Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma \textit{in situ}

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Background No one has previously examined the relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma \textit{in situ}.

Methods A case-control study was performed with 129 cases of colorectal carcinoma \textit{in situ} and 258 matched controls among examinees undergoing a health check-up in Tokyo from January 1991 to March 1993.

Results There was a significant, positive association between serum total cholesterol levels and the risk of colorectal carcinoma \textit{in situ} after adjustment for age, sex, body mass index, smoking status and alcohol consumption. Serum triglyceride levels were significantly and positively associated with colorectal carcinoma \textit{in situ} risk regardless of adjustment for the above covariates. Although there was no clear relation between colorectal carcinoma \textit{in situ} and fasting plasma glucose levels, a modest increase of colorectal carcinoma \textit{in situ} risk was observed in the highest category (>116 mg/dl) of fasting plasma glucose levels.

Conclusions The findings suggest a positive association between serum total cholesterol levels and the risk of colorectal cancer, rather than an inverse relation. The strong association with serum triglyceride levels and the weak association with fasting plasma glucose levels support the hypothesis that hyperinsulinaemia may play an important role in colorectal carcinogenesis.

Keywords Colorectal cancer, carcinoma \textit{in situ}, serum triglycerides, serum total cholesterol, fasting plasma glucose, hyperinsulinaemia

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There has long been a dispute whether low serum total cholesterol levels are related to colorectal cancer risk. According to a meta-analysis of 21 prospective studies, an inverse association between serum total cholesterol levels and colon cancer risk was restricted to the early years of follow-up.\textsuperscript{1} The observation has generally been regarded as indicating that cancer causes a decrease in serum total cholesterol levels. However, a prospective study found a positive association between serum total cholesterol levels and rectal cancer risk,\textsuperscript{2} and several other studies reported that the association between low serum total cholesterol levels and the colorectal cancer risk was observed more than 5 years before the diagnosis.\textsuperscript{3-5} Regarding colorectal adenomas, a well-established precursor of colorectal cancer,\textsuperscript{6} some studies found a weak positive association with serum total cholesterol levels,\textsuperscript{7,8} whereas others showed no measurable association.\textsuperscript{9-11}

On the other hand, McKeown-Eyssen has recently suggested that elevated levels of serum triglycerides and/or plasma glucose may be directly involved with colorectal cancer.\textsuperscript{12} This hypothesis is derived from the observation that factors associated positively with colorectal cancer, such as Western dietary patterns, alcohol use and obesity, are also positively associated with serum triglycerides and plasma glucose, while factors associated with reduced risk of colorectal cancer, such as fruits and vegetables, fish oil consumption, and exercise, are associated with lower levels of serum triglycerides and plasma glucose.\textsuperscript{12} Hyperinsulinaemia may underlie the association of serum triglycerides and/or plasma glucose.\textsuperscript{12,13} However, few studies have directly addressed the relation of colorectal cancer or adenoma risk to serum triglyceride and/or plasma glucose levels. An increased risk of colorectal adenomas was found among men with the highest level of serum triglycerides in a Japanese study,\textsuperscript{10} but the finding was not corroborated in an extended study.\textsuperscript{11} Two prospective studies suggested no or, if any, a weak.

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positive association between post-load plasma glucose and colorectal cancer.

To our knowledge, no studies have previously investigated the relation of serum lipids or plasma glucose to colorectal carcinoma in situ, which is a transitional process in the adenoma-carcinoma sequence. Investigating patients with colorectal carcinoma in situ, the current study addressed the relation of serum total cholesterol, serum triglyceride, and fasting plasma glucose levels to very early colorectal cancer.

Materials and Methods

The source population consisted of examinees in the multi-phasic health check-up programme of the PL (Perfect Liberty) Health Care Center in Tokyo, Japan during the period from January 1991 to March 1993. In all, 83,272 men and women received the medical examination including blood biochemistry and faecal occult blood test as routine procedures; about 60% of them were employees of certain companies located in Tokyo and adjacent areas, and the remaining 40% were volunteer participants.

The case subjects were a total of 129 cases, 108 men and 21 women, who were newly found to have histologically confirmed colorectal carcinoma in situ with no history of inflammatory bowel disease. Ages ranged from 34 to 73 years with a mean of 54.6. Colorectal carcinoma in situ is a cancerous lesion which does not penetrate beyond the muscularis mucosae as defined by the World Health Organization and American Joint Committee. After the health check-up, individuals with a suspicion of colorectal cancer due to a positive faecal occult blood test or other reasons were referred to university and other hospitals for a comprehensive study of the large bowel. Colonscopy and/or surgery reports along with pathology reports were returned to the Center.

