Tea Polyphenol Intake and Changes in Serum Pepsinogen Levels

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Following a phase I study, a phase II study was conducted to evaluate the effects of two different doses of tea polyphenols on serum pepsinogen levels. Subjects were patients aged 40 to 69 years who had undergone gastroscopy between 1995 and 1997 at Aichi Cancer Center Hospital, and had been found to have no disease requiring medication. Those with pepsinogen I <70 ng/ml and pepsinogen I/II ratio <6 were included in this study. Capsules containing 100 mg of tea polyphenols were administered for 1 year: 1 capsule per day for 101 patients (42 males and 59 females), and 6 capsules (equivalent to 10 cups) per day for 83 patients (30 males and 53 females). The enrollment of the 1 capsule group preceded that of the 6 capsule group, in which re-participation was allowed. Blood samples were obtained 1 year after participation from 86 participants of the 1 capsule group and 77 participants (43 new participants and 34 re-participants) of the 6 capsule group. The compliance in polyphenol capsule intake ranged from 11.4 to 105.7% (87.6% on average) of the scheduled amount for the 1 capsule group and 3.2 to 112.3% (77.8% on average) for the 6 capsule group. No serious polyphenol-related adverse effects were reported. The difference in pepsinogen I between before and after 1 year intake of the polyphenol was 3.1 ng/ml for the 43 participants of the 6 capsule group, but 3.5 ng/ml for the 1 capsule group. The mean pepsinogen I/II ratio for the 43 participants increased from 2.37 by 0.08. This increase was not larger than that for the 1 capsule group (from 2.61 by 0.11). Among 34 participants in both interventions, no significant increase in pepsinogen I and I/II ratio for the 6 capsule intervention was observed. This result suggests that additional polyphenol intake for 1 year in Japanese does not improve pepsinogen levels, which are considered to reflect stomach atrophy, a high-risk condition for stomach cancer.

Key words: Tea polyphenols — Pepsinogens — Adverse effects — Phase II trial

Epidemiologic studies suggest that green tea is a preventive agent against cancers. For stomach cancer, decreased risk has been demonstrated in case-control studies in Japan[1–3] and China,[4, 5] though little work has been done in other countries, where green tea drinking is not common. Recent biological findings on tea polyphenols support the idea that those who drink large quantities of green tea may be at a lower risk of stomach and other cancers. Tea polyphenols are anti-oxidants which prevent DNA damage by carcinogens,[6] inhibit mutagenicity of carcinogens,[7] and inhibit urokinase, which disturbs tumor growth.[8] Tea polyphenols, especially epigallocatechin gallate, reduce tumors in rats and mice,[9] and induce apoptosis in human carcinoma cell lines.[10, 11]

Atrophic gastritis is a well-known high-risk condition for stomach cancer.[12] *Helicobacter pylori (H. pylori)* infection is one of the causes of stomach atrophy.[13–15] Although it is accepted that *H. pylori* infection elevates the risk of stomach cancer,[16–19] it is not clear whether atrophic change is only a surrogate marker of the carcinogenic process or an essential step in carcinogenesis itself. If the former is correct, disturbing the progression of atrophy *per se* will not prevent stomach cancer, but if the latter is correct, atrophy prevention may become a target for preventive intervention against stomach cancer. Although the process is not fully understood, it seemed worth examining the effects of tea polyphenols on gastric atrophy to cast light on the preventive mechanism of tea polyphenols against stomach cancer. Following a phase I study (unpublished), we conducted a phase II study to observe the effects of 1-year intake of tea polyphenols on serum pepsinogens, which reflect the degree of gastric atrophy.[20] This is the first phase II study to have examined the effect of relatively long-term intake of polyphenols on pepsinogen levels.

