent-hours (MET-hr), based on the types and durations of activities reported separately for summer and winter on the baseline questionnaires. The reported activities included walking, cycling, gardening, sports and exercise, housework, home repair (do-it-yourself activities), stair climbing, and vigorous recreational activity. Each type of activity was assigned a specific MET value according to Ainsworth et al. *(45)*. Occupational activity was coded as sedentary occupation, standing occupation, manual work, heavy manual work, unemployed, or missing, as reported on the questionnaire. To create a variable for total physical activity, subjects were cross-classified on the basis of sex-specific quartiles of recreational and household activity and on categories of occupational work and were coded as inactive, moderately inactive, moderately active, active, and missing.

Information on sociodemographic and lifestyle characteristics and medical history was obtained from standardized questionnaires at study entry *(38)*. Women were classified according to menopausal status at enrollment on the basis of an algorithm that accounts for complete and combined information on menstrual status/history, type of menopause (natural, bi-/unilateral oophorectomy, hysterectomy), and use of oral contraceptives and menopausal hormones *(37)*. Current HRT use refers to the use of menopausal hormones at the time of recruitment as derived from the country-specific questionnaires or during interviews, and includes estrogen alone and combined estrogen–progestin preparations. The prevalence of HRT use within EPIC has been described in detail elsewhere *(46)*.

Statistical Analyses

We analyzed the association between anthropometric variables and risks of colon and rectal cancer separately for men and women by calculating relative risks (RRs) as incident rate ratios using Cox proportional hazards models. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age at colorectal cancer diagnosis or censoring, respectively. Subjects were grouped into quintiles on the basis of the anthropometric variables of the entire male or female cohorts, respectively. We also performed additional analyses by grouping participants into predefined well-established categories for BMI (<25, 25–<30, or ≥30 kg/m^2), waist circumference (<102 or ≥102 cm in men, and <88 or ≥ 88 in women), and waist-to-hip ratio (WHR; <0.95 or ≥0.95 in men; and <0.80 or ≥0.80 in women) *(47,48)*. Models were stratified by age at recruitment and by study center to reduce sensitivity to any violations of the proportional hazards assumption. We further adjusted the analysis for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol consumption (grams/day, continuous), physical activity (inactive, moderately inactive, moderately active, active, missing), fiber intake (grams/day, continuous), and consumption of red and processed meat, fish and shellfish, and fruits and vegetables (all grams/day, continuous). Analyses of weight, waist and hip circumference, and WHR were also adjusted for body height, and, in additional models, for body weight. We also performed additional analyses that adjusted for total energy intake; however, because the overall results did not change substantially, we did not include energy intake in our analysis. To test for linear trend across categories, we used the median anthropometric variable within quintiles as a continuous variable. In separate analyses we included body size measures as continuous variables in the models to estimate the relative risk of colon and rectal cancer per unit increase in each anthropometric variable. Differences in the associations across study centers were assessed with the chi-square test using heterogeneity statistics that are based on the inverse variance method *(49)*. To test for differences between sexes, we performed the analysis with men and women combined and added an interaction term to the model. Among postmenopausal women we further stratified the analysis by HRT use and tested for differences between HRT and non-HRT users by adding an interaction term. The proportional hazards assumption was checked by adding an interaction term of the main exposure variable with time to each model. The interaction term was not statistically significant (at the 5% level) in any model. Absolute risks were estimated from the survivor function with covariates (including age) set to sex-specific mean levels.

All P values presented are two-tailed, and $P<.05$ was considered statistically significant. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

A total of 368 277 participants were monitored for an average 6.1 ± 1.7 years, for a total of 2 254 727 person-years (Table 1). During follow-up, 1570 members of the cohort were diagnosed with colorectal cancer (984 colon, 586 rectum). Mean age at baseline was 51.7 years; 64.8% of participants were female.

We compared the age-standardized characteristics of the EPIC participants at baseline by BMI quintile for men and women, respectively (men and women in higher BMI categories were older than those in the lower BMI categories; Table 2). Alcohol

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Table 1. Cohort characteristics, the European Prospective Investigation into Cancer and Nutrition

Country	Cohort size, n		Mean age, y		Person-years		Colon cancer, n		Rectal cancer, n		Mean BMI, kg/m^2*		Mean WHR*	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
France	0	19752	0	52.8	0	167895	0	53	0	8	0	23.2	0	0.777
Italy	13895	30325	50.2	50.7	74170	187029	44	64	17	26	26.5	25.7	0.936	0.797
Spain	14986	24616	50.7	48.3	102413	162305	39	39	26	15	28.5	28.4	0.951	0.829
United Kingdom	22542	50998	53.1	47.7	118468	277133	92	91	33	54	25.4	24.5	0.914	0.769
The Netherlands	9890	27484	43.2	51.0	50057	181701	11	100	11	46	26.0	25.2	0.926	0.789
Greece	10529	14922	52.9	53.3	38776	55514	7	6	7	5	27.9	28.4	0.955	0.814
Germany	21340	27712	52.4	49.1	124150	162055	58	44	53	16	27.0	25.8	0.944	0.800
Sweden	10263	14010	59.0	57.3	79008	105781	48	58	46	42	25.6	24.4	0.933	0.782
Denmark	26286	28727	56.6	56.7	174439	193832	122	108	102	79	26.4	25.0	0.949	0.796
Total	129731	238546	52.8	51.1	761482	1493245	421	563	295	291	26.6	25.5	0.939	0.792

*Values are age adjusted. BMI = body mass index; WHR = waist-to-hip ratio.

consumption was positively related to BMI in men but inversely related to BMI in women. Both men and women in the higher BMI categories were less likely than those in the lower BMI categories to be current smokers and more likely to have a lower education level. Men in the higher BMI categories were less likely to be never smokers, whereas women in the higher BMI categories were more likely to be never smokers. Among postmenopausal women, HRT use was more common among leaner women. Subjects in the higher BMI categories had higher intake of all food groups analyzed (fruits and vegetables, fish and shellfish, and meat and meat products) than subjects in the lower BMI categories. WHR was more closely related to BMI in men than in women. Age-adjusted Pearson correlation coefficients for the association of BMI with waist and hip circumference and WHR were $r = 0.86$, $r = 0.77$, and $r = 0.56$, respectively, for men, and $r = 0.85$, $r = 0.86$, and $r = 0.43$, respectively, for women (all $P<.001$).

