[Environmental Health and Preventive Medicine 6, 184–188, October 2001]

Original Article

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

Yoshinori ITO[1] and Koji SUZUKI[1]

[1]*Department of Public Health, Fujita Health University School of Health Sciences, Aichi*

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 α-carotene (odds ratio, 0.41; 95% C.I., 0.19–0.88) and β-carotene (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 β-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, β-carotene, provitamin A

Introduction

It was reported that an intestinal type of gastric cancer occurs in stomachs that exhibit chronic atrophic gastritis[1,2]. Some studies have reported that Helicobacter pylori infection is a strong predictor for atrophic gastritis (AG)[3-6], 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[7,8]. Numerous epidemiological studies have shown that the intake of common Japanese salted foods such as Tsukemono is a significant risk factor for gastric cancer[9-12]. It has also been shown that consumption of large quantities of vegetables and fruits is associated with reduced risk of gastric cancer[9-14]. Some studies have reported that high serum β-carotene levels are a protective factor in gastric cancer incidence[15]. Other studies suggested that vitamin A from any source inhibits the development of duodenal ulcers[16]. A large number of potentially anti-carcinogenic substances are present in vegetables and fruits[17]. Furthermore, it has been found that prolonged supplementation with β-carotene or α-tocopherol acetate results in an approximately 50% decrease in ornithine decarboxylase activity in atrophic stomach mucosa[18].

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 β-carotene (BC), α-carotene (AC), lycopene (LY), β-cryptoxanthin (CR), zeaxanthin/lutein (ZL), canthaxanthin (CX), retinol (RE), and α-tocopherol (AT) were measured separately by high-performance liquid chromatography (HPLC), as reported previously[19]. Serum provitamin A (PVA) values were estimated as the sum of the AC, BC and CR values.

Received Feb. 23 2001/Accepted Jun. 27 2001
Reprint requests to: Yoshinori ITO
Department of Public Health, Fujita Health University School of Health Sciences, Dengakugakubo, Kutsukake-cho, Toyoake City, Aichi Prefecture, 470-1192, Japan
TEL&FAX: +81(562)93-9405, E-mail: yoshiito@fujita-hu.ac.jp

Serum values of total carotenes (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 ≤ 70 ng /ml and Pep I/ Pep II ratio ≤ 3.0[24]. HP infection (positivity for anti-HP antibody) was diagnosed using a serum cut-off value of anti-HP antibody set at ≥ 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 assayed 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, after adjusting for gender and age, 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

Gender	Age group	Number (%)	Atrophic gastritis (AG)		Helicobacter pylori antibody			
					Negative		Positive	
			Negative	Positive	AG negative	AG positive	AG negative	AG positive
Males	39–59	39 (100)	23 (59.0)	16 (41.0)	13 (33.3)	1 (2.6)	10 (25.6)	15 (38.5)
	60–80	37 (100)	20 (54.1)	17 (45.9)	8 (21.6)	3 (8.1)	12 (32.4)	14 (37.8)
	Total	76 (100)	43 (56.6)	33 (43.4)	21 (27.6)	4 (5.3)	22 (29.0)	29 (38.2)
Females	39–59	88 (100)	44 (50.0)	44 (50.0)	34 (38.6)	13 (14.8)	10 (11.4)	31 (35.2)
	60–80	42 (100)	28 (66.7)	14 (33.3)	16 (38.1)	6 (14.3)	12 (28.6)	8 (19.1)
	Total	130 (100)	72 (55.4)	58 (44.6)	50 (38.5)	19 (14.6)	22 (16.9)	39 (30.0)

Atrophic gastritis positive: pepsinogen I≤70 ng/ml and pepsinogen I/II ratio≤3.0.
Helicobacter pylori antibody negative: antibody levels<2.3 ELISA Value.
Heicobacter pylori antibody positive: antibody levels≥2.3 ELISA Value.