PATIENTS AND METHODS

The subjects were outpatients aged 40 to 69 years who had undergone gastroscopy between 1995 and 1997 at

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Aichi Cancer Center Hospital, and had been found by gastroscopy to have no stomach disease requiring treatment. Those who were under medication and/or had a history of gastrectomy or serious disease such as apoplexy, myocardial infarction or angina pectoris were excluded, but those with a history of cancer at other sites were included. The participants were asked to permit serum pepsinogen measurement using their residual blood, if this was preserved at the Hospital Laboratory. If there was no residual blood, they were asked to provide 2 ml of blood for pepsinogen measurement and the anti-*H. pylori* antibody test. Since mid-March 1996, all participants have been asked to supply a 2 ml blood sample to check for the *H. pylori* antibody. The patients with pepsinogen I levels less than 70 ng/ml and pepsinogen I/II ratios less than 6 were again invited to enter our intervention study to take tea polyphenol capsules for 1 year.

Recruitment was announced in a waiting room before gastroscopy was undertaken, by an 8-min video and a 2-min verbal explanation of the study purpose and process. Recruitment was conducted by the staff of the Division of Epidemiology, and participants were not advised by their doctor, in order to avoid undue influence in favor of participation. The participants were requested to sign a participation form after a further 10-min individual explanation. At that time, lifestyle data on smoking, alcohol and green tea drinking, etc., were collected. The participants in the 1 capsule intake intervention were recruited first, and then those for the 6 capsule intervention. The participants who completed the 1 capsule intervention were later allowed to participate in the 6 capsule intervention.

Tea polyphenol capsules administered were "POLYPHENON CAPSULES" (Mitsui Norin Co., Ltd., Tokyo), not decaffeinated tea extract, containing 100 mg of polyphenols per capsule, of which 50% is epigallocatechin gallate. Intake of 1 capsule per day after breakfast for 1 year was prescribed for the 1 capsule intervention group, and intake of 2 capsules after each meal for 1 year for the 6 capsule intervention group. The quantity of polyphenols in 6 capsules is equivalent to the amount in 10 cups of Japanese tea. Participants were instructed that if they forgot to take the capsules, extra capsules did not need to be taken after the next meal. Capsule intake was prohibited at times when patients were taking prescribed drugs. Capsules were provided directly to each participant at the hospital every 3 months. In order to assess compliance, participants were asked to state the number of capsules remaining at a blood test given 1 year after the beginning of the trial.

Pepsinogens were measured by radioimmunoassay (RIA) (Dainabot Co., Ltd., Tokyo) at two laboratories: at the laboratory of Aichi Cancer Center Hospital, when residual blood was preserved there at entry, and at SRL

Co., Ltd., Tokyo in other cases, and measurement 1 year later was done in the same laboratories. Thirty-seven samples were measured at both laboratories at the same time. The difference in pepsinogen I levels was 3.2 ng/ml on average with a 4.3 ng/ml standard deviation, and that in pepsinogen I/II ratio was 0.05 with 0.09 standard deviation. Anti-*H. pylori* IgG antibody was measured for the blood sent to SRL Co., Ltd. by using an enzyme immunoassay kit (Pirika Plate G Helicobacter until June 1996 and Detaminor H. Pylori antibody after July 1996). Differences in mean pepsinogen levels were subjected to a *t* test after conducting an *F*-test for equal variance, using the TTEST procedure of the SAS computer program suite. When the null hypothesis of equal variance was rejected at $P<0.05$, a *t* test for unequal variance was adopted. Regression analysis was also conducted according to the GLM procedure of SAS.[21]

RESULTS

Participation   From February 1995 to February 1996, 183 patients volunteered to participate in the 1 capsule intake intervention. Among these, 61 outpatients were found not to meet the pepsinogen criteria, 10 patients were found to be ineligible by gastroscopy, and 11 patients changed their minds. The remaining 101 patients (42 males and 59 females) consented to 1 year of polyphenol capsule intake. For the 6 capsule intake intervention, 108 patients applied from March 1996 to February 1997. Twenty-one patients did not meet the pepsinogen criteria, 4 patients changed their minds, and 83 patients (30 males and 53 females) consented to the 6 capsule intake for 1 year. Thirty-four out of the 83 were participants in the 1 capsule group. Table I shows the age distribution of the participants according to intervention group. The mean age was 58.6 years for the 1 capsule group and 57.5 years for the 6 capsule group.

