Body Size and Composition and Colon Cancer Risk in Men

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Abstract

Background: Several studies of male colon cancer have found positive associations with body size and composition. It is uncertain whether this relationship is due to non-adipose mass, adipose mass, distribution of adipose mass such as central adiposity, or all three. Methods: In a prospective cohort study of men aged 27–75 at recruitment in 1990–1994, body measurements were taken by interviewers. Fat mass and fat-free mass (FFM) were estimated from bioelectrical impedance analysis. Waist circumference and waist-to-hips ratio (WHR) estimated central adiposity. Incident colon cancers were ascertained via the population cancer registry. Altogether, 16,556 men contributed 145,433 person-years and 153 colon cancers. Results: Rate ratios (RRs) comparing men in the fourth quartile with those in the first quartile were as follows: FFM 2.3 [95% confidence interval (CI) 1.4–3.7]; height 1.9 (95% CI 1.1–3.1); waist circumference 2.1 (95% CI 1.3–3.5); WHR 2.1 (95% CI 1.3–3.4); fat mass 1.8 (95% CI 1.1–3.0); and body mass index 1.7 (95% CI 1.1–2.8). When continuous measures of FFM and WHR were modeled together, the RR for FFM per 10 kg was 1.37 (95% CI 1.04–1.80) and the RR for WHR per 0.1 unit was 1.65 (95% CI 1.28–2.13). After adjustment for FFM and WHR, the RRs for fat mass and body mass index were no longer statistically significant. Conclusion: Male colon cancer appears to be related to body size and composition by two different pathways, via central adiposity and via non-adipose mass. (Cancer Epidemiol Biomarkers Prev 2004;13(4):553–559)

Introduction

The effects of diet, energy intake, and physical activity on colon cancer risk have been widely investigated, whereas that of body size and composition less so. The literature on colon cancer and body size and composition has recently been reviewed (1). To date, many studies of colon cancer in men have investigated body mass index (BMI), with most case-control (2–9) and prospective cohort studies (10–17) finding evidence that BMI is positively associated with colon cancer. While BMI is a good measure of weight independent of height, it fails to distinguish between adipose and non-adipose body mass (18). Results from studies investigating estimates of central adiposity, such as waist circumference and waist-to-hips ratio (WHR), have been inconsistent with cohort studies finding evidence of a positive relationship (12, 14), while case-control studies have reported null relationships (2–4). It is, thus, uncertain whether a relationship of body size and composition with colon cancer risk is due to non-adipose mass, adipose mass, distribution of adipose mass such as central adiposity, or all three, acting either independently or in combination.

Measurement of body composition in terms of non-adipose mass and adipose mass, using the current ''gold standard'' methods of dual-energy X-ray absorptiometry or hydrostatic weighing, is costly and time consuming. Bioelectrical impedance analysis and skinfold measurements are cheaper and quicker to obtain, though measures of body composition based on skinfold measurements are substantially less reproducible than those based on bioelectrical impedance analysis (19).

We assessed the relationship between estimates of body size and composition and risk of colon cancer in a prospective cohort study by using direct anthropometric measurements including bioelectrical impedance analysis to estimate non-adipose mass and adipose mass.

Materials and Methods

The Cohort. The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,528 people (17,049 men) aged between 27 and 75 at baseline, 99.3% of whom were aged 40–69 (20). Recruitment occurred between 1990 and 1994. The study protocol was approved by The Cancer Council Victoria's Human Research Ethics Committee. Southern European migrants to Australia (including 2419 Italian men and 2073 Greek men) were deliberately oversampled to extend the range of lifestyle exposures and to increase genetic variation.

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Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media (*e.g.*, television, radio, newspapers). Comprehensive lists of Italian and Greek surnames were also used to target southern European migrants in the phone book and Electoral Rolls.

Passive follow-up has been conducted by record linkage to Electoral Rolls, electronic phone books and the Victorian Cancer Registry and death records until 30 June 2002. Three hundred and forty-two men have left Victoria (2.0% of all men in the cohort) and 1247 (7.3%) have died.

