

Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia

Running title: Visceral fat area and colorectal neoplasia

Shuichiro Yamamoto, MD¹; Toru Nakagawa, MD¹; Yumi Matsushita, MD, PhD²;
Suzushi Kusano, MD¹; Takeshi Hayashi, MD¹; Masataka Irokawa, MD¹;
Takatoshi Aoki, MD³; Yukunori Korogi, MD³; and Tetsuya Mizoue, MD, PhD²

¹Hitachi Health Care Center, Hitachi, Ltd.; ²Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan; ³Department of Radiology, University of Occupational and Environmental Health

Address for correspondence:

Dr. Shuichiro Yamamoto

E-mail: shuichiro.yamamoto.sr@hitachi.com

Submitted 1 July 2009 and accepted 4 October 2009.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at <http://care.diabetesjournals.org>.

Objective- Although abdominal obesity and related metabolic abnormalities are hypothesized to promote colorectal carcinogenesis, direct confirmation of this effect is required. Here, we examined the relation of early-stage colorectal neoplasia to visceral fat area and markers of insulin resistance.

Research design and methods- Subjects were participants in a comprehensive health screening conducted at the Hitachi Health Care Center, Ibaraki, Japan. During a 3-year period (2004 to 2007), a total of 108 patients with early-stage colorectal neoplasia, including 22 with early cancer, were identified among persons who received both colorectal cancer screening and abdominal computed tomography scanning. Three controls matched to each case were randomly selected from those whose screening results were negative. Conditional logistic regression analysis was used to examine the association of measures of obesity and markers of insulin resistance with colorectal neoplasia, with adjustment for smoking and alcohol drinking.

Results- Visceral fat area, but not subcutaneous fat area, was significantly positively associated with colorectal cancer, with odds ratio (95% CI) for the lowest to highest tertile of visceral fat area of 1 (reference), 2.17 (0.45, 10.46), and 5.92 (1.22, 28.65), respectively (P for trend = 0.02). Markers of insulin resistance, particularly fasting glucose, were also positively associated with colorectal cancer risk. In contrast, no associations were observed for colorectal adenomas.

Conclusions- These results suggest that visceral adipose accumulation and insulin resistance may promote the development of early-stage cancer but not adenoma in the colorectum.

While the role of obesity as a strong predictor of various chronic diseases, including type 2 diabetes and cardiovascular diseases, has been established, accumulating evidence also indicates the importance of obesity and its related metabolic disorders in the development of cancer (1). In Japan, the incidence of colorectal cancer has sharply increased over the last several decades, and is now among the highest in the world (2). This time trends, as well as findings from migrant studies (3), suggest the involvement of environmental factors in colorectal carcinogenesis. Epidemiologic studies (4, 5) have shown that colorectal cancer risk is more strongly associated with waist circumference than BMI, indicating the etiologic importance of abdominal or visceral fat disposition, rather than overall adiposity. However, given that waist circumference is only a surrogate of visceral fat mass, more direct evidence is required before the link between visceral adiposity and cancer risk can be considered conclusive.

Several studies have assessed the association between visceral fat area, as measured using computed tomography (CT) scanning, and colorectal neoplasia (6-10), but results have been mixed. For example, a Japanese study (7) demonstrated an increased prevalence of colorectal adenomas among persons with higher visceral fat area, whereas a larger, more recent study (8) did not. Given that adenomatous polyps are common but only a minority progress to cancer (11), the association with cancer should also be explored, but evidence to date is sparse. In a Turkish study (10), colorectal cancer patients tended to have a smaller rather than larger visceral fat area than controls. This

unexpected finding may have been due to weight loss in the course of cancer development, however, a possibility which highlights the importance of assessing visceral fat prior to the diagnosis of cancer or development of symptoms.

An insulin hypothesis has been proposed to explain the observed association between obesity or abdominal obesity and colorectal neoplasia (12, 13). Accumulation of visceral fat is a strong determinant of insulin resistance and hyperinsulinemia (14) and, as experimental data show (15), insulin promotes colorectal carcinogenesis. Compatible with the insulin hypothesis, epidemiologic data appear consistent in showing a positive association between colorectal neoplasia and markers of hyperinsulinemia or insulin resistance (reviewed in ref. 16). These findings notwithstanding, however, a role for insulin resistance in promoting the development of adenoma, cancer, or both in the colorectum has yet to be confirmed.