Blood samples were obtained 1 year after the start from 86 participants (34 males and 52 females) in the 1 capsule group and 77 participants (26 males and 51 females) in the 6 capsule group; 86.1% in the 1 capsule group and 92.8% in the 6 capsule group completed the follow-up. Their mean age was 58.9 years for the 1 capsule group and 57.8 years for the 6 capsule group, which did not differ substantially from that of all participants.

Compliance   Compliance with the scheduled intake among 86 participants in the 1 capsule group and 77 participants in the 6 capsule group, whose blood was sampled 1 year after the start, is shown in Fig. 1. It ranged from 11.4 to 105.7% (87.6% on average) in the 1 capsule group and from 2.2 to 112% (76.0% on average) in the 6 capsule group. Compliance of greater than 100% means that the number of remaining capsules was fewer than expected from the schedule. The interval between the start

Table I.　Age Distribution of Participants

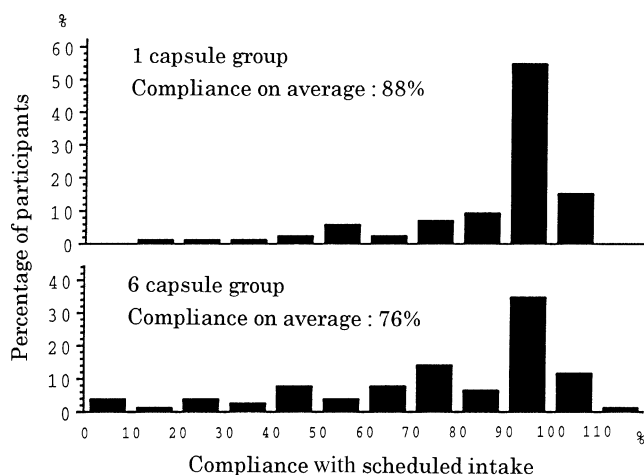| Age (years)	1 capsule group			6 capsule group		
	Males	Females	Total	Males	Females	Total
40–44	2 (5)	6 (10)	8 (8)	0 (0)	3 (6)	3 (4)
45–49	1 (2)	3 (5)	4 (4)	3 (10)	8 (13)	11 (13)
50–54	3 (7)	7 (12)	10 (10)	0 (0)	13 (25)	13 (16)
55–59	12 (28)	16 (27)	28 (28)	8 (27)	9 (19)	17 (20)
60–64	14 (33)	18 (31)	32 (32)	11 (37)	13 (25)	24 (29)
65–69	10 (13)	9 (15)	19 (19)	8 (27)	7 (13)	15 (18)
Total	42 (100)	59 (100)	101 (100)	30 (100)	53 (100)	83 (100)

% in parenthesis.

Fig. 1.　Compliance with scheduled intake of tea polyphenol capsules. The upper figure being for the 1 capsule group (*n*=86) and the lower figure for the 6 capsule group (*n*=77).

of intake and after-intake blood tests was 300 to 408 days with a mean of 366 days for the 1 capsule group, and 328 to 404 days with a mean of 368 days for the 6 capsule group. The intervals between the two blood tests were 317 to 449 days (mean 391 days) and 342 to 444 days (mean 387 days), respectively.

Adverse effects　No serious adverse effects were observed, although 1 participant was diagnosed with breast cancer a few weeks after the start of her participation; however, this was clearly not an adverse effect of the tea polyphenol intake.

In the 1 capsule group, 4 participants (3 males and 1 female) quit taking the capsules because of symptoms of discomfort: 3 stomach discomfort and 1 bowel movement while commuting to the office by train. The 3 participants with stomach discomfort discontinued participation in the study. Including the above 4 persons, 13 participants

reported experiencing discomfort as shown in Table II. Abdominal discomfort was reported by 10 participants, although one of them said that the symptom had existed prior to her entry into this study.

