Body Size and Colorectal Cancer Risk After 16.3 Years of Follow-up: An Analysis From the Netherlands Cohort Study

Original Contribution

Body Size and Colorectal Cancer Risk After 16.3 Years of Follow-up: An Analysis From the Netherlands Cohort Study

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A large body size may differentially influence risk of colorectal cancer (CRC) by anatomic location. The Netherlands Cohort Study includes 120,852 men and women aged 55–69 years who self-reported weight, height, and trouser/skirt size at baseline (1986), as well as weight at age 20 years. Derived variables included body mass index (BMI; weight (kg)/height (m)^2), BMI at age 20 years, and BMI change. After 16.3 years of follow-up (1986–2002), 2,316 CRC cases were available for case-cohort analysis. In men, the highest risk estimates were observed for body fat (per 5-unit increase in BMI, hazard ratio (HR) = 1.25, 95% confidence interval (CI): 1.05, 1.46; for highest quintile of trouser size vs. lowest, HR = 1.63, 95% CI: 1.17, 2.29 (P-trend = 0.02)) and appeared more closely associated with distal colon tumors (for BMI (5-unit increase), HR = 1.42, 95% CI: 1.13, 1.79; for highest quintile of trouser size, HR = 2.56, 95% CI: 1.55, 4.24 (P-trend < 0.01)) than with proximal colon or rectal tumors. In women, body fat was not associated with CRC risk unless it was considered simultaneously with physical activity; a large trouser/skirt size and a low level of physical activity increased risk for all subtypes. Height was associated with risk of CRC, especially distal colon tumors (highest quintile vs. lowest: HR = 1.53, 95% CI: 1.03, 2.27; P-trend = 0.05), in women only.

body height; body mass index; cohort studies; colonic neoplasms; rectal neoplasms; waist circumference

There is convincing evidence that a large body size increases the risk of colorectal cancer (CRC) (1). CRC risk has traditionally been studied according to anatomic location in the colon or rectum. However, several anatomic, embryologic, and physiologic differences exist between subanatomic locations in the colorectal tract, and therefore arising tumors may have different etiologic pathways (2–5). Thus, it may be more rational to consider CRC risk at 3 different locations: the proximal colon, distal colon, and rectum. Case-control and prospective cohort data suggest that in both men and women, body mass index (BMI) is more strongly associated with tumors of the distal colon than with tumors of the proximal colon (6–13). Several studies have suggested that waist circumference, as a proxy measure for abdominal obesity, may be a better indicator of CRC risk than BMI (14, 15) and that adult attained height as a proxy measure for early-life nutritional and socioeconomic exposures is also a convincing risk factor for CRC (1). How other indicators of body size, such as waist circumference and height, might influence CRC risk at different tumor subsites is less clear.

At present, one can only hypothesize as to how indicators of body size may influence subsite-specific pathways of colorectal carcinogenesis. Approximately 85% of tumors are thought to develop via the traditional adenoma-carcinoma pathway, characterized by mutations in the *KRAS* oncogene and the *APC* tumor suppressor gene, as well as chromosomal instability (16). Such tumors are most frequently observed in the distal colon (3). The other 15% of tumors are thought to arise via the serrated neoplasia pathway, characterized in part by a high degree of epigenetic instability and microsatellite instability (16). Such tumors are most frequently observed in the proximal colon (17–19). It has been reported that adult BMI and indicators of abdominal obesity are associated more strongly with tumors that are not characterized by

epigenetic instability (20–22). This suggests that adult body fat rather influences CRC risk via chromosomal instability and may explain the stronger associations observed between body fat and distal tumors.

Furthermore, timing of exposure may be important for defining pathways. It has been observed that a high BMI in early adulthood and a large BMI change from early adulthood to later adulthood are associated with a higher risk of CRC (13); that a high BMI at age 20 years is associated with a greater risk of having a tumor characterized by epigenetic instability (21); and that taller persons have a higher risk of tumors characterized by epigenetic instability (Hughes et al., Maastricht University, unpublished manuscript).

Here, we used data from a prospective study, the Netherlands Cohort Study (NLCS), to investigate the association between multiple indicators of body size and sex-specific risk of CRC, as well as the associations between these indicators and sex-specific CRC risk at specific tumor subsites, including the proximal colon, distal colon, rectosigmoid junction, and rectum. We considered BMI and trouser/skirt size as adult indicators of body fat, and we also considered adult attained height, BMI at age 20 years, and BMI change when assessing risk in order to study whether timing of exposure was associated with differential risk. We hypothesized that body fat would be associated more with tumors of the distal colon, whereas height might be associated more with proximal colon tumors.

MATERIALS AND METHODS

Study population and design

The NLCS includes 58,279 men and 62,573 women aged 55–69 years at baseline (1986) who completed a self-administered questionnaire involving 150 food items, as well as questions on lifestyle and health. Municipal registries from throughout the Netherlands were used to constitute an efficient sampling frame (23). The NLCS uses a case-cohort approach for data processing and analysis; case subjects were derived from the entire cohort, and the number of person-years at risk for the entire cohort was estimated from a subcohort of 5,000 persons who were randomly sampled from the full cohort at baseline. All subcohort members who reported prevalent cancer (excluding skin cancer) at baseline were excluded from the analyses, leaving 4,654 participants. Further details of the NLCS design have been published elsewhere (23–25).

Incident CRC cases were identified by annual record linkage to 9 regional cancer registries and a national pathology database (PALGA) (26). The completeness of cancer follow-up in the NLCS is almost 100% (27). CRCs were classified by anatomic location as proximal colon (*International Classification of Diseases for Oncology*, First Edition, codes 153.0, 153.1, 153.4, 153.5, and 153.6), distal colon (codes 153.2, 153.3, and 153.7), rectosigmoid (code 154.0), or rectal (code 154.1) tumors. Persons with incomplete or inconsistent baseline questionnaires were excluded. After additionally excluding persons who were missing data on variables adjusted for in the multivariate analysis, 3,197 subcohort members and 2,316 CRC cases remained. Among men, the numbers of

tumors by location were 327 proximal colon, 427 distal colon, 33 unspecified colon, 125 rectosigmoid junction, and 299 rectum; for women, the numbers were 459 proximal colon, 327 distal colon, 27 unspecified colon, 87 rectosigmoid, and 205 rectum.