Subjects. Of the 17,049 men recruited, 414 (2.4%) were excluded from analysis because they either had a diagnosis of colorectal cancer before baseline, a cancer diagnosed other than colorectal cancer diagnosed in the 5 years before baseline, or had died or been diagnosed with any cancer within the first 30 days after baseline. A further 79 men (0.5%) who did not have a complete set of valid anthropometric measurements were also excluded, leaving 16,556 men available for analysis.

Measurements. Height, weight, and waist and hips circumferences were measured once at baseline attendance for each participant according to written protocols that were based on standard procedures (21). Weight was measured to 100 g using digital electronic scales, height to 1 mm using a stadiometer, and waist and hips circumferences were measured to 1 mm using a 2-m metal anthropometric tape. Bioelectrical impedance analysis was performed with a single frequency (50 kHz) electric current produced by a BIA-101A RJL system analyzer (RJL systems, Detroit, MI). Resistance and reactance were measured with subjects in a supine position.

Questionnaire Measures. At interview, questions were asked on conventional risk factors such as country of birth, alcohol, and highest level of education. Subjects completed a validated 121-item food-frequency questionnaire (22).

Questions relating to frequency of walking, vigorous exercise (exercise ''making you sweat or feel out of breath, and includes such activities as swimming, tennis, netball, athletics, and running''), and less vigorous exercise (exercise ''which did not make you sweat or feel out of breath and includes such activities as bike riding, dancing, etc.'') over the last 6 months were asked. The reported frequency for each question was coded as follows: 0 (none), 1.5 (one or two times per week), and 4 (three or more times per week). Walking and less-vigorous exercise frequencies were added together along with two times the frequency of vigorous exercise to generate a physical activity score for each person.

Identification of Incident Colon Cancers. All subjects gave written consent allowing access to their medical records to confirm diagnoses. Cases were identified from notifications to the Victorian Cancer Registry of diagnoses of adenocarcinoma of the colon (International Classification of Diseases 9th revision rubric 153.0–153.4, 153.6–153.9, or 10th revision rubric C18.0, C18.2–C18.9). One of us (A.H.) reviewed medical records of all reported colorectal tumors and classified them according to anatomic site (rectal, and sub-site within the colon) and stage. Tumors arising in the cecum, ascending colon, hepatic flexure, and transverse colon were defined as proximal, while tumors arising in the descending and sigmoid colons were defined as distal. Stage was categorized into four groups based on the TNM staging system: stage I (T1-2, N0, M0), stage II (T3-4, N0, M0), stage III (N1-2, M0), and stage IV (M1).

Statistical Analysis. Cox's proportional hazards regression models, with age as the time axis (23), were used to estimate the rate ratios (RRs) associated with each anthropometric measure. Calculation of person-time began 30 days after baseline and ended at date of diagnosis of colon cancer or date of censoring. Subjects were censored at either the date of diagnosis of rectal cancer (International Classification of Diseases 9th revision rubric 154.0, 154.1, or 10th revision rubric C19, C20), the date of death, the date left Victoria or 30 June 2002 (the date that ascertainment of colon cases by the Victorian Cancer Registry was complete).

We used bioimpedance analysis to estimate non-adipose mass, hereafter termed fat-free mass (FFM), as $9.1536 + (0.4273 \times \text{height}^2/\text{resistance}) + (0.1926 \times \text{weight}) + (0.0667 \times \text{reactance})$ (24). Adipose mass, hereafter termed fat mass (weight − FFM), was subsequently calculated. BMI was calculated as weight in kilograms divided by the square of height in meters. WHR was also computed.

Initially, all anthropometric measures were categorized into approximate quartiles according to their baseline distribution in the entire study population and the association of each measure with risk of colon cancer analyzed separately. The lowest quartile was used as the referent category. In addition, anthropometric measures were fitted as continuous covariates to estimate linear trends on the log hazard ratio scale, and evidence for non-linear effects were tested by fitting second-order polynomial equations and using the likelihood ratio criterion.

To further examine body mass distribution as a predictor of colon cancer risk, we fitted FFM, fat mass, and WHR simultaneously as continuous variables in the same model. The selection of a parsimonious model was made by reference to the likelihood ratio test using backwards, stepwise elimination.

