The Effect of Serum Carotenoids on Atrophic Gastritis Among the Inhabitants of a Rural Area in Hokkaido, Japan

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Abstract

A total of 206 residents (76 males and 130 females) of a rural area of Hokkaido, Japan, attending a health check in August, 1997, were studied to assess the relationship between serum carotenoids and atrophic gastritis (AG). Of the participants, 91 had AG, as indicated by their serum levels of pepsinogen I and pepsinogen II. Logistic regression analysis, after adjusting for gender and age, revealed that the odds ratios for serum carotenoid levels were lower for subjects with high serum levels of \( \beta \)-carotene (odds ratio, 0.41; 95% C.I., 0.19–0.88) and \( \beta \)-cryptoxanthin (odds ratio, 0.41; 95% C.I., 0.18–0.91) than for those with low serum carotenoid levels. In addition, the odds ratios of subjects with high serum levels of \( \beta \)-cryptoxanthin (odds ratio, 0.60; 95% C.I., 0.28–1.31), provitamin A (odds ratio, 0.38; 95% C.I., 0.17–0.85), and retinol (odds ratio, 0.67; 95% C.I., 0.31–1.48) were found to be lower than the odds ratios for those with low serum levels. Odds ratios for subjects with high serum zeaxanthin/lutein levels were higher than odds ratios for those with low serum levels. These results suggest that frequent intake of foods rich in carotenoids with provitamin A activity may reduce the risk of AG.

Key words: helicobacter pylori, atrophic gastritis, green-yellow vegetables, \( \beta \)-carotene, provitamin A

Introduction

It was reported that an intestinal type of gastric cancer occurs in stomachs that exhibit chronic atrophic gastritis. Some studies have reported that Helicobacter pylori infection is a strong predictor for atrophic gastritis (AG), which is a precancerous condition associated with gastric cancer. There have also been studies, which suggested that Helicobacter pylori infection alone, was not directly associated with gastric cancer. Numerous epidemiological studies have shown that the intake of common Japanese salted foods such as Tsukemono is a significant risk factor for gastric cancer. It has also been shown that consumption of large quantities of vegetables and fruits is associated with reduced risk of gastric cancer. Some studies have reported that high serum \( \beta \)-carotene levels are a protective factor in gastric cancer incidence. Other studies suggested that vitamin A from any source inhibits the development of duodenal ulcers. A large number of potentially anti-carcinogenic substances are present in vegetables and fruits. Furthermore, it has been found that prolonged supplementation with \( \beta \)-carotene or \( \alpha \)-tocopherol acetate results in an approximately 50% decrease in ornithine decarboxylase activity in atrophic stomach mucosa.

The purpose of the present study was to determine whether serum carotenoid levels are a protective factor in AG incidence. Subjects were chosen from among the general population in Hokkaido, Japan.

Subjects and Methods

Subjects

A total of 206 subjects (76 males and 130 females) were recruited from among 986 residents of a rural area of Hokkaido, Japan, who attended a health check-up program in August, 1997. All subjects were over 39 years of age, and were gender- and age-matched. The subjects worked in either fishing, dairy farming or commerce, with roughly equal numbers from each of these fields.

Methods

Fasting serum samples were taken at the time of the health check, and the sera were separated from blood cells by centrifugation within one hour of sample collection. Biochemical analysis of the serum samples was performed using an autoanalyser (JCA-RX20, Nihon Denshi Co. Ltd.). Serum concentrations of \( \beta \)-carotene (BC), \( \alpha \)-carotene (AC), lycopene (LY), \( \beta \)-cryptoxanthin (CR), zeaxanthin/lutein (ZL), canthaxanthin (CX), retinol (RE), and \( \alpha \)-tocopherol (AT) were measured separately by high-performance liquid chromatography (HPLC), as reported previously. Serum provitamin A (PVA) values were estimated as the sum of the AC, BC and CR values.
Serum values of total carotenoids (TCR) were estimated as the sum of the AC, BC and LY values. Serum values of total carotenoids (TCA) were estimated as the sum of TCR, CR, ZL and CX values. Serum values of thiobarbituric acid-reactive substance (TBARS) were determined using the thiobarbituric acid reaction method\(^{20}\). Serum SOD activity was determined using an NADPH cytochrome c reductase-NBT method\(^{21}\). Serum values of pepsinogen I (Pep I) and II (Pep II) were estimated using the Pepsinogen RIA Kit (Dainabot Co. Ltd.), which is based on the RIA method\(^{22}\). Anti-HP antibody was detected using the HP Determiner Kit (Kyowa Medics Co. Ltd.), which is based on the ELISA method\(^{23}\). AG was serologically diagnosed, with serum cut-off values set at Pep I \(\leq 70\) ng/ml and Pep I/II Pep II ratio \(\leq 3.0\)\(^{24}\). HP infection (positivity for anti-HP antibody) was diagnosed using a serum cut-off value of anti-HP antibody set at \(\geq 2.3\) ELISA Value\(^{25}\).