To further explore these issues, we examined the relation of visceral fat mass assessed by CT and measures of insulin resistance to adenoma and cancer in the colorectum among asymptomatic screening attendants.

RESEARCH DESIGN AND METHODS

Subjects. Study subjects were participants in a comprehensive health examination conducted at the Hitachi Health Care Center, Ibaraki, Japan, during which colorectal cancer screening and, on request, abdominal CT scanning were performed. Abdominal CT scanning was introduced to encourage changes in lifestyle, such as diet and physical activity, by showing examinees a graphic

image, together with estimated data, of their own abdominal fat accumulation. In practice, it was mainly offered to persons who underwent chest CT scanning for the screening of lung cancer. Nearly one-third of all screening attendants chose to receive abdominal CT assessment. Compared with men who did not, those who underwent abdominal CT scanning were older (53 versus 46 years), more likely to be past smokers (35% versus 22%), and tended to have a higher BMI (23.9 kg/m² versus 23.6 kg/m²). In contrast, the two groups were similar in terms of alcohol drinking (more than 1 go [23 g ethanol] per day: 32% versus 29%).

During the 3-year period from April 2004 to March 2007, 47,224 examinees underwent fecal occult blood testing, which is specified as the standard procedure for colorectal cancer screening in the Japanese guidelines. Owing to limitations in colonoscopy resources, persons with a positive blood test were first invited to receive a barium enema in the health center, and only those with suspected polyp lesions were referred to a medical specialist for detailed examination by colonoscopy. Of 3,521 (8 %) who had a positive test result, half (1,738) underwent barium enema at the center. Of these, 491 (28%) with a finding suggesting colorectal neoplasia were referred to local clinics or hospitals for confirmation. Of the 280 patients who were notified by the physicians consulted that they had colorectal neoplasia, the present case series consisted of the 86 with histologically confirmed adenoma and 22 with early-stage colorectal cancer (carcinoma in situ or cancer invading within the submucosa) who received abdominal CT scanning at the time of the health check-up. Among patients with

adenomas of known size (n=82), the number with adenomas of 10 mm or greater in diameter was 15 (18%). As regard to the location of cancer, 5 cases were in the ascending colon, 2 in the transverse colon, 13 in the sigmoid colon, 1 in the rectum, and 1 was not specified. For each case, three controls matched by year of examination, sex, and age (same age) were randomly selected from among examinees who had undergone abdominal CT measurement and had a negative fecal occult blood test. No case or control had a prior history of cancer, cardiac infarction, or stroke. Informed consent was obtained from each examinee regarding the use of their data for research purposes. The protocol of present study was approved by the ethics committee of the Hitachi Health Care Center.

Abdominal CT measurement. Measurement of abdominal fat area with a CT scanner has been detailed elsewhere (17). Briefly, single slice imaging was done at the level of the umbilicus in the supine position using a Redix turbo CT (Hitachi Medico, Tokyo). Imaging conditions, which have changed since 2004, were 120 kV, 50 mA, and a 5-mm slice thickness. Visceral fat area, subcutaneous fat area, and waist circumference were calculated using the PC software application fatPointer (Hitachi Medico, Tokyo).

Subject characteristics and blood measurements. Height and weight were measured using an automated scale (Tanita BF-220) with the patient wearing a light gown. BMI was calculated as the weight in kilograms divided by height in meters squared. Fasting plasma glucose was measured by the glucose electrode technique using an ADAMS glucose GA-1170 (Arkray). Fasting serum immunoreactive insulin

($\mu\text{U/ml}$) was determined by an immunoenzymatic method using the AxSYM insulin assay (Abbott). Homeostasis model assessment-insulin resistance (HOMA-IR), an index of insulin resistance, was calculated as fasting glucose multiplied by fasting insulin divided by 405.

Covariates. Health-related lifestyles were ascertained by questionnaire. Participants entered their responses to the questionnaire directly into a computer using a custom-designed data entry system. Regarding smoking, the questionnaire enquired about smoking status and, for ever smokers, the duration and intensity of smoking. For alcohol consumption, the frequency of drinking and the amount of alcohol consumed per session was assessed in terms of *go*, a conventional unit of alcohol intake in Japan. One *go* contains approximately 23 g ethanol.

