Human Cancer Biology

Serum Interleukin-6, Insulin, and HOMA-IR in Male Individuals with Colorectal Adenoma

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Abstract

Purpose: It is widely acknowledged that chronic low-grade inflammation plays a key role in the development of obesity-related insulin resistance and type 2 diabetes. The level of circulating interleukin-6 (IL-6), one of the major proinflammatory adipokines, is correlated with obesity and insulin resistance, which are known to be risk factors for colorectal adenoma. We examined the association between the circulating level of IL-6 and the presence of colorectal adenoma.

Experimental Design: In a total colonoscopy-based cross-sectional study conducted between January and December 2008, serum levels of IL-6 were measured in samples of venous blood obtained from 336 male participants attending health checkups (118 individuals with colorectal adenoma and 218 age-matched controls) after an overnight fast.

Results: In the colorectal adenoma group, the median levels of serum IL-6 (1.24 vs. 1.04 pg/mL; P = 0.01), triglyceride, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) were to be significantly higher than those in the control group. When restricted to individuals with adenoma, levels of IL-6 were positively correlated with body mass index, insulin, and HOMA-IR. Multiple logistic analyses adjusted to include insulin or HOMA-IR showed that high levels of IL-6 were associated with the presence of colorectal adenoma. There was no significant interaction of IL-6 with HOMA-IR to modify this association.

Conclusions: Our findings suggest that increased serum levels of IL-6 are positively associated with the presence of colorectal adenoma in men, independently of insulin and HOMA-IR.

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Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide. Several epidemiologic studies have suggested that individuals with metabolic syndrome are at increased risk of colon cancer and also adenoma, which is a precursor lesion for most CRCs (1). We have shown that an increased area of visceral fat and a decreased concentration of plasma adiponectin are associated with the development of colorectal adenoma (2). Although the mechanisms underlying this association remain unclear, insulin resistance and hyperinsulinemia, in close association with visceral fat accumulation, are thought to be important etiologic factors (3).

It has been recognized that adipose tissue is not only a reservoir for surplus energy but also an active endocrine organ that contributes to metabolic homeostasis by secreting several adipokines such as adiponectin, leptin, TNF-α, interleukin-6 (IL-6), macrophage and monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and resistin (4, 5). These adipokines are able to induce a chronic state of low-grade inflammation that could play a central role in obesity-related insulin resistance and cardiovascular complications (6). Chronic inflammation is also thought to be associated with colorectal carcinogenesis (7). In addition, individuals who use aspirin/nonsteroidal anti-inflammatory drugs (NSAID), and thus possibly have lower levels of inflammation, have been shown to have a reduced risk of colorectal adenoma (8–10) and cancer (11–13).

IL-6 is one of the major proinflammatory adipokines (14), and both its expression in adipose tissue and the circulating concentration are positively correlated with obesity and insulin resistance (15). One study has shown a positive association between the circulating level of IL-6 and the risk of colorectal adenoma (16), whereas another study has found no such association (17).

In the present study, we investigated the relationship between high-sensitivity serum IL-6 levels and the presence...
Circulating IL-6 Level and Presence of Colorectal Adenoma

Translational Relevance

Obesity and insulin resistance are known to be risk factors for colorectal adenoma, which is a precursor lesion for most colorectal cancers. Chronic low-grade inflammation could play an important role in obesity-related insulin resistance and is also thought to be associated with colorectal carcinogenesis. Here, we show for the first time that circulating levels of serum interleukin (IL)-6, one of the major proinflammatory adipokines, are increased in male individuals with colorectal adenoma and associated with the presence of colorectal adenoma independently of homeostasis model assessment of insulin resistance (HOMA-IR) or insulin. These findings suggest that IL-6 may play an important role in the etiology of colorectal adenoma, although their clinical relevance is still uncertain. Further studies will be needed to clarify the mechanisms and clinical relevance of the association between IL-6 and development of colorectal adenoma. Such data might lead to a better understanding of the role of low-grade systemic inflammation in the etiology of colorectal adenoma.

