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 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 ($P_{\text{trend}} = 0.02$). 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.

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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The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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 (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 (micromunits 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
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), 1.27 (0.45–3.99; 0.09), 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 screened-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...
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 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. 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 able to detect a statistically significant 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 ant carcinogenic 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 colorectal...
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.

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

| Fasting glucose (mg/dl) | Colorectal adenoma | | Colorectal cancer | |
|------------------------|-------------------|---|-----------------|---|
|                        | 1 (low)           | 2 | 3 (high)        | P_trend | 1 (low)          | 2 | 3 (high)        | P_trend |
|                        | 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 (0.32–1.21) | 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/ml) | Colorectal adenoma | | Colorectal cancer | |
|------------------------|-------------------|---|-----------------|---|
|                        | 1 (low)           | 2 | 3 (high)        | P_trend | 1 (low)          | 2 | 3 (high)        | P_trend |
|                        | 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                | Colorectal adenoma | | Colorectal cancer | |
|------------------------|-------------------|---|-----------------|---|
|                        | 1 (low)           | 2 | 3 (high)        | P_trend | 1 (low)          | 2 | 3 (high)        | P_trend |
|                        | No. of case subjects/control subjects | 31/85 | 30/86 | 25/87 | 4/21 | 5/21 | 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 (0.43–10.81) | >0.2 |

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