Statistical analysis. Subject characteristics were compared between adenoma cases and their matched controls and between cancer cases and their matched controls. In controls, Pearson correlation coefficient was calculated to examine the linear association between visceral fat area and other exposure variables. Conditional logistic regression was used to assess the association of various obesity indexes (abdominal total fat mass, visceral fat area, subcutaneous fat area, waist circumference, and BMI) and measures of insulin resistance (insulin, glucose, HOMA-IR) with colorectal neoplasia. Odds ratios and 95% CIs for the prevalence of colorectal adenoma or cancer were calculated for the second and third (highest) tertiles of exposure, with the lowest tertile used as reference. Cutoff values for the exposure tertile were determined based on the distribution among controls for colorectal

adenomas and cancer, respectively. Analyses were performed with and without adjustment for smoking (lifetime nonsmoker, ever smoker with 1 to 600 cigarette-years, or ever smoker with more than 600 cigarette-years) and alcohol consumption (nondrinker, drinker consuming 1 *go* or less per day, or drinker consuming more than 1 *go* per day). In analyses for the relation of insulin resistance to visceral fat area and blood markers, additional adjustment was also done for BMI. All analyses were performed using SAS version 10 (SAS Institute Inc., Cary, NC). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Table 1 shows patient characteristics for colorectal adenoma and cancer and their respective controls. Patients with colorectal adenoma were more likely to smoke and consume alcohol heavily than their matched controls. In contrast, they had similar levels of obesity and markers of insulin or insulin resistance to controls. Patients with colorectal cancer were more likely to be smokers and alcohol drinkers than their matched controls, and on average had a greater BMI, waist circumference, and visceral and subcutaneous fat area than controls. Markers of insulin resistance were higher among patients with colorectal cancer than their matched controls. In control subjects, visceral fat mass was highly correlated with other measures of obesity (Pearson correlation coefficients: waist circumference, 0.82; BMI, 0.68; subcutaneous fat mass, 0.58), moderately with insulin (0.44), and weakly with fasting glucose (0.18).

As shown in Table 2, odds of having colorectal cancer were increased in subjects with a higher visceral fat mass, with

multivariable-adjusted odds ratios (95% CI) for the lowest through highest tertiles of 1 (reference), 2.17 (0.45-10.46), and 5.92 (1.22-28.65), respectively (P for trend = 0.02). Additional adjustment for BMI did not attenuate the association. In contrast, subcutaneous fat mass was materially unrelated to colorectal cancer prevalence, with a multivariable-adjusted odds ratio (95% CI) for the highest versus lowest tertile of 1.08 (0.29-4.00). Higher levels of BMI or waist circumference were also associated with increased prevalence of colorectal cancer, with multivariable-adjusted odds ratios (95% confidence interval; trend P) for the highest versus lowest tertile of visceral fat area of 4.38 (0.82-23.25; 0.09) and 2.03 (0.57-7.25; >0.2) for BMI and waist circumference, respectively. With regard to colorectal adenoma, no association was seen with any measure of obesity, including visceral fat mass.

As shown in Table 3, odds of colorectal cancer tended to increase with increasing fasting plasma glucose concentration and, to a lesser extent, with increasing fasting plasma insulin concentration and HOMA-IR. Multivariable odds ratios (95% CI; trend P) for the highest versus lowest tertiles of glucose, insulin, and HOMA-IR were 4.40 (0.99-19.59; 0.04), 1.84 (0.47-7.15; >0.2), and 3.10 (0.71-13.54; 0.15), respectively. Additional adjustment for BMI attenuated the association with insulin and HOMA-IR, but did not greatly change that with glucose. In contrast, no measurable association was seen between colorectal adenoma and any of the three blood measurements.

CONCLUSIONS

Among participants in a health

screening program who underwent abdominal CT measurement, we found increased odds of early colorectal cancer in subjects with greater visceral fat mass, but not in those with greater subcutaneous fat mass. Markers of insulin resistance were also associated with a higher prevalence of colorectal cancer. In contrast, these associations were not observed for colorectal adenoma. To our knowledge, this study is the first to provide direct evidence of an association between visceral adiposity and colorectal cancer risk.

