

## Glucose Intolerance, Plasma Insulin Levels, and Colon Adenomas in Japanese Men

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**Hyperinsulinemia may be related to colon carcinogenesis. Several studies have suggested that diabetes mellitus is related to increased risk of colon cancer. We examined cross-sectionally the relation of fasting plasma insulin levels and glucose tolerance status to colon adenomas. In a consecutive series of 951 men undergoing total colonoscopy for a health examination at the Japan Self Defense Forces Fukuoka Hospital from April 1998 to August 1999, we identified 233 cases of colon adenomas and 497 controls with normal colonoscopy. Glucose tolerance status was determined by a 75-g oral glucose tolerance test, and subjects were classified as normal, impaired glucose tolerance (IGT) or non-insulin dependent diabetes mellitus (NIDDM). Plasma insulin levels were measured after subjects had fasted overnight. Logistic regression analysis and analysis of covariance was used to control for age and obesity. While plasma insulin levels were unrelated to colon adenomas, NIDDM was associated with a significantly increased risk of colon adenomas. There was no association between IGT and colon adenomas. NIDDM was more strongly associated with proximal colon adenomas. The findings suggest that long-term hyperinsulinemic status associated with NIDDM may increase the risk of colon adenomas, and subsequently of colon cancer.**

Key words: Colon adenomas — Glucose tolerance — Plasma insulin — Japanese men — NIDDM

Hyperinsulinemia or insulin resistance is of interest in connection with colon carcinogenesis.<sup>1,2)</sup> Insulin is an important growth factor for colonic mucosa cells,<sup>3,4)</sup> and colon cancer tissue has insulin and insulin-like growth factor I receptors.<sup>5,6)</sup> Insulin was also shown to promote colon tumor and the growth of colonic aberrant crypt foci in rats.<sup>7,8)</sup> Several prospective and case-control studies have observed an increased risk of colon or colorectal cancer associated with diabetes mellitus,<sup>9–16)</sup> although such an association has not always been found.<sup>17)</sup> Further evidence for the role of hyperinsulinemia in colon carcinogenesis is derived from the consistent epidemiological findings that both physical inactivity and obesity are related to increased risk of colon cancer.<sup>2)</sup> Physical inactivity and obesity are strongly associated with hyperinsulinemia or insulin resistance.<sup>18,19)</sup> Few studies have directly addressed the relation between plasma insulin levels and colon cancer. A recent prospective study showed that plasma insulin levels at 2 h after glucose load were significantly positively associated with the risk of colorectal cancer.<sup>20)</sup>

Colorectal adenomas are a well-established precancerous lesion.<sup>21)</sup> Previously, non-insulin dependent diabetes mellitus (NIDDM) was shown to be associated with a

moderately increased risk of sigmoid colon adenomas.<sup>22)</sup> Several, but not all, studies have also found a positive association of physical inactivity and obesity with colon or colorectal adenomas.<sup>23–27)</sup> This paper investigated the relation of fasting plasma insulin levels and glucose intolerance as determined by a 75-g oral glucose tolerance test to the prevalence of colon adenomas.

### MATERIALS AND METHODS

**Subjects** Study subjects were men aged 30 years or older who received a voluntary health check-up or a preretirement health examination at the Self Defense Forces (SDF) Fukuoka Hospital from April 1998 to August 1999. In the consecutive series of 1365 men, 951 underwent total colonoscopy. Excluded were those with a prior history of colectomy ( $n=1$ ), gastrectomy ( $n=2$ ), or colorectal polypectomy ( $n=48$ ), those under dietary or drug treatment for diabetes mellitus ( $n=32$ ), and those whose glucose tolerance status was not determined ( $n=7$ ); four men had two conditions for exclusion. Of the remaining 866 men, 369 had at least one colorectal polyp, and 497 had normal colonoscopy. Numbers of men by histological diagnosis were: carcinoid 3, adenoma 253, hyperplastic polyp 37, lipoma 2, and inflammatory or normal tissue 74. Cases having rectal adenomas alone ( $n=20$ ) were excluded. The present analysis included 233 men with colon adenomas as cases and 497 men with normal colonoscopy as

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controls. The cases included 14 men having adenomas at the rectum. Numbers of cases with an adenoma of less than 5 mm, 5–9 mm, and 10 mm or greater in diameter were 153, 58, and 22, respectively.

**Health examination** Routine medical examinations were done during a 3-day (voluntary health check-up) or 5-day (preretirement health examination) admission, and included total colonoscopy and a 75-g oral glucose tolerance test. A 75-g oral glucose tolerance test was done after subjects had fasted overnight. Plasma glucose concentration was measured by the glucose oxidase method (Shinotest Co., Ltd., Tokyo). Fasting plasma insulin concentrations were measured by the enzyme immunoassay method at the hospital laboratory using a commercial kit (Dainabot Co., Ltd., Tokyo). Subjects were classified as normal, impaired glucose tolerance (IGT), or NIDDM in accordance with the World Health Organization criteria.<sup>28)</sup> Body weight and height were recorded, and body mass index ( $\text{kg}/\text{m}^2$ ) was used as a measure of obesity.

