Research Article

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Comparison of Associations of Body Mass Index, Abdominal Adiposity, and Risk of Colorectal Cancer in a Large Prospective Cohort Study

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Abstract

Background: Increased body mass index (BMI) is an established colorectal cancer risk factor. High waist circumference or waist-hip-ratio (WHR) may better reflect an abnormal metabolic state and be more predictive of colorectal cancer risk than BMI.

Methods: We examined BMI, waist circumference, WHR, and hip circumference in relation to colorectal cancer risk among 203,177 participants followed for 10 years. We derived standardized colorectal cancer risk estimates for each anthropometric parameter and compared predictive characteristics (Harrell's C-index). In women, we examined whether hormone replacement therapy (HRT) use modified the associations between anthropometric measures and colorectal cancer.

Results: We ascertained 2,869 colorectal cancers. In men, increased colon cancer risks were associated with BMI [HR per SD, 1.14; 95% confidence interval (CI), 1.08–1.20], waist circumference (HR per SD, 1.17; 95% CI, 1.08–1.27), and WHR (HR per SD, 1.09; 95% CI, 1.04–1.14). In women, anthropometric variables were unrelated to colon cancer. For men and women, anthropometric variables were unrelated to rectal cancer. Compared with BMI, waist circumference and WHR did not materially influence colon cancer prediction models [C-index changes: −0.0041 and 0.0046 (men); 0.0004 and 0.0005 (women)]. In current HRT users, colon cancer was inversely or suggestively inversely associated with waist circumference (HR per SD, 0.78; 95% CI, 0.63–0.97) and WHR (HR per SD, 0.88; 95% CI, 0.76–1.01), but positively related to hip circumference (HR per SD, 1.39; 95% CI, 1.13–1.71).

Conclusion: BMI, waist circumference, and WHR show comparable positive associations with colon cancer in men. Associations between anthropometric measures and colon cancer are weak or null in women, but there is some evidence for effect modification by HRT.

Impact: These findings may improve our understanding of the relation of adiposity to colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 22(8); 1383–94. ©2013 AACR.*

Introduction

Increased body mass index (BMI), as an approximation of total body adiposity, is an established colorectal cancer risk factor. Our systematic review and meta-analysis of 29 prospective studies reported relative risks for colon cancer per 5 kg/m^2 BMI increment of 1.24 and 1.09 in men and women, respectively, and that associations are greater for colon versus rectal cancer (1).

Few prospective studies have evaluated relations between abdominal adiposity, approximated by waist circumference and waist-to-hip ratio (WHR), and colorectal cancer risk.

Five cohorts in men (2–6) and four in women (2, 4, 7, 8) found positive associations between high versus low waist circumference and/or WHR and colon cancer risk, with summarized relative risks of 1.81 in men and 1.50 in women (9). A small number of studies (3–7) have suggested that measures of abdominal adiposity may be more predictive for colon cancer risk than BMI.

This supposition is appealing as hypothesized biologic mechanisms underpinning the link between adiposity and colon cancer include insulin resistance and metabolic dysfunction (10), and conventionally, abdominal adiposity is

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considered to be more closely related with insulin resistance than total body fat (11), and may be a stronger predictor for cardiovascular disease and type II diabetes than BMI (12, 13). However, as pointed out by Huxley and colleagues (14), this comparison is not trivial—it requires comparisons of equivalent population-specific standardized increments per anthropometric measure, and formal discrimination testing. Furthermore, waist circumference is a composite of subcutaneous and visceral adipose tissues (VAT)—proportions of which vary by age and gender—and the latter being most strongly related to insulin resistance and metabolic dysfunction. Finally, there is a paucity of prospective data on the association between hip circumference and colorectal cancer risk. A higher hip circumference may be associated with reduced cardiovascular risk (15, 16) but parallel hypotheses have seldom been explored in relation to cancer risk.

For women, associations between measures of abdominal adiposity and colon cancer risk may be weaker than in men (4, 5), raising a hypothesis that additional sex-related biologic mechanisms may prevail. Data from the Women's Health Initiative randomized trial showed that hormonal replacement therapy (HRT) use is associated with reduced colon cancer risk (17), and in turn, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported that associations between BMI and colon cancer risk in women may be attenuated (to null) in the presence of HRT use (2).

The primary objective of the current study was to derive standardized colorectal cancer risk estimates for each anthropometric parameter and compare predictive characteristics with respect to colorectal cancer risk. The secondary objective tested the hypothesis that the associations between anthropometric measures and colorectal cancer risk in women vary according to HRT use. We extend previous studies of associations of BMI (18) and weight gain (19) in relation to colorectal cancer risk using the NIH-AARP Diet and Health Study, in which comprehensive, prospectively collected data for anthropometric exposures and HRT are available.

Materials and Methods

Study population and case identification

The NIH-AARP Diet and Health Study is a large prospective cohort study of AARP members, recruited in 1995 to 1996 from 6 U.S. states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). A self-administered baseline questionnaire that requested information on diet, physical activity, anthropometry, chronic diseases, and lifestyle factors was completed by a total of $N = 566{,}401$ individuals, ages 50 to 71 years. A subcohort of $N = 334{,}907$ participants completed a second questionnaire mailed in 1996, which included determination of waist circumference and hip circumference, which in turn, were used to derive WHR. The Special Studies Institutional Review Board (IRB) of the U.S. National Cancer Institute, Rockville, MD approved the study.

Of participants who completed the second questionnaire, we excluded those with a previous diagnosis of cancer at baseline ($N = 14{,}565$) and before the second questionnaire ($N = 4{,}295$). Furthermore, we excluded participants without data on height ($N = 2{,}766$), weight ($N = 3{,}513$), waist circumference ($N = 73{,}055$), or hip circumference ($N = 11{,}015$). We also excluded subjects with extreme values (defined as more than three interquartiles ranges outside the 75th and 25th percentiles) of waist circumference or hip circumference ($N = 3{,}037$) and those with BMI less than 18.5 kg/m^2 ($N = 2{,}342$) or more than 60 kg/m^2 ($N = 32$). As smoking is an important risk factor for colon cancer, we also excluded $N = 6{,}618$ participants with missing information on smoking status. We also excluded $N = 10{,}383$ proxy respondents and $N = 109$ persons with less than 18 days of follow-up. After exclusions, this subcohort comprised 203,177 participants (124,208 men and 78,969 women) and formed the basis for the present analysis. We determined that the characteristics of this subcohort were similar to those of the overall cohort (Supplementary Table S1).

