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Anthropometry-based obesity phenotypes and risk of colorectal adenocarcinoma: a large prospective cohort study in Norway.

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Abstract

Background: Whether obesity phenotypes measured by different anthropometric indices are associated with a risk of colorectal adenocarcinoma by anatomical location is unclear.

Patients and Methods: A collection of harmonized population-based cohort studies (Cohort of Norway, CONOR) with 143,477 participants was conducted between 1994 and 2010. General, abdominal, gluteofemoral obesity, and other type were assessed by body mass index (BMI), waist circumference, hip circumference (HC), and body adiposity index (BAI) adjusted by BMI or/and waist circumference. Cox proportional hazards regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of obesity relative to a risk of colorectal adenocarcinoma.

Results: In total, 2044 incident cases of colorectal adenocarcinoma were identified. We observed a positive association between WC (≥86(women) or ≥96(men) versus<75(women) or <88 (men)) and adenocarcinoma in the proximal colon (HR 1.92, 95% CI: 1.47-2.50) and distal colon(HR 1.71, 95% CI: 1.25-2.33) when adjusted for BMI. The association with WC was especially evident in men. BMI was not associated with adenocarcinoma in the colon or rectum after adjusting for WC. No associations were found between HC and colorectal adenocarcinoma. When adjusted by BMI plus WC, BAI was negatively associated with adenocarcinoma in the proximal or distal colon

Conclusion: Abdominal, not general or gluteofemoral obesity, was associated with an increased risk of adenocarcinoma in the proximal and the distal colon, especially in men. Muscularity may be negatively associated with risk of adenocarcinoma in the proximal colon.

Key words: Anthropometrics; Waist circumference; Abdominal obesity; Muscularity; Adenocarcinoma; Colon; Rectum; CONOR; HUNT

Introduction

General obesity (measured using body mass index (BMI)) and abdominal or central obesity (measured by waist circumference) increases the risk of colorectal cancer.[1-3] The risk of colorectal cancer associated with obesity is also influenced by sex, age, menopausal status, and ethnicity.[4-7] However, direct measurements of subcutaneous and visceral obesity by computer tomography (CT) have shown inconsistent results.[8-10] It is conceivable, therefore, that the causal relation between obesity and colorectal cancer may not be as simple as assumed. In addition to different environmental conditions and hereditary factors, the selection of anthropometric indices to substitute phenotypes of obesity may have profound effects on the prediction of colorectal cancer risk.

Several anthropometric indices for the measurement of obesity have been developed and applied in epidemiological studies. As the most commonly used anthropometric parameter, BMI is a good index for general obesity, but not sensitive for more specific obese phenotypes, e.g. abdominal obesity.[11] The latter is widely recognized as the key factor related to diabetes, cardiovascular diseases, and cancer.[12,13] Waist circumference and waist to hip ratio have been demonstrated as two important indices for abdominal obesity.[11] Waist to height ratio (or called waist to stature ratio) has been associated with cardiovascular diseases as a new parameter of abdominal obesity, but reports on colorectal cancer are rare.[14,15] Hip circumference has been suggested as a measurement of gluteofemoral obesity, which has been negatively associated with a risk of chronic diseases, including cancer.[16] As a newly developed anthropometric parameter, waist to height index (WHI) was associated with an increased risk of colorectal cancer in female Japanese subjects, but no further study has been reported.[17] Another newly introduced anthropometric parameter, body adiposity index (BAI), has been recognized as an index ofestimating percentage of body fat, but the largely inconsistent results achieved with body adiposity index warrant more explorations of this index.

Collectively, a series of anthropometric parameters, representing specific obesity phenotypes, have been developed during the past decades, but few studies have compared these anthropometric indices and how they are associated differently with colorectal cancer risk by anatomical location.

In the present study, the association between different anthropometric indices for obesity and colorectal adenocarcinoma by anatomical location were investigated in a large, prospective, population-based cohort study in Norway: the CONOR study. Since adenocarcinoma is the dominating histological type (more than 90%) and different histological types of colorectal cancer may entail different causality, only the risk of adenocarcinoma has been assessed in the current study.

Materials and Methods

Study population

Detailed information on the design of, and data collection in, the CONOR study has been described previously.[18] Briefly, CONOR was performed in collaboration between the Norwegian Institute of Public Health and the Universities of Bergen, Oslo, Tromsø, and Trondheim (NTNU). Data from 10 regional epidemiological studies were merged into a national database to study risk factors for a wide range of diseases. In total,180,553 participants from 10 epidemiology studies were included in the CONOR study.[19]After excluding repeated participants (7310 with two follow-ups), prevalent cancer cases (906), individuals who died or migrated before the baseline survey (6075), missing waist circumference, hip circumference, height or weight data (21234), and missing smoking data (1551), a total of 143,477 participants remained for the final analysis. Anthropometric data were harmonized throughout all the studies based on common questionnaires/similar clinical measurements.

Follow-up and identification of colorectal cancer cases

The CONOR cohort was followed-up based on linkage to the Norwegian Cancer Register (NCR) and Statistics Norway, using the unique 11-digit national identity number of Norwegian citizens. Colorectal cancer was registered in the NCR according to the International Classification of Diseases, 7th edition (ICD-7). The ICD-7 codes were used to identify the colorectal cancer cases by anatomical location, including: the proximal colon (ICD-7 codes 1530, 1531, and 1536, including the cecum, ascending colon, transverse colon, hepatic flexure, the splenic flexure and appendix); the distal colon (ICD-7 codes 1532 and 1533, including the descending colon, the sigmoid colon); the rectum(ICD-7 code 1540, including the rectum and rectosigmoid junction). The participants were enrolled into the cohort at the baseline until diagnosis of colorectal cancer, death, censored (i.e. lost to follow-up, emigration or diagnosis of other malignancies), or end of follow-up on December 31, 2010, whichever occurred first.

Assessment of anthropometric data

Body weight (in kilograms(kg), to one decimal place) and height (in centimeters(cm), to one decimal place) were manually recorded until the year 2000 and thereafter an electronic height and weight scale was used. BMI was calculated as body weight (kg) divided by the square of height(meters square). Waist circumference was measured at the umbilicus to the nearest centimeter and with the subject standing and breathing normally. Hip circumference was measured as the maximum circumference around the buttocks. Waist to hip ratio and waist to height ratio was calculated from measurements of waist circumference, hip circumference or height. Waist to height index was calculated by the formula of waist circumference (cm)/height (m)/height (m).[17] The body adiposity index was computed by the formula of (hip circumference(cm)/height(meter)$^{1.5}$)-18.