The present association between greater visceral fat area and increased prevalence of colorectal cancer is consistent with earlier epidemiologic data showing a link between colorectal cancer and waist circumference or waist-hip ratio (4, 5). In contrast, we observed no association with subcutaneous fat mass. This finding indicates that visceral but not subcutaneous adipose disposition is involved in the promotion of colorectal carcinogenesis. Among studies that have measured visceral fat area using CT scanning in association with colorectal neoplasia (6-10), only one study (10) examined the association with colorectal cancer. Contrary to expectations, this study found a higher prevalence of colorectal cancer in subjects with low rather than high visceral fat area. The authors speculated that this finding might have been to weight loss induced by cancer progression. In our study, cancer cases included in the analysis were all screening-detected and early stage, and thus the results were unlikely to have been influenced by cancer-induced weight loss.

In contrast to the positive finding for colorectal cancer, we observed no association between any measure of obesity, including visceral fat area, and the prevalence of

colorectal adenoma. Findings among studies that have measured abdominal fat area using CT are mixed: a significant positive association with visceral adiposity in a Japanese study (7) was subsequently both supported (9) and challenged (8, 10). Further, in an ancillary study to the Polyp Prevention Trial (6), visceral fat area measured on CT was not associated with adenoma recurrence. The reason for this discrepancy among adenoma studies is not clear. Given that smoking is a strong determinant of both the prevalence of colorectal adenoma (18) and body weight (19), the null finding in our study might be attributable, at least in part, to the high proportion of subjects with a history of smoking (73%). The relation of obesity measures to colorectal adenoma might only be detected in populations with no or low-level exposure to smoking, as suggested by a positive finding among nonsmokers (7). Alternatively, if the major role of obesity in colorectal carcinogenesis is to enlarge existing adenomas, the present null finding might be ascribable to the small number of cases with large adenomas (10 mm or larger: n=15).

The insulin hypothesis has been proposed to explain the association between obesity or visceral adiposity and colorectal cancer (12, 13). Prospective studies have shown an increased risk of colorectal cancer among persons with higher levels of postprandial insulin (4); C-peptide (20, 21), a measure of average insulin secretion; and fasting glucose (4) at baseline, although the association with fasting insulin was less clear (4). In accordance with these data, we observed an increase, albeit without statistical significance, in the odds of colorectal cancer in subjects with higher levels of markers of insulin resistance,

particularly fasting glucose. With regard to colorectal adenoma, although some studies have demonstrated an elevated risk among persons with higher levels of fasting insulin (22) or fasting glucose (23), our data do not support a role of insulin resistance in the development of colorectal adenoma. Recently, Tabuchi et al. (24) reported similar findings in health check-up attendants who underwent total colonoscopy: hyperglycemia was associated with an increased risk of colorectal cancer, but not with colorectal adenoma. Similarly, Chung et al. (25) demonstrated that glucose concentrations were more strongly associated with colorectal cancer than adenoma. Further studies are required to determine whether insulin resistance and resulting conditions, including hyperinsulinemia and hyperglycemia, are more strongly involved in the development of cancer than in that of adenoma.

The present study has several methodological advantages over previous studies that directly measured visceral adiposity accumulation using CT. Controls were randomly selected from a population of screening attendants among whom the cases arose, and abdominal CT measurement was done prior to the diagnosis of colorectal neoplasia, precluding the possibility of bias in the selection of controls and assessment of exposure, both of which are major concerns in case-control studies.

Several limitations of the study also warrant mention. First, the number of cases with colorectal cancer was small (n=22). Nevertheless, we were able to detect a statistically significant association with visceral fat area. Second, although the controls were selected from among examinees with a negative screening result, they were not confirmed to be polyp-free,

and thus may have included patients with colorectal adenomas, leading to attenuation of the association. Given the low probability that the control series included patients with undetected cancer, however, we believe that the present estimates for cancer were not subject to serious bias. Third, physical activity, a convincing protective factor for colorectal cancer (1), was not controlled in the analysis; in any case, such control would not be methodologically valid if physical activity exerted an anti-carcinogenic effect by decreasing visceral fat. An additional limitation was the lack of consideration of dietary factors. Finally, since the majority of study subjects were male employees working for a large-scale company in Japan, the results may not be generalizable to populations with different backgrounds.

In conclusion, the present study of screening participants who underwent abdominal CT scanning provides direct evidence for the hypothesis that visceral fat accumulation and insulin resistance promote

carcinogenesis of the colorectum. Since adipose tissue secretes various hormones which may play a role in the development and progression of cancer not only through their effect on insulin resistance but also by directly controlling cell proliferation, the biological mechanisms linking visceral fat disposition to cancer risk should be further explored.