Study participants were followed up through December 31, 2006 by periodic linkage of the cohort to the National Change of Address database maintained by the U.S. Postal Service, other address change update services, and from cohort members' notifications. Incident colon and rectal cancers were identified through 10 state cancer registries (including Texas and Nevada) using the International Classification of Diseases for Oncology (ICD-O-3) codes for colon cancer (C18.0–C18.9) and rectal cancer (C19 and C20).

Quality control studies report that there is only 5% loss of follow-up in this cohort (20). Vital status was ascertained by linking the cohort to the U.S. Social Security Administration Death Master File. Follow-up searches of presumed deaths in the National Death Index (NDI) Plus were used to verify deaths and to gain information on the cause of death.

Exposure ascertainment

Self-reported body weight and height were assessed in the baseline questionnaire; waist and hip circumferences were obtained from the second questionnaire. Participants were instructed to measure their waist circumference and hip circumference using a tape measure to the nearest 0.25 inch while standing. Waist circumference was to be measured 1 inch above the navel, if this was not the waistline. Hip circumference was defined as the largest circumference between the upper edge of the pelvis and the femur. In a cohort study contemporaneous to ours, comparisons between self-reported and technician-measured waist circumference have yielded correlation coefficients of 0.80 in men and 0.83 in women and for hip circumference have yielded values of 0.74 in men and 0.86 in women, and deemed sufficiently accurate for identifying relationships in epidemiologic studies (21).

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Correlations between self-reported and technician-measured BMI values exceed 0.9 for both men and women (22).

Statistical analysis

We used age as the underlying time metric from the age of return of the second questionnaire to the age of diagnosis of colon or rectal cancer, move out of the registry ascertainment area, death, or December 31, 2006, whichever came first. The relationships between BMI, waist circumference, WHR, and hip circumference were evaluated using Spearman correlation coefficients in men and women separately. Cox proportional hazards regression was used to estimate the HRs and 95% confidence intervals (CIs) for colon and rectal cancer, separately, according to gender-specific quintiles of BMI, waist circumference, WHR, and hip circumference. In addition, participants were categorized into predefined World Health Organization (WHO) categories for waist circumference and WHR (23).

Three models were constructed to examine the associations between BMI, waist circumference, WHR, hip circumference, and colon and rectal cancer risk. In model 1, we adjusted for age only. In model 2—the main model—we additionally adjusted for multiple lifestyle factors (listed in footnote to Table 2). Height at baseline was included as a continuous variable in analyses of waist circumference and hip circumference, and waist circumference and hip circumference were mutually adjusted to assess whether each were independently related to colon or rectal cancer risk. In model 3, we additionally adjusted for BMI (continuous) to assess the impact of abdominal fat distribution on colon and rectal cancer independent of its relation with general adiposity.

Tests for linear trend were conducted using the continuous variables. For comparability across the four anthropometric measures, we calculated the HRs per SD for each anthropometric parameter. For cancer risk discrimination, we used model 2 Cox models and the resulting predictions to assess measures of discrimination for censored time-to-event data using Harrell's C-index (24). We tested for potential interactions between anthropometric parameters, gender, age, colonic sub-site, and HRT use using likelihood ratio tests.

All statistical tests were two-sided and P values were considered statistically significant at the 0.05 level. Analysis was conducted using SAS version 9.2 (SAS Institute).

Results

Baseline characterizations

During 1,879,060 person-years of follow-up, 2,143 incident colon cancers (1,463 men; 680 women) and 726 incident rectal cancers (536 men; 190 women) were identified. Baseline characteristics of the participants by gender-specific quintiles of waist circumference are summarized in Table 1. Men and women in the highest quintile of waist circumference tended to be less educated and less physically active than those in the lowest quintile. In contrast, participants with high waist circumference were more likely to have diabetes, to have formerly smoked 20 or more cigarettes per day, to use nonsteroidal anti-inflammatory drugs (NSAID), and to have higher intakes of total energy, red meat, and alcohol than those with a low waist circumference. In women, current HRT use was inversely related to waist circumference.

The correlation coefficients between BMI and waist circumference, hip circumference, and WHR were 0.75, 0.65, and 0.36 in men and 0.78, 0.78, and 0.41 in women (Supplementary Table S2). The mean, SDs, and quintile-cutoff points for the 4 parameters are shown in Supplementary Table S3.

Associations with cancer risk

Age-adjusted and multivariate-adjusted associations between BMI, waist circumference, WHR, and hip circumference and colon cancer risk are presented in Table 2. In men in age-adjusted models (model 1), the HRs per SD increases in BMI, waist circumference, WHR, and hip circumference were statistically significantly positive. After additional adjustment for potential confounding variables (model 2), risk estimates were attenuated but remained statistically significant for BMI, waist circumference, and WHR, but not hip circumference. The HRs per SD increase in model 2 were 1.14 (95% CI, 1.08–1.20) for BMI; 1.17 (95% CI, 1.08–1.27) for waist circumference; and 1.09 (95% CI, 1.04–1.14) for WHR. After adjustment for BMI (model 3), the associations for waist circumference and WHR remained statistically significantly positive.

For women, borderline positive associations were observed for waist circumference and WHR in relation to colon cancer in the age-adjusted model (model 1). After multivariate adjustment, no significant associations between BMI, waist circumference, WHR, or hip circumference and colon cancer risk were evident (model 2). Tests for interaction with gender revealed significant effect modification for waist circumference ($P = 0.042$) but not for BMI ($P = 0.170$), WHR ($P = 0.308$), or hip circumference ($P = 0.117$).

We analyzed associations for BMI, waist circumference, WHR, and hip circumference with rectal cancer risk using the 3 models and found no statistically significant associations in the multivariate models (Supplementary Table S4).

