

Association of Laboratory data on Lifestyle-related Factors with the Risk of Colorectal Adenoma and Cancer: A Retrospective Cohort Study with Long-term Follow-up Total Colonoscopy

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ABSTRACT

AIM: Lifestyle-related factors, in particular hyperglycemia, have been positively related to the risk of colorectal adenoma or cancer in most, but not all, studies.

METHODS: We conducted a retrospective cohort study using data from 611 individuals who had at least 10-year follow-up with total colonoscopy for colorectal adenoma or cancer. Blood glucose, cholesterol, triglycerides, and uric acid as "lifestyle-related factors" were measured in all patients at their first TCS.

RESULTS: By Kaplan-Meier analysis, comparing the cumulative incidence of colorectal adenoma or cancer, the rate in cases with a blood glucose level of 110 mg/dL or more was significantly higher than in cases with less than 110 mg/dL ($p=0.013$ by the log-rank test, glucose < 110 vs. glucose 110-125, $p=0.014$, glucose < 110 vs. glucose ≥ 126). Cox's proportional hazards model showed that a high level of blood glucose (110 mg/dL or more) was more strongly associated with an increased risk of adenoma or cancer relative to that in cases with a level of less than 110 mg/dL [hazard ratio (HR), 1.65; 95% CI, 1.33-1.94]. There was no significant difference in the cumulative incidence of adenoma or cancer according to the levels of cholesterol, triglycerides, or uric acid. Moreover, this relationship was also found in patients of older age (>50 years) and in the adenoma and cancer groups (HR, 1.4, 95% CI, 1.09-1.71; HR, 1.3, 95% CI, 0.98-1.63).

CONCLUSION: Our results suggest that hyperglycemia increases the risk of colorectal adenoma or cancer in Japanese adults as determined by long-term follow-up with total colonoscopy.

Key words: Colorectal adenoma; Colorectal cancer; Lifestyle; Hyperglycemia; Risk factor

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INTRODUCTION

Colorectal cancer (CRC) is a common and possibly fatal disease in many countries, including Japan. Most colorectal cancers develop from precancerous adenomatous polyps. Only a fraction of polyps become cancerous lesions and the progression from adenoma to carcinoma is believed to take at least ten years^[1]. The slow transition from polyps to colorectal cancer in most patients allows us to prevent cancer by removing adenomatous polyps. An understanding of the growth process and risk factors of adenomatous polyps is important for preventing colorectal cancer by interventions at an appropriate time.

The results of epidemiological studies have shown that lifestyle factors, such as high-fat diet, alcohol, physical inactivity, and obesity, are associated with an increased risk of CRC^[2,3]. Because all these risk factors are related to glucose metabolism, it is suggested that colorectal cancer development is mediated through chronic hyperinsulinemia and hyperglycemia^[4]. Many studies have suggested that diabetes mellitus is associated with an elevated risk of CRC^[5-7]. Hyperglycemia is also correlated with a high risk of colorectal adenoma^[8,9]. However, whether lifestyle-related factors other than a hyperglycemic state constitute risk for developing adenomatous polyps is still unclear.

Although many studies have reported that the risk of colorectal adenoma or cancer is positively related to the levels of serum lipids and plasma glucose^[10,11], the relationship of the risk of CRC with these two factors has not been investigated by long-term follow-up total colonoscopy (TCS). In the present study, we examined the cumulative incidence of colorectal adenoma and cancer in 611 patients who had been followed-up using TCS for at least 10 years. In addition, we investigated the relationship between the incidence of colorectal adenoma or cancer and lifestyle-related factors, in particular, blood or serum levels of glucose and lipids.

MATERIALS AND METHODS

Study population and procedures

The subjects were 651 patients who underwent initial TCS between February 1985 and August 2002 at the Japan Self-Defense Forces Central Hospital, and could be followed-up for at least 10 years after the initial of TCS. Patients had undergone the follow-up TCS two or more times at more than 1-year intervals by September 2012. The standard bowel preparation was done with 2- or 3-liter oral lavage fluid of polyethylene glycol electrolyte sodium. We excluded 40 subjects in whom the initial TCS revealed carcinoid tumors, inflammatory bowel disease, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer syndrome, or advanced colorectal cancer (Figure 1). We defined the advanced colorectal cancer as a cancer lesion penetrating beyond the lamina propria mucosae.

Adenoma or cancer of 5 mm or more in diameter was indicated by follow-up TCS and histologically diagnosed, and this time was regarded as a censoring point.