In the 6 capsule group, 3 male participants quit taking the capsules (2 because of diarrhea and 1 because of abdominal discomfort), and 2 of the 3 participants ceased participation in the study. The reported symptoms were 5 abdominal discomfort (1 participant had had the discomfort before participation), 5 diarrhea, 1 constipation, 1 sleeplessness, and 1 resumption of menstruation with abdominal pain. One participant experienced diarrhea and sleeplessness, so in total 12 participants (14.4%) reported adverse effects. This percentage was not significantly higher than that in the 1 capsule group (12.9%, 13 of 101). Concerning diarrhea, the frequency was significant higher in the 6 capsule group than in the 1 capsule group ($P<0.05$ by Fisher's exact test).

Changes in pepsinogens　The changes in pepsinogens for the 86 patients in the 1 capsule group and the 43 patients newly participating in the 6 capsule group are shown in Tables III and IV. Pepsinogen I increased by 3.5 ng/ml on average (standard error, SE=1.3) for the 1 capsule group, and 3.1 ng/ml on average (SE=1.8) for the 6 capsule group; the difference was not significant. No significant difference was observed in the pepsinogen I/II ratio change between the 1 capsule group (mean±SE, 0.11±0.07) and the 6 capsule group (0.06±0.08). When stratified by sex, age or compliance with the scheduled intake, no significant difference was observed between the two groups. The increases in pepsinogen I and I/II ratio for those with compliance of 80% or greater were not significantly larger than that for those with compliance of less than 80% in either group. Similarly, the differences were not significant when the groups were divided at the compliance values of 50%, 60% or 70%.

When subjects were divided according to the initial value of pepsinogen I/II ratio before intervention at value 3, which is commonly used in the definition of gastric

Table II.   Adverse Effects Reported by Participants

Adverse effect	1 capsule group			6 capsule group		
	Males $n=42$	Females $n=59$	Total $n=101$	Males $n=30$	Females $n=53$	Total $n=83$
Abdominal discomfort	2	8	10	2	3	5
Abdominal pain	0	1	1	0	0	0
Diarrhea	0	0	0	1	4	5[a]
Inconvenient bowel movement[b]	1	0	1	0	0	0
Constipation	0	1	1	0	1	1
Sleeplessness	0	0	0	0	1	1
Resumption of menstruation		0	0		1	1
Total	3	10	13	3	10	13

a) $P<0.05$ by Fisher's exact test (0/101 vs. 5/83).
b) Bowel movement while commuting to the office by train.

Table III.   Increase and Standard Error (SE) of Mean Pepsinogen I for the 1 Capsule Group and the 6 Capsule Group

	1 capsule group			6 capsule group		
	(*n*)	Before[a]	Increase±SE	(*n*)	Before[a]	Increase±SE
All subjects	(86)	41.4	3.5±1.3	(43)	39.6	3.1±1.8
Sex						
males	(34)	41.4	6.0±2.6	(15)	38.7	1.3±2.3
females	(52)	41.3	1.9±1.3	(28)	40.0	4.1±2.5
Age						
40–49 years	(10)	40.8	1.0±1.8	(6)	40.4	4.7±4.0
50–59 years	(30)	45.2	2.1±2.1	(20)	39.1	1.5±1.5
60–69 years	(46)	39.0	5.0±2.2	(17)	39.7	4.5±4.1
Compliance						
<80%	(18)	41.3	6.6±2.1	(25)	41.7	1.1±1.9
≥80%	(68)	41.4	2.7±1.6	(18)	36.6	6.0±3.5
Pepsinogen I/II ratio before tea capsule intake						
<3	(60)	38.5	3.4±1.5	(32)	39.8	3.8±2.3
3–6	(26)	48.0	3.8±2.5	(11)	38.9	1.1±2.2
H.pylori antibody						
positive[b]	(36)	43.7	4.6±2.4	(23)	39.8	5.4±2.6
negative	(5)	34.9	2.3±1.6	(16)	36.8	1.2±2.9
not tested	(45)	40.2	2.8±1.6	(4)	49.2	−2.1±5.4
Tea						
≤2 cups/day	(24)	38.2	4.5±1.8	(7)	33.8	0.1±2.4
3–5 cups/day	(39)	42.7	3.8±2.4	(20)	34.6	2.8±2.2
≥6 cups/day	(23)	42.5	2.1±1.9	(16)	48.3	4.9±4.0
Smoking						
smoker	(7)	39.3	1.5±1.0	(4)	36.4	2.9±6.1
non-smoker	(79)	41.5	3.7±1.4	(39)	39.9	3.2±1.9
Alcohol						
every day	(15)	44.1	8.1±4.4	(7)	44.3	−0.1±3.2
1–4 times/w	(11)	34.7	8.9±4.6	(8)	29.0	3.8±1.0
less	(60)	41.9	1.4±1.2	(28)	41.4	3.8±2.7