We repeated analyses in model 2 for colon cancer risk, categorizing the indicator parameters by WHO cutoff-points for waist circumference and WHR (23). In men, we found significant associations for waist circumference (HR for >94 cm vs. $\leq$ 94 cm, 1.14; 95% CI, 1.00–1.29; HR for waist circumference >102 cm vs. $\leq$ 102 cm, 1.16; 95% CI, 1.01–1.33); but not for WHR (HR for >0.9 vs. $\leq$ 0.9, 1.12; 95% CI, 0.97–1.28). Among women, there were no associations for waist circumference (HR for >80 cm vs. $\leq$ 80 cm, 1.06; 95% CI, 0.88–1.29; HR for >88 cm vs. $\leq$ 88 cm, 1.06;

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Table 1. Baseline characteristics of study participants in the NIH-AARP Diet and Health Study by waist circumference

	Quintile of waist circumference (range in cm)									
	Men					Women				
	1	2	3	4	5	1	2	3	4	5
Characteristic	**<89.5**	**89.5–<93.5**	**93.5–<99.0**	**99.0–<106.5**	**≥106.5**	**<73.6**	**73.6–<80.0**	**80.0<–86.0**	**86.0–<94.5**	**≥94.5**
Participants, *n*	26,934	19.994	25,583	24,840	26,857	14,933	16,512	14,145	17,464	15,915
Age at entry, y	62.6	63.2	63.3	63.4	63.1	61.7	62.5	62.9	63.2	63.0
Height, m	1.75	1.78	1.79	1.79	1.80	1.62	1.63	1.64	1.64	1.64
Weight, kg	72.4	79.3	83.9	89.0	100.9	56.7	62.0	67.0	73.2	85.2
BMI, kg/m^{2}[a]	23.5	25.2	26.3	27.7	31.1	21.7	23.3	25.1	27.3	31.6
Waist circumference, cm	85.3	91.5	95.9	101.9	112.9	68.7	76.3	82.5	89.7	103.8
Hip circumference, cm	94.8	99.1	102.0	105.5	112.8	94.0	98.4	102.3	106.8	116.4
WHR[b]	0.90	0.93	0.94	0.97	1.00	0.73	0.78	0.81	0.84	0.90
Caucasian, %	91.0	93.9	95.2	95.8	96.0	93.3	93.3	91.8	91.6	91.9
Family history of cancer, %	46.7	48.2	48.9	49.3	49.3	52.0	52.5	53.1	53.7	53.4
Family history of CRC, %	15.2	14.9	15.1	15.8	15.5	19.1	19.8	19.8	19.8	19.9
Diabetes status, %	5.3	6.7	7.4	8.9	14.6	1.7	2.1	3.4	5.8	12.8
Education level, %										
Less than high school	3.9	3.9	3.9	3.9	5.0	3.0	3.4	4.1	5.0	5.9
High school graduate	12.5	13.0	13.1	13.3	15.1	20.9	22.2	23.3	25.0	25.0
Some college	30.4	30.7	31.7	32.1	34.8	37.2	36.1	36.9	37.6	37.7
College graduate	24.2	24.8	24.5	24.5	22.1	18.8	18.6	17.4	15.5	14.8
Postgraduate	29.1	27.6	26.8	26.2	23.1	20.0	19.7	18.3	17.0	16.6
Married, %	83.1	86.8	87.9	88.8	87.1	47.5	48.9	47.9	47.3	42.4
Smoking status, %										
Never	36.9	33.6	32.6	29.8	26.0	48.2	47.8	46.6	46.2	45.2
Former (<20 cig./d)	31.5	32.7	31.4	30.4	27.3	28.5	28.9	28.5	28.0	27.3
Former (≥20 cig./d)	19.6	24.3	27.8	32.1	38.7	8.3	10.5	11.7	13.3	16.6
Current (<20 cig./d)	7.3	5.7	4.7	4.2	4.0	11.7	9.6	9.3	8.8	7.1
Current (≥20 cig./d)	4.6	3.8	3.5	3.5	4.1	3.3	3.3	3.9	3.7	3.8
Physical activity, %										
Low	17.5	19.8	22.3	26.0	34.7	23.3	25.9	29.7	34.8	45.1
Intermediate	50.3	53.9	54.0	53.7	49.6	50.3	52.0	51.9	49.9	43.4
High	32.2	26.3	23.8	20.3	15.7	26.5	22.1	18.4	15.3	11.5
Dietary intakes										
Total energy, kcal/d	1,990	1,982	2,013	2,045	2,147	1,508	1,527	1,560	1,620	1,682
Alcohol drinker, %	80.1	81.9	82.3	82.0	80.3	76.8	77.4	75.9	73.2	66.4
Alcohol, g/d[d]	20.7	20.4	21.8	23.1	24.0	8.4	8.9	8.9	8.9	7.8
Fiber, g/d	22.1	21.1	20.9	20.6	20.8	18.7	18.1	18.2	18.1	18.2
Folate, mcg/d	467.0	451.5	449.7	446.0	453.0	380.6	376.0	377.9	379.7	382.5
Calcium, mg/d	817.9	811.0	817.9	822.7	860.5	713.4	717.7	724.5	735.9	752.4
Fruits and vegetables, servings/d	6.6	6.3	6.2	6.1	6.1	6.5	6.3	6.2	6.1	6.0
Red meat, g/d	64.5	70.3	74.8	79.5	92.7	36.9	40.3	43.5	49.4	55.6
Regular NSAID use, %[c]	63.7	67.0	68.7	69.4	71.1	60.0	63.6	65.5	67.4	69.0
HRT use, %										
Never	—	—	—	—	—	36.8	37.3	40.3	44.1	50.4
Current	—	—	—	—	—	55.0	54.0	50.1	46.1	39.2
Past	—	—	—	—	—	8.0	8.5	9.4	9.7	10.3
Duration of HRT use, y	—	—	—	—	—	6.9	6.8	6.8	6.6	6.4

NOTE: All values, except age, waist circumference, and number of participants were directly standardized to the age distribution of the cohort.
Abbreviations: CRC, colorectal cancer; —, not applicable.
[a]Weight/height^{2}.
[b]Waist circumference/hip circumference (no units).
[c]Defined as 2 to 3 times use per month or more.
[d]Among drinkers only; numbers do not add to 100% because of rounding.