We examined relative risks of colon cancer by quintile of anthropometric variables in men and women (Table 3). In both sexes, there was a statistically significant trend of increasing relative risks of colon cancer across quintile of height (for men [≥180.5 cm versus < 168.0 cm], RR = 1.40, 95% CI = 0.99 to 1.98; $P_{trend} = 0.04$; for women [≥167.5 cm versus <156.0 cm], RR = 1.79, 95% CI = 1.30 to 2.46; $P_{trend}<.001$; Table 3). On a continuous scale, a 5-cm higher body height was related to an increased risk of colon cancer in both men (RR = 1.09, 95% CI = 1.01 to 1.18; $P = .02$) and women (RR = 1.12, 95% CI = 1.04 to 1.20; $P = .003$) ($P = .33$ for difference in the association between men and women).

Among men, weight and BMI were associated with a higher risk of colon cancer (weight ≥ 90.0 kg versus <71 kg, RR = 1.43, 95% CI = 1.02 to 2.02; $P_{trend} = .007$; BMI ≥ 29.4 kg/m^2 versus <23.6 kg/m^2, RR = 1.55, 95% CI = 1.12 to 2.15; $P_{trend} = .006$; Table 3) but not among women. Per unit increase, higher body weight and BMI were associated with colon cancer risk in men (per 5 kg of higher body weight, RR = 1.09, 95% CI = 1.04 to 1.13; $P<.001$; per kg/m^2 higher BMI, RR = 1.05, 95% CI = 1.02 to 1.08; $P<.001$). However, among women the association was weaker and only marginally statistically significant (per 5 kg higher body weight, RR = 1.04, 95% CI = 1.00 to 1.08; $P = .03$; $P = .35$ for difference to men; per kg/m^2 higher BMI, RR = 1.02, 95% CI = 1.00 to 1.04; $P = .07$; $P = .04$ for difference to men).

In both sexes, waist circumference was positively related to risk of colon cancer (for men [≥103.0 cm versus <86.0 cm], RR = 1.39, 95% CI = 1.01 to 1.93; $P_{trend} = .001$; for women [≥89.0 cm versus <70.2 cm], RR = 1.48, 95% CI = 1.08 to 2.03; $P_{trend} = .008$)). Per 5 cm higher waist circumference, the relative risk for men was 1.10 (95% CI = 1.05 to 1.56; $P<.001$) and for women was 1.07 (95% CI = 1.03 to 1.12; $P<.001$; $P = .48$ for difference between men and women). In contrast, hip circumference was statistically significantly positively related to colon cancer in men (per 5 cm higher hip circumference, RR = 1.12, 95% CI = 1.05 to 1.21; $P = .002$) but not in women (RR = 1.04, 95% CI = 0.99 to 1.09; $P = .10$; $P = .15$ for difference between men and women).

WHR was positively related to colon cancer risk in both men (RR per 0.1 higher WHR, RR = 1.24, 95% CI = 1.05 to 1.46; $P = .01$) and women (per 0.1 higher WHR, RR = 1.24, 95% CI = 1.10 to 1.39; $P<.001$) ($P = .92$ for difference between men and women). In fact, of all anthropometric parameters, WHR showed the strongest association with colon cancer (highest versus lowest quintile for men, RR = 1.51, 95% CI = 1.06 to 2.15; $P_{trend} = .006$; for women, RR = 1.52, 95% CI = 1.12 to 2.05; $P_{trend} = .002$). The estimated absolute 5-year rate of developing colon cancer per 100000 subjects were, for men, 203 cases (95% CI = 155 to 250) in the highest quintile of WHR and 131 cases (95% CI = 91 to 170) in the lowest and, for women, 129 cases (95% CI = 102 to 156) in the highest quintile of WHR and 86 (95% CI = 63 to 108) in the lowest. We found no statistically significant heterogeneity across study centers for any of the associations of the anthropometric measures with colon cancer risk in men or women ($P_{heterogeneity} = 0.34–0.92$). We examined the consistency of our findings by excluding 239 patients diagnosed during the first 2 years of follow-up, to eliminate the possible effects of changes in body weight and fat distribution in the prediagnostic disease phase. After exclusion, the relative risk of colon cancer per 0.1 higher WHR was 1.26 (95% CI = 1.04 to 1.52; $P = .02$) in men, and 1.25 (95% CI = 1.09 to 1.42; $P = .001$) in women. Thus, these patients did not bias the results.

There was no statistically significant association of any of the anthropometric measures with rectal cancer (Table 4). The apparent nonlinear relationship for WHR in men may be due to the low number of case patients in the reference category.