Materials and Methods

Study population

From among 967 participants in health checkup examinations conducted at Tohoku Central Hospital, Yamagata, Japan, between January and December 2008, we attempted to recruit 840 who underwent colonoscopy as part of health checkups for this study. Ten individuals declined to participate (giving a response rate of 98.8%). We screened the remaining 830 subjects, among whom 708 were considered eligible for this study on the basis of the following exclusion criteria: a history of bowel resection (n = 12), presence of malignant neoplasia (n = 1), chronic myeloid leukemia, renal failure (n = 1), and chronic inflammatory diseases (n = 42) such as chronic hepatitis (n = 11), asthma (n = 10), chronic rhinitis (n = 9), thyroid disease (n = 7), chronic sinusitis (n = 2), inflammatory bowel disease (n = 1), atopic dermatitis (n = 1), chronic prostatitis (n = 1), and collagen diseases (n = 0), incomplete colonoscopy (n = 21) because of poor bowel preparation or failure to carry out cecal intubation, and regular use of NSAIDs including aspirin (n = 42) and anti-hyperglycemic drugs (n = 22). None of the subjects had colorectal adenocarcinoma. From among 537 individuals who were found to be free of adenomatous polyps throughout the entire large intestine, we excluded 84 who had a history of colorectal polyp resection to yield a control group. We identified 171 individuals with colorectal adenoma on the basis of their endoscopic findings. Because there were few female individuals with colorectal adenoma (n = 20), we restricted the present study to male subjects. For age matching, we stratified the male subjects into 5 age categories (<40, 40–49, 50–54, 55–59, and ≥60 years) and then randomly selected individuals from each category in the control group (n = 332) and the adenoma group (n = 151). This stratified sampling yielded a final total of 336 study subjects comprising 118 males with colorectal adenoma and 218 age-matched male controls (6 cases and 12 controls in their 30s, 42 cases and 87 controls in their 40s, 64 cases and 105 controls in their 50s, and 6 cases and 14 controls in their 60s; Fig. 1).

This study was approved by the ethics committee of Tohoku Central Hospital. Written informed consent was obtained from all subjects before entering the study.

Clinical evaluation

From all subjects, we collected clinical information concerning smoking, alcohol consumption, familial history, and history of treatment and medication from a self-completed questionnaire distributed during the physical checkup. We defined current smoking as at least one cigarette daily for the previous 12 months and alcohol consumption as more than 25 g of alcohol daily. Trained nurses determined blood pressure using a standardized protocol. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Samples of venous blood were drawn from all subjects after an overnight fast before bowel preparation for colonoscopy. These samples were immediately subjected to analysis of the serum levels of high-density lipoprotein, low-density lipoprotein, serum triglyceride, fasting plasma glucose (FPG), and fasting plasma insulin (FPI). Concurrently, residual serum samples were immediately stored at −80°C until assay of IL-6. Insulin sensitivity was evaluated by homeostasis model assessment and calculated as follows: homeostasis model assessment of insulin resistance (HOMA-IR) = FPI × FPG/405, where FPI is expressed as μIU/mL and FPG as mg/dL.

Laboratory assay

Assays of IL-6 were conducted using serum stored at −80°C. Serum concentrations of IL-6 were determined in duplicate using a commercially available high-sensitivity sandwich ELISA kit for human IL-6 (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Inc.), in accordance with the manufacturer’s instructions. The measurements were conducted in a blind manner with regard to case or control sample status. The values presented here were the average IL-6 concentrations of duplicate samples. The intraclass correlation coefficient between duplicates was 0.9936. According to the kit manufacturer, the mean minimum detection limit of IL-6 was 0.039 pg/mL, and the IL-6 concentration was not below this limit in any of the samples.
Detection of colorectal adenoma by colonoscopy