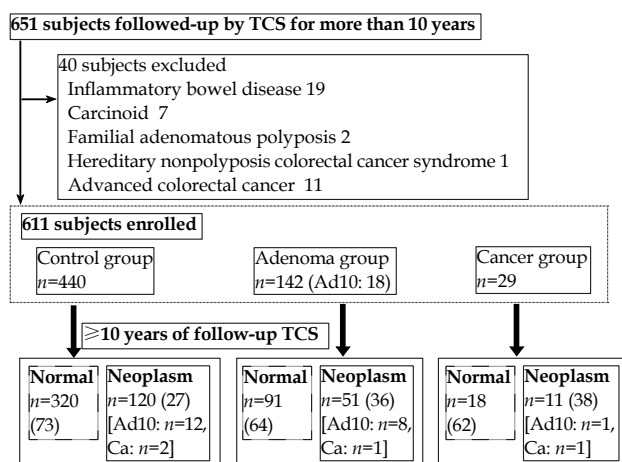


Figure 1 Flow of Subjects in study cohort. () : %; Ad10: The size of adenoma is equal to or larger than 10 mm in diameter; Ca: Carcinoma; Neoplasm: adenoma or cancer; Cancer group: the depth of cancer invasion limited to within the the lamina propria mucosae.

Laboratory methods

Blood glucose, cholesterol, triglycerides (TG), and uric acid (UA) as “lifestyle-related factors” were measured in all patients at their first TCS. Blood samples were collected after 12 hours of fasting. Serum cholesterol, TG, and UA were measured by enzymatic methods (SHINO Company, Tokyo, Japan), and were measured directly using a Hitachi 7250 automatic chemistry analyzer. The blood level of glucose was also measured by Glucose Neo SHINO-test (mutarotase-glucose oxidase method) using the same autoanalyzer.

Statistical analysis

Fasting blood glucose levels were categorized as 109 or lower, 110 to 125, and 126 or more mg/dL (<6.9, 7.0-7.7, and >7.8 mmol/L). Cholesterol, TG, and uric UA were also classified into two or three categories using the tertiles in the distributions of subjects.

These continuous variables were compared using analysis of variance (ANOVA) with Tukey's test. Factors associated with colorectal adenoma or cancer occurrence were assessed using univariable and multivariable Cox proportional hazards analyses to calculate the hazard ratios (HR) and 95% confidence intervals (CI) for the occurrence of colorectal adenoma or cancer. The explanatory variables analyzed were baseline blood glucose, total cholesterol, TG,

and UA. Other explanatory variables included age, sex, the period of survey, the number of TCS procedures, and three groups at the initial TCS (e.g. control, adenoma, and carcinoma groups). Kaplan-Meier cumulative survival curves were used for graphical presentation of time to colorectal adenoma or cancer occurrence, and the log-rank test was used to assess differences between groups in colorectal adenoma or cancer occurrence.

All data analyses were performed using SPSS version 8.02 software (SPSS Inc., Chicago, IL, USA); a significance level of 0.05 was used for statistical inferences.

RESULTS

In this study, 611 patients who had undergone long-term follow-up using total colonoscopy (TCS) for at least 10 years were analyzed. One patient in the control group died of lung cancer at 16 years since the initial TCS, when he was 52 years old. Table 1 shows the base line clinical characteristics of the three groups (440 patients in the control group, 142 in the adenoma group, and 29 in the cancer group). There were no significant differences in sex, the period of survey, the level of blood glucose, cholesterol, TG, and UA among the three groups. The predominance of males in each group was attributable to the fact that the majority of patients at our hospital were soldiers. The median age in the control group was significantly younger than in adenoma and carcinoma groups ($p=0.002$, 0.001), but there was no difference between adenoma and carcinoma groups ($p=0.85$). The numbers of TCS procedures were significantly different in the ascending order of normal, adenoma, and cancer groups (control vs. adenoma, $p=0.001$; control vs. cancer, $p=0.0001$). The median size of adenoma in the adenoma group was 7 mm (interquartile range, 5-9), and 18 cases (13%) had adenoma of 10 mm or more in diameter. The median number of adenomas was 1 (interquartile range, 1-2). Forty-four (31%) were in the right colon (defined as cecum, ascending colon, and transverse colon), and 62 (51%) were in the left colon (defined as descending colon, sigmoid colon, and rectum). Twenty-six (18%) cases were multiple adenomas in both right and left colons. In the cancer group, all patients were defined as in the early stage of CRC and twenty-two (76%) cases were located in the left colon. Table 2 shows the median and interquartile range of blood glucose, cholesterol, TG, and UA. The level of blood glucose in the cancer group tended to be higher than in the control and adenoma groups, but the difference was not significant (control vs. adenoma, $p=0.656$; control vs. cancer, $p=0.053$). There was no significant difference in the levels of cholesterol, TG, and UA among the three groups.