We further divided participants into groups based on well-established risk categories for BMI, waist circumference, and

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Table 2. Characteristics of study participants in the European Prospective Investigation into Cancer and Nutrition by body mass index (BMI)*

	Men, quintile of BMI, kg/m^2					Women, quintile of BMI, kg/m^2				
	1	2	3	4	5	1	2	3	4	5
	Range	<23.6	23.6–25.3	25.4–27.0	27.1–29.3	≥29.4	<21.7	21.7–23.6	23.7–25.7	25.8–28.8	≥28.9
Characteristic	Mean	22.0	24.6	26.3	28.2	32.0	20.2	22.7	24.7	27.2	32.7
N		25 946	25 948	25 947	25 956	25 934	47 736	47 683	47 706	47 714	47 707
Mean age, y		50.3	52.6	53.3	53.8	54.0	46.7	49.7	51.7	53.3	54.1
Mean alcohol intake, g/day		20.0	21.3	22.2	23.3	24.7	9.6	9.6	8.9	7.9	6.0
Smoking status†, %											
Never smoker		33.9	32.0	30.3	27.9	26.5	52.7	52.9	53.5	56.8	62.6
Past smoker		29.9	36.1	39.1	41.1	42.1	23.0	25.0	24.6	22.7	19.8
Current smoker		34.9	30.4	29.0	29.5	29.9	23.1	21.2	21.1	19.7	16.6
Education†, %											
No school degree or primary school		21.7	24.8	28.5	35.4	42.5	14.6	19.4	26.5	35.7	47.1
Technical or professional school		24.3	25.2	25.8	25.3	23.7	24.2	26.2	26.0	24.6	21.3
Secondary school		15.7	16.0	15.2	13.8	12.9	24.7	23.2	21.6	19.0	15.3
University degree		34.7	30.8	27.4	22.6	17.8	31.6	26.2	21.3	16.2	11.2
Total physical activity†, %											
Inactive		19.8	20.4	20.2	19.9	19.9	19.0	17.8	16.2	14.0	11.4
Moderately inactive		28.9	28.2	28.4	28.9	29.1	37.1	33.4	30.9	28.5	26.6
Moderately active		35.7	34.9	35.5	35.3	36.2	34.8	38.5	42.2	46.9	51.5
Active		13.1	13.9	13.3	13.6	13.1	8.0	9.0	9.2	9.2	9.2
Menopausal status†, %											
Premenopausal		—	—	—	—	—	33.3	33.6	33.8	33.8	33.9
Perimenopausal		—	—	—	—	—	13.1	13.0	12.6	12.4	11.9
Postmenopausal		—	—	—	—	—	45.9	45.6	45.6	45.0	44.6
Surgical postmenopausal		—	—	—	—	—	2.4	2.8	3.1	3.8	4.7
HRT use among postmenopausal women†, %											
No		—	—	—	—	—	69.6	71.4	73.7	78.1	84.4
Yes		—	—	—	—	—	28.3	26.4	24.2	20.2	14.2
Mean weight, kg		68.2	75.5	80.1	85.2	95.7	54.1	60.3	64.8	70.5	83.1
Mean height, cm		175.8	175.2	174.5	173.8	172.7	163.3	162.8	162.0	160.9	159.4
Mean waist circumference, cm		83.7	89.7	93.8	98.4	107.4	69.2	74.0	78.3	83.9	95.1
Mean hip circumference, cm		94.2	97.9	100.3	103.0	108.8	91.9	96.3	99.7	104.0	113.4
Mean waist-to-hip ratio		0.89	0.92	0.94	0.96	0.99	0.75	0.77	0.79	0.80	0.84
Mean fiber intake, g/day		24.6	24.4	24.4	24.7	25.1	22.9	22.8	22.7	22.7	23.0
Mean fruit and vegetable intake, g/day		393.0	417.2	434.3	465.2	496.5	466.2	477.2	485.9	507.8	538.3
Mean fish and shellfish intake, g/day		34.9	37.1	38.9	41.1	43.4	29.2	30.7	31.7	33.2	34.2
Mean red and processed meat intake, g/day		95.5	102.1	105.7	110.1	116.4	59.8	63.6	67.5	70.6	73.6

*All values except age, BMI, and number of subjects are age standardized. HRT = hormone replacement therapy.

†Numbers do not add up to 100% because of missing values; — = not applicable.

WHR, respectively. Compared with nonoverweight subjects (BMI < 25 kg/m^2), the relative risk for colon cancer was 1.00 (95% CI = 0.80 to 1.26) for overweight men (BMI = 25–29.9 kg/m^2) and 1.16 (95% CI = 0.96 to 1.40) for overweight women, and 1.41 (95% CI = 1.06 to 1.88; P_{trend} = .03) for obese men (BMI ≥ 30 kg/m^2) and 1.07 (95% CI = 0.82 to 1.38; P_{trend} = .41) for obese women. Among men, those with a waist circumference of at least 102 cm had a higher risk for colon cancer than those with a waist circumference of less than 102 cm (RR = 1.37, 95% CI = 1.10 to 1.70; P = .004), whereas among women, risk did not differ between those with a waist circumference at least 88 cm versus less than 88 cm (RR = 1.18; 95% CI = 0.97 to 1.43; P = .10). However, men in the higher WHR category had a higher risk of colon cancer (≥0.95 versus <0.95, RR = 1.44, 95% CI = 1.17 to 1.76; P<.001), and the same was true for women (≥0.80 versus <0.80, RR = 1.27, 95% CI = 1.06 to 1.51; P = .008). The absolute 5-year rate of colon cancer per 100 000 individuals was 206 cases (95% CI = 167 to 245) for men with a WHR of at least 0.95 and 144 cases (95% CI = 117 to 171) for men with a WHR less than 0.95, 115 cases (95% CI = 95 to 135) for women with a WHR of at least 0.80, and 91 cases (95% CI = 76 to 106) for women with a WHR less than 0.80.