Table 2 The odds ratios of serum levels of carotenoids, retinol and α-tocopherol for atrophic gastritis

Independent variable		Model 1: Odds ratio (95%C.I.)			p value	Model 2: Odds ratio (95%C.I.)			p value
		Low	Middle	High	for trend	Low	Middle	High	for trend
Total carotenoids	(μmol/L)	1.00	0.80 (0.41–1.58)	0.66 (0.30–1.45)	0.58	1.00	0.73 (0.34–1.60)	0.80 (0.32–2.03)	0.73
Total carotenes	(μmol/L)	1.00	0.53 (0.27–1.05)[a]	0.46 (0.21–1.00)[b]	0.10	1.00	0.35 (0.15–0.80)[b]	0.45 (0.17–1.17)	0.04
Lycopene	(μmol/L)	1.00	0.75 (0.38–1.48)	0.73 (0.34–1.58)	0.66	1.00	0.61 (0.28–1.30)	0.80 (0.33–1.96)	0.42
α-Carotene	(μmol/L)	1.00	0.49 (0.25–0.96)[b]	0.41 (0.19–0.88)[b]	0.04	1.00	0.39 (0.18–0.86)[b]	0.33 (0.13–0.82)[b]	0.02
β-Carotene	(μmol/L)	1.00	0.54 (0.28–1.08)[a]	0.41 (0.18–0.91)[b]	0.07	1.00	0.36 (0.15–0.83)[b]	0.35 (0.13–0.94)[b]	0.04
β-Cryptoxanthin	(μmol/L)	1.00	0.36 (0.18–0.71)[c]	0.60 (0.28–1.31)	0.01	1.00	0.32 (0.14–0.72)[c]	0.51 (0.21–1.26)	0.02
Zeaxanthin & lutein	(μmol/L)	1.00	1.22 (0.62–2.41)	1.18 (0.53–2.60)	0.85	1.00	1.20 (0.55–2.60)	1.40 (0.56–3.52)	0.77
Provitamin A	(μmol/L)	1.00	0.49 (0.24–0.96)[b]	0.38 (0.17–0.85)[b]	0.04	1.00	0.29 (0.13–0.69)[c]	0.27 (0.10–0.73)[c]	0.01
Retinol	(μmol/L)	1.00	0.84 (0.42–1.65)	0.67 (0.31–1.48)	0.61	1.00	0.89 (0.39–2.01)	0.79 (0.30–2.11)	0.90
α-Tocopherol	(μmol/L)	1.00	1.35 (0.68–2.68)	0.85 (0.39–1.88)	0.37	1.00	1.60 (0.70–3.62)	1.39 (0.49–3.97)	0.53
SOD activity	(unit)	1.00	1.37 (0.69–2.71)	0.63 (0.32–1.26)	0.19	1.00	1.73 (0.73–3.92)	0.49 (0.21–1.10)[a]	0.08
TBARS	(μmol/L)	1.00	1.02 (0.98–1.05)	1.31 (0.68–2.54)	0.43	1.00	0.76 (0.36–1.62)	1.35 (0.63–2.90)	0.44

The odds ratios and 95% confidence intervals (C.I.) were calculated using logistic regression analysis after separating the subjects into three groups according to their quartile distribution for serum component levels: low, within the first quartile; middle, second to third qartile; high, in the fourth quartile (n=206).
Model 1: adjusting for gender and age; Model 2: adjusting for gender, age, habits of alcohol drinking (1: non-drinker, 2: irregular drinker and 3: regular drinker) and smoking status (1: never smoked, 2: former smoker and 3: current smoker), and serum levels of Helicobacter pylori antibody, total cholesterol and GPT activity.
[a]: $p<0.10$, [b]: $p<0.05$, [c]: $p<0.01$.

Table 3 The odds ratios of serum levels of carotenoids, retinol, α-tocopherol, and other serum components for atrophic gastritis with or without Helicobacter pylori antibody