Nine experienced gastroenterologists conducted colonoscopic examinations using conventional video-endoscopes (PCF-240I, PCF-Q260I, CF-240I, CF-240AI, CF-Q260AI, CF-H260AI; Olympus Medical Systems). All subjects underwent bowel preparation using 2 L of polyethylene glycol-electrolyte solution (MUBEN; Nihon Pharmaceutical Co. Ltd.). The endoscopists were unaware of the clinical and laboratory findings at the time of the examinations. To obtain an accurate endoscopic diagnosis of whether lesions were adenomatous polyps, indigo carmine solution was sprayed on the surface of each lesion during colonoscopic examination, and the pit pattern was analyzed. This procedure, as described previously (18), is known to be highly accurate for differential diagnosis of neoplastic (adenoma and adenocarcinoma) and nonneoplastic (hyperplastic) polyps. All of the colonoscopy recordings were double checked by the chief gastroenterologist (H. Saito) at Tohoku Central Hospital.

Statistical analyses

For comparison between the colorectal adenoma group and the control group, we analyzed continuous variables and categorical variables using the 2-tailed Wilcoxon rank-sum test or the χ² test, respectively. The Kruskal–Wallis test was used to compare some continuous variables in each of the quartile IL-6 groups. The Spearman rank test was used to evaluate correlations between the serum IL-6 level and some continuous variables adjusted for age. We computed the ORs and 95% confidence interval (CI) using logistic regression model analysis. The categories of covariates included in the logistic regression models were as follows: age, current smoking (yes or no), alcohol consumption (yes or no), family history of CRC (yes or no), quartiles of BMI (<22.39, 22.39 to <23.98, 23.98 to <25.94, ≥25.94 kg/m²), quartiles of insulin (<2.95, 2.95 to <4.55, 4.55 to <7.55, ≥7.55 μIU/mL), and quartiles of HOMA-IR (<0.66, 0.66 to <1.06, 1.06 to <1.74, ≥1.74). We then investigated possible interaction between IL-6 and HOMA-IR to modify its association with colorectal adenoma for 8 combinations of quartiles of IL-6 and the dichotomized 75th percentile value of HOMA-IR (1.73). On the basis of the likelihood ratio test with 3 degrees of freedom, we statistically evaluated these interactions. We determined the cutoff points for quartiles of each biomarker/index on the basis of the distribution of all the subjects combined. Differences at a value of P < 0.05 were considered to be significant. We carried out all statistical calculations using SAS Enterprise Guide v. 4.2 (SAS Institute, Inc.).
## Results

### Selected characteristics of the individuals with adenoma

The selected characteristics of the 336 enrolled male subjects are presented in Table 1. There were no significant differences between the colorectal adenoma group and the control group in the proportions of current smokers, alcohol consumers, presence of a family history of CRC, regular use of antihypertensive or anti-lipemic drugs, median age, BMI, or blood pressure. In comparison with the control group, individuals in the colorectal adenoma group had significantly higher median levels of serum triglyceride ($P < 0.01$), and HOMA-IR values ($P < 0.01$). In individuals with colorectal adenoma, the Spearman correlation coefficients after adjustment for age between IL-6 and BMI, insulin, or HOMA-IR were significantly higher in the highest quartiles in both controls and individuals with colorectal adenoma. Furthermore, the Spearman correlation coefficients after adjustment for age between IL-6 and triglyceride in the quartiles in both controls and individuals with colorectal adenoma were also significantly higher in the highest quartiles in both controls and individuals with colorectal adenoma. No significant difference in the median level of triglyceride was observed among the quartiles in both controls and individuals with colorectal adenoma. In individuals with colorectal adenoma, the Spearman correlation coefficients after adjustment for age between IL-6 and BMI, insulin, or HOMA-IR were 0.330, 0.314, and 0.220, respectively. In addition, we observed a statistically significant trend of increasing univariate or multivariate-adjusted odds ratios for colorectal adenoma according to the quartiles of IL-6, insulin, and HOMA-IR, which were 2.22 (95% CI, 1.54–5.64), 3.45 (95% CI, 1.73–6.87), and 3.19 (95% CI, 1.60–6.35) for IL-6, insulin, and HOMA-IR, respectively. In addition, we observed a statistically significant trend of increasing univariate or multivariate-adjusted odds ratios for colorectal adenoma according to the quartiles of IL-6, insulin, and HOMA-IR, which were 2.22 (95% CI, 1.54–5.64), 3.45 (95% CI, 1.73–6.87), and 3.19 (95% CI, 1.60–6.35) for IL-6, insulin, and HOMA-IR, respectively.

