Visceral Fat Area and Markers of Insulin Resistance in Relation to Colorectal Neoplasia

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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 (2004–2007), a total of 108 patients with early-stage colorectal neoplasia, including 22 with early cancer, were identified among individuals who received both colorectal cancer screening and abdominal computed tomography scanning. Three control subjects matched to each case subject 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 ratios (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 ($P_{trend} = 0.02$). 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 tissue accumulation and insulin resistance may promote the development of early-stage cancer but not adenoma in the colorectum.

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Although the role of obesity as a strong predictor of various chronic diseases, including type 2 diabetes and cardiovascular disease, 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 trend, as well as findings from migrant studies (3), suggests the involvement of environmental factors in colorectal carcinogenesis. Epidemiological studies (4,5) have shown that colorectal cancer risk is more strongly associated with waist circumference than with BMI, indicating the etiological 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 individuals 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), patients with colorectal cancer tended to have a smaller rather than larger visceral fat area than that in control subjects. This unexpected finding may have been due to weight loss in the course of cancer development, however, a possibility that highlights the importance of assessing visceral fat before 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, epidemiological data appear consistent in showing a positive association between colorectal neoplasia and markers of hyperinsulinemia or insulin resistance (rev. in 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 individuals who underwent screening.

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RESEARCH DESIGN AND METHODS

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 offered mainly to individuals who underwent chest CT scanning for the screening of lung cancer. Nearly one-third of all individuals who underwent screening chose to receive abdominal CT assessment. Compared with men who did not, those who underwent abdominal CT scanning were older (53 vs. 46 years), were more likely to be past smokers (35 vs. 22%), and tended to have a higher BMI (23.9 vs. 23.6 kg/m²). In contrast, the two groups were similar in terms of alcohol drinking (> 1 *go* [23 g ethanol]/day: 32 vs. 29%). A *go* is a conventional unit of alcohol intake in Japan.

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, individuals 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 checkup. Among patients with adenomas of known size ($n = 82$), the number with adenomas of ≥10 mm in diameter was 15 (18%). Regarding the location of cancer, 5 cases were in the ascending colon, 2 were in the transverse colon, 13 were in the sigmoid colon, 1 was in the rectum, and 1 was not specified. For each case subject, three control subjects 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 subject had a prior history of cancer, cardiac infarction, or stroke. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The protocol of the 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). In brief, single slice imaging was done at the level of the umbilicus in the supine position using a Redix Turbo CT scanner (Hitachi Medico, Tokyo, Japan). 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).

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 the square of height in meters. Fasting plasma glucose was measured by the glucose electrode technique using an ADAMS Glucose GA-1170 (Arkray). Fasting serum immunoreactive insulin (microunits per milliliter) was determined by an immunoenzymatic method using the AxSYM insulin assay (Abbott). Homeostasis model assessment of 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 inquired about smoking status and for ever-smokers it inquired about 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*. One *go* contains ~23 g ethanol.

Statistical analysis

Subject characteristics were compared between case subjects with adenomas and their matched control subjects and between case subjects with cancer and their matched control subjects. In control subjects, Pearson correlation coefficients were calculated to examine the linear associations 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, and HOMA-IR) with colorectal neoplasia. Odds ratios (ORs) 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 control subjects for colorectal adenomas and cancer, respectively. Analyses were performed with and without adjustment for smoking (lifetime nonsmoker, ever-smoker with 1–600 cigarette-years, or ever-smoker with >600 cigarette-years), and alcohol consumption (nondrinker, drinker consuming ≤1 *go*/day, or drinker consuming >1 *go*/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, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows patient characteristics for colorectal adenoma and cancer and their respective control subjects. Patients with colorectal adenomas were more likely to smoke and consume alcohol heavily than their matched control subjects. In contrast, they had levels of obesity and markers of insulin or insulin resistance similar to those of control subjects. Patients with colorectal cancer were more likely to be smokers and alcohol drinkers than their matched control subjects and on average had a greater BMI, waist circumference, and visceral and subcutaneous fat area than control subjects. Markers of insulin resistance were higher among patients with colorectal cancer than among their matched control subjects. In control subjects, visceral