Trained health care nurses administered a questionnaire on health and daily lifestyle at the time of the health examination, as previously described\(^{26}\). Subjects were asked about lifestyle habits, including smoking, alcohol consumption and dietary intake of primary foods and drinks. We obtained informed consent to use the collected personal information and serum in epidemiological studies of prevention of lifestyle-related diseases. Participants indicated their consent by writing their signature in the designated space on the questionnaire.

All statistical analyses were performed using logistic regression analysis (statistical package: StatView 5.0, Power Macintosh), after adjusting for gender and age (Model 1) or adjusting for gender, age, smoking, alcohol consumption, and serum levels of anti-HP antibody, total cholesterol and GPT activity (Model 2). These variables were associated with serum carotenoid levels. Serum levels of the various assayd carotenoids, SOD activity and TBARS were classified into three groups, according to their quartile distribution: low group, within the first quartile; middle group, second to third quartile; high group, in the fourth quartile.

Results

Characteristics of the study subjects

Table 1 shows the characteristics of the subjects in the present study. AG was diagnosed in 43.4% of all males and 44.6% of all females. Of the male subjects, 5.3% were AG-positive/anti-HP-negative, 27.6% were AG-negative/anti-HP-negative, 38.2% were AG-positive/anti-HP-positive, and 29.0% were AG-negative/anti-HP-positive. Of the female subjects, 14.6% were AG-positive/anti-HP-negative, 38.5% were AG-negative/anti-HP-negative, 30.0% were AG-positive/anti-HP-positive, and 16.9% were AG-negative/anti-HP-positive. The number of subjects older than 60 years who were positive for both AG and anti-HP antibody was not high in either gender, compared with subjects younger than 59 years.

The odds ratios of serum carotenoids among subjects with atrophic gastritis

The odds ratios for serum values of AC, BC, and CR were low for subjects with middle or high serum carotenoid levels, compared with subjects with low serum carotenoid levels (Table 2), and these differences were significant for subjects with high serum levels of AC and BC. The odds ratios for serum levels of PVA and TCR were significantly lower in subjects with high serum carotenoid levels than in subjects with low levels. However, the odds ratios for subjects with high serum levels of ZL or AT were not significantly lower than those for subjects with low serum levels. The odds ratios for subjects with high serum TBARS values were higher than those for subjects with low serum levels, but this difference was not significant. The odds ratios for subjects with high serum SOD activity were lower than those for subjects with low serum levels, but this difference was not significant. Furthermore, the odds ratios obtained after adjusting for gender, age, smoking, alcohol consumption, serum anti-HP antibody levels, total serum cholesterol level and serum GPT activity (Model 2) tended to show greater differences between groups than the results obtained after adjusting for gender and age (Model 1).

In subjects with HP antibody-negative AG, the odds ratios for serum levels of AC, BC, TCR, PVA, RE and AT were lowest for the subjects with high serum levels, but these differences were not significant (Table 3). The odds ratios of serum SOD activity were also lowest for the subjects with high serum SOD activity, whereas the odds ratios for high serum levels of ZL and TBARS were highest, but neither of these differences was significant.

In subjects with HP antibody-positive AG, the odds ratios for serum levels of AC, PVA and RE were lowest among subjects with high serum levels, and these differences were significant for subjects with middle or high serum AC levels. The odds ratios for subjects with middle serum levels of BC were significantly lower than those of the other 2 quartile-based classifications. However, the odds ratios for subjects with high serum LY, CR and TCR levels were not the lowest of the 3 quartile-based classifications.

