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A nested case–control study of stomach cancer in relation to green tea consumption in Japan

Y Hoshiyama*[,1], T Kawaguchi[1], Y Miura[2], T Mizoue[3], N Tokui[3], H Yatsuya[4], K Sakata[5], T Kondo[4], S Kikuchi[6], H Toyoshima[4], N Hayakawa[7], A Tamakoshi[8], Y Ohno[8] and T Yoshimura[3] for the Japan Collaborative Cohort Study Group[†]

[1]Department of Public Health, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa, Tokyo 142-8555, Japan; [2]Department of Nursing, Saitama University, Saitama, Japan; [3]Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Fukuoka, Japan; [4]Department of Public Health/Health Information Dynamics, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Department of Public Health, Wakayama Medical University, Wakayama, Japan; [6]Department of Public Health, Aichi Medical University, Aichi, Japan; [7]Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan; [8]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

To evaluate whether green tea consumption provides protection against stomach cancer, the relative risks (RRs) were calculated in the Japan Collaborative Study for Evaluation of Cancer Risk, sponsored by the Ministry of Health and Welfare (JACC Study). The study was based on 157 incident cases and 285 controls aged 40–79 years. Cox proportional hazards regression analysis was used to estimate the RRs for stomach cancer. It was found that green tea consumption had no protective effect against stomach cancer. After adjustment for age, smoking status, *H. pylori* infection, history of peptic ulcer, and family history of stomach cancer along with certain dietary elements, the risks associated with drinking one or two, three or four, five to nine, and 10 or more cups of green tea per day, relative to those of drinking less than one cup per day, were 1.3 (95% confidence interval (CI): 0.6–2.8), 1.0 (95% CI: 0.5–1.9), 0.8 (95% CI: 0.4–1.6), and 1.2 (95% CI: 0.6–2.5), respectively (*P* for trend = 0.899). We found no inverse association between green tea consumption and the risk of stomach cancer.
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Stomach cancer is the second most common cancer worldwide (Parkin *et al*, 1999). In Japan, this cancer is the leading cause of cancer death among women and the second among men (Statistics and Information Department, Minister's secretariat, Ministry of Health and Welfare Japan, 2000). It has recently been reported that green tea consumption is inversely associated with the risk of stomach cancer; in other words, it has a protective effect. Green tea polyphenols have various anticarcinogenic effects, such as strong antioxidant activity, and inhibition of nitrosation and cell proliferation.

Although case–control studies (Kono *et al*, 1988; Yu and Hsieh, 1991; Yu *et al*, 1995; Ji *et al*, 1996; Inoue *et al*, 1998; Setiawan *et al*, 2001) have found a reduced risk of stomach cancer in association with green tea consumption, prospective studies (Galanis *et al*, 1998; Nakachi *et al*, 2000; Nagao *et al*, 2001; Tsubono *et al*, 2001) have not. A recent prospective study found that green tea had a protective effect against stomach cancer. Urinary tea polyphenols have been associated with protection from the risk of stomach cancer, while controlling *Helicobacter pylori* infection. Past studies did not consider the presence or absence of a history of infection with *H. pylori*, a strong risk factor for stomach cancer (Asaka *et al*, 1997). Assuming that green tea consumption is related to *H. pylori* infection, when a subject has a history of infection with *H. pylori* and consumes a large quantity of green tea, the protective effect, if any, would be masked. The present nested case–control study aimed to examine the association between green tea consumption and the risk of stomach cancer, while controlling *H. pylori* infection and other potential confounders, using data from the Japan Collaborative Cohort (JACC) Study, a Japan-wide population-based prospective study. This is the first study to analyse the effects of green tea consumption while controlling *H. pylori* infection.