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Table 2. HRs and 95% CIs for risk of incident colon cancer by gender across categories of anthropometric measures in the NIH-AARP Diet and Health Study

	Men					Women				
Measure	**PY**	**Cases[a]**	**Model 1**	**Model 2**	**Model 3**	**PY**	**Cases[a]**	**Model 1**	**Model 2**	**Model 3**
BMI[b] (quintile)										
1	227,769	242	1.0	1.0		147,050	125	1.0	1.0	
2	228,277	255	1.06 (0.89–1.26)	1.04 (0.87–1.24)		148,971	133	1.03 (0.81–1.32)	1.04 (0.81–1.32)	
3	229,123	281	1.18 (0.99–1.40)	1.13 (0.95–1.35)		148,758	135	1.03 (0.81–1.32)	1.01 (0.79–1.29)	
4	227,671	330	1.40 (1.19–1.66)	1.31 (1.10–1.55)		147,802	143	1.10 (0.87–1.40)	1.02 (0.80–1.31)	
5	225,231	355	1.59 (1.35–1.87)	1.42 (1.19–1.68)		148,408	144	1.14 (0.90–1.45)	0.96 (0.74–1.23)	
P_{trend}[d]			<0.001	<0.001				0.251	0.477	
Per SD			1.19 (1.13–1.25)	1.14 (1.08–1.20)				1.05 (0.97–1.13)	0.97 (0.90–1.05)	
WC (quintile)										
1	248,658	223	1.0	1.0	1.0	141,001	114	1.0	1.0	1.0
2	184,690	213	1.24 (1.03–1.49)	1.18 (0.97–1.43)	1.15 (0.95–1.40)	155,739	122	0.91 (0.71–1.18)	0.90 (0.70–1.17)	0.91 (0.70–1.18)
3	235,126	303	1.38 (1.16–1.63)	1.26 (1.05–1.52)	1.22 (1.00–1.47)	132,999	119	1.01 (0.78–1.31)	0.95 (0.73–1.25)	0.97 (0.74–1.28)
4	227,550	314	1.46 (1.23–1.74)	1.28 (1.05–1.55)	1.21 (0.99–1.49)	163,568	176	1.19 (0.94–1,51)	1.06 (0.81–1.40)	1.10 (0.83–1.45)
5	242,048	410	1.83 (1.56–2.16)	1.45 (1.16–1.82)	1.32 (1.03–1.70)	147,683	149	1.14 (0.89–1.45)	0.90 (0.63–1.27)	0.95 (0.66–1.37)
P_{trend}[d]			<0.001	<0.001	0.007			0.042	0.838	0.859
Per SD			1.24 (1.18–1.30)	1.17 (1.08–1.27)	1.14 (1.04–1.26)			1.08 (1.00–1.16)	0.99 (0.88–1.12)	1.01 (0.89–1.16)
WHR[c] (quintile)										
1	227,096	245	1.0	1.0	1.0	149,032	121	1.0	1.0	1.0
2	236,193	292	1.11 (0.93–1.31)	1.08 (0.91–1.28)	1.06 (0.89–1.25)	151,823	126	0.96 (0.75–1.23)	0.92 (0.72–1.18)	0.92 (0.72–1.19)
3	223,657	267	1.06 (0.89–1.26)	1.01 (0.85–1.21)	0.98 (0.82–1.16)	146,523	140	1.06 (0.83–1.36)	0.98 (0.77–1.26)	0.99 (0.77–1.27)
4	205,108	264	1.14 (0.96–1.35)	1.06 (0.89–1.27)	1.00 (0.84–1.20)	147,387	140	1.03 (0.81–1.32)	0.90 (0.70–1.15)	0.91 (0.70–1.17)
5	246,016	395	1.46 (1.24–1.71)	1.29 (1.10–1.52)	1.17 (0.99–1.38)	146,225	153	1.12 (0.88–1.42)	0.90 (0.70–1.15)	0.91 (0.70–1.18)
P_{trend}[d]			<0.001	<0.001	0.044			0.045	0.997	0.836
Per SD			1.13 (1.08–1.19)	1.09 (1.04–1.14)	1.05 (1.00–1.11)			1.08 (1.00–1.17)	1.00 (0.92–1.08)	1.01 (0.93–1.10)
HC (quintile)										
1	217,058	243	1.0	1.0	1.0	146,956	131	1.0	1.0	1.0
2	255,289	249	0.84 (0.71–1.01)	0.78 (0.65–0.93)	0.77 (0.65–0.93)	150,767	121	0.90 (0.70–1.15)	0.93 (0.72–1.19)	0.94 (0.73–1.21)
3	235,050	307	1.13 (0.95–1.34)	0.95 (0.79–1.14)	0.94 (0.78–1.13)	146,136	143	1.07 (0.85–1.36)	1.10 (0.85–1.43)	1.13 (0.87–1.48)
4	212,115	307	1.25 (1.06–1.48)	0.96 (0.78–1.17)	0.95 (0.77–1.16)	163,789	151	1.01 (0.80–1.27)	1.01 (0.76–1.33)	1.06 (0.78–1.43)
5	218,559	357	1.43 (1.21–1.68)	0.91 (0.72–1.16)	0.89 (0.70–1.14)	133,341	134	1.13 (0.89–1.44)	1.04 (0.74–1.48)	1.15 (0.77–1.71)
P_{trend}[d]			<0.001	0.952	0.829			0.201	0.940	0.557
Per SD			1.18 (1.12–1.24)	1.00 (0.93–1.09)	0.99 (0.91–1.08)			1.05 (0.97–1.13)	1.01 (0.89–1.13)	1.04 (0.90–1.21)

NOTE: Model 1: The model is derived from Cox regression using age as the underlying time metric; Model 2: The multivariate models were adjusted for education (less than 12 y, 12 y or high school, post-high school or some college, college graduate, or postgraduate), race/ethnicity (Caucasian or non-Caucasian), smoking status (never smoker, former smoker with 20 cig./d or less, former smoker with more than 20 cig./d, current smoker with 20 cig./d or less, or current smoker with more than 20 cig./d), marital status (married or living as married; divorced, widowed, separated, or never married), physical activity (never or rarely, 1 to 3 times/mo, 1 to 2 times/wk, 3 to 4 times/wk, 5 or more times/wk), NSAID use (yes or no), family history of colorectal cancer (yes or no), diabetes status (yes or no), dietary intakes of total energy, fiber, folate, calcium, red meat, fruits and vegetables (all in quartiles), alcohol (yes or no), HRT (women only; never, current, or past). In addition, the multivariate model for waist circumference was adjusted for hip circumference (continuous) and the multivariate model for hip circumference was adjusted for waist circumference (continuous). Multivariate models for waist circumference, hip circumference, and WHR were further adjusted for height (continuous); Model 3: The multivariate model 2 was further adjusted for BMI (continuous).

Abbreviations: HC, hip circumference; PY, person years; WC, waist circumference.

[a]Number of patients with colon cancer.

[b]Weight/height^2.

[c]Waist circumference/hip circumference.

[d]P_{trend} (two-sided) across categories is based on the continuous variable and was calculated using Cox regression.