Independent variable		Helicobacter pylori antibody negative				Helicobacter pylori antibody positive			
		Odds ratio (95%C.I.)			p value	Odds ratio (95%C.I.)			p value
		Low	Middle	High	for trend	Low	Middle	High	for trend
Total carotenoids	(μmol/L)	1.00	0.79 (0.24–2.60)	0.62 (0.16–2.40)	0.79	1.00	0.80 (0.31–2.05)	0.79 (0.26–2.40)	0.88
Total carotenes	(μmol/L)	1.00	0.43 (0.13–1.35)	0.42 (0.12–1.46)	0.27	1.00	0.43 (0.16–1.19)	0.51 (0.16–1.69)	0.24
Lycopene	(μmol/L)	1.00	0.61 (0.19–1.92)	0.60 (0.17–2.15)	0.65	1.00	0.74 (0.28–1.93)	0.84 (0.28–2.51)	0.83
α-Carotene	(μmol/L)	1.00	0.49 (0.16–1.52)	0.40 (0.11–1.45)	0.30	1.00	0.30 (0.10–0.89)[b]	0.27 (0.08–0.88)[b]	0.04
β-Carotene	(μmol/L)	1.00	0.66 (0.21–2.06)	0.35 (0.09–1.35)	0.29	1.00	0.33 (0.12–0.95)[b]	0.43 (0.13–1.46)	0.10
β-Cryptoxanthin	(μmol/L)	1.00	0.37 (0.12–1.18)[a]	0.49 (0.13–1.95)	0.25	1.00	0.41 (0.16–1.07)[a]	0.71 (0.24–2.09)	0.16
Zeaxanthin & lutein	(μmol/L)	1.00	0.52 (0.16–1.73)	0.96 (0.27–3.47)	0.46	1.00	1.84 (0.70–4.81)	1.23 (0.41–3.70)	0.42
Provitamin A	(μmol/L)	1.00	0.35 (0.11–1.08)[a]	0.32 (0.09–1.16)[a]	0.12	1.00	0.40 (0.14–1.13)	0.37 (0.11–1.25)	0.16
Retinol	(μmol/L)	1.00	0.99 (0.31–3.22)	0.64 (0.15–2.81)	0.77	1.00	0.49 (0.17–1.43)	0.37 (0.11–1.18)[a]	0.22
α-Tocopherol	(μmol/L)	1.00	0.90 (0.27–3.00)	0.70 (0.18–2.65)	0.86	1.00	1.30 (0.51–3.33)	0.97 (0.32–2.97)	0.78
SOD activity	(unit)	1.00	1.02 (0.30–3.44)	0.48 (0.13–1.78)	0.26	1.00	1.80 (0.64–5.06)	0.63 (0.24–1.63)	0.34
TBARS	(μmol/L)	1.00	1.19 (0.41–3.47)	1.61 (0.51–5.10)	0.42	1.00	0.74 (0.29–1.86)	1.09 (0.43–2.76)	0.86

The odds ratios and 95% confidence intervals (C.I.) were calculated using logistic regression analysis, after adjusting for gender and age.
The subjects were classified according to their quartile distribution for serum component levels: low, within the first quartile; middle, second to third quartile; high, in the fourth quartile. (n=94 for Helicobacter pylori antibody negative and n=112 for Helicobacter pylori antibody positive).
[a]: $p<0.10$, [b]: $p<0.05$.

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[27] that have been studied[26]. 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[28].

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[24,29]. In the present study, the only 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[24,29]. In previous studies, the sensitivity for HP antibody was greater than 85%[25] using ELISA, and the sensitivity for AG positivity was greater than 90%[22] using RIA.

Some studies have suggested that HP infection is not directly associated with gastric cancer[7,8], whereas others reported evidence

that suggested that HP infection carries a significant risk of gastric cancer[30,31]. Previous studies have indicated a correlation between lipid peroxidation and an increased risk of AG[6]. 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[32,33], because AC and BC are important antioxidants[17,34]. 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[4,10]. In addition, it has been reported that BC supplementation increases the rate of regression of cancer precursor lesions[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[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[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[16].

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[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.

Acknowledgements

This study was supported in part by a Grant-in Aid for the Monbusho Cancer Research Program. It was conducted in cooperation with Prof. H. Nakano (Director of Digestive Internal Medicine at Fujita Health University). The authors are grateful to all participants and staff of the health check-up for residents of Y-town, Hokkaido, Japan (Director: Professor Emeritus K. Aoki).