**Statistical analysis** Logistic regression analysis was done to examine the relation of plasma insulin levels and glucose tolerance status to colon adenomas, controlling for age and body mass index. Insulin levels were classified into four categories at the quartiles in the distribution of cases and controls combined. Indicator variables were created to represent the categories of insulin levels and glucose tolerance status. Continuous variables were used for age and body mass index. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) were

obtained from logistic regression coefficients and standard errors. Comparison of means was done by unpaired *t* test, and adjusted means were calculated by analysis of covariance. The distribution of plasma insulin concentrations was skewed to the right side, and natural logarithms of the values were used for the comparison of means. Presented means of plasma insulin levels were always geometric means. Two-sided *P* values less than 0.05 were regarded as statistically significant. All computations were done by using the Statistical Analysis System software available at Kyushu University Computer Center (SAS Institute, Inc., Cary, NC).

## RESULTS

Age ranges were 33–58 years in adenoma cases and 30–61 years in the controls; the mean age of adenoma cases (49.3 year) was significantly greater than that of the controls (48.1 year) ( $P=0.002$ ). Body mass index in the adenoma group did not materially differ from that of the control group (23.8 versus 23.5,  $P=0.25$ ).

An approximately 2-fold increase was observed in the prevalence odds of colon adenomas associated with NIDDM, but not with IGT, as compared with normal glucose tolerance (Table I). The ORs did not change at all after adjustment for body mass index. The prevalence odds of colon adenoma did not vary according to plasma insulin levels regardless of adjustment for body mass index (Table II).

Table I. Glucose Tolerance Status and Colon Adenomas

Glucose tolerance	No. of cases	No. of controls	Age-adjusted OR (95% CI)	Age- and BMI-adjusted OR (95% CI)
Normal	169	386	1.0	1.0
IGT	42	90	1.0 (0.7–1.5)	1.0 (0.6–1.5)
NIDDM	22	21	2.2 (1.2–4.2)	2.2 (1.1–4.0)

OR, odds ratio; CI, confidence interval; BMI, body mass index; IGT, impaired glucose tolerance; NIDDM, non-insulin dependent diabetes mellitus.

Table II. Fasting Plasma Insulin Levels and Colon Adenomas

Plasma insulin <sup>a)</sup> ( $\mu\text{U}/\text{ml}$ )	No. of cases	No. of controls	Age-adjusted OR (95% CI)	Age- and BMI-adjusted OR (95% CI)
0.2–3.0	57	129	1.0	1.0
3.1–4.5	54	126	1.0 (0.6–1.5)	0.9 (0.6–1.5)
4.6–6.5	61	120	1.2 (0.8–1.8)	1.1 (0.7–1.7)
6.6–35.8	61	122	1.2 (0.8–1.8)	1.1 (0.6–1.7)

OR, odds ratio; CI, confidence interval; BMI, body mass index.

a) Categorized at quartiles in the distribution of cases and controls combined.

Table III. Age-adjusted Geometric Means of Fasting Plasma Insulin Concentrations ( $\mu\text{U/ml}$ ) in Colon Adenoma Cases and Controls by Glucose Tolerance Status

Glucose tolerance	Adenoma cases	Controls
Normal	4.2 (3.8–4.5)	4.2 (3.9–4.4)
IGT	5.3 (4.4–6.5)	5.3 (4.6–6.1)
NIDDM	5.5 (4.2–7.3)	5.4 (4.0–7.1)

Values in parentheses are 95% confidence intervals. IGT, impaired glucose tolerance; NIDDM, non-insulin dependent diabetes mellitus.

Age-adjusted geometric means of plasma insulin levels were 4.5 (95% CI 4.1–4.8) in adenoma cases and 4.4 (95% CI 4.2–4.6) in the controls. While plasma insulin levels were progressively higher in the IGT and NIDDM groups compared with the group of normal glucose tolerance in both adenoma cases and controls, the means of insulin concentrations were almost equal among adenoma cases and the controls in each stratum of glucose tolerance status (Table III).

When the association with glucose tolerance status was examined for proximal and distal adenomas separately, a more pronounced increase in the OR associated with NIDDM was noted for proximal colon adenomas (Table IV). The prevalence odds of distal adenomas increased only modestly (statistically nonsignificantly), among those with NIDDM. Plasma insulin levels were unrelated to either proximal or distal adenomas, whether or not the size of adenoma was taken into account (data not shown).