We examined each obesity phenotype with one specific anthropometric index. BMI was used for general obesity, waist circumference for abdominal obesity, hip circumference for gluteofemoral obesity, and body adiposity index for one uncertain type. Due to the limited space of the manuscript and also in order to complement the results using other related indices, the results of waist to hip ratio, waist to height ratio and waist to height index were further showed in supplemental tables.

Other data collected at the baseline survey included: marital status, country of birth, years of education, smoking, alcohol consumption, physical activity, anti-hypertensive drug use, and self-reported diabetes.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between the anthropometric indices and colorectal cancer were estimated using Cox proportional hazard models. BMI was grouped into four categories (<22.5, 22.5-25, 25-30, >30 kg/m^2). The categorization of BMI was slightly different from the WHO standardization because of small size of cohort members in the group of BMI less than 18.5. Waist circumference was divided into three categories based on sex-specific cut-offs (women: <75, 75-85.9, ≥86; men <88, 88-95.9, ≥96 cm). Hip circumference was categorized into two groups (<101 cm and ≥101 cm), and waist to height ratio three groups (<0.5, 0.5- and ≥0.6). Other anthropometric data were analyzed based on continuous variables. Waist to hip ratio and waist to height ratio were multiplied by 10 in the model to decrease the significant fluctuation of the small values, and are interpreted as 1/10 change. WHI was divided by 10 and was interpreted as a per 10 units increase, while body adiposity index was divided by 5 and interpreted as a per 5 units increase.

Analyses of BMI were conducted with and without adjustment for waist circumference. The analyses of waist circumference, hip circumference, waist to hip ratio, waist to height ratio, and waist to height index were performed both with and without inclusion of BMI in the models.[20] Body adiposity index was analyzed with adjustment for BMI or/and waist circumference. An interaction between sex and anthropometric indices (BMI, waist circumference, waist to height ratio, and waist to height index) was found. Therefore, further sex-stratified analyses of anthropometric measurements were performed. P values for trend were computed based on continuous variables of median values of categories of BMI, waist circumference, or waist to height ratio.

Compared with weight and height, waist circumference and hip circumference had a significant number of missing values (20,902 in total) because both were not measured in 1994, the first round of the survey. We analyzed the data based on three approaches. First, we removed all of the participants with missing waist circumference or hip circumference data. Second, we imputed waist circumference based on a sex-specific model adjusted for age, sex, smoking, alcohol drinking, education, physical activity, height and weight. Third, we analyzed the data when using missing waist circumference as a separate category. Since the overall results were not changed materially, we kept results based on the first approach in the main report.

For each anthropometric indicator, we analyzed data based on a crude model adjusted for age and sex and a multivariable model adjusted for all potential confounders, but we only reported the results based on multivariable models because the overall results were not changed. We selected confounders based on previous etiological studies on colorectal cancer together with stepwise selection approaches. The following co-variables were included in the multivariable model: age (<50, 50-60, ≥60), education (none/primary school/secondary school, high school, university), currently daily smoking (yes, no), alcohol drinking (never/seldom, several times per week, about once a week, 2-3 times per month, about once a month), physical activity (none, <1,1-2, ≥3 hours/week). There are approximately 10% to 20% missing values for education, alcohol drinking and physical activity. We treated the missing values as a separate category or deleted them from the total dataset for analyses. Since the final results did not materially alter, we only included the results based on missing values as separate categories in order to keep as many participants and colorectal cancer cases as possible for the whole study. Furthermore, we excluded the first two years of follow-up in order to decrease the potential bias of reverse causality; the results were similar and are not shown.

The proportional hazards assumption was tested on the basis of Schoenfeld residuals afterfitting a Cox regression model. None of the variables violated the assumption except for the age groups. The age groups were, thus, treated as a strata factor in the model. A two-sided test with a significance level (α) of 0.05 was chosen. All analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Ethics

The present study was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (ID: 2012/853/REK midt). The individual studies included in CONOR were all approved by their respective ethics committees. All participants signed an informed consent form.

Results

Basic characteristics

During an average of 11.3 years of follow-up, 2044 incident cases of colorectal adenocarcinoma(853 in the proximal colon, 606 in the distal colon and 555 in the rectum, 30 cases with specified locations) were identified. Of these cases, 1101 (54 %) were men and 943 (46 %) were women (Table 1). The average age at study entry was 64.5 years for cases and 50.9 years for non-cases. Cases were less educated (35.3% of cases versus 22.6% of the total cohort in the lowest education categ3ory), had more family history of cancer (32.9% versus 25.3%), less physical activity (10.9% versus 6.3% for 3 or more hours per week) and alcohol drinking (13% versus 12% for drinking alcohol several times per week), whereas daily smoking seemed to be more common in the total cohort members (Table 1).

General obesity (body mass index, BMI) and colorectal adenocarcinoma

The highest BMI category (BMI>30) was associated with colorectal adenocarcinoma when the multivariable models were not adjusted for waist circumference (HR 1.17, 95% CI: 1.02-1.34), but the association disappeared when the models were adjusted for waist circumference (HR 0.90, 95% CI: 0.76-1.06)(Table 2). The risk estimates were similar for each anatomical location within the colon and rectum (Table 2). Interestingly, a negative association of BMI with proximal colon adenocarcinoma was observed when adjusted for waist circumference

(HR 0.77, 95%CI: 0.59-0.99, Table 2). This association was attenuated in the sex-stratified analyses but still existed, especially in women (Table 3).