At the long-term follow-up by TCS, the cumulative incidence of adenoma or cancer occurred in 120 cases (27%) in the control group, 51 cases (36%) in the adenoma group, and 11 cases (38%)

Table 1 Clinical characteristics of the 611 study subjects.

	Control group (n=440)	Adenoma group (n=142)	Cancer group (n=29)
Age, years ¹	45 (41-52)	50 (43-55) ³	48 (41-52) ⁴
Male sex ²	413 [94]	135 [95]	27 [94]
Survey period ¹	12.7 (10.8-14.1)	11.9 (10.4-13.9)	11.3 (10.3-13.1)
Number of TCS ¹	4 (3-6)	6 (4-7) ³	6 (4-8) ⁴
Adenoma/carcinoma			
Size (mm) ¹		7 (5-9)	12 (8-17)
Number ¹		1 (1-2)	
Location (n/%)			
C/A/T		7/19/18	2000/4/3
D/S/R		11/45/16	2006/10/6
Both		26	

¹ Median (interquartile range); ² n [%]; ³ p -value<0.001 vs. control; ⁴ p -value<0.0001 vs. control; C: Cecum; A: Ascending colon; T: Transverse colon; D: Descending colon; S: Sigmoid colon; R: Rectum.

Table 2 Laboratory data of the 611 study subjects.

	Control group (n=440)	Adenoma group (n=142)	Cancer group (n=29)	P Value*
Glucose (mg/dL) ¹	101 (94-108)	100 (93-110)	101 (94-108)	0.053
<109	334 [76]	109 [76]	16 [55]	
110-125	70 [16]	22 [16]	9 [31]	
>126	36 [8]	11 [8]	4 [14]	
Cholesterol (mg/dL) ¹	200 (176-221)	202 (178-223)	200 (176-221)	0.967
<209	323 [73]	104[73]	21 [73]	
210-240	82 [19]	27 [19]	5 [17]	
>241	35 [8]	11 [8]	3 [10]	
TG (mg/dL) ¹	110 (81-168)	121 (88-175)	110 (81-168)	0.769
<149	293 [66]	92 [65]	19 [66]	
150-200	73 [17]	26 [18]	5 [17]	
>201	74 [17]	24 [17]	5 [17]	
Uric acid (mg/dL) ¹	5.8 (5.1-6.6)	5.7 (4.8-6.7)	5.8 (4.8-6.3)	0.671
<6.9	363 [83]	115 [81]	25 [86]	
>7.0	77 [17]	27 [19]	4 [14]	

¹ Median (interquartile range), n[%].

in the cancer group (Figure 1). Cancer was histologically detected in two cases in the control group and in one case each in adenoma and cancer groups. Figure 2 shows Kaplan-Meier curves of the cumulative incidence rate of adenoma or cancer among control, adenoma, and cancer groups. Although the cumulative incidence rate of adenoma or cancer in the adenoma and cancer groups was higher in the observation period of more than 10 years than in the normal group, there was no significant difference among the three groups (control vs. adenoma, $p=0.064$; control vs. cancer, $p=0.121$). Comparing the cumulative incidence of colorectal adenoma or cancer, the rate in cases with a blood glucose level of 110 mg/dL or more was significantly higher than in cases with less than 110 mg/dL ($p=0.013$, glucose<109 vs. glucose 110-125, $p=0.014$, glucose<109 vs. glucose >126) (Figure 3). However, there was no significant difference in the cumulative incidence of adenoma or cancer according to the levels of cholesterol, TG, and UA.