In analyses that also adjusted for body weight, waist and hip circumference and WHR were not statistically significantly related to risk of colon cancer in men, whereas WHR remained statistically significant in women (Table 5). Results were similar when we adjusted these analyses for BMI instead of for weight and height (highest versus lowest WHR quintile adjusted

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Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) of colon cancer across quintiles of anthropometric measures in the European Prospective Investigation into Cancer and Nutrition

Men				Women			
Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡	Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡
Height, cm				Height, cm			
<168.0	79	1 (Referent)	1 (Referent)	<156.0	80	1 (Referent)	1 (Referent)
168.0–172.4	84	1.09 (0.79 to 1.50)	1.10 (0.80 to 1.52)	156.0–159.9	106	1.34 (0.99 to 1.80)	1.33 (0.99 to 1.80)
172.5–176.1	86	1.14 (0.82 to 1.57)	1.16 (0.84 to 1.60)	160.0–163.2	141	1.72 (1.29 to 2.30)	1.71 (1.28 to 2.28)
176.2–180.4	91	1.26 (0.91 to 1.74)	1.29 (0.93 to 1.79)	163.3–167.4	128	1.68 (1.25 to 2.27)	1.66 (1.23 to 2.24)
≥180.5	81	1.33 (0.95 to 1.87)	1.40 (0.99 to 1.98)	≥167.5	108	1.82 (1.33 to 2.50)	1.79 (1.30 to 2.46)
P_{trend}§		.06	.04	P_{trend}§		<.001	<.001
Weight, kg				Weight, kg			
<71.0	72	1 (Referent)	1 (Referent)	<56.9	83	1 (Referent)	1 (Referent)
71.0–76.9	68	0.94 (0.67 to 1.31)	0.91 (0.65 to 1.28)	56.9–62.0	100	1.20 (0.89 to 1.60)	1.14 (0.84 to 1.53)
77.0–82.7	79	1.12 (0.81 to 1.54)	1.06 (0.76 to 1.48)	62.1–67.4	108	1.19 (0.89 to 1.59)	1.10 (0.82 to 1.49)
82.8–89.9	93	1.33 (0.97 to 1.82)	1.24 (0.89 to 1.73)	67.5–74.9	137	1.35 (1.02 to 1.78)	1.23 (0.91 to 1.64)
≥90.0	109	1.57 (1.16 to 2.13)	1.43 (1.02 to 2.02)	≥75.0	135	1.40 (1.06 to 1.86)	1.25 (0.93 to 1.70)
P_{trend}§		<.001	.007	P_{trend}§		.02	.14
BMI, kg/m^2				BMI, kg/m^2			
<23.6	64	1 (Referent)	1 (Referent)	<21.7	87	1 (Referent)	1 (Referent)
23.6–25.3	85	1.20 (0.86 to 1.66)	1.18 (0.85 to 1.63)	21.7–23.5	96	0.92 (0.69 to 1.23)	0.92 (0.68 to 1.23)
25.4–27.0	74	1.03 (0.74 to 1.45)	1.00 (0.71 to 1.41)	23.6–25.7	120	1.02 (0.77 to 1.35)	1.02 (0.77 to 1.35)
27.1–29.3	88	1.24 (0.89 to 1.72)	1.19 (0.85 to 1.66)	25.8–28.8	137	1.09 (0.83 to 1.44)	1.09 (0.83 to 1.45)
≥29.4	110	1.64 (1.19 to 2.25)	1.55 (1.12 to 2.15)	≥28.9	123	1.04 (0.78 to 1.39)	1.06 (0.79 to 1.42)
P_{trend}§		.002	.006	P_{trend}§		.46	.40
Waist circumference, cm				Waist circumference, cm			
<86.0	63	1 (Referent)	1 (Referent)	<70.2	62	1 (Referent)	1 (Referent)
86.0–91.8	57	0.75 (0.53 to 1.08)	0.73 (0.50 to 1.04)	70.2–75.8	91	1.13 (0.81 to 1.56)	1.10 (0.80 to 1.52)
91.9–96.5	78	1.03 (0.74 to 1.44)	0.97 (0.69 to 1.36)	75.9–80.9	125	1.27 (0.93 to 1.73)	1.23 (0.90 to 1.68)
96.6–102.9	95	1.20 (0.87 to 1.66)	1.10 (0.79 to 1.53)	81.0–88.9	135	1.29 (0.95 to 1.76)	1.25 (0.91 to 1.70)
≥103.0	125	1.56 (1.14 to 2.14)	1.39 (1.01 to 1.93)	≥89.0	149	1.53 (1.12 to 2.09)	1.48 (1.08 to 2.03)
P_{trend}§		<.001	.001	P_{trend}§		.004	.008
Hip circumference, cm				Hip circumference, cm			
<95.2	71	1 (Referent)	1 (Referent)	<93.7	83	1 (Referent)	1 (Referent)
95.2–98.9	62	0.93 (0.66 to 1.31)	0.90 (0.64 to 1.27)	93.7–97.9	90	1.03 (0.76 to 1.39)	0.99 (0.73 to 1.34)
99.0–101.9	97	1.13 (0.83 to 1.55)	1.08 (0.78 to 1.48)	98.0–101.9	137	1.16 (0.88 to 1.52)	1.09 (0.82 to 1.44)
102.0–105.9	76	1.36 (0.98 to 1.89)	1.27 (0.90 to 1.78)	102.0–107.9	108	1.10 (0.82 to 1.47)	1.02 (0.76 to 1.38)
≥106.0	110	1.51 (1.11 to 2.06)	1.37 (0.99 to 1.90)	≥108.0	142	1.28 (0.97 to 1.70)	1.20 (0.89 to 1.60)
P_{trend}§		<.001	.01	P_{trend}§		.07	.19
WHR				WHR			
<0.887	48	1 (Referent)	1 (Referent)	<0.734	68	1 (Referent)	1 (Referent)
0.887–0.922	72	1.19 (0.83 to 1.72)	1.16 (0.80 to 1.68)	0.734–0.768	94	1.06 (0.78 to 1.46)	1.07 (0.78 to 1.47)
0.923–0.952	77	1.19 (0.83 to 1.72)	1.15 (0.79 to 1.65)	0.769–0.802	113	1.13 (0.83 to 1.53)	1.15 (0.84 to 1.56)
0.953–0.989	109	1.63 (1.15 to 2.31)	1.54 (1.08 to 2.19)	0.803–0.845	125	1.17 (0.86 to 1.58)	1.19 (0.88 to 1.61)
≥0.990	110	1.63 (1.15 to 2.31)	1.51 (1.06 to 2.15)	≥0.846	160	1.48 (1.10 to 2.00)	1.52 (1.12 to 2.05)
P_{trend}§		<.001	.006	P_{trend}§		.003	.002

*Number of colon cancer patients. BMI = body mass index; WHR = waist-to-hip ratio.