a) Mean before tea capsule intake.
b) Antibody positive means 1+, 2+, or 3+ for Pirika Plate G Helicobacter and Elisa Value 2.3 or over for Detaminor H. Pylori.

Table IV.   Increase and Standard Error (SE) of Mean Pepsinogen I/II Ratio for the 1 Capsule Group and the 6 Capsule Group

	1 capsule group			6 capsule group		
	(*n*)	Before[a]	Increase±SE	(*n*)	Before[a]	Increase±SE
All subjects	(86)	2.61	0.11±0.07	(43)	2.37	0.08±0.06
Sex						
males	(34)	2.58	0.11±0.12	(15)	2.63	0.14±0.10
females	(52)	2.62	0.11±0.09	(28)	2.22	0.06±0.07
Age						
40–49 years	(10)	3.56	−0.31±0.12	(6)	2.82	−0.11±0.44
50–59 years	(30)	2.59	0.08±0.10	(20)	2.37	0.16±0.07
60–69 years	(46)	2.41	0.22±0.11	(17)	2.20	0.06±0.10
Compliance						
<80%	(18)	3.02	0.18±0.16	(25)	2.23	0.09±0.08
≥80%	(68)	2.50	0.09±0.08	(18)	2.56	0.07±0.07
Pepsinogen I/II ratio before tea capsule intake						
<3	(60)	1.92	0.14±0.08	(32)	1.70	0.02±0.04
3–6	(26)	4.18	0.04±0.14	(11)	4.31	0.28±0.18
H.pylori antibody						
positive[b]	(36)	2.31	−0.04±0.08	(23)	1.85	0.02±0.06
negative	(5)	4.28	−0.22±0.08	(16)	3.15	0.23±0.12
not tested	(45)	2.65	0.27±0.11	(4)	2.21	−0.14±0.11
Tea						
<2 cups/day	(24)	2.72	0.01±0.09	(7)	2.68	0.03±0.11
3–5 cups/day	(39)	2.34	0.08±0.09	(20)	2.18	0.17±0.09
≥6 cups/day	(23)	2.93	0.27±0.18	(16)	2.47	0.00±0.09
Smoking						
smoker	(7)	2.46	−0.12±0.14	(4)	3.12	−0.19±0.18
non-smoker	(79)	2.62	0.13±0.07	(39)	2.29	0.11±0.06
Alcohol						
every day	(15)	2.58	0.24±0.18	(7)	2.81	0.21±0.09
1–4 times/w	(11)	2.60	0.14±0.18	(8)	1.88	0.05±0.18
less	(60)	2.61	0.07±0.08	(28)	2.40	0.06±0.07

a) Mean before tea capsule intake.
b) Antibody positive means 1+, 2+, or 3+ for Pirika Plate G Helicobacter and Elisa Value 2.3 or over for Detaminor H. Pylori.

atrophy, no significant difference in the changes of pepsinogen I or I/II ratio was observed. Those with anti-*H. pylori* antibody showed a lower pepsinogen I/II ratio than those with a negative result. The difference in the pepsinogen I/II ratio for the antibody-negative participants was marginally significant ($P=0.053$) between the 1 capsule group (5 persons) and the 6 capsule group (16 persons). Among the antibody-positive participants in the 6 capsule group ($n=47$), 3 became negative and 1 became borderline, while in the 1 capsule group ($n=36$), 1 became negative and 4 became borderline. Smoking, tea and alcohol drinking did not affect the changes in pepsinogen levels.