The following variables were considered as potential confounders: country of birth (Australia, Greece, Italy, United Kingdom); highest level of education (primary school, some high/technical school, completed high school, and completed tertiary degree/diploma); current physical activity (0, >0–3, >3–4, >4); total dietary energy intake (log transformed); meat, fruit, vegetable, and cereal intake (servings/day); multivitamin and fiber supplements (yes/no); and current alcohol consumption (0, 1–39, 40–59, 60+ g/day). Adjustments for total dietary energy intake and meat, fruit, vegetable, and cereal intake were made excluding those in the top 1% and bottom 1% of total dietary energy intake. For each anthropometric measure, all potential confounders were initially included in the model (full model). Backwards stepwise elimination was then performed with each covariate being removed from the model if the RRs of the anthropometric measures changed by less than 5% compared with the full model (25). If a potential confounder changed the estimate for any anthropometric

RR by more than 5%, it was included in the final models for all other measures. As a consequence, country of birth and highest level of education were included as covariates in all final models.

Statistical analyses were performed using STATA/SE 7.0 (Stata Corporation, College Station, TX). $P < 0.05$ (two-sided) was considered statistically significant. Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves (26) showed no evidence that proportional hazard assumptions were violated for any of the anthropometric measures. Polytomous logistic regression models, adjusting for age (as a continuous variable), country of birth, and highest level of education, were used to test for heterogeneity in the odds ratios (ORs) between proximal and distal colon cancers, and for early (I and II) and late (III and IV) stage disease (27). Age, country of birth, and level of education were all constrained to be equal between sub-sites, while country of birth and education were both constrained to be equal between stages.

Results

A total of 153 colon cancers (146 were histopathologically confirmed, and the other 7 were metastatic) was identified during 145,433 person-years of follow-up from 1991 to 2002. Approximately 85% of the cases were over 60 years old at the time of diagnosis and the mean age at diagnosis of colon cancer was 66.6 years (range 43.8–79.1 years). Descriptive statistics for selected baseline characteristics of the study sample are shown in Table 1. The means of height, BMI, FFM, fat mass, and WHR all differed by age, country of birth, and highest level of education. Mean values of the anthropometric measures for cases and non-cases are shown in Table 2. The means of age, and of all anthropometric measurements, were greater in cases than non-cases.

Relationships between individual anthropometric measures and risks of colon cancer, adjusted for age, country of birth, and highest level of education, are presented in Table 3. Height, weight, waist circumference, FFM, fat mass, BMI, and WHR were all moderately associated with increased risk of colon cancer, with RRs for the highest quartile *versus* the lowest quartile ranging from 1.7 to 2.3 (all $P < 0.05$). Using the continuous form of the covariates revealed similar inferences about risk of colon cancer as the quartile measures. No statistically significant association was observed with hips circumference ($P = 0.1$).

There was no evidence of deviation from linear effects on the log risk scale for any of the anthropometric measures (results not shown). Excluding the first 2 years of follow-up did not materially change the RRs (data not shown).

FFM and height were moderately correlated ($r = 0.56$). FFM remained moderately associated with colon cancer risk after adjustment for height [RR per 10 kg of FFM = 1.43, 95% confidence interval (CI) 1.04–1.96], whereas after adjustment for FFM, the RR for height was reduced and no longer statistically significant (RR per 10 cm of height = 1.20, 95% CI 0.89–1.61).

Fat mass was moderately correlated with FFM and WHR (both $r \approx 0.50$), while FFM and WHR were only weakly correlated with each other ($r = 0.21$). When we modeled the continuous forms of FFM, fat mass, and WHR together (Table 4), the RRs for FFM and WHR reduced slightly but both measures remained independent predictors of colon cancer risk. To illustrate the joint effect of these two variables, the RR for an increase of 10 kg of FFM and 0.1 of WHR in the same individual was 2.25 (95% CI 1.64–3.09), while the RR for an increase of 15 kg of FFM and 0.15 of WHR (representing the difference between the 10th percentile and the 90th percentile of each variable) was 3.38 (95% CI 2.11–5.44). On the other hand, after adjustment for FFM and WHR, the point estimate of the RR for fat mass dropped to below unity, and was no longer statistically significant. The same pertained to BMI when it was substituted for fat mass in a model that included FFM and WHR (result not shown).