†Crude model is derived from Cox regression using age as the underlying time variable and stratified by center and age at recruitment.

‡Multivariable models for height and BMI were based on the crude model with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous). Multivariable model for weight, waist, hip, and WHR were further adjusted for height (continuous).

§P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald chi-square statistic.

for BMI in men, RR = 1.19, 95% CI = 0.80 to 1.77; P_{trend} = .26; in women, RR = 1.46, 95% CI = 1.06 to 2.01; P_{trend} = .01). Conversely, no statistically significant association was observed for BMI after adjustment for WHR among men or women.

When we restricted the analysis to women who were postmenopausal at baseline (including 424 postmenopausal women who developed colon cancer), the results were similar to those in women overall (data not shown). Among postmenopausal women, 336 colon cancer patients (75.1%) reported no HRT use at baseline, and 81 patients (23.3%) reported HRT use; for the remaining 7 patients, information on HRT use was unavailable. The positive associations for waist circumference and WHR with risk of colon cancer were restricted to postmenopausal women who did not use HRT at baseline (Table 6) (for difference between postmenopausal women with and without HRT use for the association of colon cancer with waist circumference, P = .05; and for the association with WHR, P = .19). HRT alone was not statistically significantly related to colon cancer risk in postmenopausal women.

Discussion

In this large prospective cohort study, we found that body weight and BMI were statistically significantly related to colon

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Table 4. Relative risks (RRs) and 95% confidence intervals (CIs) of rectal cancer across quintiles of anthropometric measures in the European Prospective Investigation into Cancer and Nutrition

Men				Women			
Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡	Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡
Height, cm				Height, cm			
<168.0	53	1 (Referent)	1 (Referent)	<156.0	50	1 (Referent)	1 (Referent)
168.0–172.4	74	1.32 (0.91 to 1.90)	1.30 (0.90 to 1.87)	156.0–159.9	61	1.03 (0.70 to 1.51)	1.03 (0.70 to 1.52)
172.5–176.1	57	0.99 (0.67 to 1.47)	0.97 (0.65 to 1.44)	160.0–163.2	83	1.24 (0.86 to 1.80)	1.25 (0.86 to 1.81)
176.2–180.4	59	1.03 (0.69 to 1.52)	1.00 (0.67 to 1.49)	163.3–167.4	53	0.80 (0.53 to 1.21)	0.81 (0.54 to 1.23)
≥180.5	52	1.03 (0.68 to 1.56)	1.00 (0.66 to 1.52)	≥167.5	44	0.77 (0.49 to 1.18)	0.78 (0.50 to 1.21)
P_{trend}§		.66	.55	P_{trend}§		.09	.12
Weight, kg				Weight, kg			
<71.0	49	1 (Referent)	1 (Referent)	<56.9	53	1 (Referent)	1 (Referent)
71.0–76.9	59	1.15 (0.78 to 1.68)	1.17 (0.80 to 1.73)	56.9–62.0	45	0.76 (0.51 to 1.14)	0.81 (0.54 to 1.21)
77.0–82.7	57	1.10 (0.75 to 1.62)	1.14 (0.76 to 1.70)	62.1–67.4	60	0.92 (0.63 to 1.34)	1.01 (0.69 to 1.49)
82.8–89.9	67	1.26 (0.87 to 1.83)	1.30 (0.87 to 1.94)	67.5– 74.9	67	0.93 (0.64 to 1.34)	1.04 (0.71 to 1.53)
≥90.0	63	1.18 (0.81 to 1.73)	1.22 (0.80 to 1.86)	≥75.0	66	0.92 (0.63 to 1.33)	1.06 (0.71 to 1.57)
P_{trend}§		.36	.36	P_{trend}§		.94	.44
BMI, kg/m^2				BMI, kg/m^2			
<23.6	52	1 (Referent)	1 (Referent)	<21.7	47	1 (Referent)	1 (Referent)
23.6–25.3	52	0.89 (0.60 to 1.31)	0.88 (0.60 to 1.30)	21.7–23.5	44	0.77 (0.51 to 1.16)	0.78 (0.51 to 1.18)
25.4–27.0	58	0.98 (0.67 to 1.44)	0.96 (0.66 to 1.40)	23.6–25.7	72	1.11 (0.77 to 1.62)	1.14 (0.78 to 1.66)
27.1–29.3	69	1.15 (0.80 to 1.67)	1.11 (0.77 to 1.62)	25.8–28.8	63	0.92 (0.63 to 1.36)	0.95 (0.64 to 1.41)
≥29.4	64	1.12 (0.77 to 1.62)	1.05 (0.72 to 1.55)	≥28.9	65	1.03 (0.70 to 1.52)	1.06 (0.71 to 1.58)
P_{trend}§		.28	.47	P_{trend}§		.58	.51
Waist circumference, cm				Waist circumference, cm			
<86.0	40	1 (Referent)	1 (Referent)	<70.2	40	1 (Referent)	1 (Referent)
86.0–91.8	52	1.09 (0.72 to 1.65)	1.06 (0.70 to 1.61)	70.2–75.8	54	1.08 (0.71 to 1.63)	1.10 (0.73 to 1.66)
91.9–96.5	60	1.18 (0.79 to 1.77)	1.15 (0.76 to 1.73)	75.9–80.9	55	0.91 (0.60 to 1.37)	0.94 (0.62 to 1.42)
96.6–102.9	65	1.23 (0.82 to 1.84)	1.18 (0.78 to 1.77)	81.0–88.9	72	1.18 (0.79 to 1.76)	1.22 (0.82 to 1.83)
≥103.0	76	1.37 (0.93 to 2.04)	1.27 (0.84 to 1.91)	≥89.0	70	1.18 (0.79 to 1.78)	1.23 (0.81 to 1.86)
P_{trend}§		.08	.21	P_{trend}§		.28	.22
Hip circumference, cm				Hip circumference, cm			
<95.2	53	1 (Referent)	1 (Referent)	<93.7	49	1 (Referent)	1 (Referent)
95.2–98.9	53	1.07 (0.73 to 1.57)	1.07 (0.73 to 1.58)	93.7–97.9	46	0.92 (0.61 to 1.38)	0.97 (0.65 to 1.46)
99.0–101.9	73	1.12 (0.78 to 1.60)	1.12 (0.78 to 1.61)	98.0–101.9	70	1.05 (0.72 to 1.52)	1.14 (0.78 to 1.66)
102.0–105.9	52	1.18 (0.80 to 1.74)	1.19 (0.79 to 1.78)	102.0–107.9	64	1.16 (0.79 to 1.71)	1.27 (0.86 to 1.88)
≥106.0	61	1.07 (0.73 to 1.56)	1.05 (0.70 to 1.56)	≥108.0	62	1.00 (0.67 to 1.47)	1.10 (0.74 to 1.64)
P_{trend}§		.66	.77	P_{trend}§		.75	.44
WHR				WHR			
<0.887	23	1 (Referent)	1 (Referent)	<0.734	41	1 (Referent)	1 (Referent)
0.887–0.922	64	2.15 (1.33 to 3.47)	2.07 (1.28 to 3.35)	0.734–0.768	47	0.90 (0.59 to 1.37)	0.88 (0.58 to 1.34)
0.923–0.952	71	2.17 (1.35 to 3.49)	2.06 (1.28 to 3.32)	0.769–0.802	60	1.03 (0.69 to 1.55)	1.01 (0.68 to 1.52)
0.953–0.989	56	1.62 (0.99 to 2.64)	1.49 (0.91 to 2.45)	0.803–0.845	65	1.07 (0.72 to 1.60)	1.04 (0.69 to 1.56)
≥0.990	78	2.17 (1.35 to 3.49)	1.93 (1.19 to 3.13)	≥0.846	78	1.26 (0.85 to 1.87)	1.20 (0.81 to 1.79)
P_{trend}§		.04	.16	P_{trend}§		.11	.17