### Association of IL-6, insulin, and HOMA-IR with presence of colorectal adenoma

Using logistic regression analysis models, we computed the ORs of colorectal adenoma according to the quartiles of the levels of IL-6, insulin, and HOMA-IR values (Table 3). On the basis of the results of univariate analysis, the highest IL-6 quartile (OR, 2.08; 95% CI, 1.09–3.97), the highest insulin quartile (OR, 2.95; 95% CI, 1.54–5.64), and the highest HOMA-IR quartile (OR, 2.65; 95% CI, 1.39–5.04) were significantly associated with the presence of colorectal adenoma. Multivariate-adjusted ORs of colorectal adenoma for the highest compared with the lowest quartile were 2.22 (95% CI, 1.13–4.38), 3.45 (95% CI, 1.73–6.87), and 3.19 (95% CI, 1.60–6.35) for IL-6, insulin, and HOMA-IR, respectively. In addition, we observed a statistically significant trend of increasing univariate or multivariate-adjusted odds ratios for colorectal adenoma according to the quartiles of IL-6, insulin, and HOMA-IR, which were 2.22 (95% CI, 1.13–4.38), 3.45 (95% CI, 1.73–6.87), and 3.19 (95% CI, 1.60–6.35) for IL-6, insulin, and HOMA-IR, respectively.

### Factors associated with an increased IL-6 level

We conducted quartile analysis of the IL-6 level to assess the factors associated with high IL-6 levels. Although no significant differences in the proportion of current smokers or current alcohol consumers were observed among the IL-6 quartiles, the proportion of current smokers tended to be higher as the quartiles became higher (data not shown, $P = 0.12$). In both controls and individuals with colorectal adenoma, the median age was significantly higher in the highest rather than in the lowest IL-6 quartile (Table 2). In individuals with colorectal adenoma, the median BMI ($P = 0.04$), level of fasting insulin ($P < 0.01$), and value of HOMA-IR ($P < 0.01$) were also significantly higher in the highest rather than in the lowest IL-6 quartile. No significant difference in the median level of triglyceride was observed among the quartiles in both controls and individuals with colorectal adenoma. In individuals with colorectal adenoma, the Spearman correlation coefficients after adjustment for age between IL-6 and BMI, insulin, or HOMA-IR were 0.330, 0.314, and 0.220, respectively. In addition, we observed a statistically significant trend of increasing univariate or multivariate-adjusted odds ratios for colorectal adenoma according to the quartiles of IL-6, insulin, and HOMA-IR, which were 2.22 (95% CI, 1.13–4.38), 3.45 (95% CI, 1.73–6.87), and 3.19 (95% CI, 1.60–6.35) for IL-6, insulin, and HOMA-IR, respectively.
ORS for colorectal adenoma across the quartiles of IL-6 quartile range of the upper quartile. Within the minimum, and the highest datum still within the 1.5 internal individual range of the upper quartile.

Comparison of serum IL-6 concentrations between individuals with colorectal adenoma and controls. Box plot: the bottom and top of each box represent the 25th and 75th percentiles, and the band near the middle of the box is the median of the serum IL-6 concentration in the individuals with adenoma and the controls. Whiskers: the lowest datum is within the minimum, and the highest datum still within the 1.5 internal quartile range of the upper quartile.