Abdominal obesity (waist circumference) and colorectal adenocarcinoma

Waist circumference(cm, ≥86(women) or ≥96(men) versus <75(women) or <88 (men))was positively associated with adenocarcinoma of the proximal and the distal colon (HR 1.51, 95%CI: 1.24-1.83 and HR 1.48, 95% CI: 1.18-1.86, respectively), and the association became stronger when the model was adjusted for BMI (HR 1.92, 95% CI: 1.47-2.50 and HR 1.71, 95% CI: 1.25-2.33, respectively)(Table 2). For the rectum, no association was observed (HR 1.16, 95% CI: 0.93-1.46; HR 1.12, 95% CI: 0.82-1.54, with or without adjustment for BMI, respectively).The positive association between waist circumference and adenocarcinoma of the proximal and distal colon was evident in both sexes, especially in men (Table 3).A positive association was further observed for rectal adenocarcinoma in women (HR 2.07, 95%: 1.17-3.68) (Table 3).

Gluteofermoral obesity (hip circumference) and colorectal adenocarcinoma

Positive associations were found between HC(<101 cm versus ≥101) and adenocarcinoma in the proximal and the distal colon (HR 1.23, 95% CI: 1.07-1.42; HR 1.19, 95%CI: 1.01-1.40, respectively), but not in the rectum (HR 1.03, 95% CI: 0.87-1.22) (Table 2).These associations were more evident in men (Table 3), but disappeared with adjustments for BMI plus waist circumference (Table 2).

Body adiposity index (BAI) and colorectal cancer

Body adiposity index was not associated with colorectal adenocarcinoma (HR 0.98, 95%CI: 0.93-1.04)(Table 2). However, when the analyses were further adjusted for BMI or BMI plus waist circumference, negative associations were observed for adenocarcinoma of the proximal and the distal colon (adjustment for BMI, HR 0.88, 95%CI: 0.78-0.99; HR 0.81, 95%CI: 0.70-0.94) (Table 2).

BMI and waist circumference

All of the results in this section were analyzed based on a comparison with the normal BMI (22.5-25kg/m^2) and lower waist circumference category (women <80cm, men <94cm). In the low BMI category (<22.5 kg/m^2), higher waist circumference indicated an increased risk of colorectal adenocarcinoma, especially in the proximal colon and rectum. The latter was a surprisingly increased HR which was not observed in the aforementioned analyses (HR 2.37; 95%CI: 1.09-5.12), however, only seven cases of rectal adenocarcinoma were identified in this group. In the normal BMI group, HR are 1.31 (95%CI: 0.95-1.80) and 1.44 (95%CI: 0.97-2.14) for proximal colon and distal colon respectively when a higher waist circumference compared to the lower category. (Table 5). In the overweight group (BMI 25-30kg/m^2), a higher waist circumference displayed an elevated risk of colon adenocarcinoma, especially in the distal colon, but not the rectum. Similar high circumference results can be found in the obese group (BMI≥30 kg/m^2) (Table 5), but a lower circumference may still entail an increased risk of adenocarcinoma in the proximal colon (HR), although the results were not statistically significant due to too few cases.

Other anthropometric indices and colorectal adenocarcinoma

Waist to hip ratio (per 1/10 increase) was positively associated with adenocarcinoma in the proximal and distal colon (HR 1.28, 95%CI: 1.16-1.42 and HR 1.20, 95%CI:1.06-1.36, respectively), and the associations remained almost similar when adjusted for BMI

(Supplemental Table 1). In the sex-stratified analyses, positive associations remained for the proximal colon in both sexes(Supplemental Table 1).

Waist to height ratio (per 1/10 increase) was positively associated with adenocarcinoma in the proximal colon regardless of adjustment for BMI (HR 1.18, 95%CI: 1.06-1.31; HR 1.26, 95%CI: 1.07-1.49, with or without adjustment for BMI) (Supplemental Table 1). This association remained for categorical variables of Waist to height ratio (Supplemental Table 1). No association was observed for adenocarcinoma in the rectum, regardless of adjustment for BMI (Table 2). In the sex-stratified analysis, a persistent association with colon adenocarcinoma was observed in men, especially in the proximal colon(Supplemental Table 1).

WHI was associated with adenocarcinoma in the proximal colon (HR1.18, 95%:1.01-1.39) but this association disappeared when adjusted for BM I (Supplemental Table 1). Similar results could be found in the sex-stratified analysis (Supplemental Table 2).

Discussion

Abdominal obesity, represented by waist circumference, waist to hip ratio, or waist to height ratio, seemed to be the most important obesity phenotype that had the strongest association with adenocarcinoma in the proximal and the distal colon, but no association with adenocarcinoma in the rectum. General obesity, represented by body mass index (BMI), seemed to not be associated with colorectal adenocarcinoma when adjusted for abdominal obesity. While gluteofemoral obesity, represented by hip circumference, was not associated with colorectal adenocarcinoma.

The strengths of the current study included the large population-based cohort design with a long follow-up period, where anthropometric measures were objectively assessedby standard protocols rather than being self-reported. Potential confounders such as smoking, consuming alcohol, education, and physical activity were adjusted for as well. The Norwegian Cancer Register and Statistics Norway provided outcomes of cancer and death with a high validity. Weaknesses of the study included the possibility of residual confounding produced by missing information of nutrients/diet. For missing values, we performed sensitivity analyses based on imputation, deletion, or treating as a separate category. The overall results, however, were consistent and conclusions were not changed. We also realize that the anthropometric measures of abdominal obesity may not separate visceral obesity from subcutaneous fat. Each of them probably have different effects on cancer incidence, while visceral fat may be worse. Nevertheless, the mutual adjustment of waist circumference and BAI may provide more evidence for this issue.