Assessment of anthropometric variables, diet, and physical activity

Height (cm), body weight (kg), and body weight at age 20 years (kg) were self-reported on the baseline questionnaire. BMI was calculated as weight (kg)/height (m)^2. Participants were also asked to report their lower-body clothing (trouser or skirt) size from their clothing label (in Dutch sizes). Trouser/skirt size has been shown to be an adequate proxy measure for waist circumference when predicting cancer risk in the NLCS (28).

Both occupational physical activity in the longest-/last-held job and baseline nonoccupational physical activity were used to assess risk, depending on sex (Simons et al., Maastricht University, unpublished manuscript). For analyses of men, occupational physical activity was used. Participants were asked to report job title(s) and job duration(s) on the baseline questionnaire. Assessment of physical activity at work was based on the job held for the longest amount of time. Total energy expenditure was based on a rating system developed by Hettinger et al. (29). Men were classified into 3 energy expenditure groups: <8 kJ/minute, 8–<12 kJ/minute, and ≥12 kJ/minute. For analyses with women, nonoccupational physical activity was used to assess risk, because most women of this generation had not held a job or had worked for only a short period of time. It was calculated by totaling the number of minutes per day spent cycling/walking to work, going to shops, and walking the dog and the number of hours spent per week engaging in gardening/odd jobs, recreational cycling/walking, and sports/exercise, as reported on the baseline questionnaire. Women were classified as having a low (<30 minutes/day), intermediate (30–90 minutes/day), or high (>90 minutes/day) level of physical activity.

Statistical analyses

Data were analyzed with Stata, version 10 (StataCorp LP, College Station, Texas), separately for men and women. Cox proportional hazards analysis using the case-cohort approach was used to estimate hazard ratios and 95% confidence intervals for the association between total CRC risk and BMI (per 5-unit increase, in sex-specific quintiles), BMI at age 20 years (per 5-unit increase, in sex-specific quintiles), BMI change (<0, 0–<4, 4–<8, or ≥8 units; categories were based on a previous NLCS publication (30)), trouser/skirt size (per 2-unit size increase, in 5 sex-specific categories), and height (per 5-cm increase, in sex-specific quintiles). To test for a linear trend across categories, we used the median anthropometric variable within quintiles/categories as a continuous variable. Statistical significance was defined as $P < 0.05$ (2-sided testing).

Multivariate models. We adjusted for potential confounders selected a priori from the literature and those that introduced more than a 10% change in hazard ratios. Selected a

priori were age, family history of CRC (yes/no), smoking status (never smoker, ex-smoker, or current smoker), socioeconomic status (educational level), total energy intake (kcal/day), alcohol intake (0, 0.1–4, 5–14, 15–29, or $\geq$30 g/day), recreational physical activity (<30, 30–90, or >90 minutes/day) for women, and occupational physical activity at the longest-held job (<8, 8–<12, or $\geq$12 kJ/minute) for men. No variables introduced more than a 10% change in the hazard ratios. BMI change was additionally adjusted for BMI at age 20 years, and height was additionally adjusted for body weight (30). We also considered a model for women that included additional adjustment for oral contraceptive use (ever, never), duration of oral contraceptive use (years), use of hormone replacement therapy (ever, never), and duration of hormone replacement therapy (years). This extra adjustment did not influence effect estimates, and results are not presented.

Interaction with physical activity. Evidence suggests that among persons with lower physical activity, BMI becomes a more important indicator of colon cancer risk (9) and that underlying population levels of physical activity can impair or enhance the ability to identify colon cancer associations with other risk factors (31). We created a 2-way interaction between trouser/skirt size and physical activity. Categories of physical activity were based on self-reported recreational physical activity (women) and occupational physical activity (men), and trouser/skirt size was dichotomized on the basis of sex-specific median size. We used trouser/skirt size because evidence suggests that fat distribution is more important than body weight or BMI for CRC risk, especially in women (14). We also considered this interaction for colonic and rectal tumors separately.

For all analyses, the proportional hazards assumption was tested using scaled Schoenfeld residuals and visual inspection of the hazard curves. Furthermore, we repeated the analyses according to duration of follow-up by splitting the follow-up time at 8 years (<8 years vs. $\geq$8 years). To account for the additional variance introduced by sampling the subcohort from the entire cohort, we estimated standard errors using the robust option.

Tests for heterogeneity. We conducted tests for heterogeneity to evaluate differences between sublocalizations of tumors (e.g., proximal colon vs. distal colon), using the competing-risks procedure in Stata. However, the standard error for the difference in the log hazard ratios from this procedure assumes independence of both estimated hazard ratios, which would overestimate that standard error and thus overestimate the *P* value for their difference. Therefore, we estimated these *P* values and the associated confidence intervals on the basis of a bootstrapping method that was developed for the case-cohort design, as described previously (32). Each bootstrap analysis was based on 1,000 replications.

RESULTS

Descriptive characteristics

For both men and women, a higher trouser/skirt size corresponded with increasing BMI, and total energy intake was highest in the third quintile of BMI. Furthermore, the great-

est proportion of persons with a university-level education was observed in the lowest quintile of BMI, as was the greatest proportion of current smokers. In men, levels of occupational physical activity were relatively similar across quintiles of BMI, whereas in women, higher levels of recreational physical activity were reported by persons in the lowest quintile of BMI (Tables 1 and 2).