Apart from height and FFM, we observed stronger effects of anthropometric measures on risk of cancer for the distal colon compared with that for the proximal colon, although none of the differences between sub-sites was statistically significant (Table 5). Apart from height, the effect was stronger for late stage (Table 6), although none of these differences by stage was statistically significant.

Table 1. Number of men, mean values (SDs in parentheses) for height, weight, BMI, FFM, fat mass, and WHR, by age at baseline, country of birth, and education level

	No. of men	Height (cm)	Weight (kg)	BMI (kg/m^2)	FFM (kg)	Fat mass (kg)	WHR (unit)
Age at baseline							
<50	5120	174.8 (7.2)	81.8 (12.4)	26.8 (3.7)	58.2 (5.8)	23.6 (8.3)	0.91 (0.06)
50–59	5177	172.3 (7.3)	81.3 (11.6)	27.4 (3.5)	57.4 (5.7)	23.9 (7.6)	0.93 (0.06)
≥60	6259	170.6 (7.0)	79.7 (11.5)	27.4 (3.6)	56.1 (5.7)	23.6 (7.6)	0.93 (0.06)
Country of birth							
Australia	10,786	174.4 (6.7)	81.3 (12.2)	26.7 (3.6)	57.7 (5.8)	23.6 (8.1)	0.92 (0.06)
United Kingdom	1355	173.1 (7.2)	80.1 (11.3)	26.7 (3.4)	56.8 (5.5)	23.2 (7.4)	0.91 (0.06)
Greece	2045	168.2 (6.1)	80.4 (11.2)	28.4 (3.4)	55.9 (5.6)	24.6 (7.4)	0.94 (0.06)
Italy	2370	166.6 (6.9)	79.4 (10.7)	28.6 (3.3)	55.6 (5.6)	23.7 (6.9)	0.94 (0.06)
Education level							
Primary school	3103	167.1 (6.7)	79.9 (11.1)	28.6 (3.4)	55.5 (5.6)	24.4 (7.2)	0.95 (0.06)
Some high school	5153	172.3 (6.8)	81.6 (12.5)	27.5 (3.7)	57.4 (5.9)	24.2 (8.3)	0.93 (0.06)
Completed high school	4103	173.2 (6.9)	80.9 (11.8)	27.0 (3.5)	57.3 (5.7)	23.6 (7.8)	0.92 (0.06)
Degree/diploma	4197	175.8 (6.7)	80.5 (11.5)	26.0 (3.3)	57.9 (5.6)	22.7 (7.6)	0.90 (0.06)

Table 2. Mean values and SDs for each anthropometric measurement for cases and non-cases

	Cases (n = 153)		Non-cases (n = 16,403)	
	Mean	(SD)	Mean	(SD)
Age at baseline (years)	61.2	(6.7)	55.1	(8.8)
Height (cm)	172.6	(6.7)	172.4	(7.4)
Weight (kg)	83.4	(11.8)	80.8	(11.8)
Waist circumference (cm)	97.8	(10.6)	93.5	(10.0)
Hips circumference (cm)	102.4	(7.0)	101.1	(7.0)
FFM (kg)	58.0	(5.6)	57.1	(5.8)
Fat mass (kg)	25.3	(8.2)	23.7	(7.8)
BMI (kg/m^2)	28.0	(3.6)	27.2	(3.6)
WHR	0.95	(0.07)	0.92	(0.06)

Discussion

We found about a 2-fold greater risk of male colon cancer, comparing the fourth with the first quartile, for height, weight, waist circumference, and WHR, as well as for FFM estimated from bioelectrical impedance. Fat mass and BMI were less strongly associated with risk. When modeled together, the RR for FFM was reduced but remained significant, and the RR for WHR (or for waist circumference) changed little, but the RRs for fat mass and for BMI became negligible and not significant. That is, in males, there appear to be two independent effects of body composition on risk of colon cancer; one associated with non-adipose mass and the other with central adiposity.

We had virtually complete follow-up in this prospective study as the identification of incident colon cancers was done by record linkage to the Victorian population cancer registry that has complete coverage of the cohort participants. As only 342 men have left Victoria, it is unlikely that we have missed more than two or three cases. Surveillance bias was unlikely, as during this period there was no organized screening program for colorectal cancer. Furthermore, for most of our body size measures, we observed the strongest relationships for late-stage disease, for which the incidence would not be as influenced by early detection.