General and abdominal obesity have been associated with colorectal cancer in many studies. In a large European cohort study, obesity was associated with a higher relative risk of cancer in the colon than cancer of the rectum[20]. This is consistent with our results. However, whether general or abdominal obesity played the leading role was not clear in the previous studies.[20,21] In our study, abdominal adiposity (mainly determined by waist circumference, waist to hip ratio or waist to height ratio) was statistically associated with colon cancer especially in men irrespective of BMI. On the other hand, BMI was not associated with colon cancer when adjusted for waist circumference. This suggests that abdominal adiposity is a more important risk factor for colon cancer than general adiposity. However, as Hu et al. pointed out, in a disease model with waist circumference and BMI, waist circumference would still reflect abdominal adiposity, but BMI would probably be more a measure of lean body mass since body fatness is to a large extent accounted for by waist circumference, especially in older adults[11]. This might well explain the negative association of BMI with the proximal colon adenocarcinoma when the analysis was adjusted for waist circumference. On the other hand, for a given BMI, individuals with an elevated waist circumference will likely have more abdominal fat and, thus, more visceral, liver, and ectopic fat and therefore a higher risk of obesity-related metabolic disorders. In the sex-stratified analyses, a positive association of waist circumference with adenocarcinoma in the proximal and distal colon persisted, especially in men. This is consistent with the study from a Chinese cohort. [22]Surprisingly, a strongly positive association of waist circumference with rectal adenocarcinoma in women was observed. A positive, but not strong association, was also observed for waist to hip ratio or waist to height ratio with female rectal adenocarcinoma. As this has been rarely reported in previous studies, further evidence is warranted. When we examined the risk of colorectal adenocarcinoma for a given BMI and waist circumference, we found a consistently increased risk of abdominal obesity represented by a higher waist circumference regardless of lower or normal BMI, overweight, or obesity. This further strengthened our conclusion regarding the pivotal role of abdominal obesity on adenocarcinoma in the proximal and distal colon.

There is increasing evidence that the anatomical position of adipose tissue determines the effects on the individual and predicts the associated morbidity from cancer.[16,23]This has led to the addition of the new anthropometric indices of obesity in addition to BMI and waist circumference. Gluteofemoral body fat, assessed by hip circumference, is associated with a protective lipid and glucose profile, as well as a decrease in cardiovascular and metabolic risk.[24] However, the association between hip circumference and cancer is inconclusive.[25,26] The present study found that an increasing hip circumference was associated with an increased risk of adenocarcinoma of the colon, while this association disappeared with additional adjustments for BMI and waist circumference. This indicates that gluteofemoral obesity is not associated with colorectal cancer. Furthermore, since BMI cannot reflect the percentage of body fat (e.g., with a high BMI may be due to lean muscular mass rather than body fat), the body adiposity index has therefore been purposely developed. In our study, body adiposity index was negatively associated with adenocarcinoma in the proximal and the distal colon when adjusted for BMI or BMI plus waist circumference. This seemed to be similar to the association between BMI and colorectal adenocarcinoma. If this reflects the true association, body adiposity index may indicate the percentage of muscular mass for a given BMI or BMI plus waist circumference, because BMI or waist circumference has represented the body fat. Since body adiposity index was still an anthropometric index under debate, this result may need further validating studies.

Other anthropometric indices have also been investigated in previous studies. Waist to height ratio is associated with cancer and cardio-metabolic risks.[27,28] In a study among Taiwanese adults, a Waist to height ratio >0.5 was an indicator of centralized obesity, even among ‘healthy’ individuals according to BMI and waist circumference.[29] A recent systemic review and meta-analysis also demonstrated that waist to height ratio is a better screening tool for adult cardiometabolic risk factors than waist circumference and BMI.[27] As far as we know, no data has been reported about the association between waist to height ratio and colorectal cancer. In our study, we found a consistent association between waist to height ratio and an increased risk of adenocarcinoma of the proximal and distal colon, but not the rectum. Moreover, waist to height ratio is a simple and easily understood anthropometric index, which may carry much valuable public health implications, e.g., waist to height ratio may allow the same boundary values (0.5) for children and adults, women and men.[30] As a newly developed index, waist to height index (WHI is a composite index proposed by a Japanese study.[17] In our study, however, waist to height index (per 10 units of increase) was not associated with an increased risk of colorectal adenocarcinoma.

Abdominal fat is comprised of fat stored subcutaneously (e.g., subcutaneous adipose tissue) and the adipose tissue located in the abdominal cavity. The latter has been commonly described as intra-abdominal or visceral adipose tissue. Visceral adiposity is the best adiposity predictor of liver fat content which is closely related to features of metabolic syndrome. Abdominal obesity, metabolic syndrome, insulin resistance and modifications in levels of adipocytokines seem to be of great importance for the underlying mechanisms linking obesity to colorectal cancer, whichis certainly a multifactorial process.[3] Adipose tissue is a highly active tissue that secrets various cytokines, chemokines, and hormones.[31] Some of these cytokines can act directly in the promotion of cancer.[13,32] Circulating insulin levels increase with obesity and many obese patients are insulin resistant. Chronic hyperinsulinemia decreases insulin growth factor binding proteins 1 and 2, resulting in an increase in circulating insulin and, more importantly, insulin growth factor. This in turn results in decreased apoptosis and increased cell proliferation in the target tissues.[23] Studies have shown a correlation of an elevated C-peptide (a surrogate of circulating insulin) with colorectal cancer.[32] Furthermore, adipokines (leptin and adiponectin) secreted by adipose tissue have been associated with carcinogenesis.[33,34] Leptin is apro-inflammatory hormone and has also been shown to be directly tumorigenic. Adiponectin levels, which are decreased in obese individuals, are associated with a lower risk of colorectal cancer.[33,34] Further carcinogenesis has been proposed for obesity-driven low-grade inflammation. Inflammatory cells are present in abundance in visceral adipose tissue and the secretion of inflammatory mediators into the body creates a chronic inflammatory state that is thought to generate a protumorigenic environment.[31] Systemic pro-inflammatory markers, such as C-reactive protein and interleukin-6, are elevated in the obese due to obesity-driven low-grade inflammation.[13]

In conclusion, obesity, especially abdominal obesity, was positively associated with adenocarcinoma of the proximal and distal colon, but not certainly with the rectum. Obesity control, with a focus on abdominal obesity, will be an important factor in the prevention of malignancy of the colon.