**Figure 2.** Comparison of serum IL-6 concentrations between individuals with colorectal adenoma and controls. Box plot: the bottom and top of each box represent the 25th and 75th percentiles, and the band near the middle of the box is the median of the serum IL-6 concentration in the individuals with adenoma and the controls. Whiskers: the lowest datum is within the minimum, and the highest datum still within the 1.5 internal quartile range of the upper quartile.

ORS for colorectal adenoma across the quartiles of IL-6 ($P_{\text{trend}} = 0.01$), insulin ($P_{\text{trend}} < 0.01$), and HOMA-IR ($P_{\text{trend}} < 0.01$). Upon additional adjustment for HOMA-IR or insulin, a significantly positive association between the quartiles of IL-6 and presence of colorectal adenoma was observed. We then conducted a sensitivity analysis by excluding subjects with values of IL-6 (4.412 pg/mL), insulin (13.4 μIU/mL), and HOMA-IR (3.29) above the 95th percentile, but the results were essentially the same as those above. When cases were restricted to those in which the largest adenoma was 5 mm ($n = 78$) or more in diameter ($n = 40$), or those with one adenoma ($n = 71$) or more adenomas ($n = 47$), the quartiles of IL-6, insulin, and HOMA-IR were not associated with large adenomas or multiple adenomas (data not shown).

**Association of IL-6 with the presence of colorectal adenoma in relation to HOMA-IR**

To explore whether IL-6 interacted with the value of HOMA-IR to modify its association with the presence of colorectal adenoma, we computed the ORs of colorectal adenoma by stratifying the study subjects into 8 groups according to the quartiles of IL-6 concentration as well as the value of HOMA-IR (Table 4). We adopted a HOMA-IR value higher than 1.73 (75th percentile) as a cutoff index of insulin resistance. The highest IL-6 quartile with a high HOMA-IR value was significantly associated with the presence of colorectal adenoma (multivariate OR, 4.55; 95% CI, 1.74–11.93). We observed no significant interaction of IL-6 quartiles with the dichotomized value of HOMA-IR ($P_{\text{interaction}} = 0.68$).

**Discussion**

In this study, high-sensitivity serum IL-6 concentrations were higher in male individuals with colorectal adenoma than in controls. In these individuals with colorectal adenoma, the IL-6 level was positively correlated with age, BMI, insulin, and HOMA-IR, whereas in controls, IL-6 was positively correlated with age. Increased levels of IL-6 were associated with the presence of colorectal adenoma, independent of insulin and the HOMA-IR value, which showed a stronger association with the presence of colorectal adenomas than IL-6. No significant interaction of IL-6 quartiles with the dichotomized value of HOMA-IR was observed.

To our knowledge, only two previous studies have investigated the relationship between the circulating level of IL-6 and the risk of colorectal adenoma (16, 17). Our findings for colorectal adenoma agree with the results of a cross-sectional study in which Kim and colleagues (16) found a positive association with the highest tertiles of IL-6 compared with the lowest tertiles. In that study, however, the levels of IL-6 were below the detection limit (<0.104 pg/mL) in about 50% of the individuals with colorectal adenoma and 65% of the controls, and thus no clear difference in the IL-6 level was demonstrable between the groups. In contrast, IL-6 levels were within the detectable range in all of our subjects using the high-sensitivity ELISA kit, allowing us to show differences in the levels of IL-6 between individuals with colorectal adenoma and controls at the low end of the concentration range. On the other hand, another case–control study of a multiethnic population showed no association between the serum concentration of IL-6 and colorectal adenoma risk (17). The present study population was rather smaller in size than those of these two previous studies, which included 873 participants (16) and 810 multiethnic participants (17), respectively. To confirm the association between the level of IL-6 and colorectal adenoma, large-scale studies or studies covering a wide range of ethnic groups will be needed.