*Number of rectal cancer patients. BMI = body mass index; WHR = waist-to-hip ratio.

†Crude model is derived from Cox regression using age as the underlying time variable and stratified by center and age at recruitment.

‡Multivariable models for height and BMI were based on the crude model with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous). Multivariable model for weight, waist, hip, and WHR were further adjusted for height (continuous).

§P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable using the Wald chi-square statistic.

cancer risk in men but only weakly related to risk in women. In contrast, both waist circumference and WHR were strongly related to colon cancer risk in both sexes. Thus, WHR conveyed statistically significant information beyond body weight for colon cancer risk in women, but not in men. These data support the hypothesis that abdominal obesity is a risk factor for colon cancer in both sexes and suggest that fat distribution is more important than body weight or BMI for disease risk in women. Further, our results indicate that the association of body fat accumulation and risk of colon cancer in postmenopausal women may be associated with HRT use. That is, waist circumference and WHR were statistically significantly related to risk of colon cancer among nonusers but not among users of HRT, although the difference was only marginally statistically significant. Finally, results from our study support the hypothesis that height is related to colon cancer risk in both sexes.

Previous studies have primarily used body weight or BMI to assess the association of obesity with colon cancer risk. Similar to our findings (Table 3), most of these studies found positive associations of these measurements for men but weaker or no associations for women *(1–30)*. However, these measurements may not be ideal because the changes in physiologic functions that accompany obesity depend to a certain extent on regional adipose tissue distribution. Intra-abdominal visceral obesity is related to elevated blood pressure and insulin levels, insulin resistance, and dyslipidemia, and several studies have shown that

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Table 5. Relative risk (RRs) and 95% confidence intervals (CIs) of colon cancer across quintiles of waist and hip circumference and waist-to-hip ratio (WHR) after controlling for body weight in men and women of the European Prospective Investigation into Cancer and Nutrition*

Men		Women	
Measure	Multivariable RR (95% CI)	Measure	Multivariable RR (95% CI)
Waist circumference, cm		Waist circumference, cm	
<86.0	1 (Referent)	<70.2	1 (Referent)
86.0–91.8	0.67 (0.46 to 0.98)	70.2–75.8	1.10 (0.79 to 1.53)
91.9–96.5	0.85 (0.59 to 1.23)	75.9–80.9	1.22 (0.87 to 1.70)
96.6–102.9	0.91 (0.61 to 1.35)	81.0–88.9	1.23 (0.85 to 1.77)
≥103.0	1.01 (0.62 to 1.65)	≥89.0	1.44 (0.92 to 2.26)
P_{trend}†	.50	P_{trend}†	.12
Hip circumference, cm		Hip circumference, cm	
<95.2	1 (Referent)	<93.7	1 (Referent)
95.2–98.9	0.81 (0.57 to 1.16)	93.7–97.9	0.95 (0.70 to 1.29)
99.0–101.9	0.89 (0.63 to 1.26)	98.0–101.9	1.00 (0.74 to 1.36)
102.0–105.9	0.97 (0.65 to 1.43)	102.0–107.9	0.89 (0.63 to 1.27)
≥106.0	0.88 (0.55 to 1.39)	≥108.0	0.94 (0.60 to 1.46)
P_{trend}†	.85	P_{trend}†	.72
WHR		WHR	
<0.887	1 (Referent)	<0.734	1 (Referent)
0.887–0.922	1.08 (0.75 to 1.57)	0.734–0.768	1.06 (0.78 to 1.46)
0.923–0.952	1.02 (0.70 to 1.49)	0.769–0.802	1.13 (0.83 to 1.54)
0.953–0.989	1.32 (0.91 to 1.91)	0.803–0.845	1.16 (0.85 to 1.58)
≥0.990	1.18 (0.79 to 1.76)	≥0.846	1.46 (1.06 to 2.00)
P_{trend}†	.27	P_{trend}†	.01

*Multivariable models were derived from Cox regression using age as the underlying time variable and stratified by center and age at recruitment with additional adjustment for height (continuous), weight (continuous), smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol consumption (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous).