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Table 1. Characteristics of colorectal adenocarcinoma cases and cohort members in CONOR

Variables	Cohort participants	Colorectal Adenocarcinoma	Colon		Rectum
			Proximal colon	Distal colon	
Total	143477	2044	853	606	555
Sex, n(%)					
Men	70033(49)	1101(54)	410(48)	332(55)	343(62)
Women	73444(51)	943(46)	443(52)	274(45)	212(38)
Age at examination					
Mean (SD[a])	50.9(16)	64.5(12)	65.8(11)	63.4(12)	63.5(12)
Age by groups (%)					
<50	81232(57)	341(17)	119(14)	117(19)	103(19)
50-59	17559(12)	269(13)	96(11)	91(15)	80(14)
≥60	44686(31)	1434(70)	638(75)	398(66)	372(67)
Education, n(%)					
None/primary school/secondary school	32423(23)	724(35)	320(38)	198(33)	198(36)
High school	44964(31)	468(23)	193(22)	136(22)	134(24)
University	29227(20)	237(12)	88(10)	94(16)	51(9)
Missing	36863(26)	615(30)	252(30)	178(29)	172(31)
Smoking status, n(%)					
Not daily smoker	101341(71)	1542(75)	653(77)	461(76)	402(72)

Daily smoker	42136(29)	502(25)	200(23)	145(24)	153(28)
Alcohol consumption last year, n(%)					
Never/seldom	41694(29)	690(34)	316(37)	182(30)	185(33)
About 1-3 times per month	45233(32)	465(23)	174(20)	149(25)	135(24)
About once a week	26106(18)	331(16)	123(14)	116(19)	89(16)
Several times per week	17187(12)	265(13)	104(13)	77(13)	80(14)
Missing	13257(9)	293(14)	136(16)	82(13)	66(13)
Physical activity, n(%)					
None	43492(30)	720(35)	318(37)	225(37)	167(30)
Less than once a week	30222(21)	342(17)	117(14)	108(18)	113(20)
1-2 hours per week	28226(20)	284(14)	113(13)	86(14)	84(15)
3 or more hours per week	15581(11)	129(6)	49(6)	41(7)	36(7)
Missing	25956(18)	569(28)	256(30)	146(24)	155(28)
[b]Family history of cancer, n(%)	36309(25)	672(33)	385(33)	211(35)	169(31)
Diabetes, n(%)	4463(4)	122(6)	57(7)	31(5)	33(6)
[c]Cardiovascular diseases, n(%)	11373(8)	301(15)	137(16)	78(13)	81(15)
Asthma, n(%)	12087(8)	210(10)	99(12)	62(10)	46(8)
Body mass index (BMI), mean (SD)	26.2(4.1)	27.0(4.1)	27.1(4.1)	27.0(4.0)	27.0(4.1)
Waist circumference (cm), mean (SD)	86.9(12.1)	90.7(11.8)	90.6(12.2)	90.6(11.5)	91.0(11.5)
Hip circumference (cm), mean (SD)	101.6(7.8)	102.7(7.6)	102.9(7.8)	102.8(7.4)	102.5(7.5)
Waist to hip ratio*10 (WHR), mean (SD)	8.5(0.9)	8.8(0.9)	8.8(0.9)	8.8(0.9)	8.9(0.8)

Waist to height ratio*10 (WHtR), mean (SD)	5.1(0.7)	5.3(0.7)	5.4(0.7)	5.3(0.6)	5.3(0.6)
Waist to height index, (WHI) mean (SD)	30.1(4.5)	31.6(4.4)	31.9(4.5)	31.3(4.2)	31.4(4.3)
Body adiposity index (BAI), mean (SD)	27.9(4.9)	28.4(4.7)	29.2(5.1)	28.4(4.7)	28.3(5.0)

a: SD, standard deviation

b. Family history of cancer: self-reported cancer among parents, siblings and children

c. Cardiovascular diseases: including angina pectoris, myocardial infarction and stroke.

Table 2. HR and 95% CI for risk of colorectal adenocarcinoma in relation to anthropometric characteristics

Anthropometric indices	Colorectal adenocarcinoma by anatomical location[a]							
	Total		Proximal colon		Distal colon		Rectum	
		HR(95%CI)		HR(95%CI)		HR(95%CI)		HR(95%CI)
Total	2044		853		606		555	
Overall obesity:								
Body mass index (BMI)								
Not adjusted for waist circumference								
<22.5	234	0.97(0.82-1.14)	97	0.95(0.74-1.21)	72	1.06(0.79-1.42)	60	0.87(0.64-1.19)
22.5-25	435	Reference	181	Reference	122	Reference	127	Reference
25-30	942	1.03(0.92-1.15)	389	1.01(0.85-1.21)	286	1.13(0.91-1.39)	251	0.94(0.76-1.16)
>30	433	1.17(1.02-1.34)	186	1.15(0.93-1.41)	126	1.26(0.98-1.62)	117	1.14(0.88-1.47)
P value for trend		0.008		0.11		0.10		0.13
Adjusted for waist circumference								
<22.5	234	1.08(0.91-1.28)	97	1.10(0.84-1.43)	72	1.23(0.90-1.68)	60	0.91(0.66-1.26)
22.5-25	435	Reference	181	Reference	122	Reference	127	Reference
25-30	942	0.88(0.77-1.00)	389	0.80(0.65-0.98)	286	0.94(0.74-1.19)	251	0.90(0.71-1.15)
>30	433	0.90(0.76-1.06)	186	0.77(0.59-0.99)	126	0.94(0.69-1.29)	117	1.07(0.78-1.49)
P value for trend		0.17		0.04		0.37		0.41
Abdominal obesity:								
Waist Circumference (cm)								
Not adjusted for BMI								
<75(women) or <88 (men)	388	Reference	148	Reference	111	Reference	120	Reference
75-85.9(women) or 88-95.9(men)	699	1.16(1.02-1.31)	281	1.17(0.96-1.43)	214	1.27(1.01-1.60)	195	1.08(0.86-1.36)
≥86(women) or ≥96(men)	957	1.37(1.22-1.55)	424	1.51(1.24-1.83)	281	1.48(1.18-1.86)	240	1.16(0.93-1.46)
P value for trend		<.0001		<.0001		0.0006		0.19
Adjusted for BMI								
<75(women) or <88 (men)	388	Reference	148	Reference	111	Reference	120	Reference
75-85.9(women) or 88-95.9(men)	699	1.26(1.09-1.46)	281	1.34(1.07-1.69)	214	1.42(1.08-1.85)	195	1.09(0.84-1.43)