Obesity, which is the main determinant of insulin resistance and hyperinsulinemia in a non-diabetic state, is a known risk factor for CRC and adenoma (2, 3). Although the biologic mechanisms of this potential association have not been fully elucidated, obesity-related insulin resistance and subsequent hyperinsulinemia are likely involved in colorectal carcinogenesis (19). It has also been shown that adipose tissue releases a wide variety of biologically functional molecules, including TNF-α and IL-6 (20). In fact, IL-6 is increased in obese individuals relative to lean ones (21). It is known that an increase in the circulating level of IL-6 is linked to the development of insulin resistance (15, 22) and that associated hyperinsulinemia might be involved in the
Circulating IL-6 Level and Presence of Colorectal Adenoma

Table 2. Factors associated with IL-6 levels

<table>
<thead>
<tr>
<th>Quartile of IL-6, pg/mL</th>
<th>&lt;0.804</th>
<th>≥0.804 to &lt;1.098</th>
<th>≥1.098 to &lt;1.619</th>
<th>≥1.619</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases/controls</td>
<td>23/61</td>
<td>27/57</td>
<td>31/53</td>
<td>37/47</td>
</tr>
</tbody>
</table>

Control

- **Age, y**
  - Median: 46 (43–51)
  - Median: 50 (45–57)
  - Median: 51 (46–54)
  - Median: 54 (51–59)
  - *P* = 0.01

- **BMI, kg/m²**
  - Median: 23.1 (21.4–25.4)
  - Median: 24.1 (22.6–25.7)
  - Median: 24.1 (22.8–25.5)
  - Median: 23.7 (22.3–25.7)
  - *P* = 0.18

- **Triglyceride, mg/dL**
  - Median: 125 (94–149)
  - Median: 127 (93–220)
  - Median: 141 (109–193)
  - Median: 128 (87–199)
  - *P* = 0.44

- **Fasting insulin, µU/mL**
  - Median: 4.1 (3.0–5.9)
  - Median: 4.0 (2.6–7.0)
  - Median: 4.5 (2.8–6.7)
  - Median: 4.4 (2.7–7.2)
  - *P* = 0.91

- **HOMA-IR**
  - Median: 0.96 (0.70–1.39)
  - Median: 0.88 (0.59–1.70)
  - Median: 0.98 (0.66–1.55)
  - Median: 0.97 (0.57–1.46)
  - *P* = 0.93

Colorectal adenoma

- **Age, y**
  - Median: 47 (43–54)
  - Median: 47 (45–55)
  - Median: 53 (48–56)
  - Median: 53 (50–57)
  - *P* = 0.02

- **BMI, kg/m²**
  - Median: 22.6 (21.6–24.6)
  - Median: 25.4 (22.7–26.7)
  - Median: 24.5 (22.7–26.9)
  - Median: 24.9 (23.2–26.6)
  - *P* = 0.04

- **Triglyceride, mg/dL**
  - Median: 1.19 (73–206)
  - Median: 1.70 (99–226)
  - Median: 1.80 (105–231)
  - Median: 1.88 (98–256)
  - *P* = 0.12

- **Fasting insulin, µU/mL**
  - Median: 3.3 (2.3–6.1)
  - Median: 6.8 (3.8–10.4)
  - Median: 5.8 (3.1–7.8)
  - Median: 6.5 (4.0–10.8)
  - *P* < 0.01

- **HOMA-IR**
  - Median: 0.76 (0.52–1.41)
  - Median: 1.42 (0.85–2.33)
  - Median: 1.38 (0.65–1.75)
  - Median: 1.45 (0.93–2.39)
  - *P* < 0.01

NOTE: Results are expressed as median (IQR).

*P* values were evaluated by the Kruskal–Wallis test for median value difference in each of the quartile IL-6 groups in controls or individuals with colorectal adenoma.

BMI is the weight in kilograms divided by the square of the height in meters.