ACKNOWLEDGMENTS

We thank Dr Keita Sasajima (Saitama Red Cross Hospital) for his helpful comments; and Ms Kae Saito and Yuho Mizoue (International Medical Center of Japan) for their assistance in the preparation of the manuscript.

This work was supported by Grants-in-Aid for Cancer Research, for the Third Term Comprehensive 10-Year Strategy for Cancer Control, and for Health Science Research from the Ministry of Health, Labour and Welfare of Japan.

Disclosure. All authors declare no conflict of interest.

REFERENCES

1. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington, DC: American Institute for Cancer Research, 2007.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
3. Shimizu H, Mack TM, Ross RK, Henderson BE. Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. *J Natl Cancer Inst* 1987;78:223-228.
4. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999;91:1147-1154.
5. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guerne G, Bergmann MM, Linseisen J, Becker N, Trichopoulou A, Trichopoulos D, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Van Guelpen B, Palmqvist R, Berglund G, Gonzalez CA, Dorronsoro M, Barricarte A, Navarro C, Martinez C, Quiros JR, Roddam A, Allen N, Bingham S, Khaw KT, Ferrari P, Kaaks R, Slimani N, Riboli E. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98:920-931.
6. Sass DA, Schoen RE, Weissfeld JL, Weissfeld L, Thaete FL, Kuller LH, McAdams M, Lanza E, Schatzkin A. Relationship of visceral adipose tissue to recurrence of adenomatous polyps. *Am J Gastroenterol* 2004;99:687-693.
7. Otake S, Takeda H, Suzuki Y, Fukui T, Watanabe S, Ishihama K, Saito T, Togashi H, Nakamura T, Matsuzawa Y, Kawata S. Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. *Clin Cancer Res* 2005;11:3642-3646.
8. Schoen RE, Weissfeld JL, Kuller LH, Thaete FL, Evans RW, Hayes RB, Rosen CJ. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. *Gastroenterology* 2005;129:464-475.
9. Oh TH, Byeon JS, Myung SJ, Yang SK, Choi KS, Chung JW, Kim B, Lee D, Byun JH, Jang SJ, Kim JH. Visceral obesity as a risk factor for colorectal neoplasm. *J Gastroenterol Hepatol* 2008;23:411-417.
10. Erarslan E, Turkay C, Koktener A, Koca C, Uz B, Bavbek N. Association of visceral fat accumulation and adiponectin levels with colorectal neoplasia. *Dig Dis Sci* 2009;54:862-868.
11. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology* 1987;93:1009-1013.
12. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control* 1995;6:164-179.
13. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 1994;3:687-695.

14. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982;54:254-260.
15. Koohestani N, Tran TT, Lee W, Wolever TM, Bruce WR. Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. *Nutr Cancer* 1997;29:69-76.
16. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr* 2007;86(suppl.):836-842.
17. Nakagawa T, Yamamoto S, Irokawa M. Development of the Automated Diagnosis CT Screening System for Visceral Obesity. *Asian Pacific Journal of Disease Management* 2008;2:31-38.
18. Botteri E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB. Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008;134:388-395.
19. Mizoue T, Ueda R, Tokui N, Hino Y, Yoshimura T. Body mass decrease after initial gain following smoking cessation. *Int J Epidemiol* 1998;27:984-988.
20. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000;92:1592-1600.
21. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, Stampfer MJ. A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst* 2004;96:546-553.
22. Keku TO, Lund PK, Galanko J, Simmons JG, Woosley JT, Sandler RS. Insulin resistance, apoptosis, and colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev* 2005;14:2076-2081.
23. Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H, Kono S. Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. *Int J Epidemiol* 1998;27:794-798.
24. Tabuchi M, Kitayama J, Nagawa H. Hyperglycemia and hypertriglyceridemia may associate with the adenoma-carcinoma transition in colorectal epithelial cells. *J Gastroenterol Hepatol* 2008;23:985-987.
25. Chung YW, Han DS, Park YK, Son BK, Paik CH, Lee HL, Jeon YC, Sohn JH. Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case-control study in Korea. *Dig Liver Dis* 2006;38:668-672.