A major strength of our study is that our measures of body size at baseline were made by direct physical examination according to standard protocols. A particular issue for bioelectric impedance analysis is the absence of a standard equation to estimate FFM. Numerous attempts have been made to develop algorithms for a variety of populations using various methods of validation (19, 24, 28–33). We chose a formula that had been developed using subjects of similar ethnicity, age, and BMI distribution to our own (24) and that had been validated using sound statistical techniques. FFM measured by bioelectric impedance analysis has been shown to be highly correlated with FFM measured by dual-energy X-ray absorptiometry (r = 0.85) (24). Another concern is that the use of bioelectric impedance analysis to calculate adipose and non-adipose body components assumes that subjects have normal levels of body hydration (30, 34, 35), a status that is difficult to assess in large epidemiological studies. There is evidence from an experimental study, however, that body dehydration has a strong effect on fat mass but has virtually no effect on FFM (35). Thus, any between-subject variability in hydration level in the current study would have resulted in greater attenuation of the relationship between fat mass and colon cancer than between FFM and colon cancer.

Table 3. Colon cancer risk in relation to anthropometric measurements (in approximate quartiles): RRs[a] and 95% CIs

Variable	Person-years	Cases	RR	95% CI	P value
Height (cm)					
<167.5	36,716	36	1.0		
167.5–172.4	37,157	44	1.4	(0.9–2.2)	
172.5–177.4	35,749	34	1.3	(0.8–2.2)	
>177.4	35,812	39	1.9	(1.1–3.1)	
Linear model (per 10 cm)	145,433	153	1.43	(1.12–1.83)	0.004
Weight (kg)					
<73.0	36,445	28	1.0		
73.0–79.7	36,536	31	1.1	(0.7–1.9)	
79.8–87.4	36,175	47	1.8	(1.1–2.9)	
>87.4	36,277	47	1.9	(1.2–3.1)	
Linear model (per 10 kg)	145,433	153	1.26	(1.11–1.43)	<0.001
Waist circumference (cm)					
<87.0	34,618	22	1.0		
87.0–92.9	36,174	19	0.8	(0.4–1.4)	
93.0–99.3	38,153	48	1.7	(1.0–2.8)	
>99.3	36,488	64	2.1	(1.3–3.5)	
Linear model (per 10 cm)	145,433	153	1.37	(1.18–1.60)	<0.001
Hips circumference (cm)					
<96.5	35,206	28	1.0		
96.5–100.7	37,332	35	1.1	(0.7–1.9)	
100.8–104.9	33,746	41	1.4	(0.9–2.3)	
>104.9	39,150	49	1.4	(0.9–2.2)	
Linear model (per 10 cm)	145,433	153	1.20	(0.97–1.48)	0.1
FFM (kg)					
<53.0	34,772	25	1.0		
53.0–56.4	36,202	37	1.6	(1.0–2.7)	
56.5–60.4	36,519	46	2.2	(1.3–3.5)	
>60.4	37,941	45	2.3	(1.4–3.7)	
Linear model (per 10 kg)	145,433	153	1.59	(1.22–2.06)	0.001
Fat mass (kg)					
<18.7	37,786	25	1.0		
18.7–23.2	37,106	39	1.6	(0.9–2.6)	
23.3–28.3	35,715	48	2.0	(1.2–3.2)	
>28.3	34,826	41	1.8	(1.1–3.0)	
Linear model (per 10 kg)	145,433	153	1.33	(1.09–1.61)	0.004
BMI (kg/m^2)					
<24.8	35,653	26	1.0		
24.8–26.9	36,331	37	1.3	(0.8–2.2)	
27.0–29.2	36,555	39	1.4	(0.8–2.3)	
>29.2	36,894	51	1.7	(1.1–2.8)	
Linear model (per 5 kg/m^2)	145,433	153	1.29	(1.04–1.60)	0.02
WHR					
<0.88	35,854	23	1.0		
0.88–0.92	36,238	27	1.1	(0.6–1.8)	
0.93–0.96	36,715	39	1.3	(0.8–2.3)	
>0.96	36,626	64	2.1	(1.3–3.4)	
Linear model (per 0.1 unit)	145,433	153	1.78	(1.40–2.28)	<0.001

[a]All models adjusted for age at attendance, country of birth, and highest level of education.