≥86(women) or ≥96(men)	957	1.56(1.32-1.84)	424	1.92(1.47-2.50)	281	1.71(1.25-2.33)	240	1.12(0.82-1.54)
P value for trend		<.0001		<.0001		0.001		0.49
Gluteofemoral obesity								
Hip circumference (cm)								
Not adjusted for BMI								
<101	816	Reference	322	Reference	237	Reference	238	Reference
≥101	1227	1.14(1.04-1.25)	531	1.23(1.07-1.42)	368	1.19(1.01-1.40)	317	1.03(0.87-1.22)
Adjusted for BMI								
<101	816	Reference	322	Reference	237	Reference	238	Reference
≥101	1227	1.12(1.00-1.25)	531	1.28(1.07-1.53)	368	1.16(0.94-1.43)	317	0.95(0.77-1.18)
Adjusted for BM and waist circumference								
<101	816	Reference	322	Reference	237	Reference	238	Reference
≥101	1227	1.02(0.90-1.15)	531	1.12(0.93-1.35)	368	1.05(0.84-1.30)	317	0.92(0.73-1.15)
Muscularity								
Body adiposity index (BAI, continuous, per 5 units)								
Not adjusted for BMI or waist circumference	2043	0.98(0.93-1.04)	853	0.98(0.91-1.07)	605	0.95(0.86-1.06)	555	1.03(0.92-1.15)
Adjusted for BMI	2043	0.87(0.81-0.94)	853	0.88(0.78-0.99)	605	0.81(0.70-0.94)	555	0.95(0.81-1.10)
Adjusted for waist circumference	2043	0.88(0.83,0.94)	853	0.86(0.78,0.95)	605	0.84(0.74,0.95)	555	0.99(0.88,1.13)
Adjusted for BMI and waist circumference	2043	0.86(0.80-0.94)	853	0.87(0.77-0.98)	605	0.81(0.70-0.93)	555	0.94(0.81-1.10)

a. adjusted for education, smoking status, alcohol drinking, physical activity, family history of cancer, study center, and/or anthropometrics when appropriate, stratified by age groups.

Table 3. HR and 95% CI for risk of colorectal adenocarcinoma in relation to anthropometric characteristics in men

Anthropometric indices	Total		Proximal colon		Distal colon		Rectum	
	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)
Body mass index (BMI)								
Not adjusted for waist circumference								
<22.5	86	0.89(0.69-1.14）	31	0.86(0.57-1.30)	23	0.86(0.54-1.39)	30	0.91(0.60-1.38)
22.5-25	238	Reference	88	Reference	66	Reference	81	Reference
25-30	561	1.02(0.87-1.19)	207	1.01(0.79-1.30)	176	1.16(0.87-1.54)	169	0.90(0.69-1.18)
30	216	1.30(1.08-1.57)	84	1.37(1.01-1.85)	67	1.48(1.05-2.09)	63	1.11(0.79-1.54)
P value for trend		0.002		0.03		0.009		0.59
Adjusted for waist circumference								
<22.5	103	0.96(0.74-1.24)	31	1.02(0.66-1.57)	23	1.03(0.63-1.70)	36	0.87(0.56-1.34)
22.5-25	279	Reference	88	Reference	66	Reference	94	Reference
25-30	644	0.91(0.76-1.08)	207	0.77(0.58-1.02)	176	0.98(0.72-1.35)	205	0.97(0.72-1.31)
30	246	1.08(0.86-1.36)	84	0.86(0.59-1.25)	67	1.20(0.79-1.83)	75	1.26(0.82-1.92)
P value for trend		0.59		0.39		0.52		0.25
Waist Circumference (cm)								
Not adjusted for BMI								
<75(women) or <88 (men)	216	Reference	70	Reference	54	Reference	86	Reference
75-85.9(women) or 88-95.9(men)	364	1.16(0.98-1.38)	125	1.23(0.92-1.65)	120	1.55(1.12-2.14)	116	0.93(0.70-1.23)
≥86(women) or ≥96(men)	521	1.37(1.17-1.61)	215	1.73(1.31-2.28)	158	1.71(1.24-2.34)	141	0.93(0.71-1.23)
P value for trend		<.0001		<.0001		0.002		0.65
Adjusted for BMI								
<75(women) or <88 (men)	216	Reference	71	Reference	54	Reference	86	Reference
75-85.9(women) or 88-95.9(men)	364	1.20(1.00-1.46)	129	1.39(1.00-1.95)	120	1.57(1.09-2.27)	116	0.90(0.65-1.24)
≥86(women) or ≥96(men)	521	1.37(1.10-1.70)	217	2.05(1.41-2.97)	158	1.62(1.06-2.45)	141	0.82(0.57-1.20)
P value for trend		0.01		<.0001		0.05		0.31
Hip circumference (cm)								
Not adjusted for BMI								
<101	419	Reference	141	Reference	124	Reference	145	Reference
≥101	682	1.21(1.07-1.37)	269	1.41(1.15-1.73)	208	1.24(0.99-1.56)	198	1.02(0.82-1.26)
Adjusted for BMI								
<101	419	Reference	141	Reference	124	Reference	145	Reference
≥101	682	1.14(0.99-1.32)	269	1.39(1.09-1.78)	208	1.09(0.83-1.42)	198	0.99(0.76-1.28)
Adjusted for BMI and waist circumference								
<101	419	Reference	141	Reference	124	Reference	145	Reference
≥101	682	1.07(0.92-1.25)	269	1.20(0.92-1.56)	208	0.99(0.75-1.31)	198	1.04(0.79-1.38)
Body adiposity index (BAI, continuous, per 5 units)								

Not adjusted for BMI or waist circumference	1101	1.07(0.97-1.18)	410	1.12(0.95-1.31)	332	1.08(0.90-1.30)	343	1.02(0.85-1.22)
Adjusted for BMI	1101	0.94(0.83-1.07)	410	0.97(0.79-1.20)	332	0.88(0.70-1.11)	343	0.96(0.76-1.21)
Adjusted for BMI and waist circumference	1101	0.94(0.83-1.07)	410	0.97(0.79-1.19)	332	0.89(0.70-1.12)	343	0.96(0.76-1.22)

Table 4. HR and 95% CI for risk of colorectal adenocarcinoma in relation to anthropometric characteristics in women