Two controls were selected randomly from the computer file of the examinees for each case, matching for sex, age (exact year), date of examination (within one month), and history of prior health check-up at the Center (0 or >1). In all, 258 controls were selected for the study. Control subjects were selected among those who had neither a history of colorectal cancer nor inflammatory bowel disease and who had not been diagnosed as having colorectal carcinoma in situ or cancer. Control subjects did not necessarily undergo colonoscopy or barium enema unless they showed any sign or symptom suggestive of colorectal cancer. Controls were not excluded for the reason of prevalent colorectal adenomas because information on colorectal adenomas was not available.

Blood samples were collected after an overnight fast without taking any kind of drug at the time of health check-up examination. Serum triglyceride (mg/dl), serum total cholesterol (mg/dl) and plasma glucose (mg/dl) levels were determined enzymatically using commercially available kits. Adjusted mean levels and their difference between in situ cases and controls of the three biochemical variables were calculated by the analysis of covariance. Covariates included in the model were sex, age (year), and body mass index (BMI) (classified into quartiles <21.5, 21.6-23.4, 23.5-25.1, 25.2+ kg/m²), cigarette smoking (non-smokers, 1-15, 16-30, 31+ cigarettes/day), and alcohol consumption (non-drinkers, 1-20, 21-40, 41+ g/day). Indicator variables were used for the categories of BMI, cigarette smoking and alcohol consumption. Logistic regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence interval (CI) for categories of serum total cholesterol, serum triglycerides, and fasting plasma glucose. Trend of the association was assessed by a logistic regression model, assigning the mean of each category group as a representative value. A P-value (two-sided) <0.05 was considered as statistically significant. All statistical computations were done by the SPSS statistical software version 6.0 (SPSS Inc., Chicago).

Results

Table 1 shows the mean levels of the three biochemical variables in colorectal carcinoma in situ cases and controls. Serum triglyceride levels were significantly higher in cases than in controls. Serum total cholesterol levels were also higher among cases, but the difference failed to reach the statistical significance. There was no material difference in fasting plasma glucose levels between cases and controls.

In Table 2, adjustment was made for BMI, smoking status and alcohol consumption as well as sex and age. Serum total cholesterol levels were significantly higher among cases than controls after the adjustment, whereas the difference in fasting plasma glucose levels did not change. The difference in serum triglyceride levels was slightly more pronounced.

Table 3 shows the relation of the three biochemical variables to the risk of carcinoma in situ in terms of crude and adjusted OR. Serum triglyceride levels were significantly and positively associated with increased risk of colorectal carcinoma in situ whether covariates were adjusted or not. After adjustment for sex, age, BMI, smoking status, and alcohol consumption, a significant and positive trend was observed for the risk of carcinoma in situ in relation to serum total cholesterol levels. A twofold increase was observed for the risk of colorectal carcinoma in situ in the highest category (≥116 mg/dl) of fasting plasma glucose levels, although the increase was not statistically significant and the trend was far from statistically significant.

When serum total cholesterol and triglycerides were mutually adjusted for, the association with triglycerides remained highly significant while that with total cholesterol was weakened.

Table 1: Mean levels of serum lipids and fasting plasma glucose among cases of colorectal carcinoma in situ and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 129)</th>
<th>Controls (n = 258)</th>
<th>Difference (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>202.6</td>
<td>195.6</td>
<td>7.0 (-0.6-14.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>148.7</td>
<td>108.7</td>
<td>40.0 (15.7-64.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>104.8</td>
<td>100.9</td>
<td>3.9 (-1.4-9.1)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Based on independent t-test.
Furthermore, the presence of colorectal adenomas was not colorectal cancer suggesting that the inverse association described in the study of the large bowel, and they may have had undiagnosed colorectal carcinoma in situ: adjusted OR for the highest versus lowest category was 2.1 (95% CI: 1.1-4.0).

However, it is unconceivable that faecal occult blood positivity are not solely attributable to cigarette smoking alone actually resulted in a significant association. But a positive association between serum total diacolesterol and colorectal adenoma occurrence was detected primarily on the basis of the faecal occult blood test. As reported elsewhere, the present study. Cases of colorectal carcinoma in situ were day and the serum total cholesterol levels was -0.18 (P = 0.0005), and was noted between the risk of carcinoma in situ and serum total cholesterol; the Spearman's correlation coefficient between the number of cigarettes smoked per day and the serum total cholesterol levels was -0.18 (P = 0.0001). As reported elsewhere, cigarette smoking was positively associated with the risk of carcinoma in situ. Adjustment for cigarette smoking alone actually resulted in a significant association between serum total cholesterol levels and the risk of colorectal carcinoma in situ: adjusted OR for the highest versus lowest category was 2.1 (95% CI: 1.1-4.0).