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95% CI, 0.87–1.29) and WHR (HR for >0.85 cm vs. ≤0.85 cm, 0.99; 95% CI, 0.84–1.16).

We undertook stratified analyses to assess the effect of age (above vs. below the median) on associations in women. We noted a suggestive positive relation between BMI and colon cancer among younger women (those younger than age 67 years) in the age-adjusted analysis (HR per SD, 1.08; 95% CI, 0.99–1.19) but that association became null after multivariate adjustment (Supplementary Table S5). We also conducted stratified analyses by colonic sub-site (proximal vs. distal location) in women. We noted suggestive positive relations between anthropometric variables and distal colon cancer in age-adjusted analyses (HR for BMI per SD, 1.12; 95% CI, 1.00–1.28; HR for waist circumference per SD, 1.12; 95% CI, 0.98–1.27; HR for WHR per SD, 1.14; 95% CI, 1.00–1.30), but those associations were considerably attenuated and were statistically nonsignificant in the multivariate models (Supplementary Table S6).

Direct comparisons between anthropometric measures

To test the relative predictive characteristics of the four anthropometric measures, we defined the null model including all confounding variables but none of the anthropometric variables, and compared whether the addition of BMI, waist circumference, WHR, and hip circumference, separately, improved predictive characteristics model fit (Table 3). BMI, waist circumference, WHR, and hip circumference conducted equally well in colon cancer risk prediction. Single and joint additions of BMI, waist circumference, WHR, and hip circumference to a null model did not materially improve the model fit. Compared with BMI, waist circumference and WHR did not materially influence the prediction models for colon cancer (C-index changes, −0.0040 and 0.0046 for men; 0.0004 and 0.0005 for women).

Associations stratified by HRT

To assess whether the null associations observed between anthropometric measures and risk of colon and rectal cancer in women were due to effect modification by HRT, we conducted stratified analyses in women according to current versus never HRT use at baseline (Table 4). After multivariate adjustment (model 2), current HRT use was inversely associated with colon cancer (compared with never HRT users, HR per SD, 0.63; 95% CI, 0.53–0.75). Among current users of HRT, waist circumference was inversely (HR per SD, 0.78; 95% CI, 0.63–0.97) and WHR was suggestively inversely (HR per SD, 0.88; 95% CI, 0.77–1.01) associated with colon cancer in model 2, whereas hip circumference was positively associated with colon cancer (HR per SD, 1.39; 95% CI, 1.13–1.71), but there was no association for BMI. Among never users of HRT, BMI was inversely associated with colon cancer (HR per SD, 0.89; 95% CI, 0.80–0.99). There were no associations between waist circumference, WHR, or hip circumference with colon cancer risk in never HRT users. Tests for interaction by HRT use revealed significant effect modification for hip circumference ($P = 0.018$) but not for waist circumference ($P = 0.728$), WHR ($P = 0.171$), or BMI ($P = 0.165$).

We noted in the stratified analyses of women with current HRT use that colon cancer risk estimates changed substantially between model 1 and model 2 for waist circumference. We explored this further, adding one potential confounder at a time to model 1 and noted that the greatest change in risk estimate was through the additions of hip circumference and BMI (Supplementary Table S7).

To further examine potential effect modification of HRT of the relations of anthropometric variables to colon cancer risk, we analyzed HRs for BMI, waist circumference, WHR, and hip circumference with risk expressed relative to quintile 1 in never HRT users (Fig. 1). After multivariate adjustment (model 2), current HRT use was associated with reduced risk of colon cancer across the lower (but not uppermost) quintiles of BMI and hip circumference and reduced risk associated with increasing waist circumference and WHR (Supplementary Table S8).

We repeated all analyses for rectal cancer risk and found no associations or interactions (Supplementary Tables S9 and S10).

We excluded the first 2 years of follow-up from date of the second questionnaire, and found no material influences on our findings (Supplementary Table S11).

Discussion

Main findings

In this large prospective study of men and women, our primary findings showed significant positive associations with colon cancer in men for BMI, waist circumference, and WHR, but not for hip circumference. BMI, waist circumference, and WHR were equally discriminatory for colon cancer risk. There were no associations with BMI, waist circumference, WHR, or hip circumference for colon cancer risk in women, and no associations between anthropometric variables and rectal cancer risk in men or women. In secondary analyses, there was some evidence for effect modification by HRT, but the patterns of direction of these relations were complex. Specifically, among current users of HRT, waist circumference was inversely associated with colon cancer, whereas hip circumference was positively associated with colon cancer.

Context of other studies

The observations in this study on the associations between BMI and colon cancer risk in men are consistent with our updated meta-analyses of 22 prospective studies (25). For women, associations between BMI and colon cancer risk are generally either modestly positive or null. For associations among waist circumference, WHR, and colon cancer risk, our findings for men are consistent with those reported in five other studies (2–6), which reported relative risk estimates for high versus low waist circumference or WHR ranging from 1.39 (2) to 3.3. (5). In

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Table 3. Changes in risk discrimination for colon cancer risk for men and women after addition of anthropometric measures to the null model

	Null model	BMI[a]	Waist circumference	WHR[b]	Hip circumference	BMI[a] + waist circumference	BMI[a] + WHR[b]	BMI[a] + hip circumference
Men								
−2 log *L*	33,666.8	33,640.9	33,627.8	33,654.8	33,642.5	33,627.4	33,637.0	33,636.6
AIC	33,746.8	33,722.9	33,709.8	33,736.8	33,724.5	33,711.4	33,721.0	33,720.6
C-index	0.7455 (0.6996, 0.7889)	0.7380 (0.6916, 0.7818)	0.7339 (0.6874, 0.7780)	0.7425 (0.6964, 0.7861)	0.7376 (0.6913, 0.7815)	0.7338 (0.6873, 0.7779)	0.7371 (0.6907, 0.7810)	0.7363 (0.6899, 0.7803)
C-index change	Reference	−0.0076 (−0.0079, −0.0071)	−0.0116 (−0.0122, −0.0109)	−0.0030 (−0.0032, −0.0029)	−0.0079 (−0.0083, −0.0074)	−0.0117 (−0.0123, −0.0110)	−0.0085 (−0.0089, −0.0080)	−0.0092 (−0.0097, −0.0087)
Women								
−2 log *L*	14,974.2	14,973.8	14,974.2	14,997.2	14,974.2	14,973.6	14,973.8	14,973.0
AIC	15,058.2	15,059.8	15,060.2	15,060.2	15,060.2	15,061.6	15,061.8	15,061.0
C-index	0.6833 (0.6112, 0.7512)	0.6828 (0.6107, 0.7507)	0.6832 (0.6112, 0.7512)	0.6833 (0.6112, 0.7512)	0.6834 (0.6113, 0.7513)	0.6827 (0.6106, 0.7507)	0.6827 (0.6107, 0.7507)	0.6825 (0.6104, 0.7505)
C-index change	Reference	−0.0005 (−0.0006, −0.0005)	−0.0001 (−0.0001, −0.0001)	0.0000 (0.0000, 0.0000)	0.0001 (0.0001, 0.0001)	−0.0006 (−0.0006, −0.0006)	−0.0005 (−0.0006, −0.0005)	−0.0008 (−0.0009, −0`.0008)