Table 4. RR (95% CI in parentheses) of risk of colon cancer and FFM (per 10 kg), WHR (per 0.1 unit) and fat mass (per 10 kg) and deviance for each model fitted

Model[a]	FFM	Fat mass	WHR	Deviance
Individual	1.59 (1.22–2.06)			2533.6
		1.33 (1.09–1.61)		2537.2
			1.78 (1.40–2.28)	2524.5
Full	1.40 (1.03–1.90)	0.96 (0.75–1.23)	1.68 (1.27–2.22)	2519.5
Parsimonious	1.37 (1.04–1.80)		1.65 (1.28–2.13)	2519.6

[a]All models adjusted for age at baseline, country of birth, and highest level of education.

As the algorithm to compute FFM and fat mass includes height, weight, resistance, and reactance, in theory, any measurement errors in these would have reduced the precision of FFM and fat mass estimates. In practice, however, these measurement errors are generally small so the consequences for precision are likely to have been minimal. Although it is possible that dietary intake, physical activity, and current alcohol consumption could have confounded these relationships, the RRs did not differ by more than 5% after adjustment for our measures of these lifestyle factors. Furthermore, in multivariate modeling of measures that are highly correlated with one another, there is a potential for the covariates with the least amount of measurement error—instead of those that are biologically important—to be credited as being the better predictors. In this regard, it is important to note that FFM was more predictive than height when included in the same model, even though height would have been measured with greater precision.

Previous cohort studies (14, 36, 37) have found an association with height and risk of colon cancer, although case-control studies (2–4) have not confirmed this. Height and FFM are correlated, and our analyses suggest that FFM is an independent risk factor that diminishes, if not fully explains, the association of cancer risk with height. Height and FFM reflect the net result of nutrition during childhood and adolescence and the action of growth factors including androgens and insulin-like growth factor (IGF). One study has shown that patients with acromegaly (the disease caused by abnormal overproduction of growth hormone) are 13.5 times more likely to develop colorectal cancer than those without (38). The administration of testosterone in adult life is known to increase muscle mass and anabolic steroids are used by athletes and body builders for this purpose (39). Dwarf rats administered with growth hormones had increased body weight, colon weight, and surface area (40).

It has been speculated that different environmental factors may be responsible for distal and proximal colon cancer (41), but only a few studies (mainly case-control) have reported separately on risk by site (2–4, 6, 8, 14). Most (2, 3, 6, 8) but not all (4) studies found a stronger effect of BMI for the distal colon. The Health Professionals Follow-up Study (14) reported a ''slightly stronger'' association with waist circumference for distal colon cancer compared with proximal colon cancer. We found

Table 5. OR[a] (95% CIs in parentheses) of proximal and distal colon cancer risk in relation to anthropometric measurements

	Proximal colon	Distal colon	*P* value[b]
	n = 70	*n* = 78	
Height (per 10 cm)	1.61 (1.14–2.27)	1.29 (0.93–1.79)	0.3
Weight (per 10 kg)	1.23 (1.02–1.49)	1.27 (1.07–1.51)	0.8
Waist circumference (per 10 cm)	1.24 (0.99–1.56)	1.46 (1.18–1.80)	0.3
Hips circumference (per 10 cm)	1.13 (0.82–1.55)	1.25 (0.93–1.68)	0.6
FFM (per 10 kg)	1.73 (1.18–2.52)	1.45 (1.00–2.11)	0.5
Fat mass (per 10 kg)	1.21 (0.90–1.62)	1.42 (1.09–1.86)	0.4
BMI (per 5 kg/m^2)	1.18 (0.86–1.62)	1.38 (1.03–1.84)	0.5
WHR (per 0.1 unit)	1.51 (1.04–2.17)	1.96 (1.41–2.73)	0.3

[a]All ORs (per unit of change) were adjusted for age, country of birth, and highest level of education. The covariates were constrained to be equal for proximal and distal colon cancer.
[b]Test of heterogeneity in the ORs between proximal and distal colon cancer using polytomous logistic regression.