Associations with overall CRC in men

Age-adjusted results are not presented, since they were comparable with multivariate results. Associations between body size and CRC risk in men are presented in Table 3. With respect to body fat, BMI modeled per 5-unit increase was associated with total CRC (hazard ratio (HR) = 1.25, 95% confidence interval (CI): 1.05, 1.46). When BMI was modeled in quintiles, associations did not reach statistical significance. Stronger associations were observed with respect to trouser size; a statistically significant association was observed when comparing persons with the largest trouser size to those with the smallest size (HR = 1.63, 95% CI: 1.17, 2.29; *P*-trend = 0.02).

With respect to BMI at age 20 years, BMI change, and height, associations with overall CRC did not reach statistical significance.

Associations by tumor subsite in men

All indicators of body fat appeared to be most strongly associated with tumors of the distal colon. Increasing BMI (per 5 units) was associated with both distal (HR = 1.42, 95% CI: 1.13, 1.79) and rectosigmoid (HR = 1.49, 95% CI: 1.05, 2.11) tumors. A statistically significant trend was observed over quintiles of BMI for these two subsites (*P* = 0.05). BMI at age 20 years was associated only with tumors of the distal colon (5-unit increase: HR = 1.09, 95% CI: 1.00, 1.19; highest quintile vs. lowest: HR = 1.47, 95% CI: 1.03, 2.08 (*P*-trend = 0.05)). With respect to a positive BMI change, there was a suggested dose-response association for tumors of the distal colon (*P*-trend = 0.05). The strongest association was observed with respect to trouser size and the distal colon (largest size vs. smallest: HR = 2.56, 95% CI: 1.55, 4.24; *P*-trend < 0.01).

With respect to height, an inverse association was observed for rectosigmoid tumors (5-cm increase: HR = 0.77, 95% CI: 0.65, 0.93; highest quintile vs. lowest: HR = 0.38, 95% CI: 0.17, 0.83 (*P*-trend = 0.01)).

The strengths of the associations did not differ when data were split according to duration of follow-up (<8 years vs. $\geq$8 years). Tests for heterogeneity between tumor subtypes were not statistically significant for any risk factors considered.

Associations with overall CRC in women

In women, there were no statistically significant associations between BMI, BMI at age 20 years, BMI change, or trouser/skirt size and overall CRC risk (Table 4).

Height, modeled per 5-cm increase, was associated with a higher risk of total CRC (HR = 1.09, 95% CI: 1.01, 1.17). There was also an association when the highest quintile was

Table 1. Baseline Characteristics of Male Subcohort Members[a] According to Quintile of Body Mass Index, Netherlands Cohort Study, 1986

	Quintile of BMI[b]														
	1 (Lowest) (n = 289)			2 (n = 282)			3 (n = 280)			4 (n = 265)			5 (Highest) (n = 249)		
	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median
Age at baseline, years		61.0 (4.3)			61.0 (4.1)			60.9 (4.2)			61.0 (4.2)			61.2 (4.2)	
Total energy intake, kcal		2,115 (445)			2,194 (485)			2,202 (480)			2,147 (505)			2,172 (523)	
Weight, kg		67.9 (6.1)			74.2 (5.6)			77.4 (5.4)			81.4 (6.3)			88.9 (8.9)	
Height, cm		177.5 (6.7)			177.1 (6.6)			176.7 (6.0)			176.7 (6.5)			176.0 (6.5)	
Baseline BMI			22.0			23.7			24.9			26.1			28.4
BMI at age 20 years			18.9			20.5			21.7			22.9			24.7
Trouser size		50 (2)			50 (2)			52 (2)			52 (2)			54 (2)	
Occupational physical activity, kJ/minute															
<8	63			61			62			60			60		
8–<12	26			25			24			26			26		
≥12	11			13			14			14			14		
Level of education															
Primary school	18			19			23			27			29		
Junior/senior high school	18			19			21			22			21		
Higher vocational school	39			40			36			33			35		
University	24			23			20			18			15		
Smoking status															
Never smoker	12			11			11			12			14		
Ex-smoker	47			54			57			59			57		
Current smoker	41			35			32			30			29		
Alcohol intake, g/day															
0	20			11			13			11			10		
0.1–4	22			17			19			24			21		
5–14	24			30			29			29			25		
15–29	21			26			23			22			28		
≥30	14			16			17			15			16		
Family history of colorectal cancer															
No	96			95			93			96			95		
Yes	4			5			7			4			5		

Abbreviations: BMI, body mass index; SD, standard deviation.
[a] Subcohort members who were not missing data for the given exposure or any of the considered baseline characteristics.
[b] Weight (kg)/height (m)^2. Range of BMI values: quintile 1, 16.1–23.0; quintile 2, 23.1–24.2; quintile 3, 24.3–25.3; quintile 4, 25.4–27.0; quintile 5, 27.1–39.6.

Table 2. Baseline Characteristics of Female Subcohort Members[a] According to Quintile of Body Mass Index, Netherlands Cohort Study, 1986