NOTE: Null model included age at baseline (continuous), education (less than 12 y, 12 y or high school, post-high school or some college, college graduate, or postgraduate), race/ethnicity (Caucasian or non-Caucasian), smoking status (never smoker, former smoker with 20 cig./d or less, former smoker with more than 20 cig./d, current smoker with 20 cig./d or less, or current smoker with more than 20 cig./d), marital status (married or living as married, divorced, widowed, separated, or never married), physical activity (never or rarely, 1 to 3 times/mo, 1 to 2 times/wk, 3 to 4 times/wk, 5 or more times/wk), NSAID use (yes or no), family history of colorectal cancer (yes or no), diabetes status (yes or no), dietary intakes of total energy, fiber, folate, calcium, red meat, fruits and vegetables (all in quartiles), alcohol (yes or no), HRT (never, current, or past).

Abbreviations: AIC, Akaike Information Criterion; −2 log *L*, −2 log likelihood.

[a]Weight/height^2.

[b]Waist circumference/hip circumference.

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Table 4. HRs and 95% CIs for risk of incident colon cancer across categories of anthropometric measures in women stratified by HRT use in the NIH-AARP Diet and Health Study

	Never HRT use				Current HRT use			
Measure	**Cases[a]**	**Model 1**	**Model 2**	**Model 3**	**Cases[a]**	**Model 1**	**Model 2**	**Model 3**
BMI[b] (quintile)								
1	70	1.0	1.0		49	1.0	1.0	
2	73	1.01 (0.73–1.41)	1.00 (0.73–1.40)		49	0.99 (0.67–1.47)	1.00 (0.67–1.49)	
3	73	0.92 (0.67–1.28)	0.91 (0.65–1.27)		46	0.98 (0.65–1.47)	0.97 (0.65–1.46)	
4	82	0.98 (0.71–1.35)	0.94 (0.67–1.30)		45	1.05 (0.70–1.57)	0.99 (0.66–1.50)	
5	78	0.83 (0.60–1.14)	0.74 (0.53–1.04)		50	1.43 (0.97–2.12)	1.27 (0.84–1.92)	
P_{trend}[d]		0.171	0.034			0.043	0.241	
Per SD		0.93 (0.84–1.03)	0.89 (0.80–0.99)			1.14 (1.00–1.30)	1.09 (0.95–1.25)	
WC (quintile)								
1	60	1.0	1.0	1.0	47	1.0	1.0	1.0
2	66	0.91 (0.64–1.29)	0.96 (0.67–1.37)	0.98 (0.69–1.40)	49	0.96 (0.65–1.44)	0.81 (0.53–1.21)	0.80 (0.53–1.21)
3	60	0.86 (0.60–1.24)	0.93 (0.64–1.35)	0.97 (0.66–1.42)	47	1.02 (0.68–1.52)	0.82 (0.53–1.26)	0.82 (0.52–1.27)
4	102	1.07 (0.78–1.48)	1.18 (0.81–1.70)	1.26 (0.87–1.85)	53	1.07 (0.72–1.61)	0.67 (0.42–1.07)	0.67 (0.41–1.08)
5	88	0.92 (0.66–1.27)	1.04 (0.66–1.64)	1.17 (0.72–1.91)	43	1.50 (1.01–2.22)	0.50 (0.27–0.91)	0.49 (0.26–0.94)
P_{trend}[d]		0.982	0.553	0.229		0.186	0.022	0.029
Per SD		1.00 (0.91–1.10)	1.05 (0.90–1.23)	1.11 (0.94–1.33)		1.09 (0.96–1.25)	0.78 (0.63–0.97)	0.77 (0.61–0.97)
WHR[c] (quintile)								
1	52	1.0	1.0	1.0	67	1.0	1.0	1.0
2	68	1.10 (0.77–1.58)	1.09 (0.76–1.56)	1.12 (0.78–1.61)	47	0.70 (0.48–1.02)	0.68 (0.47–0.99)	0.65 (0.45–0.95)
3	84	1.26 (0.89–1.79)	1.24 (0.88–1.76)	1.31 (0.92–1.86)	43	0.69 (0.47–1.01)	0.63 (0.43–0.93)	0.59 (0.40–0.87)
4	77	1.02 (0.72–1.45)	0.97 (0.68–1.39)	1.04 (0.73–1.49)	44	0.76 (0.52–1.12)	0.66 (0.45–0.98)	0.59 (0.40–0.88)
5	95	1.17 (0.83–1.63)	1.05 (0.75–1.49)	1.17 (0.82–1.68)	38	0.72 (0.49–1.08)	0.58 (0.38–0.87)	0.49 (0.32–0.76)
P_{trend}[d]		0.203	0.578	0.219		0.468	0.069	0.018
Per SD		1.07 (0.97–1.18)	1.03 (0.93–1.15)	1.07 (0.96–1.20)		0.95 (0.83–1.09)	0.88 (0.76–1.01)	0.83 (0.72–0.97)
HC (quintile)								
1	73	1.0	1.0	1.0	48	1.0	1.0	1.0
2	72	1.01 (0.73–1.39)	1.01 (0.72–1.41)	1.04 (0.74–1.46)	40	0.78 (0.52–1.19)	0.85 (0.55–1.30)	0.84 (0.54–1.29)
3	79	1.07 (0.78–1.47)	1.06 (0.75–1.50)	1.13 (0.79–1.61)	47	0.97 (0.65–1.45)	1.11 (0.71–1.71)	1.08 (0.69–1.68)
4	85	0.98 (0.71–1.33)	0.92 (0.63–1.35)	1.03 (0.69–1.54)	51	1.00 (0.67–1.48)	1.20 (0.74–1.92)	1.14 (0.69–1.88)
5	67	0.85 (0.61–1.18)	0.73 (0.45–1.18)	0.91 (0.53–1.56)	53	1.54 (1.05–2.28)	2.05 (1.15–3.64)	1.87 (0.98–3.59)
P_{trend}[d]		0.263	0.120	0.714		0.004	0.002	0.015
Per SD		0.95 (0.86–1.04)	0.88 (0.75–1.03)	0.97 (0.80–1.17)		1.21 (1.07–1.38)	1.39 (1.13–1.71)	1.37 (1.06–1.77)