†P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald chi-square statistic.

upper-body fat distribution is independently associated with a higher risk of developing diabetes and cardiovascular disease *(50)*. Higher body weight is more closely related to abdominal obesity than to lower-body obesity in men but more closely related to gluteofemoral obesity in women *(31)*. Similarly, in our cohort WHR was more closely related to BMI in men than in women. Hence, assuming that it is primarily visceral and not nonvisceral adipose tissue that is involved in tumorigenic processes, body weight and BMI may not accurately reflect the colon cancer risk that is associated with abdominal fat accumulation, at least in women.

Few prospective studies have examined the association of body fat distribution—as reflected by waist and hip circumference—and colon cancer risk *(11,13,14,19,21,51)*. Among these studies, we are aware of only one report *(21)* that presented results for men and women separately. In this report, from the Framingham Study *(21)*, which included 306 colon cancer case patients, waist circumference was an equally strong risk factor for colon cancer in men and women, and it was a stronger risk factor than BMI in both sexes. A report from the Cardiovascular Health Study, which included 102 men and women with colorectal cancer, found that waist circumference and WHR were statistically significantly related to risk of colorectal cancer but that BMI was not; however, this analysis did not present sex-specific results *(51)*.

Our findings are in contrast with reports from the Melbourne Collaborative Cohort Study *(19)* and the Health Professionals Follow-up Study *(13)*, which found an association between WHR and colon cancer risk in men even after adjustment for BMI, and with reports from the Iowa Women's Health Study *(11)* and the Nurses' Health Study *(14)*, which found statistically significantly positive associations in women between BMI but not WHR and risk of colon cancer. However, most of these studies *(11,13,14)* relied on self-reported anthropometric data, which limits the interpretability of these results.

The pathophysiology underlying the association between obesity and increased colon cancer risk is unclear. Some authors have suggested that components of the metabolic syndrome, particularly insulin resistance and subsequent hyperinsulinemia, are the underlying link, which may reflect the growth-promoting effects of insulin *(52–54)*. These speculations are also supported by studies that found subjects with type 2 diabetes to be at increased risk of colon cancer *(55,56)*. Hyperinsulinemia is also related to increased levels of bioavailable insulin-like growth factor 1, which is known to have cancer-promoting effects *(57–60)*. Further potential mediators include leptin, which stimulates growth of colonic epithelial cells *(61–63)*, and adiponectin, which has antiangiogenic and antitumor activities *(64,65)*. We are now analyzing the relationship of these and other biomarkers with risk of colon and rectal cancer in EPIC.

Postmenopausal HRT has been associated with reduced risk of colon cancer in observational studies *(33)*, a finding that has been supported by the results of the Women's Health Initiative intervention trial of estrogen plus progestin use *(34–36)*. HRT has been hypothesized to reduce the risk of colon cancer by reducing the likelihood of estrogen receptor methylation *(66,67)*. In our study we found that, among postmenopausal women, the positive association of waist circumference and WHR with risk of colon cancer was not apparent in women who used HRT at baseline (Table 6). We are aware of only one case–control study that has examined the interaction between HRT use and adiposity on colon cancer risk, with body weight assessed in colon cancer

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Table 6. Relative risks (RRs) and 95% confidence intervals (CIs) of colon cancer across quintiles of anthropometric measures in postmenopausal women stratified by hormone replacement therapy (HRT) use at baseline in the European Prospective Investigation into Cancer and Nutrition*

	No HRT use		HRT use	
Measure	N†	RR (95% CI)	N†	RR (95% CI)
Weight‡, kg				
<56.9	48	1 (Referent)	15	1 (Referent)
56.9–62.0	56	1.05 (0.71 to 1.56)	16	1.04 (0.50 to 2.18)
62.1–67.4	61	0.99 (0.67 to 1.46)	15	0.95 (0.44 to 2.03)
67.5–74.9	82	1.08 (0.74 to 1.57)	23	1.55 (0.74 to 3.22)
≥75.0	89	1.13 (0.77 to 1.67)	12	1.01 (0.43 to 2.37)
P_{trend}§		.49		.69
BMI, kg/m^2				
<21.7	40	1 (Referent)	21	1 (Referent)
21.7–23.5	50	0.96 (0.63 to 1.45)	15	0.69 (0.35 to 1.35)
23.6–25.7	77	1.21 (0.82 to 1.78)	17	0.80 (0.41 to 1.56)
25.8–28.8	83	1.11 (0.75 to 1.64)	20	1.10 (0.57 to 2.10)
≥28.9	86	1.12 (0.75 to 1.67)	8	0.72 (0.31 to 1.70)
P_{trend}§		.52		.88
Waist circumference‡, cm				
<70.2	25	1 (Referent)	17	1 (Referent)
70.2–75.8	48	1.30 (0.80 to 2.11)	21	1.07 (0.55 to 2.06)
75.9–80.9	71	1.35 (0.85 to 2.14)	17	0.79 (0.39 to 1.57)
81.0–88.9	85	1.39 (0.88 to 2.19)	17	0.90 (0.44 to 1.83)
≥89.0	106	1.68 (1.06 to 2.64)	9	0.76 (0.32 to 1.80)
P_{trend}§		.02		.46
Hip circumference‡, cm				
<93.7	43	1 (Referent)	23	1 (Referent)
93.7–97.9	46	0.93 (0.61 to 1.41)	17	0.71 (0.37 to 1.36)
98.0–101.9	88	1.21 (0.83 to 1.76)	13	0.43 (0.21 to 0.88)
102.0–107.9	68	1.04 (0.70 to 1.54)	14	0.70 (0.34 to 1.44)
≥108.0	89	1.08 (0.74 to 1.60)	13	0.77 (0.37 to 1.61)
P_{trend}§		.69		.54
WHR‡				
<0.734	27	1 (Referent)	19	1 (Referent)
0.734–0.768	40	1.02 (0.62 to 1.66)	19	0.79 (0.41 to 1.53)
0.769–0.802	75	1.55 (1.00 to 2.42)	11	0.46 (0.21 to 0.99)
0.803–0.845	85	1.51 (0.97 to 2.34)	14	0.69 (0.34 to 1.43)
≥0.846	107	1.76 (1.14 to 2.72)	17	0.96 (0.47 to 1.94)
P_{trend}§		.002		.89