Table 6. OR[a] (95% CI in parentheses) of early- and late-stage colon cancer risk in relation to anthropometric measurements

	Early stage	Late stage	*P* value[b]
	n = 77	*n* = 70	
	RR (95% CI)	RR (95% CI)	
Height (per 10 cm)	1.58 (1.13–2.20)	1.48 (1.04–2.10)	0.8
Weight (per 10 kg)	1.20 (1.01–1.44)	1.37 (1.14–1.64)	0.3
Waist circumference (per 10 cm)	1.28 (1.03–1.59)	1.54 (1.23–1.91)	0.2
Hips circumference (per 10 cm)	1.17 (0.87–1.59)	1.27 (0.93–1.73)	0.7
FFM (per 10 kg)	1.49 (1.03–2.16)	1.92 (1.31–2.81)	0.3
Fat mass (per 10 kg)	1.24 (0.94–1.63)	1.47 (1.11–1.94)	0.4
BMI (per 5 kg/m^2)	1.14 (0.84–1.55)	1.49 (1.11–2.01)	0.2
WHR (per 0.1 unit)	1.52 (1.07–2.15)	2.21 (1.57–3.13)	0.1

[a]All ORs (per unit of change) were adjusted for age, country of birth, and highest level of education. Country of birth and highest level of education were constrained to be equal for early- and late-stage colon cancer.
[b]Test of heterogeneity in the ORs between early- and late-stage colon cancer using polytomous logistic regression.

that the association between BMI, waist circumference, and WHR and the risk of colon cancer may differ between the two sub-sites, with most of the overall associations with colon cancer explained by the distal sub-site. These results are in agreement with most studies but the current analysis lacks statistical power to detect other than large differences as it is based on only 78 distal and 70 proximal cases.

Previous studies of measures of body size and composition and the risk of male colon cancer have not directly measured adipose mass, and have instead relied on BMI. Seven case-control studies (2–6, 8, 9) and eight cohort studies (10–17) have found a consistent and moderate association with BMI at interview and at 2 and 5 years before diagnosis. We also found an association with BMI, but this was no longer evident once we adjusted for WHR. The effects of waist circumference and WHR were independent of FFM and fat mass. Moreover, our data suggest that the risk is most pronounced in men with a waist circumference that equals or exceeds their hip circumference (see Table 3). Taken together, these findings suggest that central adiposity is more important than obesity *per se*. Other prospective cohort studies (12, 14) have also found that central adiposity is important.

The association of central adiposity with colon cancer has contributed to the growing acceptance of the importance of insulin resistance to carcinogenesis, as articulated by McKeown-Eyssen (42) and Giovannucci (14, 43). Insulin resistance, which is characterized by increased plasma levels of insulin (hyperinsulinemia), is a major consequence of obesity and of central adiposity in particular (1). Increased insulin increases the level of bioactive IGF-1 (36) and both insulin and IGF-1 have been shown in animal and epidemiological studies to increase risk of colon cancer (36, 37).

In summary, our results suggest that body size and composition might be related to risk of colon cancer in men through two different pathways, via an association with central adiposity (waist and WHR) and via an association with non-adipose mass (height and FFM). From the point of view of prevention, an association between colon cancer risk and FFM has few implications, given that FFM is not amenable to intervention, and there are other good reasons to avoid anabolic steroids. Given their increased and irreducible risk, men with a large FFM might benefit more by avoiding the development of central adiposity; our estimates would predict that men in the 90th percentile of FFM and WHR are over three times more likely to develop colon cancer than men in the 10th percentile of FFM and WHR. Men might be able to avoid or reduce central adiposity by increasing their physical activity (1). Physical activity might in itself have a beneficial effect on colon cancer risk independently from adiposity (44); for example, by increasing insulin sensitivity (1). Our observations in regard to an increased risk of colon cancer with late stage lends further support to a possible protective effect of increased physical activity and reducing central adiposity in middle age. The association with stage observed in our study is supported by a cohort study that showed a strong association between large adenomas and WHR but nothing for small adenomas (14), suggesting that adiposity might be playing a role in disease progression.

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