| | Quintile of BMI[b] | | | | | | | | | | | | | | |
| | 1 (Lowest) (n = 359) | | | 2 (n = 373) | | | 3 (n = 369) | | | 4 (n = 373) | | | 5 (Highest) (n = 358) | | |
	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median	%	Mean (SD)	Median
Age at baseline, years		61.2 (4.5)			61.0 (4.3)			61.1 (4.2)			6.16 (4.2)			61.4 (4.1)	
Total energy intake, kcal		1,719 (412)			1,710 (401)			1,725 (420)			1,655 (350)			1,630 (372)	
Weight, kg		57.4 (5.6)			63.6 (4.6)			67.8 (4.9)			71.5 (5.6)			81.7 (8.5)	
Height, cm		166.2 (6.1)			165.6 (5.9)			165.9 (5.9)			164.4 (6.2)			163.9 (5.9)	
Baseline BMI			21.3			23.4			24.7			26.3			29.4
BMI at age 20 years			18.0			20.0			21.3			22.6			24.6
Trouser/skirt size		40 (2)			42 (2)			43 (2)			44 (2)			46 (2)	
Recreational physical activity, minutes/day															
<30	20			19			23			25			25		
30–<60	30			32			32			33			33		
60–90	25			26			23			21			21		
>90	25			23			23			22			22		
Level of education															
Primary school	26			27			31			38			39		
Junior/senior high school	17			24			26			25			28		
Higher vocational school	43			38			36			29			29		
University	13			12			7			8			4		
Smoking status															
Never smoker	49			58			54			65			63		
Ex-smoker	24			18			25			21			19		
Current smoker	27			24			21			14			18		
Alcohol intake, g/day															
0	28			31			32			33			37		
0.1–4	33			35			37			39			37		
5–14	22			20			18			18			15		
15–29	12			11			9			8			8		
≥30	6			3			4			3			3		
Family history of colorectal cancer															
No	94			94			93			95			94		
Yes	6			6			7			5			6		

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] Subcohort members who were not missing data for the given exposure or any of the considered baseline characteristics.

[b] Weight (kg)/height (m)^2. Range of BMI values: quintile 1, 15.4–22.1; quintile 2, 22.2–23.8; quintile 3, 23.9–25.3; quintile 4, 25.4–27.5; quintile 5, 27.6–41.4.

Table 3. Multivariate-Adjusted Hazard Ratios[a] for the Association Between Anthropometric Variables and Colorectal Cancer in Men After 16.3 Years of Follow-up, by Anatomic Location, Netherlands Cohort Study, 1986–2002

Exposure	Person-Years at Risk	Anatomic Location														
		Total Colorectal Cancer			Proximal Colon			Distal Colon			Rectosigmoid Junction			Rectum		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
BMI[b]																
Per 5-unit increase	18,595	1,211	1.25	1.05, 1.46	327	1.19	0.92, 1.54	427	1.42	1.13, 1.79	125	1.49	1.05, 2.11	299	1.02	0.79, 1.32
Q1	3,772	232	1		61	1		78	1		16	1		60	1	
Q2	3,931	238	0.95	0.74, 1.24	75	1.15	0.78, 1.70	78	0.92	0.64, 1.34	24	1.34	0.67, 2.61	59	0.92	0.61, 1.39
Q3	3,889	240	0.99	0.77, 1.28	58	0.89	0.59, 1.33	89	1.07	0.75, 1.53	24	1.34	0.69, 2.60	59	0.90	0.60, 1.35
Q4	3,688	247	1.05	0.81, 1.36	59	0.93	0.62, 1.40	89	1.10	0.77, 1.58	34	2.04	1.08, 3.82	60	0.93	0.62, 1.41
Q5	3,315	254	1.25	0.96, 1.62	74	1.35	0.90, 1.98	93	1.38	0.95, 1.98	27	1.62	0.85, 3.10	61	1.01	0.67, 1.51
P-trend			0.08			0.43			0.05			0.05			0.96	
BMI at age 20 years[c]																
Per 5-unit increase	18,595	1,211	1.15	0.97, 1.37	327	0.98	0.75, 1.27	427	1.09	1.00, 1.19	125	1.40	0.98, 2.01	299	1.12	0.86, 1.46
Q1	3,771	238	1		69	1		84	1		21	1		50	1	
Q2	4,090	240	0.92	0.72, 1.19	69	0.98	0.66, 1.44	82	0.96	0.67, 1.37	19	0.85	0.45, 1.63	62	1.18	0.77, 1.80
Q3	3,723	229	0.99	0.77, 1.28	62	0.93	0.63, 1.38	72	0.84	0.58, 1.22	26	1.24	0.68, 2.26	59	1.16	0.75, 1.79
Q4	3,622	254	1.09	0.84, 1.41	60	0.86	0.58, 1.29	89	1.03	0.72, 1.47	31	1.43	0.79, 2.60	69	1.34	0.88, 2.03
Q5	3,389	250	1.21	0.93, 1.56	67	1.05	0.72, 1.56	100	1.47	1.03, 2.08	28	1.37	0.75, 2.51	59	1.11	0.73, 1.71
P-trend			0.07			0.97			0.05			0.10			0.46	
BMI change[d]																
<0	1,646	103	0.87	0.63, 1.19	27	0.91	0.56, 1.47	36	0.87	0.56, 1.36	7	0.41	0.17, 1.02	29	0.99	0.61, 1.61
0–<4	10,298	657	1		178	1		224	1		74	1		163	1	
4–<8	5,701	375	1.07	0.88, 1.30	96	0.97	0.71, 1.32	140	1.23	0.93, 1.62	37	1.01	0.63, 1.61	91	1.02	0.75, 1.40
≥8	950	76	1.38	0.93, 2.05	26	1.59	0.93, 2.72	27	1.56	0.91, 2.65	7	1.29	0.51, 3.26	16	1.16	0.63, 2.15
P-trend			0.09			0.33			0.05			0.19			0.73	
Height, cm[e]																
Per 5-cm increase	18,595	1,211	0.96	0.89, 1.04	327	1.01	0.90, 1.13	427	0.99	0.89, 1.11	125	0.77	0.65, 0.93	299	0.95	0.85, 1.07
Q1	5,047	337	1		94	1		96	1		32	1		72	1	
Q2	2,781	167	0.85	0.65, 1.12	39	0.73	0.48, 1.12	66	1.13	0.77, 1.65	26	0.73	0.41, 1.29	62	0.84	0.56, 1.26
Q3	3,819	262	0.94	0.73, 1.20	68	0.91	0.62, 1.31	91	1.03	0.73, 1.47	34	0.90	0.51, 1.57	63	0.91	0.60, 1.37
Q4	3,480	224	0.84	0.64, 1.09	59	0.82	0.55, 1.22	84	0.96	0.65, 1.41	19	0.54	0.27, 1.06	58	0.92	0.60, 1.42
Q5	3,469	221	0.80	0.60, 1.08	67	0.90	0.59, 1.37	90	0.97	0.63, 1.48	14	0.38	0.17, 0.83	44	0.71	0.43, 1.17
P-trend			0.16			0.66			0.70			0.01			0.35	