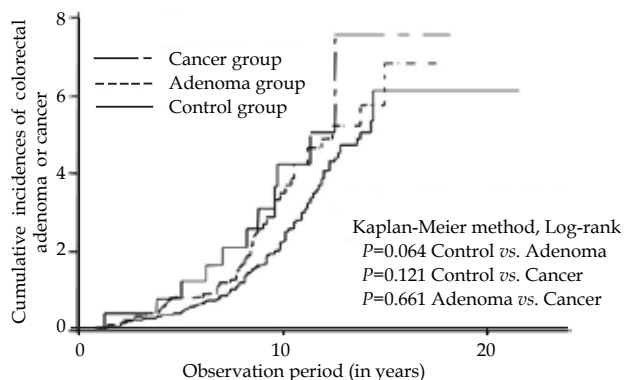


Figure 2 Cumulative incidences of colorectal adenoma or cancer during more than 10 years of follow-up TCS among three groups (control, adenoma, and cancer group) at the initial TCS.

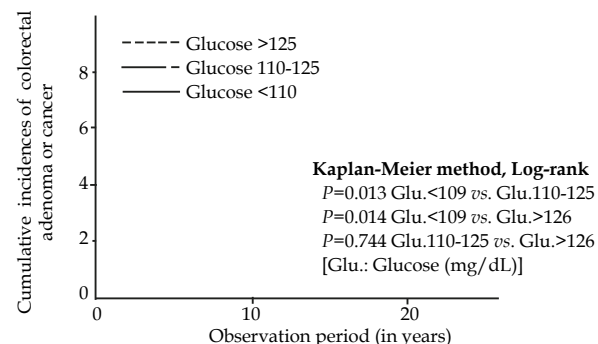


Figure 3 Cumulative incidences of colorectal adenoma or cancer during more than 10 years of follow-up TCS among subjects with different blood glucose levels at the initial TCS.

Using a univariable Cox proportional hazards model to adjust for 7 of the clinical characteristics, age, blood glucose, and adenoma group were associated with the rate of incidence of adenoma or cancer (Table 3). Serum cholesterol, TG, and UA levels were not associated with the risk of adenoma or cancer. The multivariable-adjusted model is presented in table 4. A high level of blood glucose (110 or more) and old age (>50) were significantly associated with an increased risk of adenoma or cancer (HR, 1.635; 95% CI, 1.327-1.943; 1.398, 95% CI, 1.090-1.706). Baseline presence of adenoma or cancer also had a tendency to be associated to later new incidence of adenoma or cancer (HR, 1.301, 95% CI, 0.976-1.626).

Table 3 Factors associated according to the incidence of colorectal adenoma or cancer (using a univariable Cox's proportional hazards analyses).

Risk factor	Hazard ratio	95% CI	P value
Age	1.693	1.675-1.711	<0.001
Sex	0.359	-0.531-1.249	0.024
Glucose (mg/dL)	1.013	1.007-1.019	<0.001
Cholesterol (mg/dL)	0.997	0.993-1.001	0.108
Triglyceride (mg/dL)	1.001	0.999-1.003	0.276
Uric acid (mg/dL)	0.827	0.774-0.879	0.994
Adenoma ¹	1.693	1.366-2.020	0.002
Carcinoma ¹	1.663	1.046-2.280	0.107

¹ At the initial TCS, adenoma or cancer was detected.

Table 4 Factors associated according to the incidence of colorectal adenoma or cancer (using a multivariable Cox's proportional hazards analyses).

Risk factor	Hazard ratio	95% CI	P value
Age (>50, <50)	1.398	1.090-1.706	0.033
Glucose (>110, <110 mg/dL)	1.635	1.327-1.943	0.002
Neoplasm ¹ vs. normal	1.301	0.976-1.626	0.113

¹ Neoplasm: adenoma or cancer.

DISCUSSION

There were several important findings in this study. Firstly, the cumulative occurrence rate of adenoma or cancer (almost always adenoma) in adenoma and cancer group was higher than in the control group by long-term TCS although it did not reach a statistically significant level. Many reports have stated that the incidence of adenoma or cancer is higher in cases with presence of adenoma or cancer at baseline than that in cases without these lesions^[12]. However, in these previous studies patients were observed by sigmoidoscopy at baseline and followed-up later with TCS, and the follow-up period was less than 3-5 years. It is well known that patients with adenoma tend to have multiple adenomas. In these patients, adenomas present even at baseline can be overlooked and found on a repeat TCS carried out later^[13]. Thus, these overlooked adenomas can be considered as a new development. Moreover, we suggest that it takes approximately 10 years for a small adenoma to develop into advanced adenoma (10 mm or more in diameter and/or high grade dysplasia). Therefore, we think that a long-term follow-up with TCS, i.e., more than 10 years, is necessary to determine the real longitudinal course of adenoma. In addition, colorectal adenomas are common and occur in 30 to 50 percent of adults; in this study, the incidences of colorectal adenomas in the 3 groups were the same after more than 10 years of follow-up TCS. However, the result of Cox's proportional hazards model suggest that baseline presence of cancer or adenoma slightly increases the later development of adenoma or cancer.