Anthropometric indices	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)
Body mass index (BMI)								
Not adjusted for waist ircumference								
<22.5	148	1.00(0.81-1.24)	66	0.98(0.71-1.34)	49	1.14(0.77-1.67)	30	0.83(0.53-1.32)
22.5-25	197	Reference	93	Reference	56	Reference	46	Reference
25-30	381	1.05(0.89-1.25)	182	1.02(0.79-1.31)	110	1.11(0.80-1.54)	82	1.02(0.71-1.47)
30	217	1.09(0.89-1.32)	102	1.01(0.76-1.35)	59	1.11(0.76-1.61)	54	1.24(0.83-1.86)
P value for trend		0.36		0.8		0.91		0.104
Adjusted for waist circumference								
<22.5	180	1.15(0.91-1.46)	66	1.11(0.79-1.57)	49	1.27(0.83-1.93)	30	1.04(0.63-1.73)
22.5-25	229	Reference	93	Reference	56	Reference	46	Reference
25-30	422	0.87(0.71-1.05)	182	0.84(0.64-1.12)	110	0.91(0.63-1.30)	82	0.82(0.55-1.23)
30	245	0.77(0.60-0.99)	102	0.72(0.50-1.04)	59	0.76(0.47-1.21)	54	0.88(0.53-1.48)
P value for trend		0.007		0.04		0.08		0.54
Waist Circumference (cm)								
Not adjusted for BMI								
<75(women) or <88 (men)	172	Reference	78	Reference	57	Reference	34	Reference
75-85.9(women) or 88-95.9(men)	335	1.16(0.96-1.40)	156	1.12(0.85-1.47)	94	1.03(0.74-1.44)	79	1.47(0.98-2.21)
≥86(women) or ≥96(men)	436	1.40(1.16-1.68)	209	1.33(1.02-1.74)	123	1.31(0.94-1.82)	99	1.78(1.19-2.67)
P value for trend		0.0002		0.03		0.07		0.01
Adjusted for BMI								
<75(women) or <88 (men)	172	Reference	78	Reference	57	Reference	34	Reference
75-85.9(women) or 88-95.9(men)	335	1.33(1.06-1.65)	156	1.27(0.92-1.76)	94	1.21(0.82-1.81)	79	1.63(1.01-2.63)
≥86(women) or ≥96(men)	436	1.81(1.39-2.36)	209	1.75(1.19-2.58)	123	1.78(1.10-2.88)	99	2.07(1.17-3.68)
P value for trend		<.0001		0.003		0.01		0.02
Hip circumference (cm)								
Not adjusted for BMI								
<101	397	Reference	181	Reference	113	Reference	93	Reference
≥101	545	1.09(0.95-1.24)	262	1.10(0.91-1.34)	160	1.16(0.91-1.49)	119	1.07(0.81-1.41)
Adjusted for BMI								
<101	397	Reference	181	Reference	113	Reference	93	Reference
≥101	545	1.08(0.90-1.29)	262	1.16(0.89-1.50)	160	1.29(0.92-1.80)	119	0.86(0.59-1.26)
Adjusted for BMI and waist circumference								
<101	397	Reference	181	Reference	113	Reference	93	Reference
≥101	545	0.96(0.80-1.16)	262	1.04(0.79-1.37)	160	1.16(0.81-1.65)	119	0.75(0.51-1.11)
Body adiposity index (BAI, continuous, per 5 units)								
Not adjusted for BMI or waist circumference		0.96(0.90-1.03)		0.95(0.86-1.05)	273	0.92(0.81-1.05)		1.07(0.93-1.23)
Adjusted for BMI		0.86(0.77-0.95)		0.87(0.75-1.01)	273	0.82(0.67-1.00)		0.94(0.76-1.17)
Adjusted for BMI and waist circumference		0.84(0.75-0.93)		0.85(0.73-0.99)	273	0.79(0.65-0.97)		0.92(0.74-1.14)

Table 5. HR and 95% CI for risk of colorectal adenocarcinoma in relation to normal weight obesity

Body Mass index (BMI, kg/m2)	Waist circumference (cm)	Non-cases participants	Colorectum		Proximal colon		Distal colon		Rectum	
			Cases	HR(95%CI)	Cases	HR(95%CI)	Cases	HR(95%CI)	Cases	HR(95%CI)
Lower weight (<22.5)	Women<80, men<94	23559	218	1.00(0.84-1.19)	90	1.00(0.76-1.31)	70	1.19(0.87-1.64)	53	0.80(0.58-1.12)
	Women≥80, men≥94	937	16	1.47(0.89-2.43)	7	1.42(0.66-3.06)	2	0.70(0.17-2.87)	7	2.37(1.09-5.12)
Normal weight (≥22.5 and <25)	Women<80, men<94	28671	320	Reference	128	Reference	87	Reference	101	Reference
	Women≥80, men≥94	6920	115	1.23(0.99-1.53)	53	1.31(0.95-1.80)	35	1.44(0.97-2.14)	26	0.97(0.63-1.50)
Over weight(≥25 and <30)	Women<80, men<94	23004	273	0.97(0.82-1.14)	88	0.80(0.61-1.06)	85	1.10(0.82-1.49)	94	1.02(0.77-1.35)
	Women≥80, men≥94	37440	669	1.13(0.99-1.30)	301	1.21(0.98-1.49)	201	1.30(1.01-1.68)	157	0.88(0.69-1.14)
Obese (≥30)	Women<80, men<94	443	5	1.07(0.44-2.58)	4	2.22(0.82-6.02)	1	0.77(0.11-5.55)	0	0
	Women≥80, men≥94	22503	428	1.25(1.08-1.44)	182	1.23(0.98-1.55)	125	1.41(1.06-1.86)	117	1.16(0.88-1.52)

a: normal weight without abdominal obesity; b: overweight with abdominal obesity; c: overweight without abdominal obesity; d: overweight with abdominal obesity

Supplemental Table 1. HR and 95% CI for risk of colorectal adenocarcinoma in relation to anthropometric characteristics