Thirty-four participants took part in both interventions. The mean value of pepsinogen I decreased by 0.2 ng/ml during the first 1 capsule intake period and by 2.5 ng/ml during the second 6 capsule intake period, but the difference was not significant by the paired *t* test. The mean pepsinogen I/II ratio was stable for both intervention periods: the differences were −0.03 and 0.02, respectively. The mean pepsinogen I change of the 34 participants in the 6 capsule intervention (−2.5 ng/ml) was significantly lower than the 3.2 ng/ml increase in 43 patients newly participating in the 6 capsule intervention. There was no significant difference in the change in pepsinogen I/II ratio between them (0.02 vs. 0.08).

Multivariate regression analysis was conducted to evaluate the effect of 6 capsule intake per day, standardized for sex, age, compliance, pepsinogen I or I/II ratio before intake, *H. pylori* antibody status, smoking, tea and alcohol drinking. As shown in Table V, the difference in pepsino-

Table V. Multivariate Regression Analysis for Difference in Pepsinogen I and Pepsinogen I/II Ratio before and 1 Year after Capsule Intake (*n*=129)

Variable	Pepsinogen I		Pepsinogen I/II ratio	
	β	95%CI	β	95%CI
Group				
0 for 1 capsule group				
1 for 6 capsule group	0.27	−5.30, 5.83	−0.03	−0.29, 0.23
Sex				
0 for males				
1 for females	0.42	−5.22, 6.06	0.05	−0.21, 0.32
Age in years	0.08	−0.26, 0.42	0.013	−0.003, 0.029
Compliance in %	0.06	−0.04, 0.15	−0.002	−0.006, 0.002
Pepsinogen I in ng/ml before intake	0.08	−0.06, 0.21		
Pepsinogen I/II ratio before intake			−0.02	−0.11, 0.06
H.pylori antibody[a]				
0 for negative				
1 for positive[b]	1.89	−4.81, 8.58	−0.23	−0.56, 0.09
1 for not tested	−0.81	−8.52, 6.91	0.02	−0.35, 0.38
Japanese tea[a]				
0 for 0–2 cups/day				
1 for 3–5 cups/day	−0.08	−0.99, 10.02	0.03	−0.23, 0.29
1 for ≥6 cups/day	−0.70	−6.78, 5.37	0.09	−0.18, 0.37
Smoking				
0 for non-smoker				
1 for smoker	−1.64	−9.73, 6.45	−0.19	−0.56, 0.18
Alcohol				
0 for "less"				
1 for 1 or more times/w	4.51	−1.00, 10.02	0.09	−0.17, 0.34
Intercept	−11.36		−0.48	

a) Two dummy variables were used.
b) Antibody positive means 1+, 2+, or 3+ for Pirika Plate G Helicobacter and Elisa Value 2.3 or over for Detaminor H. Pylori.

gen I or I/II ratio was negligible between the 1 capsule group and the 6 capsule group.

DISCUSSION

Stomach cancer is thought to be a good target for chemoprevention. Several trials have been conducted or are ongoing throughout the world. In the Linxian district in China, where the esophageal/gastric cardiac cancer rate was quite high and the intake of micronutrients low, a significant reduction in stomach cancer mortality (RR=0.79, 95% confidence interval=0.75–1.00) was observed for participants randomly allocated to a combination of 15 mg of β-carotene, 30 mg of vitamin E, and 50 µg of selenium intake per day after a 5-year follow-up.[22] In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study conducted in Finland for 29,000 male smokers aged 50 to 69 years, end-of-trial prevalence of gastric neoplasia was not different among 4 groups, placebo, α-tocopherol (50 mg/day) only, β-carotene (20 mg/day) only, and both, after a median supplementation time of 5.1 years.[23] In Venezuela, a double-blind, placebo-controlled trial is ongoing for 2,200 participants aged 35 to 69 years, to examine the effects of 3 year supplementation of vitamin C (750 mg/day), vitamin E (600 mg/day), and β-carotene (6 mg/day) on precancerous lesions of the stomach.[24] Double-blind, placebo-controlled trials of β-carotene and/or vitamin C are under way for precancerous lesions in Colombia[25] and in Europe,[26] and for stomach cancer incidence in Japan.[27]