Table 1. Characteristics of study subjects

	Colorectal adenoma		Colorectal cancer	
	Cases	Controls	Cases	Controls
Number	86	258	22	66
Sex, % women	3.5	3.5	4.6	4.6
Age (y)	54.0 (6.4)	54.0 (6.4)	53.8 (7.9)	53.8 (7.7)
Smoking, %				
Lifetime nonsmoker	15.1	26.0	13.6	21.2
600 cigarette-years or less	38.4	36.1	45.5	39.4
More than 600 cigarette-years	46.5	38.0	40.9	39.4
Alcohol use, %				
Non-drinker	24.4	26.7	22.7	40.9
Drinking 1 go/d or less	37.2	41.9	36.4	27.3
Drinking more than 1 go/d	38.4	31.4	40.9	31.8
Body mass index (kg/m ²)	23.7 (3.0)	23.8 (2.9)	25.5 (3.8)	23.7 (2.9)
Waist circumference (cm)	85.2 (8.5)	85.9 (8.7)	89.5 (14.6)	84.4 (8.0)
Total fat area (cm ²)	247 (101)	253 (95)	290 (120)	240 (93)
Visceral fat area (cm ²)	122 (56)	124 (52)	140 (42)	115 (54)
Subcutaneous fat area (cm ²)	125 (57)	129 (55)	150 (87)	125 (52)
Fasting glucose (mg/dl)	106 (20)	108 (19)	118 (39)	109 (20)
Fasting insulin (μ U/dl)	6.7 (4.3)	6.9 (4.1)	9.2 (7.5)	7.3 (4.4)
HOMA-IR	1.79 (1.26)	1.88 (1.27)	2.71 (2.49)	2.02 (1.36)

* Values are mean (SD) unless stated otherwise

Table 2. Associations of measures of obesity with the prevalence of adenoma and cancer in the colorectum

	Colorectal adenoma (n=86)				Colorectal cancer (n=22)			
	1 (low)	2	3 (high)	<i>P</i> _{trend}	1 (low)	2	3 (high)	<i>P</i> _{trend}
Total fat area* (cm²)	<214	214 to 288	>288		<197	197 to 287	>287	
No. of cases/controls	33/85	22/86	31/87		4/21	8/22	10/23	
Crude OR (95% CI) †	1	0.63 (0.32, 1.23)	0.87 (0.43, 1.74)	>0.2	1	2.04 (0.52, 7.96)	2.44 (0.63, 9.44)	>0.2
Multivariable OR (95% CI) ‡	1	0.64 (0.32, 1.27)	0.87 (0.43, 1.76)	>0.2	1	2.26 (0.52, 9.82)	2.76 (0.64, 11.87)	0.19
Visceral fat area* (cm²)	<103	103 to 142	>142		<92	92 to 129	>129	
No. of cases/controls	29/85	27/86	30/87		3/21	6/22	13/23	
Crude OR (95% CI) †	1	0.90 (0.44, 1.85)	1.02 (0.46, 2.24)	>0.2	1	1.88 (0.42, 8.35)	4.87 (1.11, 21.42)	0.03
Multivariable OR (95% CI) ‡	1	0.86 (0.41, 1.78)	0.99 (0.45, 2.20)	>0.2	1	2.17 (0.45, 10.46)	5.92 (1.22, 28.65)	0.02
Multivariable OR (95% CI) §	1	0.89 (0.41, 1.97)	1.08 (0.42, 2.81)	>0.2	1	2.09 (0.41, 10.70)	8.42 (0.80, 88.56)	0.08
Subcutaneous fat area* (cm²)	<106	106 to 139	>139		<101	101 to 145	>145	
No. of cases/controls	30/85	31/86	25/87		7/21	7/22	8/23	
Crude OR (95% CI) †	1	1.0 (0.55, 1.83)	0.78 (0.40, 1.52)	>0.2	1	0.96 (0.26, 3.46)	1.04 (0.30, 3.66)	>0.2
Multivariable OR (95% CI) ‡	1	1.01 (0.55, 1.87)	0.82 (0.41, 1.61)	>0.2	1	1.17 (0.30, 4.51)	1.08 (0.29, 4.00)	>0.2
Waist circumference* (cm)	<82	82 to 89	>89		<80	80 to 88	>88	
No. of cases/controls	24/83	32/87	30/88		6/21	4/22	12/23	
Crude OR (95% CI) †	1	1.28 (0.69, 2.38)	1.22 (0.61, 2.42)	>0.2	1	0.70 (0.18, 2.78)	2.01(0.58, 6.95)	>0.2
Multivariable OR (95% CI) ‡	1	1.37 (0.73, 2.55)	1.18 (0.59, 2.35)	>0.2	1	0.75 (0.18, 3.13)	2.03(0.57, 7.25)	>0.2
Body mass index (kg/m²)	<22.5	22.5 to 24.8	>24.8		<22.2	22.2 to 24.8	>24.8	
No. of cases/controls	29/84	29/85	28/89		3/20	8/23	11/23	
Crude OR (95% CI) †	1	0.98 (0.53, 1.83)	0.89 (0.46, 1.73)	>0.2	1	2.32 (0.56, 9.68)	3.65(0.81, 16.44)	>0.2
Multivariable OR (95% CI) ‡	1	0.99 (0.52, 1.86)	0.90 (0.46, 1.77)	>0.2	1	3.00 (0.61, 14.86)	4.38(0.82, 23.25)	0.09