Anthropometric indices	Colorectal adenocarcinoma by anatomical location[a]							
	Total		Proximal colon		Distal colon		Rectum	
		HR(95%CI)		HR(95%CI)		HR(95%CI)		HR(95%CI)
Total	2044		853		606			555
Waist to hip ratio (WHR, continuous, per 1/10)								
Not adjusted for BMI	2043	1.14(1.06-1.22)	853	1.28(1.16-1.42)	605	1.20(1.06-1.36)	555	1.15(1.01-1.31)
Adjusted for BMI	2043	1.22(1.13-1.31)	853	1.30 (1.16-1.46)	605	1.19(1.03-1.36)	555	1.13(0.97-1.31)
Waist to height ratio (WHtR, continuous, per 1/10)								
Not adjusted for BMI	2044	1.14(1.06-1.22)	853	1.18(1.06-1.31)	606	1.12(0.99-1.27)	555	1.13(0.98-1.29)
Adjusted for BMI	2044	1.15(1.03-1.28)	853	1.26(1.07-1.49)	606	1.08(0.88-1.32)	555	1.10(0.891.36)
Not adjusted for BMI								
<0.5	596	Reference	237	Reference	177	Reference	170	Reference
0.5-	1138	1.19(1.07-1.32)	479	1.26(1.07-1.49)	343	1.27(1.05-1.54)	303	1.06(0.87-1.30)
≥0.6	310	1.29(1.12-1.49)	137	1.37(1.10-1.71)	86	1.30(0.99-1.70)	82	1.20(0.91-1.58)
P value for trend		0.0002		0.002		0.02		
Adjusted for BMI								
<0.5	596	Reference	237	Reference	177	Reference	170	Reference
0.5-	1138	1.23(1.08-1.41)	479	1.37(1.12-1.69)	343	1.30(1.02-1.66)	303	1.04(0.81-1.34)
≥0.6	310	1.28(1.05-1.57)	137	1.49(1.09-2.02)	86	1.27(0.87-1.84)	82	1.06(0.72-1.56)
P value for trend		0.007		0.006		0.13		0.74
Waist to height index (WHI, continuous, per 10 units)								
Not adjusted for BMI	2044	1.14(1.02-1.26)	853	1.18(1.01-1.39)	606	1.07(0.88-1.30)	555	1.18(0.96-1.45)
Adjusted for BMI	2044	1.06(0.91-1.23)	853	1.17(0.93-1.46)	606	0.90(0.68-1.20)	555	1.10(0.82-1.48)

a. adjusted for education, smoking status, alcohol drinking, physical activity, family history of cancer, study center, and/or anthropometrics when appropriate, stratified by age groups.

Supplemental Table 2. HR and 95% CI for risk of colorectal adenocarcinoma in relation to anthropometric characteristics by genders

Anthropometric indices	Total				Proximal colon				Distal colon				Rectum			
	Male		Female		Male		Female		Male		Female		Male		Female	
	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)	N	HR(95%CI)
Waist to hip ratio (continuous, per 1/10)																
Not adjusted for BMI	1101	1.22(1.11-1.34)	942	1.21(1.10-1.33)	410	1.37(1.18-1.59)	443	1.21(1.06-1.40)	332	1.25(1.06-1.48)	289	1.16(0.97-1.39)	343	1.07(0.90-1.26)	212	1.26(1.03-1.54)
Adjusted for BMI	1101	1.18(1.06-1.31)	942	1.24(1.11-1.37)	410	1.34(1.13-1.60)	443	1.26(1.08-1.47)	332	1.15(0.95-1.40)	289	1.20(0.98-1.46)	343	1.05(0.86-1.27)	212	1.22(0.97-1.52)
Waist to height ratio (continuous, per 1/10)																
Not adjusted for BMI	1101	1.24(1.12-1.38)	943	1.09(0.99-1.19)	410	1.40(1.18-1.66)	443	1.08(0.94-1.23)	332	1.28(1.05-1.55)	289	1.05(0.88-1.24)	343	1.07(0.88-1.30)	212	1.20(1.00-1.45)
Adjusted for BMI	1101	1.20(1.02-1.42)	943	1.14(0.98-1.32)	410	1.50(1.16-1.95)	443	1.17(0.95-1.45)	332	1.10(0.82-1.49)	289	1.10(0.83-1.45)	343	1.02(0.76-1.38)	212	1.16(0.85-1.57)
Not adjusted for BMI																
<0.5	229	Reference	367	Reference	74	Reference	163	Reference	61	Reference	116	Reference	89	Reference	81	Reference
0.5-	700	1.20(1.03-1.40)	438	1.23(1.06-1.42)	265	1.38(1.06-1.80)	214	1.24(1.00-1.53)	224	1.50(1.12-2.01)	119	1.16(0.88-1.51)	203	0.89(0.69-1.16)	100	1.38(1.01-1.88)
≥0.6	172	1.43(1.17-1.76)	138	1.18(0.96-1.45)	71	1.79(1.27-2.51)	66	1.14(0.84-1.53)	47	1.55(1.05-2.31)	39	1.19(0.82-1.75)	51	1.09(0.76-1.56)	31	1.33(0.86-2.05)
P value for trend		0.0006		0.03		0.0007		0.2		0.014		0.27		0.85		0.08
Adjusted for BMI																
<0.5	229	Reference	367	Reference	74	Reference	163	Reference	61	Reference	116	Reference	89	Reference	81	Reference
0.5-	700	1.19(0.98-1.44)	438	1.32(1.09-1.59)	265	1.48(1.07-2.04)	214	1.37(1.04-1.81)	224	1.41(0.98-2.01)	119	1.26(0.89-1.79)	203	0.86(0.63-1.19)	100	1.36(0.91-2.02)
≥0.6	172	1.26(0.95-1.67)	138	1.30(0.97-1.73)	71	1.76(1.11-2.79)	66	1.33(0.87-2.02)	47	1.20(0.71-2.04)	39	1.40(0.81-2.41)	51	0.96(0.58-1.58)	31	1.18(0.64-2.17)
P value for trend		0.1		0.03		0.02		0.2		0.4		0.18				
Waist to height index (WHI, continuous, per 10 units)																
Not adjusted for BMI	1119	1.30(1.10-1.53)	964	1.08(0.94-1.24)	410	1.50(1.14-1.96)	447	1.07(0.88-1.31)	332	1.32(0.97-1.79)	274	0.99(0.76-1.28)	343	1.10(0.81-1.49)	213	1.30(0.98-1.71)
Adjusted for BMI	1119	1.12 (0.89-1.42)	964	1.07(0.87-1.31)	410	1.38(0.95-2.01)	447	1.13(0.84-1.50)	332	0.98(0.64-1.49)	274	0.93(0.64-1.37)	343	1.02(0.67-1.56)	213	1.20(0.79-1.82)