## DISCUSSION

While fasting plasma insulin levels were virtually unrelated to colon adenomas, NIDDM was associated with an increased risk of colon adenomas. The finding adds to evidence that NIDDM is related to increased risk of colon cancer. The lack of a positive association between plasma insulin levels and colon adenomas does not necessarily rule out a role for insulin in colon tumorigenesis. The current levels of plasma insulin may not represent the long-

term insulin levels, which are probably more relevant to the development of colon adenomas and cancer. In this regard, the finding that IGT was not associated with colon adenomas is plausible, because those with IGT had probably experienced a shorter duration of hyperinsulinemic status than those with NIDDM.

The observed magnitude of an increased risk of adenomas associated with NIDDM is compatible with the risk of colon cancer among those with diabetes mellitus reported elsewhere. Relative risks of 1.3 to 1.4 were reported for colon or colorectal cancer in men with diabetes mellitus in several studies.<sup>9–13, 15</sup> A similar excess in the risk associated with diabetes mellitus was also noted in women,<sup>12, 14</sup> although the findings in women are less consistent.<sup>9–11, 13, 15</sup>

A unique finding in the present study is that NIDDM was more strongly associated with proximal colon adenomas than with distal adenomas. We have no plausible explanation for this finding. The site-specific association may be a chance finding due to the subgroup analysis. The 95% CIs for the ORs of distal and proximal adenomas in relation to NIDDM overlapped well. At least two studies have previously addressed the relation of diabetes mellitus to proximal and distal colon cancer separately. In a prospective study in Sweden,<sup>12</sup> a slightly greater relative risk was reported for cancer of the cecum and ascending colon in men and women with diabetes mellitus; the relative risk for cancer of the cecum and ascending colon was 1.55 (95% CI 1.40–1.72) while the relative risks for cancers of the other sites ranged from 1.26 to 1.30. Likewise, in the Nurses' Health Study,<sup>14</sup> the relative risks associated with diabetes mellitus were 1.64 (95% CI 1.04–2.60) for proximal colon cancer and 1.38 (95% CI 0.88–2.15) for distal colon cancer. In these studies as well, the 95% CIs of the site-specific relative risks overlapped. Further studies are needed to consolidate a stronger association between NIDDM and proximal colon adenomas. The nonsignificant, modest increase in the OR for distal colon adenomas associated with NIDDM was consistent with the finding on sigmoid colon adenomas in the previous study of men retiring from the SDF.<sup>22</sup> In that study, NIDDM was associated with a 1.4-fold increased risk.

Table IV. Glucose Tolerance and the Risk of Proximal and Distal Colon Adenomas

Site		Normal	IGT	NIDDM
Proximal adenomas	No.	83	21	14
	OR (95% CI) <sup>a)</sup>	1.0	0.9 (0.5–1.6)	2.7 (1.3–5.7)
Distal adenomas	No.	86	21	8
	OR (95% CI) <sup>a)</sup>	1.0	1.0 (0.6–1.8)	1.6 (0.7–3.7)

IGT, impaired glucose tolerance; NIDDM, non-insulin dependent diabetes mellitus; OR, odds ratio; CI, confidence interval.

a) Adjusted for age and body mass index.

Strengths in the present study are that the study subjects underwent total colonoscopy regardless of glucose tolerance status and that diabetes mellitus was diagnosed on the basis of the standard test. Differential ascertainment or medical surveillance in association with either diabetes mellitus or colon adenomas results in a spurious, positive association between the two disease conditions. There are several weaknesses to be discussed. In the present study, only age and body mass index were taken into consideration. Information was not available regarding other factors such as physical activity, smoking, and alcohol use. Physical inactivity is a known risk factor for NIDDM,<sup>18,19)</sup> and many studies have observed a protective association between physical activity and colon adenomas.<sup>23,27)</sup> A weak, positive association between NIDDM and distal adenomas could be ascribed to physical inactivity. However, if physical inactivity is directly related to both NIDDM and colon adenomas, adjustment for physical inactivity may unmask the true association between NIDDM and colon adenomas. Cigarette smoking and alcohol use have been related to increased risk of colon adenomas,<sup>24,29,30)</sup> but it is uncertain whether these factors are associated with NIDDM. Diagnosis of NIDDM based on a single test necessarily suffers from misclassification, but undifferen-

tial misclassification does not erroneously cause a positive association. The study subjects were men in the SDF, and they probably differed from Japanese men in the general population in terms of factors related to NIDDM and colon adenomas. Thus, generalization of the present findings should be done with caution.

Finally, neither adenoma size nor multiplicity of adenomas was taken into account in the present study. Large adenomas (i.e., 10 mm or greater) and multiple adenomas are considered to have a greater potential for malignancy.<sup>21)</sup> In the present study, however, cases of such adenomas were very few. Studies on NIDDM and large or multiple colon adenomas would provide more direct evidence regarding the role of glucose intolerance in colon carcinogenesis.

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