NOTE: Model 1: The model is derived from Cox regression using age as the underlying time metric; Model 2: The multivariate models were adjusted for education (less than 12 y, 12 y or high school, post-high school or some college, college graduate, or postgraduate), race/ethnicity (Caucasian or non-Caucasian), smoking status (never smoker, former smoker with 20 cig./d or less, former smoker with more than 20 cig./d, current smoker with 20 cig./d or less, or current smoker with more than 20 cig./d), marital status (married or living as married, divorced, widowed, separated, or never married), physical activity (never or rarely, 1 to 3 times/mo, 1 to 2 times/wk, 3 to 4 times/wk, 5 or more times/wk), NSAID use (yes or no), family history of colorectal cancer (yes or no), diabetes status (yes or no), dietary intakes of total energy, fiber, folate, calcium, red meat, fruits and vegetables (all in quartiles), alcohol (yes or no), HRT (women only; never, current, or past). In addition, the multivariate model for waist circumference was adjusted for hip circumference (continuous) and the multivariate model for hip circumference was adjusted for waist circumference (continuous). Multivariate models for waist circumference, hip circumference and WHR were further adjusted for height (continuous); Model 3: The multivariate model 2 was further adjusted for BMI (continuous).

Abbreviations: HC, hip circumference; WC, waist circumference.

[a]Number of patients with colon cancer.

[b]Weight/height^2.

[c]Waist circumference/hip circumference.

[d]P_{trend} (two-sided) across categories is based on the continuous variable and was calculated using Cox regression.

contrast, for women, 4 (2, 4, 7, 8) of 6 prospective studies (2, 4, 5, 7, 8, 26) observed positive associations between waist circumference and colon cancer, with relative risks ranging from 1.4 to 1.6. (7, 8).

Additional adjustment for BMI generally attenuates the associations of waist circumference and WHR with colon cancer to a null association, as noted by others (4, 5, 26) or to a more modest positive association, as noted in the present study.

We noted an inverse association between abdominal adiposity and colon cancer risk in postmenopausal women with HRT use. Four previous studies have reported on the association between parameters of adiposity and colon cancer risk in postmenopausal women stratified by

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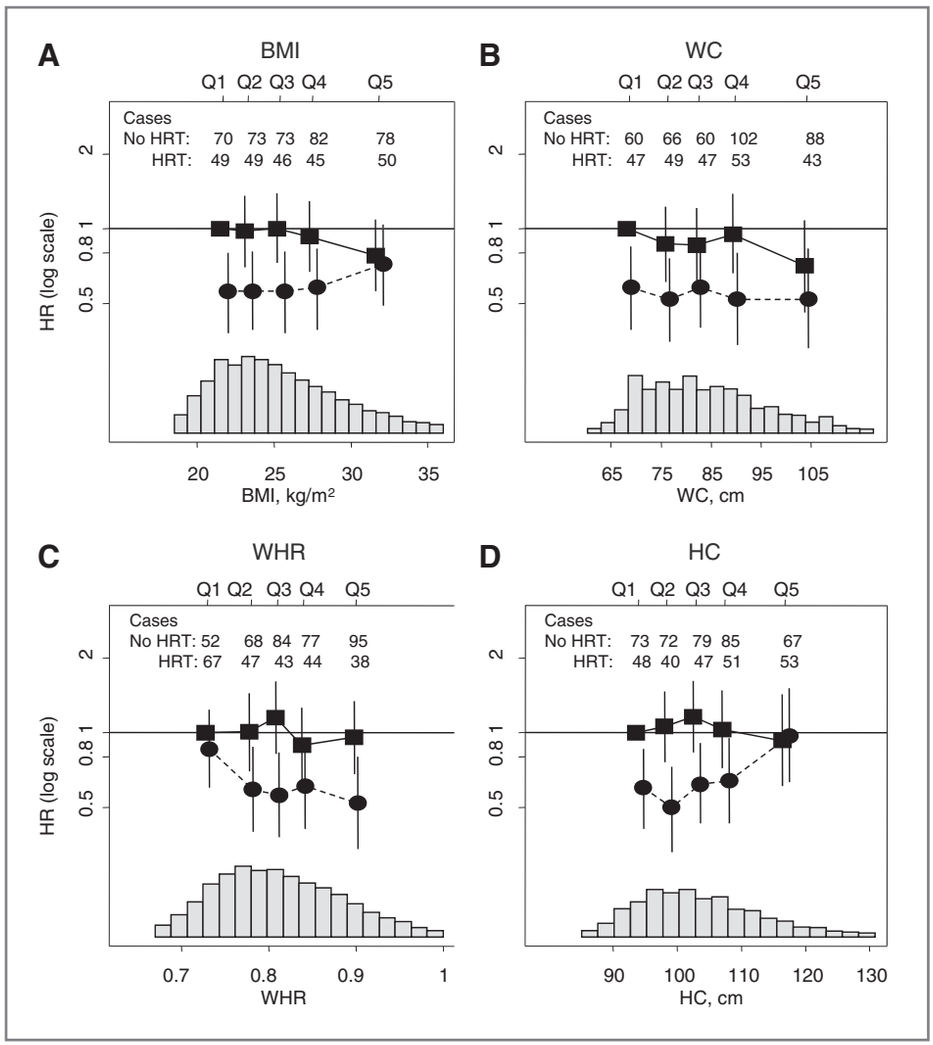

Figure 1. Hazard of colon cancer by anthropometric parameters and HRT status referent: never HRT (no HRT) and quintile 1 of anthropometric parameters. Plots of colon cancer HRs for (A) BMI, (B) waist circumference (WC), (C) WHR, and (D) hip circumference (HC) by HRT status expressed relative to quintile 1 for never HRT users. Never HRT users represented as solid line; current HRT users represented as dotted line. For each parameter, density histograms and corresponding mid-quintile points are shown. HRs are derived as per model 2 and expressed on the log scale. The number of cases for non-HRT users and current HRT users per quintile are shown as headers.