Trouser size (Dutch size in 1986)[f]	No.	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
Per 2-size increase	18,595	1,211	1.12	1.05, 1.19	327	1.09	0.99, 1.20	427	1.16	1.04, 1.29	125	1.07	0.93, 1.22	299	1.06	0.96, 1.17
Q1	2,760	128	1		43	1		32	1		15	1		35	1	
Q2	4,563	280	1.31	0.98, 1.74	70	0.96	0.62, 1.48	95	1.78	1.14, 2.78	25	1.04	0.53, 2.04	83	1.42	0.90, 2.23
Q3	6,185	421	1.46	1.11, 1.91	116	1.21	0.81, 1.80	156	2.14	1.40, 3.27	48	1.51	0.82, 2.79	87	1.09	0.70, 1.63
Q4	3,269	239	1.56	1.15, 2.10	59	1.16	0.74, 1.82	87	2.23	1.40, 3.54	26	1.51	0.76, 3.01	63	1.50	0.94, 2.39
Q5	1,819	143	1.63	1.17, 2.29	39	1.32	0.81, 2.15	57	2.56	1.55, 4.24	11	1.10	0.49, 2.49	31	1.33	0.77, 1.29
P-trend			0.02			0.14			<0.01			0.28			0.34	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; Q, quintile.

[a] Hazard ratios were adjusted for age, total energy intake (kcal/day), occupational physical activity (<8, 8–<12, or ≥12 kJ/minute), level of education (primary school, some high school, high vocational school, or university), family history of colorectal cancer (yes/no), alcohol consumption (0, 0.1–4, 5–14, or 15–29 g/day), and smoking (never smoker, ex-smoker, or current smoker).

[b] Weight (kg)/height (m)². Range of BMI values: Q1, 16.1–23.0; Q2, 23.1–24.2; Q3, 24.3–25.3; Q4, 25.4–27.0; Q5, 27.1–39.6.

[c] Range of BMI values at age 20 years: Q1, 11.8–19.8; Q2, 19.9–21.0; Q3, 21.1–22.1; Q4, 22.2–23.6; Q5, 23.7–31.8.

[d] In the model for BMI change, hazard ratios were additionally adjusted for BMI at age 20 years. Body weight change associated with categories of BMI change: −29 to 0 kg; 0.1–15 kg; 11–30 kg; 23–57 kg.

[e] In the model for height, hazard ratios were additionally adjusted for body weight (kg). Range of height values: Q1, 158–172 cm; Q2, 173–175 cm; Q3, 176–178 cm; Q4, 179–182 cm; Q5, 183–200 cm.

[f] Range of trouser sizes: Q1, 28–48; Q2, 50; Q3, 52; Q4, 54; Q5, 56–68.

compared with the lowest quintile (HR = 1.32, 95% CI: 1.03, 1.71; *P*-trend = 0.05).

Associations by tumor subsite in women

Associations by subsite in women were not as clear as those in men. With respect to body fat, women with the largest trouser/skirt size had a borderline statistically significant risk of proximal colon tumors compared with those with the smallest size (HR = 1.46, 95% CI: 0.98, 2.18), but there was no clear trend (*P*-trend = 0.46).

There was a borderline statistically significant association between height and distal colon tumors (HR = 1.11, 95% CI: 0.99, 1.24) and rectal tumors (HR = 1.14, 95% CI: 0.98, 1.32) when data were modeled per 5-cm increase. Women in the highest quintile also had a statistically significant risk of distal tumors when compared with those in the lowest quintile (HR = 1.53, 95% CI: 1.03, 2.27; *P*-trend = 0.05). This association was borderline statistically significant for rectal tumors (HR = 1.49, 95% CI: 0.98, 2.27; *P*-trend = 0.06).

When data were split at 8 years of follow-up, it appeared that associations for all anthropometric variables were attenuated over time (data not shown). Tests for heterogeneity between tumor subtypes were not statistically significant for any risk factors considered.

Interaction between trouser/skirt size and physical activity

Table 5 shows hazard ratios for the interaction between trouser size and occupational physical activity in men. Compared with the reference category of men with a small trouser size and a high level of physical activity, there were no statistically significant associations for total CRC, but men with a small trouser size and a low level of physical activity were at increased risk of distal colon tumors (HR = 1.63, 95% CI: 1.03, 2.56). A borderline statistically significant association was also observed for men with a large trouser size and all levels of physical activity with respect to tumors of the distal colon.

Compared with the reference category of women with a small trouser/skirt size and a high level of physical activity (Table 6), the greatest risk for each subtype considered appeared to be for persons with the highest trouser/skirt size and the lowest level of physical activity (for total CRC, HR = 1.83, 95% CI: 1.28, 2.63; for proximal colon tumors, HR = 1.70, 95% CI: 1.08, 2.67; for distal colon tumors, HR = 1.95, 95% CI: 1.21, 3.17; for rectal tumors, HR = 2.56, 95% CI: 1.36, 4.79). The interaction between trouser/skirt size and physical activity was statistically significant only for the proximal colon (*P* < 0.05).