Secondly, the cumulative incidence rate of adenoma or cancer in patients with a high level of blood glucose (>110 mg/dL) was significantly higher than those in the normal range (<110 mg/dL). However, the occurrence rates were not significantly different between cases with the levels of blood glucose of 110-125 mg/dL

and cases >126 mg/dL. Moreover, in multivariable proportional hazards analyses, a higher level of blood glucose (110 or more) was associated with an increased risk of adenoma. From these results, we believe that cases with a high level of blood glucose were more likely to develop adenoma or cancer than those within the normal range.

Obesity and hyperglycemia were shown to be positively related to an increased risk of colorectal adenoma, which is an important precursor of CRC^[8,14]. Unfortunately, these relationships were revealed by epidemiological studies, and there have been a few studies by short-term follow-up and only with sigmoidoscopy^[15,16]. TCS is the best way to evaluate colorectal adenoma or cancer because the physician can visualize the entire lining of the colon and remove any polyps that are found. The protective effect of TCS against colorectal adenoma or cancer is recognized to be derived from its capacity to identify all adenomatous polyps, regardless of size, and to enable their removal^[17]. We are confident that the relationship of hyperglycemia and a high incidence of adenoma or cancer became clear for the first time in the present hospital-based retrospective cohort study of a more than 10-year follow-up TCS.

In vitro studies have shown that insulin and glucose stimulate the growth of colonic mucosal cells and colonic tumor cells^[18-20] and suggest that hyperinsulinemia and hyperglycemia contribute to the growth of adenomatous cells and colonic cancer cells in humans. The risk of CRC among diabetics was found to be approximately 30 percent higher than in nondiabetics^[21-23]. Diabetes mellitus is a serious and costly disease that is becoming increasingly common in many western countries, including Japan; developing countries have lower rates (<1/10), particularly Africa and Asia. We suggest that patients with hyperglycemia receive regular screening for colon cancer with intervals shorter than those with no hyperglycemia.

In this study, we first hypothesized that biological processes involving glucose, triglycerides, cholesterol, and UA were risk factors of colon adenoma or cancer, but we could not find association with those factors except blood glucose. Many studies have shown either positive or negative associations between serum lipids and colorectal adenomas^[8,24,25]. From our findings, the relationship between serum TG and cholesterol levels and the risk of adenoma or cancer was not significant although subjects were mainly aged in their 40s to 50s. Hyperlipidemia is caused by the secondary results from metabolic or nutritional changes, and the influence of colorectal adenoma or cancer on hyperlipidemia appears after 60 years of age. Further study including on a large cohort of adenoma or cancer cases is needed to clarify the associations between serum lipid levels and risk of adenoma or cancer.

Our study has several limitations that sample size was small, study subjects were mainly male and middle-aged, and serum chemistry was examined at the initial TCS. However, advantages are the long follow-up period as long as more than 10 years, times of TCS more than 2 times, and subjects had been asymptomatic during follow-up periods meaning that we could observe colonic lesions at early stages. The population, aged 40 to 50 years, are an important group, because their incidence of colorectal adenoma or cancer and lifestyle-related factors including diabetes mellitus begins to increase in each subsequent decade. This study was performed as a retrospective cohort study, and we could not obtain other information besides blood glucose, lipids, and UA. Therefore, we could not assess other risk factors related to a subject's lifestyle, such as obesity, physical activity, alcohol consumption, and smoking status, which may be related to the development of colorectal adenoma and carcinoma in our patients. In the past study of Japanese soldiers the mean

body mass index (\pm standard deviation) was 23.80 (\pm 2.56), and their participating in recreational exercise twice per week or more accounted for 59%^[26]. We consider subjects in the present study to have the same tendency as those in the past study, and our subjects were estimated as a group who was of normal body mass index and exercises regularly.

In conclusion, irrespective of the baseline presence of colorectal adenoma or cancer, hyperglycemia as a lifestyle-related factor was significantly associated with the increased risk of colorectal adenoma or cancer. This finding provides a strong support to the role of hyperglycemia in the pathogenesis of colorectal adenoma or cancer.

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