HRT use—two prospective studies observing positive associations between adiposity and colon cancer among postmenopausal women without HRT use, but not among HRT users (2, 27); one case–control study observing an inverse association between BMI and colorectal adenoma in HRT users (28); and by contrast, one case–control study showing a positive association between BMI and colorectal cancer risk among HRT users (29). Several reasons may explain these inconsistencies, including different criteria to define HRT use and different types of HRT between study populations.

Furthermore, we found that hip circumference was positively associated with colon cancer risk in HRT users. We are aware of another report on hip circumference and colon cancer risk stratified by HRT use (2); that study observed no association of hip circumference with colon cancer risk in any of the HRT strata. In contrast, one study found a positive association between hip circumference and colorectal cancer in postmenopausal women, but did not present results stratified by HRT use (30). One study (31) found a positive association between hip circumference and premenopausal breast cancer, which among the subgroup of women with hormone receptor–positive tumors only emerged after adjustment for BMI, suggesting an interaction between gluteofemoral fat accumulation, tumor hormone receptor status, and breast cancer risk.

Biologic mechanisms

Findings from our study may provide insight into the biologic mechanisms underpinning links between obesity and colon cancer. First, waist circumference and WHR—as approximations of VAT—are positively correlated with insulin resistance, hyperinsulinemia, and chronic inflammation, conditions hypothesized to play an important role in colon carcinogenesis (10, 32). For example, insulin directly stimulates the growth of colonic cancer cells *in vitro* (32, 33), whereas hyperinsulinemia indirectly increases the bioavailability of insulin-like growth factor I (IGF-I), a key promoter of tumor development (33).

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Classic adipokines, such as leptin and adiponectin, are also preferentially secreted from VAT—adiponectin is inversely correlated with increasing fatness, is antiangiogenic, anti-inflammatory, insulin-sensitizing, and inhibits tumor growth in animals. Circulating levels are higher in women than men, an observation which may contribute to the gender differences in risk associations noted for colon cancer (34).

Second, as HRT use is associated with decreased colon cancer risk [this study and others (35, 36)], bioavailable estrogens may be relevant. Estrogens inhibit colonic epithelial cell growth via stimulation of estrogen receptors in colon cells (37, 38); they reduce bile acid synthesis, putative promoters of colon carcinogenesis (39); and they reduce bioavailable IGF-I levels in postmenopausal women (40).

The observations in our study that current use of HRT was associated with reduced risk of colon cancer with increasing waist circumference and WHR but elevated risk with increasing hip circumference, point to a complexity of biologic processes. In postmenopausal women, the primary production of estrogen occurs in the adipose tissue via aromatization of androstenedione to estrone, such that levels of bioavailable estrogen are greater in obese than lean women (41). The ratio of estradiol to testosterone may also be relevant (42).

VAT may be a particularly strong stimulus to aromatization through release of interleukin 6 (IL)-6 and TNF-α (43, 44). Sex-hormone–binding globulin is also reduced in obese postmenopausal women (45), serving to further drive higher levels of bioavailable estrogen. Thus, HRT use combined with an increased amount of VAT may offer "double" estrogen protection against colon cancer risk and outweigh the adverse effects of the VAT-associated insulin pathway.

Finally, among women, high hip circumference is strongly related to subcutaneous gluteofemoral fat accumulation (11, 46), which in turn, is the main source of leptin production (44). Leptin stimulates colonic cell growth *in vitro* (47, 48) and in human studies is associated with increased colon cancer risk independent of insulin (49). In postmenopausal women, as leptin mRNA expression in subcutaneous fat correlates positively with estrogen (50)—we speculate that hip circumference may be associated with increased colon cancer risk via an estrogen-related synthesis of leptin in the subcutaneous fat.

Strengths and limitations

Strengths of the present study include its large sample size, prospective design, colorectal sub-site classification, high follow-up rate, and detailed anthropometry data. To our knowledge, this is the first prospective study to directly compare risk estimates for colon cancer related to these anthropometric measures at 2 levels: first, by deriving standardized HRs for each parameter; and second, by comparing predictive characteristics using Harrell's C-index. This is analogous to analyses comparing BMI and abdominal adiposity measures and cardiovascular disease risk reported by the Emerging Risk Factors Collaboration (51). Finally, we addressed the hypothesis that the weaker associations observed between anthropometric measures and colorectal cancer risk in women reflects HRT use—we found that these relations are complex and warrant further research.

There are potential study limitations. First, anthropometric data were self-reported, and findings could have been affected by imprecise assessments. However, self-reported waist circumference, hip circumference, weight, and height values are sufficiently precise for use in large epidemiologic investigations (52). Second, the data informing waist circumference and hip circumference are from respondents to the second questionnaire, who represent a proportion of the overall cohort. However, characteristics of this subcohort were similar to those of the overall cohort, suggesting that selection bias was not likely responsible for our findings. Third, this study represents the largest cohort to date to evaluate associations across individual anthropometric parameters and risks of colon and rectal cancer, but larger sample sizes may be required to adequately explore interactions between highly correlated measures.

Unanswered questions and future research

Important questions remain. First, there is a need to replicate these analyses in other populations to test the generalizability of our findings. Second, previous studies indicate that estrogen therapy and combined estrogen–progesterone therapy may have distinct associations with colon cancer (17, 53, 54)—these associations need to be tested in the context of interactions with a variety of anthropometric measures. Finally, there is a need to test alternative measures of VAT—such as computed tomography (CT) scan–derived estimates—and associations with colorectal cancer risk. We hypothesize that these indicators have stronger predictive characteristics than currently used anthropometry, and more likely to identify clinically relevant high-risk individuals.

Disclosure of Potential Conflicts of Interest

A.G. Renehan is a consultant/advisory board member of Novo Nordisk. A.R. Hollenbeck is a consultant/advisory board member of Love/Avon Army of Women Scientific Advisory Committee and Society of Psychologists in Management Board of Directors. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.R. Hollenbeck, A.J. Cross
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Keimling, A.G. Renehan, G. Behrens, A.J. Cross, M.F. Leitzmann

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Writing, review, and/or revision of the manuscript: M. Keimling, A.G. Renehan, G. Behrens, B. Fischer, A.R. Hollenbeck, A.J. Cross, M.F. Leitzmann
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