DISCUSSION

We observed that in men, body fat, as indicated by BMI, BMI at age 20 years, BMI change, and trouser size, appeared to be more associated with distal tumors than with tumors at other anatomic subsites; however, associations with respect to height were less clear. Body size appeared to be unrelated to CRC outcomes in women, except for height, which was

Table 4. Multivariate-Adjusted Hazard Ratios[a] for the Association Between Anthropometric Variables and Colorectal Cancer Endpoints in Women After 16.3 Years of Follow-up, by Anatomic Location, Netherlands Cohort Study, 1986–2002

Exposure	Person-Years at Risk	Anatomic Location														
		Total Colorectal Cancer			Proximal Colon			Distal Colon			Rectosigmoid Junction			Rectum		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
BMI[b]																
Per 5-unit increase	27,195	1,106	0.98	0.88, 1.10	459	1.02	0.87, 1.18	327	0.95	0.79, 1.14	87	1.01	0.74, 1.38	205	1.05	0.83, 1.31
Q1	5,238	228	1		94	1		70	1		16	1		42	1	
Q2	5,623	211	0.88	0.69, 1.13	87	0.88	0.63, 1.23	62	0.85	0.58, 1.24	17	1.08	0.53, 2.21	41	1.00	0.63, 1.58
Q3	5,499	223	0.94	0.73, 1.20	94	0.99	0.71, 1.40	58	0.81	0.55, 1.19	26	1.86	0.94, 3.69	38	0.87	0.54, 1.40
Q4	5,606	222	0.91	0.71, 1.16	95	0.98	0.70, 1.37	64	0.85	0.58, 1.23	13	0.85	0.40, 1.84	40	0.93	0.58, 1.49
Q5	5,229	222	0.97	0.76, 1.24	89	0.91	0.65, 1.28	73	1.04	0.72, 1.50	15	1.06	0.50, 2.26	44	1.07	0.67, 1.60
P-trend			0.90			0.84			0.84			0.93			0.90	
BMI at age 20 years[c]																
Per 5-unit increase	27,195	1,106	1.04	0.90, 1.19	459	1.03	0.84, 1.25	327	1.05	0.85, 1.31	87	0.91	0.61, 1.35	205	1.06	0.82, 1.36
Q1	5,628	213	1		90	1		60	1		19	1		38	1	
Q2	5,247	227	1.21	0.95, 1.56	100	1.28	0.90, 1.76	67	1.22	0.83, 1.79	18	1.09	0.56, 1.13	43	1.26	0.78, 2.01
Q3	5,212	236	1.25	0.98, 1.61	96	1.15	0.82, 1.60	74	1.36	0.95, 1.99	18	0.97	0.50, 1.89	46	1.34	0.84, 2.13
Q4	5,576	212	1.08	0.84, 1.38	87	0.98	0.70, 1.38	65	1.21	0.82, 1.79	15	0.85	0.42, 1.72	35	0.98	0.60, 1.61
Q5	5,532	218	1.12	0.87, 1.43	86	1.14	0.81, 1.62	61	1.09	0.74, 1.62	17	1.07	0.54, 2.12	43	1.29	0.80, 2.07
P-trend			0.68			0.97			0.68			0.89			0.62	
BMI change[d]																
<0	3,268	134	0.94	0.73, 1.22	51	0.86	0.60, 1.23	44	1.08	0.72, 1.60	12	1.26	0.63, 2.50	19	0.67	0.39,1.14
0–<4	12,177	507	1		212	1		147	1		37	1		97	1	
4–<8	8,787	343	0.89	0.74, 1.06	144	0.86	0.67, 1.10	98	0.89	0.67, 1.20	26	0.97	0.56, 1.68	69	0.96	0.68, 1.35
≥8	2,963	122	0.95	0.73, 1.24	52	0.98	0.68, 1.40	38	1.00	0.67, 1.50	12	1.40	0.69, 2.82	20	0.83	0.49, 1.39
P-trend			0.55			0.86			0.58			0.83			0.78	
Height, cm[e]																
Per 5 cm	27,195	1,106	1.09	1.01, 1.17	459	1.04	0.95, 1.15	327	1.11	0.99, 1.24	87	1.02	0.82, 1.25	205	1.14	0.98, 1.32
Q1	6,353	250	1		104	1		68	1		24	1		49	1	
Q2	4,932	186	0.96	0.75, 1.23	89	1.11	0.80, 1.54	62	1.17	0.80, 1.72	10	0.53	0.25, 1.12	20	0.52	0.30, 0.89
Q3	5,599	209	0.97	0.77, 1.24	103	1.15	0.83, 1.58	49	0.84	0.56, 1.25	13	0.61	0.30, 1.24	40	0.93	0.60, 1.45
Q4	5,708	231	1.03	0.81, 1.31	78	0.83	0.59, 1.18	76	1.28	0.88, 1.86	23	1.02	0.55, 1.86	45	1.04	0.68, 1.59
Q5	4,603	230	1.32	1.03, 1.71	85	1.19	0.84, 1.70	72	1.53	1.03, 2.27	17	0.90	0.44, 1.84	51	1.49	0.98, 2.27
P-trend			0.05			0.67			0.05			0.78			0.06	

Trouser/skirt size (Dutch size in 1986)[f]	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
Per 2-size increase	27,195	1.03	0.98, 1.09	459	1.06	0.98, 1.14	327	1.02	0.94, 1.11	87	1.03	0.90, 1.18	205	1.04	0.94, 1.16
Q1	5,317	1		80	1		66	1		15	1		36	1	
Q2	6,861	1.02	0.80, 1.29	126	1.20	0.86, 1.67	80	0.89	0.62, 1.28	20	1.07	0.54, 2.13	52	1.08	0.68, 1.71
Q3	7,586	0.90	0.71, 1.14	114	0.95	0.68, 1.33	83	0.83	0.58, 1.19	29	1.38	0.73, 2.60	52	0.96	0.61, 1.53
Q4	4,761	0.98	0.76, 1.27	76	0.97	0.67, 1.39	57	0.92	0.62, 1.36	19	1.39	0.68, 2.87	44	1.28	0.79, 2.08
Q5	2,670	1.17	0.87, 1.58	63	1.46	0.98, 2.18	41	1.15	0.74, 1.80	4	0.58	0.19, 1.78	21	1.07	0.59, 1.93
P-trend		0.62			0.46			0.72			0.90			0.56	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; Q, quintile.