### Table 1 Subject characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age group</th>
<th>Number (%)</th>
<th>Atrophic gastritis (AG)</th>
<th>Helicobacter pylori antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG negative</td>
<td>AG positive</td>
</tr>
<tr>
<td>Males</td>
<td>39–59</td>
<td>39 (100)</td>
<td>23 (59.0)</td>
<td>16 (41.0)</td>
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<td>60–80</td>
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<td>Total</td>
<td>76 (100)</td>
<td>43 (56.6)</td>
<td>33 (43.4)</td>
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<tr>
<td>Females</td>
<td>39–59</td>
<td>88 (100)</td>
<td>44 (50.0)</td>
<td>44 (50.0)</td>
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<td>60–80</td>
<td>42 (100)</td>
<td>28 (66.7)</td>
<td>14 (33.3)</td>
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<tr>
<td></td>
<td>Total</td>
<td>130 (100)</td>
<td>72 (55.4)</td>
<td>58 (44.6)</td>
</tr>
</tbody>
</table>

Atrophic gastritis positive: pepsinogen I \(\leq 70\) ng/ml and pepsinogen I/II ratio \(\leq 3.0\).

Helicobacter pylori antibody negative: antibody levels < 2.3 ELISA Value.

Helicobacter pylori antibody positive: antibody levels \(\geq 2.3\) ELISA Value.

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among subjects with HP antibody-positive AG. The odds ratios for subjects with high serum levels of SOD activity were lower than those for subjects with low levels. The odds ratios for subjects with high serum levels of TBARS and AT were similar to those of subjects with low levels.

**Discussion**

The present subjects live in an area in which health check-ups have been conducted for inhabitants over 40 years of age every August for the past 15 years. Prior history of disease, dietary habits and other lifestyle habits of the present study population did not appear to be different from those of other Japanese populations that have been studied. However, there appeared to be significant differences between serum values of carotenoids, RE and TBARS of the present subjects and those of Japanese subjects in previous studies. In two previous studies, the morbidity of AG was found to correlate with serum levels of pepsinogen I and serum ratios of pepsinogen I to pepsinogen II. In the present study, the method used for AG diagnosis was serological testing. The cut-off values used for the present AG diagnosis were similar to those used in previous studies involving Japanese subjects. In previous studies, the sensitivity for HP antibody was greater than 85% using ELISA, and the sensitivity for AG positivity was greater than 90% using RIA. Some studies have suggested that HP infection is not directly associated with gastric cancer, whereas others reported evidence...
that suggested that HP infection carries a significant risk of gastric cancer\textsuperscript{36,37}. Previous studies have indicated a correlation between lipid peroxidation and an increased risk of AG\textsuperscript{4}. This correlation is consistent with 2 of the present findings: 1) the odds ratio of subjects with high serum TBARS values tended to be relatively high; 2) high serum values of carotenoids such as BC, AC and CR correlated with a reduced risk of AG. Furthermore, in the present study, the odds ratios for high serum levels of carotenoids such as AC and BC were low in subjects with AG who were positive for anti-HP antibody, but these odds ratios were not low in subjects with AG who were negative for anti-HP antibody. The simultaneous occurrence of AG and HP infection might be due in part to oxidative reactions\textsuperscript{32,33}, because AC and BC are important antioxidants\textsuperscript{37,38}. The present inverse correlation between AG and serum carotenoid levels might be due to reductions in carotenoid levels resulting from oxidative processes.

Recently, some studies have found that green-yellow vegetables rich in BC reduce the risk of both AG and HP infection\textsuperscript{4,10}. In addition, it has been reported that BC supplementation increases the rate of regression of cancer precursor lesions\textsuperscript{35} and results in an approximately 50% decrease in ornithine decarboxylase activity in atrophic stomach mucosa, as ornithine decarboxylase activity plays a role in tumor promotion\textsuperscript{18}. However, in another study, BC supplementation for 5 years had no major impact on the occurrence of neoplastic changes in the stomachs of older male smokers with AG\textsuperscript{36}. However, in the present study, AG apparently inversely correlated with both RE and carotenoids with provitamin A activity. It was found that HP-infection increased the risk of duodenal ulcer and RE might inhibit the development of its ulcer\textsuperscript{40}.

RE and its derivatives have chemopreventive effects at some sites of cancer. These effects are due to antioxidant activity, effects on cell differentiation and proliferation, and suppression of some malignant transformations\textsuperscript{37,38}.

The present results suggest that AG inversely correlates with high serum levels of carotenoids with provitamin A activity. Therefore, high intake of vegetables and fruits rich in these carotenoids might reduce the risk of AG.

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References

Serum Carotenoids and Atrophic Gastritis in Japanese Subjects