HOMA-IR = FPI (µU/mL) × FPG (mg/dL)/405.

High levels of IL-6 appeared to contribute to the development of colorectal adenoma via insulin resistance and subsequent hyperinsulinenia in the present individuals with colorectal adenoma.

Table 3. ORs of colorectal adenoma according to quartiles of IL-6, insulin and HOMA-IR

<table>
<thead>
<tr>
<th>Measurement</th>
<th>1 OR (95% CI)</th>
<th>2 OR (95% CI)</th>
<th>3 OR (95% CI)</th>
<th>4 OR (95% CI)</th>
<th><em>P</em>&lt;sub&gt;trend&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, range, pg/mL</td>
<td>&lt;0.804</td>
<td>≥0.804 to &lt;1.098</td>
<td>≥1.098 to &lt;1.619</td>
<td>≥1.619</td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>23/61</td>
<td>27/57</td>
<td>31/53</td>
<td>37/47</td>
<td></td>
</tr>
<tr>
<td>Univariate 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.25 (0.64–2.43)</td>
<td>1.55 (0.80–2.98)</td>
<td>2.08 (1.09–3.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.26 (0.62–2.56)</td>
<td>1.52 (0.75–3.08)</td>
<td>2.22 (1.13–4.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.15 (0.53–2.31)</td>
<td>1.47 (0.71–3.04)</td>
<td>2.03 (1.04–4.08)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.20 (0.58–2.49)</td>
<td>1.52 (0.74–3.15)</td>
<td>2.06 (1.02–4.15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin, range, µU/mL</td>
<td>&lt;2.95</td>
<td>≥2.95 to &lt;4.55</td>
<td>≥4.55 to &lt;7.55</td>
<td>≥7.55</td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>22/62</td>
<td>27/57</td>
<td>26/58</td>
<td>43/41</td>
<td></td>
</tr>
<tr>
<td>Univariate 1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.33 (0.68–2.60)</td>
<td>1.26 (0.64–2.47)</td>
<td>2.95 (1.54–5.64)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.44 (0.69–2.98)</td>
<td>1.50 (0.73–3.10)</td>
<td>3.45 (1.73–6.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HOMA-IR&lt;sup&gt;f&lt;/sup&gt;, range</td>
<td>&lt;0.66</td>
<td>≥0.66 to &lt;1.06</td>
<td>≥1.06 to &lt;1.74</td>
<td>≥1.74</td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
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<td>42/42</td>
<td></td>
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<tr>
<td>Univariate 1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.21 (0.62–2.35)</td>
<td>1.23 (0.63–2.40)</td>
<td>2.65 (1.39–5.04)</td>
<td>&lt;0.01</td>
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<tr>
<td>Model 1&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.00 (reference)</td>
<td>1.47 (0.71–3.04)</td>
<td>1.60 (0.77–3.31)</td>
<td>3.19 (1.60–6.35)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age, current smoking (yes or no), alcohol consumption (yes or no), family history of CRC (yes or no), and BMI (quartiles).
<sup>b</sup>Further adjusted for HOMA-IR (quartiles).
<sup>c</sup>Further adjusted for insulin (quartiles).
<sup>d</sup>HOMA-IR = FPI (µU/mL) × FPG (mg/dL)/405.
Beside this indirect effect, IL-6 may have a direct carcinogenic effect on the large intestine. In fact, IL-6 is a potent stimulator of colon cancer cell proliferation and tumor growth (23). In Apcmin mice, which develop intestinal tumors, IL-6 has been shown to stimulate the proliferation of premalignant enterocytes (7). Thus, high levels of IL-6 appear to have a direct role in promoting the development of colorectal adenoma. In the present individuals with colorectal adenoma, the association with IL-6 was independent of HOMA-IR or insulin. Therefore, our data suggest that IL-6 may exert its carcinogenic effect, at least partly, through mechanisms other than an indirect one via insulin resistance. However, simultaneous measurement of HOMA-IR, insulin, and IL-6 is probably associated with some degree of variation, and residual confounding factors would be large even after statistical adjustment for such variations. Further studies will be needed to clarify the mechanism whereby IL-6 is associated with the development of colorectal adenoma.