*Relative risks derived from multivariable Cox regression models using age as the underlying time variable and stratified by center and age at recruitment with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol consumption (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous). BMI = body mass index; WHR = waist-to-hip ratio.

†Number of colon cancer patients.

‡Relative risks for weight, waist and hip circumference, and WHR are also adjusted for height (continuous).

§P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald chi-square statistic.

patients and population-based control subjects *(20)*. Contrary to our findings, in that report *(20)* a positive association between BMI and colon cancer risk was observed for postmenopausal women on HRT only. The reasons for this discrepancy are unclear; however, differences between HRT users and nonusers in the association of obesity with postmenopausal breast cancer risk similar to our observations for colon cancer have previously been reported *(37)*. Because the differences between HRT users and non users were only marginally statistically significant in our study, we cannot rule out a role for chance. Clearly, our findings need to be confirmed in future studies and to be put in context with the complex effects observed in interventional studies of HRT use on women's health, e.g., their detrimental effects on the cardiovascular system *(34)*.

In our analysis, height was related to risk of colon cancer (Table 3), a finding that is in agreement with previous studies *(68)*. The magnitude of this association was similar in men and women. Height has been related to several types of cancer, including colon, breast, pancreatic, and prostate cancer *(37,69)*, and it was recently estimated that 18% of total cancers are attributable to factors related to tallness *(69)*. Tallness is related to having more cells in the body structure, which may increase the probability of malignant transformation *(70)*. Postnatal growth depends largely on a complex interaction between nutrition, growth hormones (GH, insulin-like growth factor), and sex hormones, all of which have been suggested to be involved in cancer development *(71)*. For example, evidence from animal and human studies suggests that restricted caloric intake in early life is related to lower adult cancer risk *(72–74)*. Adult height may also reflect increased exposure to GH, insulin-like growth factor 1, and insulin in preadulthood that may predispose to cancer development in later life *(57,58,75,76)*. These speculations are supported by studies that found patients with GH excess (e.g., acromegaly) to be at increased cancer risk, particularly for colon cancer *(77,78)*.

In agreement with most previous reports, we found no statistically significant association between body size and risk of rectal

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cancer (Table 4) *(2–5,12,17,27,30)*. This finding suggests differences in tumor susceptibility between colon and rectum, although the potential mechanisms accounting for these differences need further investigation.

Our study has strengths and limitations. Among the strengths are its prospective design and the large sample size, which included several European countries. Also, all body measures were assessed directly at baseline, in contrast to self-reported data used in most previous studies. Among the limitations were slight differences in the method of assessment of waist and hip circumference between centers in EPIC; however, we found similar results for the associations of body size with risk of colon and rectal cancer across centers, which also reduces the possibility of residual confounding by geographic region. The combination of related measures in our analysis may lead to imprecision and instability of the risk estimates; however, the width of the confidence intervals did not substantially change when we combined body weight with waist or hip circumference or WHR, therefore indicating that these combinations did not substantially decrease precision. Nevertheless, the anthropometric parameters we used—although being standard, well established, and routinely used for disease risk assessment—may be imperfect measures of body size or underlying true biologic risk factors, and this situation may complicate the interpretation of our findings when considering these measures simultaneously.

Within EPIC we currently have standardized information about exposure variables available at baseline only, which neglects modifications in subjects' exposure status during follow-up. However, any potential misclassification should be nondifferential and, if anything, is expected to bias our results toward the null.

Information on menopausal status was available at baseline only; we were therefore unable to stratify our analysis by menopausal status at time of cancer diagnosis. Previous studies have suggested that the association of BMI with risk of colon cancer may be stronger in, or even limited to, premenopausal women *(20,23,79)*. In our analysis, only 33% of women were premenopausal at baseline; it is therefore reasonable to assume that most women were postmenopausal (or at least perimenopausal) at the time of cancer diagnosis. In line with this hypothesis, when we restricted the analysis to women who were postmenopausal at baseline, our findings were almost identical to those using all women. Although our study included many colon cancer case patients, stratification may have limited the power to detect statistically significant associations of waist circumference or WHR with risk of colon cancer among postmenopausal women with HRT use. However, in this group the point estimates of risk showed no substantial variation across quintiles of measures of obesity, arguing against a substantial association with colon cancer risk. Despite excluding participants with reported cancers at baseline, we cannot exclude the possibility that some subjects had underlying yet undiagnosed colon or rectal cancer. However, results did not appreciably change when we excluded subjects with a follow-up time of less than 2 years.

In conclusion, in this study we found that abdominal obesity is an equally strong risk factor for colon cancer in men and women, whereas body weight and BMI were associated with colon cancer risk in men but not in women. These data suggest that fat distribution is a more important risk factor than body weight and BMI for colon cancer in women. Also, our study suggests that the relationship between abdominal obesity and colon cancer risk may vary according to HRT use; however, these findings require confirmation in future studies. Our data give further credence to public health efforts aiming to reduce the prevalence of obesity to prevent cancer and other chronic diseases. Measurement of waist circumference or WHR should be included in current guidelines to maintain a healthful lifestyle for disease prevention *(80)*.

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NOTES

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