[a] Hazard ratios were adjusted for age, total energy intake (kcal/day), recreational physical activity (<30, 30–<60, 60–90, or >90 minutes/day), level of education (primary school, some high school, high vocational school, or university), family history of colorectal cancer (yes/no), alcohol consumption (0, 0.1–4, 5–14, or 15–29 g/day), and smoking (never smoker, ex-smoker, or current smoker).

[b] Weight (kg)/height (m)^2. Range of BMI values: Q1, 15.4–22.1; Q2, 22.2–23.8; Q3, 23.9–25.3; Q4, 25.4–27.5; Q5, 27.6–41.4.

[c] Range of BMI values at age 20 years: Q1, 11.3–19.0; Q2, 19.1–20.6; Q3, 20.7–21.8; Q4, 21.9–23.3; Q5, 23.4–46.9.

[d] In the model for BMI change, hazard ratios were additionally adjusted for BMI at age 20 years. Body weight change associated with categories of BMI change: −50 to 0 kg; 0.1–12 kg; 9–25 kg; 18–62 kg.

[e] In the model for height, hazard ratios were additionally adjusted for body weight (kg). Range of height values: Q1, 143–160 cm; Q2, 161–164 cm; Q3, 165–167 cm; Q4, 168–170 cm; Q5, 171–186 cm.

[f] Range of trouser/skirt sizes: Q1, 36–40; Q2, 42; Q3, 44; Q4, 46; Q5, 48–56.

related positively to cancers of the distal colon and rectum. In general, our observations, especially in men, highlight the importance of examining CRC risks according to tumor subsite, because stronger associations were observed for individual subsites than with overall risk.

Strengths of this study include the prospective cohort design and the large population, in combination with sufficient follow-up time to allow precise analysis of CRC risk at different subsites. The NLCS has almost complete ascertainment of CRC cases, and follow-up of the subcohort is almost 100%. Although measures of body size in this study were obtained by self-report, there are many examples in the literature showing that this method is a reasonably valid and reliable tool for assessing body weight and height in cohort studies (33–36). A weakness of this study was the small number of rectosigmoid and rectal tumors and the subsequently limited statistical power.

Investigators in several case-control studies have considered the association between BMI and site-specific tumors of the colon in men, and they have generally reported a stronger risk for tumors of the distal colon than for tumors of the proximal colon (6–10). This is supported by the results of a recent prospective cohort study carried out by Laake et al. (11). In our study, we considered several indicators of body fat in addition to BMI, including BMI at age 20 years, BMI change, and trouser/skirt size as a proxy for waist circumference, and we consistently observed an elevated risk of distal colon tumors as compared with tumors at other subsites. Although we did not observe statistically significant heterogeneity between proximal and distal colon tumors as Laake et al. (11) did, the bootstrapping method we used is quite conservative. The weaker associations that we observed with respect to associations between body fat and the rectum align with previous research (1), but we also observed a positive association between BMI and tumors of the rectosigmoid junction. To our knowledge, no other prospective study has considered the association between anthropometric measures and the rectosigmoid junction. This association is plausible, because the rectosigmoid junction and distal colon are anatomically linked. Our findings should be replicated in other prospective studies, but they support the hypothesis that the etiology of CRC tumors differs between anatomic subsites of the colorectal tract in men.

We did not observe clear associations between BMI, BMI at age 20 years, or BMI change and CRC risk in women, but our results suggest that women with a high trouser/skirt size are at increased risk of proximal colon tumors, although this association did not reach statistical significance. In contrast, positive associations between BMI and distal colon tumors have been reported in prospective cohort studies of Swedish (12) and Norwegian (11) women. In an American cohort, both BMI and waist circumference were associated with proximal and distal tumors (13). The proportion of obese women in the NLCS is small, and perhaps this prevented us from detecting associations of similar strength. It has also been suggested that the impact of a given risk factor along the length of the large bowel may differ according to the prevalence of other environmental factors and, thus, according to sex and country (2).

Alternatively, it is plausible that a metabolic profile reflecting a combination of risk factors has a greater influence

Table 5. Multivariate-Adjusted Hazard Ratios[a] for the Interaction Between Occupational Physical Activity and Trouser Size in the Risk of Colorectal Cancer Among Men, Netherlands Cohort Study, 1986–2002

| Trouser Size[b] | Physical Activity | | | | | | | | | | | |
| | Low | | | | Intermediate | | | | High | | | |
	No. of Cases	PY at Risk	HR	95% CI	No. of Cases	PY at Risk	HR	95% CI	No. of Cases	PY at Risk	HR	95% CI
Total colorectal cancer												
≤52	632	10,139	1.20	0.90, 1.60	249	4,392	1.03	0.76, 1.39	123	2,293	1	
>52	263	3,821	1.15	0.83, 1.61	123	1,490	1.38	0.95, 2.02	75	940	1.34	0.87, 2.06
Proximal colon												
≤52	169	10,139	1.03	0.67, 1.58	83	4,392	1.10	0.70, 1.72	37	2,293	1	
>52	81	3,821	1.14	0.70, 1.84	29	1,490	1.07	0.61, 1.89	15	940	0.84	0.42, 1.67
Distal colon												
≤52	233	10,139	1.63	1.03, 2.56	66	4,392	1.10	0.70, 1.72	30	2,293	1	
>52	103	3,821	1.54	0.95, 2.54	41	1,490	1.72	0.98, 3.03	26	940	1.76	0.94, 3.30
Rectum												
≤52	140	10,139	0.94	0.61, 1.45	68	4,392	0.92	0.59, 1.45	40	2,293	1	
>52	51	3,821	0.89	0.52, 1.53	37	1,490	1.51	0.86, 2.66	22	940	1.41	0.75, 2.67

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

[a] Hazard ratios were adjusted for trouser size, physical activity, total energy intake, family history of colorectal cancer, socioeconomic status, alcohol consumption, and smoking status.