In contrast to several previous studies, our findings support a positive association between serum total cholesterol and colorectal cancer suggesting that the inverse association described in the present study is cross-sectional, it is an advantage that we investigated patients with very early colorectal cancer. It is unlikely that carcinoma in situ alters the levels of serum lipids and fasting plasma glucose. The measured biochemical levels are thus considered to have reflected the levels prior to the occurrence of cancerous lesions. There are some weaknesses in the present study. Cases of colorectal carcinoma in situ were detected primarily on the basis of the faecal occult blood test while controls were selected regardless of results of this test. However, it is unconceivable that faecal occult blood positivity is linked with either serum lipids levels or plasma glucose concentrations. Control subjects did not necessarily undergo a study of the large bowel, and they may have had undiagnosed colorectal carcinoma in situ or early stage cancer, but this type of misclassification would only attenuate the true association. Furthermore, the presence of colorectal adenomas was not taken into consideration in selecting controls, but because cases were not excluded for having colorectal adenomas, the comparability between cases and controls was preserved. We cannot rule out the possibility that the observed association may have been ascribed to common factors linked with both the disease and biochemical variables.

Adjusted OR for the highest versus lowest level of serum triglycerides was 2.6 (95% CI: 1.2-5.8, trend P = 0.005), and the corresponding value for serum total cholesterol was 1.7 (95% CI: 0.8-3.5, trend P = 0.18).

Discussion

This study first addressed the relation of serum lipids and plasma glucose to colorectal carcinoma in situ. Although the present study is cross-sectional, it is an advantage that we investigated patients with very early colorectal cancer. It is unlikely that carcinoma in situ alters the levels of serum lipids and fasting plasma glucose. The measured biochemical levels are thus considered to have reflected the levels prior to the occurrence of cancerous lesions. There are some weaknesses in the present study. Cases of colorectal carcinoma in situ were detected primarily on the basis of the faecal occult blood test while controls were selected regardless of results of this test. However, it is unconceivable that faecal occult blood positivity is linked with either serum lipids levels or plasma glucose concentrations. Control subjects did not necessarily undergo a study of the large bowel, and they may have had undiagnosed colorectal carcinoma in situ or early stage cancer, but this type of misclassification would only attenuate the true association. Furthermore, the presence of colorectal adenomas was not taken into consideration in selecting controls, but because cases were not excluded for having colorectal adenomas, the comparability between cases and controls was preserved. We cannot rule out the possibility that the observed association may have been ascribed to common factors linked with both the disease and biochemical variables.

There was no clear relation between serum total cholesterol and carcinoma in situ in terms of either crude mean or crude OR. However, after adjustment for sex, age, BMI, smoking status, and alcohol consumption, a significant and positive association was noted between the risk of carcinoma in situ and serum total cholesterol levels. This change was largely ascribed to cigarette smoking. In the present data, cigarette smoking was associated with the risk of carcinoma in situ. Adjusted OR for the highest versus lowest level of serum triglycerides was 2.6 (95% CI: 1.2-5.8, trend P = 0.005), and the corresponding value for serum total cholesterol was 1.7 (95% CI: 0.8-3.5, trend P = 0.18).

Table 2 Adjusted mean levels of serum lipids and fasting plasma glucose among colorectal carcinoma in situ cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Controls</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>204.2</td>
<td>194.1</td>
<td>10.1 (2.8-17.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>149.8</td>
<td>107.6</td>
<td>42.2 (21.7-62.8)</td>
<td>0.00006</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>104.7</td>
<td>100.9</td>
<td>3.8 (-0.8-8.3)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, body mass index as classified into the quartile category (<21.5, 21.6-23.4, 23.5-25.1, 25.2+ kg/m²), cigarette smoking (non-smokers, 1-15, 16-30, 31+ cigarettes/day), and alcohol consumption (non-drinkers, 1-20, 21-40, 41+ g/day).