Note: OR, odds ratio * Measured by abdominal computer tomography at the umbilical level in supine position; † Crude; ‡ Adjusted for smoking and alcohol drinking; § Additionally adjusted for BMI

Table 3. Associations of glucose, insulin, and HOMA-IR with the prevalence of adenoma and cancer in the colorectum

	Colorectal adenoma (n=86)				Colorectal cancer (n=22)			
	1 (low)	2	3 (high)	<i>P</i> _{trend}	1 (low)	2	3 (high)	<i>P</i> _{trend}
Fasting glucose (mg/dl)	<100	100 to 108	>108		<99	99 to 108	>108	
No. of cases/controls	32/74	24/93	30/91		4/21	6/22	12/23	
Crude OR (95% CI) [†]	1	0.57 (0.30, 1.08)	0.73 (0.39, 1.36)	>0.2	1	1.69 (0.36, 7.96)	3.12 (0.76, 12.74)	0.09
Multivariable OR (95% CI) [‡]	1	0.62 (0.32, 1.19)	0.76 (0.40, 1.42)	>0.2	1	1.76 (0.35, 8.69)	4.40 (0.99, 19.59)	0.04
Multivariable OR (95% CI) [§]	1	0.62 (0.32, 1.20)	0.76 (0.41, 1.44)	>0.2	1	2.17 (0.41, 11.50)	4.07 (0.86, 19.37)	0.07
Fasting insulin (μ U/dl)	<4.7	4.7 to 7.4	>7.4		<5	5 to 7.8	>7.8	
No. of cases/controls	29/85	29/83	28/90		5/21	8/22	8/23	
Crude OR (95% CI) [†]	1	1.02 (0.57, 1.85)	0.91 (0.50, 1.66)	>0.2	1	1.55 (0.45, 5.32)	1.38 (0.40, 4.76)	>0.2
Multivariable OR (95% CI) [‡]	1	1.14 (0.61, 2.12)	1.08 (0.58, 2.03)	>0.2	1	1.65 (0.38, 7.28)	1.84 (0.47, 7.15)	>0.2
Multivariable OR (95% CI) [§]	1	1.15 (0.62, 2.15)	1.15 (0.57, 2.31)	>0.2	1	1.88 (0.39, 9.03)	1.29 (0.28, 5.84)	>0.2
HOMA-IR	<1.2	1.2 to 2.05	>2.05		1.33	1.33 to 2.04	>2.04	
No. of cases/controls	31/85	30/86	25/87		4/21	8/22	9/23	
Crude OR (95% CI) [†]	1	0.95 (0.53, 1.72)	0.79 (0.43, 1.45)	>0.2	1	1.85 (0.52, 6.62)	1.89 (0.51, 6.94)	>0.2
Multivariable OR (95% CI) [‡]	1	1.08 (0.58, 2.00)	0.89 (0.47, 1.68)	>0.2	1	2.60 (0.62, 10.97)	3.10 (0.71, 13.54)	0.15
Multivariable OR (95% CI) [§]	1	1.08 (0.58, 2.03)	0.91 (0.45, 1.83)	>0.2	1	2.63 (0.60, 11.41)	2.20 (0.45, 10.81)	>0.2

Note: OR, odds ratio; † Crude; ‡ Adjusted for smoking and alcohol drinking; § Additionally adjusted for BMI