A recent study of a large population has confirmed that the level of IL-6 increases with age (24). Smoking may also have an association with increased levels of IL-6 (25). Our results in both the colorectal adenoma group and the controls support these previous findings. Older age and smoking are known to be risk factors for colorectal adenoma (26, 27), although no significant intergroup differences in median age or the proportion of current smokers were evident in our study population. Therefore, in the present study, age and smoking did not appear to be major potential confounding factors affecting the level of IL-6 and the presence of colorectal adenoma.

Our study had several strengths. First, all of the subjects who underwent total colonoscopy and colorectal adenomas were carefully evaluated using noninvasive chromendoscopy. This probably minimized any likelihood of misclassification between the colorectal adenoma group and the control group. Second, none of the subjects had any missing values for the serum IL-6 level, thus allowing detailed statistical analyses.

A major limitation of this study was its cross-sectional and observational nature, making it difficult to establish causal relationships. However, colorectal adenomas themselves are unlikely to affect the circulating levels of IL-6. Furthermore, measurement of the serum IL-6 level at a single time point made it unclear whether a continuous increase in the level of IL-6 affected the development of colorectal adenoma. Therefore, to confirm whether the long-term role of IL-6 in the development of colorectal adenoma is one of chronic low-grade inflammation, a prospective study will be needed. In addition, because the number of female individuals with colorectal adenoma in the baseline subjects was too small to allow detailed analysis, we conducted this study only in men. Therefore, it is uncertain whether our present findings would also be representative of females with colorectal adenoma. As estrogen is a well-known inhibitor of IL-6 secretion (28), investigation of this issue in women may need to take menstrual status into account. Finally, this study was limited with regard to case ascertainment with no histologic confirmation of adenoma. Further studies based on histologic diagnosis will thus be needed.

In conclusion, our study has indicated that an increased level of serum IL-6 is associated with the presence of colorectal adenoma in men, independently of insulin resistance and hyperinsulinemia. To our knowledge, this is the first study to have examined the association of IL-6 with insulin resistance and the presence of colorectal adenoma. Our findings suggest that IL-6 may be involved in the development of colorectal adenoma via a pathway different from that associated with insulin resistance and that low-grade systemic inflammation may play an active role in the etiology of colorectal adenoma.

### Table 4. Association of IL-6 with the presence of colorectal adenoma according to value of HOMA-IR

<table>
<thead>
<tr>
<th>Quartile of IL-6, pg/mL</th>
<th>HOMA-IRa</th>
<th>Univariate</th>
<th>Multivariate-adjustedb</th>
<th>P trendc</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.004 (OR [95% CI])</td>
<td>&gt;0.004 to &lt;1.096 (OR [95% CI])</td>
<td>&gt;1.096 to &lt;1.619 (OR [95% CI])</td>
<td>≥1.619 (OR [95% CI])</td>
<td></td>
</tr>
<tr>
<td>&lt;1.73 (cases/controls)</td>
<td>18/52</td>
<td>12/12</td>
<td>8/10</td>
<td>17/11</td>
</tr>
<tr>
<td>≥1.73 (cases/controls)</td>
<td>5/9</td>
<td>12/12</td>
<td>8/10</td>
<td>17/11</td>
</tr>
</tbody>
</table>

aHOMA-IR = FPI (µIU/mL) × FPG (mg/dL)/405.
bValues are P interaction instead of P trend-.
cAdjusted for age, current smoking (yes or no), alcohol consumption (yes or no), family history of CRC (yes or no), and BMI (quartiles).

dHOMA-IR = FPI (µIU/mL) × FPG (mg/dL)/405.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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