There have been no intervention studies with tea polyphenols reported so far. Our phase II study showed that a 1-year intervention with tea polyphenol capsules did not affect the pepsinogen levels on average. This result might have been expected, because atrophic gastritis is thought to be irreversible and tea drinking is a common habit among the Japanese, especially among the older generation. Possible explanations of our results are

as follows: 1) additional tea polyphenol intake may improve atrophy or disturb the progression, but 1 year is too short to observe the effect, 2) it does not improve atrophy for those who already drink much tea, 3) it may work against atrophic change only at an earlier stage, and/ or 4) tea polyphenols do not work against atrophy, even if they are effective against stomach carcinogenesis. Interpretations 1) and 4) may be possible, but 2) and 3) seem unlikely because no difference was observed after stratification of the amount of daily tea drinking, or among those with a pepsinogen I/II ratio >3.

In this study, anti-*H. pylori* antibody-negative participants in the 6 capsule group showed a marginally significant increase in pepsinogen I/II ratio compared with those in the 1 capsule group. However, since the comparison was based on 5 vs. 16 participants, and since the result was observed among dozens of subgroup analyses, it may have occurred by chance.

The examination of adverse effects is essential before chemopreventive agents are applied in the population at large. The majority of Japanese are familiar with adverse effects as well as the beneficial ones of tea through daily life experience, but formal reports on adverse effects have not been published except for one on green tea-induced asthma.[28] Although it has not been published, a phase I study with 10 volunteers (5 male research staff members and 5 nurses at Aichi Cancer Center), where 6 capsules per day for 3 months were administered, was conducted in 1994 before this phase II study. Blood pressure was taken and blood tests (urea nitrogen, creatinine, uric acid, glucose, total cholesterol, HDL cholesterol, triglyceride, γ-GTP, GOT, GPT, LDH, Fe, total iron binding capacity, saturation % of Fe, white blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count; pepsinogens I and II were not measured) were administered 4 times; at the start of intake, 6 weeks after, at the end of intake (3 months after the start), and 6 weeks after the end of intake. No adverse effects were found in blood pressure or the blood tests. However, 1 female participant complained of sleeplessness; as a result, her compliance was 63.3% of the scheduled dose. Sleeplessness was observed in the 6 capsule group of the phase II study. It had been expected that the quantity of caffeine in the capsules would be enough to disturb the sleep of caffeine-sensitive persons, as strong tea does. Loose stools might also be caused by tea polyphenols, because it has been found that tea catechins influence flora in the large intestine: lactobacilli and bifidobacteria increase while enterobacteriaceae decrease.[29] Abdominal discomfort may be partly due to tea polyphenols, as it is commonly observed that drinking strong tea on an empty stomach causes abdominal discomfort. It may also have been partly due to participants' illnesses, as participants in the phase II study were recruited from outpatients who had undergone gastroscopy for reasons including abdominal discomfort.

This is the first intervention study to report the effects of tea polyphenols on gastric atrophy in terms of pepsinogen levels; in this study, an additional tea polyphenol intake equivalent to 10 cups per day was compared with a negligible additional amount, in a situation where the majority of participants drank 3 cups of tea or more in a day. Since this study did not directly relate to the carcinogenic process, but rather examined tea polyphenols' influence on gastric atrophy, it remains unclear whether the gastric atrophy is indeed a useful biomarker for chemoprevention trials against stomach cancer. However, this study made it clear that the effect of tea polyphenol intake for 1 year on gastric atrophy is limited, which discourages us from conducting randomized trials on tea polyphenols as a means of reducing pepsinogen levels in the Japanese population.

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