Table 1—*Characteristics of study subjects*

	Colorectal adenoma		Colorectal cancer	
	Case subjects	Control subjects	Case subjects	Control subjects
n	86	258	22	66
Sex (% women)	3.5	3.5	4.6	4.6
Age (years)	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	38.4	36.1	45.5	39.4
>600 cigarette-years	46.5	38.0	40.9	39.4
Alcohol use (%)				
Nondrinker	24.4	26.7	22.7	40.9
Drinking ≤1 *go*/day	37.2	41.9	36.4	27.3
Drinking >1 *go*/day	38.4	31.4	40.9	31.8
BMI (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 (μU/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

Data are means ± SD unless stated otherwise.

fat mass was highly correlated with other measures of obesity (Pearson correlation coefficients: waist circumference 0.82, BMI 0.68, and subcutaneous fat mass 0.58), moderately with insulin (0.44), and weakly with fasting glucose (0.18).

As shown in Table 2, the odds of having colorectal cancer were increased in subjects with a higher visceral fat mass, with multivariable-adjusted ORs (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_{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 OR 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 ORs (95% CI; P_{trend}) 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, the 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 ORs (95% CI; P_{trend}) 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 epidemiological data showing a link between colorectal cancer and waist circumference or waist-to-hip ratio (4,5). In contrast, we observed no association with subcutaneous fat mass. This finding indicates that visceral but not subcutaneous adipose tissue 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 showed 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 due to weight loss induced by cancer progression. In our study, cancer in subjects included in the analysis was 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 may be ascribable to the small number of case subjects with large adenomas (≥10 mm: 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 individuals with higher

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

	Colorectal adenoma				Colorectal cancer			
	1 (low)	2	3 (high)	P_{trend}	1 (low)	2	3 (high)	P_{trend}
n		86				22		
Total fat area (cm^2)*	<214	214–288	>288		<197	197–287	>287	
No. of case subjects/control subjects	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 (cm^2)*	<103	103–142	>142		<92	92–129	>129	
No. of case subjects/control subjects	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 (cm^2)*	<106	106–139	>139		<101	101–145	>145	
No. of case subjects/control subjects	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	82–89	>89		<80	80–88	>88	
No. of case subjects/control subjects	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
BMI (kg/m^2)	<22.5	22.5–24.8	>24.8		<22.2	22.2–24.8	>24.8	
No. of case subjects/control subjects	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

*Measured by abdominal CT at the umbilical level in supine position. †Crude. ‡Adjusted for smoking and alcohol drinking. §Additionally adjusted for BMI.

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 individuals 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 checkup participants 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 with adenoma. Further studies are required to de-

termine 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. Control subjects were randomly selected from a population of screening participants, among whom the cases arose, and abdominal CT measurement was done before the diagnosis of colorectal neoplasia, precluding the possibility of bias in the selection of control subjects 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 case subjects with colorectal cancer was small (n = 22). Nevertheless, we were able to detect a statistically significant association with visceral fat area. Second, although the control subjects 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 subjects 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 for in the analysis; in any case, such control would not be methodologically valid if physical activity exerted an anticarcinogenic effect by decreasing visceral fat. An additional limitation was the lack of consideration of dietary factors. Finally, because 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 summary, 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 colorec-

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

	Colorectal adenoma				Colorectal cancer			
	1 (low)	2	3 (high)	P_{trend}	1 (low)	2	3 (high)	P_{trend}
n		86				22		
Fasting glucose (mg/dl)	<100	100–108	>108		<99	99–108	>108	
No. of case subjects/control subjects	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 (μU/dl)	<4.7	4.7–7.4	>7.4		<5	5–7.8	>7.8	
No. of case subjects/control subjects	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	1.2–2.05	>2.05		1.33	1.33–2.04	>2.04	
No. of case subjects/control subjects	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

*Crude. †Adjusted for smoking and alcohol drinking. ‡Additionally adjusted for BMI.

tum. Because adipose tissue secretes various hormones that 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.

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, Tjønneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec 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, Quirós 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 re-

view. 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 Pac J Dis Manage 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