References

1) Correa P. The gastric precancerous process. Cancer Survey 1983; 2: 438–450.
2) Kato I, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsumura A, Kameya A, Kano T. Atrophic gastritis and stomach cancer risk: cross-sectional analyses. Jpn. J. Cancer Res. 1992; 83: 1041–1046.
3) Kawaguchi H, Haruma K, Komoto K, Yoshihara M, Sumii K, Kajiyama. Helicobacter pylori infection is the major risk factor for atrophic gastritis. Am. J. Gastroent. 1996; 91: 959–969.
4) Tsugane S, Kabuto M, Imai H, Gey F, Tei Y, Hanaoka T, Sugano K, Watanabe S. Helicobacter pylori, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. Cancer Causes and Control 1993; 4: 297–305.
5) Namekata T, Miki K, Kimmey M, Fritsche T, Hughes D, Moore D, Suzuki K. Chronic atrophic gastritis and Helicobacter pylori infection among Japanese Americans in Seattle. Am. J. Epidemiol. 2000; 151: 820–830.
6) Correa P. Helicobacter pylori and gastric carcinogenesis. Am. J. Surg. Path. 1995; 19: S37–S43.
7) Watanabe Y, Kurita JH, Mizuno S, Mukai M, Inokuchi H, Miki K, Ozasa K, Kawai K. Helicobacter pylori infection and gastric cancer. A nested case-control study in a rural area of Japan. Digest. Diseases Sciences 1997; 42: 1383–1387.
8) Hwang H, Dwyer J, Russell RM. Diet, Helicobacter pylori infection, food preservation and gastric cancer risk: are there new roles for preventative factors? Nutr. Rev. 1994; 52: 75–83.
9) Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya. Japan. Jpn. J. Cancer Res. 1985; 76: 705–716.
10) Kato I, Taminaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, Kameya A, Kano T, Ikari A. A prospective study of atrophic gastritis and stomach cancer risk. Jpn. J. Cancer Res. 1992; 83: 1137–1142.
11) Kono S, Hirohata T. A review on the epidemiology of stomach cancer. J. Epidemiol. 1994; 4: 1–11.
12) The Committee for Study of Cancer Prevention Guidelines in Japanese Society for Cancer Epidemiology. Lifestyle and Cancer of Major Sites (Seikatsu Syukan To Syuyou Bui No Gann), Japan, Kyusyu University Press, 1998; 7–14. (in Japanese).
13) Ziegler RG. Vegetables, fruits, and carotenoids and the risk of cancer. Am. J. Clin. Nutr. 1991; 53: 251S–259S.
14) Kim Y-I, Manson JB. Nutrition chemoprevention of gastrointestinal cancers: a critical review. Nutr. Rev. 1996; 54: 259–279.
15) Steinmetz KA, Potter JD. Vegetables, fruits and cancer. I. Epidemiology. Cancer Causes Control 1991; 2: 325–357.
16) Aldoori WH, Giovannucci EL, Stampfer MJ, Rimm EB, Wing AL, Willett WC. Prospective study of diet and the risk of duodenal ulcer in men. Am. J. Epidemiol. 1997; 145: 42–50.
17) Bendich A, Olsen JA. Biological actions and carotenoids. FASEB J. 1989; 3: 1927–1932.
18) Burkin YV, Draudin-Krylenko VA, Orlov EN, Kuvshinov YP, Poddubny BK, Vorobyeva OV, Shabanov MA. Effect of prolonged β-carotene or DL-α-tocopherol acetate supplementation on ornithine decarboxylase activity in human atrophic stomach mucosa. Cancer Epidemiol. Biomark. Prev. 1995; 4: 865–870.
19) Ito Y, Ochiai J, Sasaki R, Suzuki S, Kushuhara Y, Morimitsu Y, Otani M, Aoki K. Serum concentrations of carotenoids, retinol, and α-tocopherol in healthy persons determined by high-performance liquid chromatography. Clin. Chim. Acta 1991; 194: 131–144.
20) Yagi K. A simple fluorometric assay for lipoperoxide in blood plasma. Biochem. Med. 1976; 15: 212–216.
21) Shinohara R, Ishiguro I. Detection methods of free radical related substances and the system for their elimination. Jpn. J. Clin. Path.