Table 3 Numbers of cases and controls, odds ratio (OR), adjusted OR and 95% confidence interval (CI) of colorectal carcinoma in situ according to the levels of serum lipids and fasting plasma glucose

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>&lt;170</td>
<td>23</td>
<td>55</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>171-195</td>
<td>39</td>
<td>81</td>
<td>1.2 (0.6-2.1)</td>
<td>1.1 (0.6-2.1)</td>
</tr>
<tr>
<td></td>
<td>196-220</td>
<td>29</td>
<td>64</td>
<td>1.1 (0.6-2.1)</td>
<td>1.2 (0.6-2.5)</td>
</tr>
<tr>
<td></td>
<td>221+</td>
<td>38</td>
<td>58</td>
<td>1.6 (0.8-3.0)</td>
<td>2.0 (1.0-4.1)</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.17</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>&lt;70</td>
<td>23</td>
<td>67</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>71-110</td>
<td>39</td>
<td>92</td>
<td>1.2 (0.7-2.3)</td>
<td>1.1 (0.6-2.2)</td>
</tr>
<tr>
<td></td>
<td>111-150</td>
<td>28</td>
<td>61</td>
<td>1.3 (0.7-2.6)</td>
<td>1.3 (0.6-2.7)</td>
</tr>
<tr>
<td></td>
<td>151+</td>
<td>39</td>
<td>38</td>
<td>3.0 (1.6-5.7)</td>
<td>3.0 (1.4-6.4)</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.0003</td>
<td>P = 0.0008</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>&lt;95</td>
<td>52</td>
<td>103</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>96-105</td>
<td>43</td>
<td>95</td>
<td>0.9 (0.5-1.5)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td></td>
<td>106-115</td>
<td>14</td>
<td>38</td>
<td>0.7 (0.4-1.5)</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td></td>
<td>116+</td>
<td>20</td>
<td>22</td>
<td>1.8 (0.9-3.6)</td>
<td>2.0 (0.9-4.4)</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.12</td>
<td>P = 0.11</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, body mass index as classified into the quartile category (<21.5, 21.6-23.4, 23.5-25.1, 25.2+ kg/m²), cigarette smoking (non-smokers, 1-15, 16-30, 31+ cigarettes/day), and alcohol consumption (non-drinkers, 1-20, 21-40, 41+ g/day).
in these early studies is probably ascribed to the advanced cancer stage. The findings do not imply that elevated levels of serum total cholesterol lead to the occurrence of colorectal cancer. High intake of saturated fat or meat is known to increase serum total cholesterol levels.23,24 and these dietary factors are involved with colorectal cancer, possibly through increased hepatic secretion of bile acids.25-27

Serum triglycerides was most strongly related to increased risk of colorectal carcinoma in situ in the present study. Previous studies have only suggested a weak, positive association between serum triglycerides and colorectal polyps.10-12 The present finding is the first, direct evidence for the link between hypertriglyceridaemia and colorectal cancer. The observed association between serum triglycerides and colorectal carcinoma in situ may be ascribed to increased secretion of faecal bile acids associated with elevated levels of serum triglycerides.12 Yet hyperinsulinaemia or insulin resistance seems to be a more plausible mechanism underlying the association. Hyperinsulinaemia is proven to be closely related to hypertriglyceridaemia according to an animal experimental study28 and epidemiological studies.29,30 Obesity, physical activity, and low dietary polyunsaturated fat to saturated fat ratio are major determinants of insulin resistance and hyperinsulinaemia, and appear to be related to colon cancer risk.13,14 Insulin is an important growth factor for colonic mucosal cells and is a mitogen of colonic carcinoma cells in vitro.31-33

Hyperglycaemia is also a condition associated with hyperinsulinaemia or insulin resistance. The present study, however, did not find a strong, positive association between fasting plasma glucose and colorectal carcinoma in situ. A statistically non-significant, modest increase in the risk of colorectal carcinoma in situ was observed for the highest category of fasting plasma glucose levels. In the present study, the subjects who belonged to the remaining three categories had almost normal fasting plasma glucose levels according to the National Diabetes Data Group standard.34 In healthy individuals with normal glucose tolerance, fasting plasma glucose levels were found to be unrelated to either the degree of insulin resistance or plasma insulin response to 75 g oral glucose challenge.35,36 Thus, the lack of clear association between colorectal cancer and fasting plasma glucose levels is not surprising among subjects whose glucose tolerance is almost normal. The highest category of fasting plasma glucose levels (≥116 mg/dl) probably included many subjects with impaired glucose tolerance or non-insulin dependent diabetes mellitus, approximately 50-80%,37-39 among whom plasma insulin levels are relatively higher.40 Thus our findings are regarded as weak evidence for the hypothesis that hyperinsulinaemia increases colorectal cancer risk. Because hyperinsulinaemic status is determined by various factors such as insulin resistance, dietary habits, and postprandial β-cell response, fasting plasma glucose levels may be a crude measure which clarifies the relation between hyperinsulinaemia and colorectal cancer risk.

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References