[b] Dutch size in 1986.

on cancer risk than do the individual effects of body size and obesity (37, 38). Because evidence suggests that fat distribution is more important than body weight or BMI for CRC risk, especially in women (14), we investigated the interaction with physical activity using trouser/skirt size. Our observations for women were intriguing. As noted above, we did not observe statistically significant associations with respect to trouser/skirt size in our general analysis. However, when we considered the interaction between trouser/skirt size and physical activity, it appeared that women with a large trouser/skirt size and the lowest level of physical activity were at the greatest risk of CRC compared with women with a small trouser/skirt

Table 6. Multivariate-Adjusted Hazard Ratios[a] for the Interaction Between Nonoccupational Physical Activity and Trouser/Skirt Size in the Risk of Colorectal Cancer Among Women, Netherlands Cohort Study, 1986–2002

| Trouser/Skirt Size[b] | Physical Activity | | | | | | | | | | | |
| | Low | | | | Intermediate | | | | High | | | |
	No. of Cases	PY at Risk	HR	95% CI	No. of Cases	PY at Risk	HR	95% CI	No. of Cases	PY at Risk	HR	95% CI
Total colorectal cancer												
≤44	159	4,471	1.45	1.08, 1.94	357	12,026	1.25	0.97, 1.60	122	5,054	1	
>44	97	2,283	1.83	1.28, 2.63	116	4,447	1.14	0.82, 1.59	51	1,617	1.44	0.95, 2.18
Proximal colon*												
≤44	89	4,471	1.60	1.10, 2.31	203	12,026	1.40	1.02, 1.93	63	5,054	1	
>44	52	2,283	1.70	1.08, 2.67	66	4,447	1.16	0.76, 1.77	33	1,617	1.69	1.03, 2.79
Distal colon												
≤44	63	4,471	1.28	0.86, 1.91	141	12,026	1.08	0.77, 1.52	54	5,054	1	
>44	42	2,283	1.95	1.21, 3.17	50	4,447	1.18	0.74, 1.84	17	1,617	1.12	0.61, 2.03
Rectum												
≤44	38	4,471	1.67	0.98, 2.85	86	12,026	1.43	0.89, 2.29	25	5,054	1	
>44	27	2,283	2.56	1.36, 4.79	35	4,447	1.70	0.93, 3.10	12	1,617	1.66	0.77, 3.54

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

* P for interaction < 0.05.

[a] Hazard ratios were adjusted for trouser/skirt size, physical activity, total energy intake, family history of colorectal cancer, socioeconomic status, alcohol consumption, and smoking status.

[b] Dutch size in 1986.

size and a high level of physical activity. This risk was highest for rectal tumors; however, the interaction was statistically significant only for tumors of the proximal colon. These findings require confirmation in other prospective studies, but they support case-control data (9, 39). They also highlight that underlying population levels of physical activity can impair or enhance the ability to identify CRC associations with other risk factors (31), such as body fat.

Height is a reflection of earlier life exposures, such as childhood energy intake (40). In our study, height was associated with increased risk of CRC in women, which is in accordance with previous research (1, 13, 14, 41, 42). In a recent report, Oxentenko et al. (13) suggested that risk is greater for tumors of the proximal colon, whereas our data suggest that risk is greater for tumors of the distal colon. However, in the former study, Oxentenko et al. did not report conducting tests for heterogeneity, and in our study, such tests did not reach statistical significance. We did not observe any association with respect to height and CRC risk in men, and we actually observed an inverse association for tumors of the rectosigmoid junction. We cannot explain this observation, and we suggest that it may be a chance finding. We have shown previously in the NLCS population that energy restriction during childhood is inversely related to later CRC risk (43); therefore, while we have not observed strong associations between height and CRC in the present study, it is plausible that early-life nutritional factors may influence different carcinogenic pathways than later-life exposure to increased body fat (13).

We can only speculate as to why body size and body fat in particular might differentially influence the etiology of colorectal tumors at different subsites. Obesity is associated with a chronic state of low-grade inflammation and thus increased circulatory levels of inflammatory markers like C-reactive protein, interleukin-6, and tumor necrosis factor α (44). These in turn may induce insulin resistance and hyperinsulinemia. It is hypothesized that such conditions influence CRC risk (45–47); however, it remains unclear how they directly or indirectly influence specific tumor subsites. There are some distinct differences between the proximal colon and the distal colon, both anatomically and genetically (3–5). The distal colon is associated more with physical/chemical stimuli and associated less with water absorption and electrolyte transport than the proximal colon (3). It has been shown that tumors characterized by chromosomal instability are more associated with tumors of the distal colon, whereas epigenetic changes like methylation are more associated with tumors of the proximal colon (48). Interestingly, recent studies have suggested that overweight and obesity do not appear to differentially influence CRC risk via epigenetic mechanisms and microsatellite instability (20, 22, 49). Based on the observation that body fat appears to be associated with a higher risk of distal colon tumors, a plausible hypothesis is that obesity and its associated process may influence risk via the chromosomal instability pathway. However, to our knowledge, this has not been investigated in any population-based studies. It is clear that the association between metabolic and hormonal risk factors and CRC is complex, and more research in this area is needed to elucidate clear mechanisms and how these mechanisms might differ with respect to tumor subsite.

In this Dutch population, body fat—especially abdominal fat, as indicated by trouser size—was associated with tumors of the distal colon in men. In women, the influence of body fat on CRC risk may differ according to level of physical activity. Height was associated with CRC risk only in women. More research is needed to fully elucidate how body size may influence subsite-specific pathways of CRC carcinogenesis.

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