1989; 37: 1006–1012. (in Japanese).
22) Samloff IM, Varis K, Ihamaki T,Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal history. Gastroenterology 1982; 83: 204–209.
23) Evans DJ, Evans DG, Graham DY, Klein PD. A sensitive and specific serologic test for detection of campylobacter pylori infection. Gastroenterology 1989; 96: 1004–1008.
24) Kabuto M, Imai H, Tsugane S, Watanabe S. Correlation between atrophic gastritis prevalence and gastric cancer mortality among middle-aged men in 5 areas in Japan. J. Epidemiol. 1993; 3: 35–39.
25) Tani T, Kurimoto S, Sawamura T, Nakano H. Evaluation of five commercial kits for detection of Helicobacter pylori antibodies. Eisei Kensa 1997; 46: 1521–1524. (In Japanese)
26) Ito Y, Suzuki S, Yagyu K, Sasaki R, Suzuki K, Aoki K. Relationship between serum carotenoid levels and cancer death rates in the residents, living in a rural area of Hokkaido, Japan. J. Epidemiol. 1997; 7: 1–8.
27) Research group on evaluation of risk factors for cancer by large-scale cohort study (Chairman K. Aoki) (1996). Baseline results of a large-scale cohort study on evaluation of risk factors on cancer. Secretariat Office of the Research Committee: Aichi Cancer Center, Nagoya.
28) Ito Y, Shimizu H., Yoshimura T, Hashimoto T, Hayakawa N, Shinohara R, Takatsuka N, Tokui, N, Kasamatsu T, Suzuki K. Relationship between serum levels of lipid peroxides and carotenoids among residents of Japan. Vitamins 1997; 71: 427–434. (in Japanese)
29) Miki K, Ichinose M, Kawamura N, Matsushima M, Ahmad HB, Kimura M, Sano J, Tashiro T, Kakei N, Oka H, Furihata C, Takahashi K. The significance of low serum pepsinogen levels to detect stomach cancer associated with extensive chronic gastritis in Japanese subjects. Jpn. J. Cancer Res. 1989; 80: 111–114.
30) Miehlke S, Hackelsberger A, Meining A, von Arnim U, Muller P, Ochsenkuhn T, Lehn N, Malfertheiner P, Stolte M, Bayerdorffer E. Histological diagnosis of Helicobacter pylori gastritis is predictive of a high risk of gastric carcinoma. Int. J. Cancer 1997; 73: 837–839.
31) Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. Gastroenterology 1998; 114: 1169–1179.
32) Farinati F, Cardin R, Libera GD, Herszenyi L, Marafin C, Molari A, Plebani M, Rugge M, Naccarato R. The role of antioxidants in the chemoprevention of gastric cancer. Eur. J. Cancer Prev. 1994; 3 (Suppl 2): 93–97.
33) Sanjose S, Munoz N, Sobala G, Vivas J, Peraza S, Cano E, Castro D, Sanchez V, Andrade O, Tompkins D, Schorah CJ, Axon ATR, Benz M, Oliver W. Antioxidants, Helicobacter pylori and stomach cancer in Venezuela. Eur. J. Cancer Prev. 1996; 5: 57–62.
34) Burton GN, Ingold KV. β-Carotene: an unusual type of lipid antioxidant. Science 1984; 224: 569–573.
35) Correa P, Fontham ETH, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, Mera R. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-Helicobacter pylori therapy. J. Natl. Cancer Inst. 2000; 92: 1881–1888.
36) Varis K, Taylor PR, Sipponen P, Samloff IM, Heinonen OP, Albanes D, Harkonen M, Huttunen JK, Laxen F, Virtamo J, The Helsinki Gastritis Study Group. Gastric cancer and premalignant lesions in atrophic gastritis: a controlled trial on the effect of supplementation with alpha-tocopherol and beta-carotene. Scand. J. Gastroent. 1998; 33: 294–300.
37) Goodman de WS. Vitamin A and retinoids in health and disease. New Eng. J. Med. 1984; 310: 1023–1031.
38) Moriwaki H, Muto Y, Shidoji Y, Okuno M. Cancer prevention and treatment by retinoids. Vitamins 1993; 67: 387-396. (in Japanese).