MATERIAL AND METHODS

JACC Study

This study was part of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (the JACC Study), a nationwide multicentre collaborative study to prospectively evaluate various risk or protective factors for cancer mortality and

*Correspondence: Dr Y Hoshiyama, E-mail: yhkiss@med.showa-u.ac.jp
† See the appendix for the investigators (name and affiliation) involved in the JACC Study
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incidence. Details of the study design were reported previously. Briefly, the cohort included 110 792 men and women (46 465 and 64 327, respectively), aged 40–79 years at recruitment, who were enrolled from 1988 to 1990. Enrollment was based on the participants of a general health checkup periodically provided by the 45 municipalities involved. The informed consent procedures were approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, and the Ethical Board of the Nagoya University School of Medicine, Japan.

At the time of recruitment, baseline characteristics were gathered by a self-administered questionnaire, which covered the medical history and included items such as drinking and smoking, level of education, and family history of several medical conditions including cancer. About one-third of the cohort members ($n=39\,293$) also donated a residual serum sample (about 2 ml) to be used for the general health checkup. This sample was partitioned into 0.3–0.5 ml aliquots and stored at −80°C, until laboratory analyses were performed. The *H. pylori* antibody level was measured in the serum using HM-CAPTM (Enteric Products, Westbury, NY, USA) with an antigen from Japanese (J-HM-CAP). The cutoff value was determined at 2.3, which was recommended in the manufacturer's instructions.

Follow-up and identification of stomach cancer cases, and selection of control subjects

The vital status of each participant was checked annually by each regional research centre, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications to review their population register sheets. The incidence of cancer was ascertained in 24 study areas ($n=65\,184$) and coded according to the tenth revision of the International Classification of Disease and the second edition of the International Classification of Diseases for Oncology. These data were collected at the central office of the Research Committee.

We first restricted the subjects to those who lived in the study areas where cancer incidence was ascertained. We then excluded 857 participants with a self-reported history of cancer. From the remaining 64 327 subjects, diagnosis of stomach cancer at 12 or more months after cohort recruitment was documented in 804 subjects until the end of 1997. Serum had been obtained from 218 cases of the initial 804 cases. However, seven cases without sufficient serum for the laboratory analyses and one case without an eligible control subject were excluded. Thus, the study reported here included 210 cases in total. There were no differences between those selected for the case–control study nested within the cohort and those who were not selected in terms of the variables included in the multivariate model. The lag time between blood sampling and stomach cancer diagnosis varied between 12 and 113 months (median, 50 months). Each of these subjects was matched with two control subjects with respect to sex, age at recruitment (as near as possible), and study area, who had also provided an adequate baseline blood sample, and who were alive and free of confirmed cancer by the end of 1997. Owing to a lack of eligible subjects, a few sets ($n=10$) contained only one control, and thus there was a total of 410 controls.

Since questions on the daily consumption of green tea were not included in the questionnaire in seven areas (four rural areas and three urban/rural areas), we excluded these data (49 cases and 88 controls). Of the 161 cases and 322 controls remaining, eight cases (5.0%) and 38 controls (11.8%) had green tea consumption data missing from the questionnaire; so these too were excluded. Owing to a lack of eligible subjects, 16 sets were further excluded. The remaining 151 cases and 265 controls were included in the present analysis.

Data processing

Cox proportional hazard regression analysis was used. The relative risk (RR) and its 95% confidence interval (CI) were calculated based on the regression coefficient and its standard error (Cox, 1972), for an indicator term corresponding to the level of an independent variable. For multivariate analysis, several factors were listed as potential confounders according to epidemiological studies (Boeing, 1991; Hoshiyama and Sasaba, 1992; World Cancer Research Fund, 1997; Hoshiyama *et al*, 2002; Yatsuya *et al*, 2002). Trends of association were assessed by the regression model assigning scores (0–4) to the levels of the independent variables. Statistical significance (two-sided) was based on the ratio of the regression coefficient and its standard error. Statistical analysis (PHREG procedure) was performed using the Statistical Analysis System (SAS Institute, 1983).

RESULTS

Table 1 compares the characteristics of the cases and the controls. The consumption of green tea varied substantially. The proportion with a history of *H. pylori* infection was higher for the cases than for the controls. The proportion with a family history of stomach cancer was also higher for the cases than for the controls. The proportion of current smokers was also higher for the cases than for the controls. The cases consumed rice, miso soup, green-yellow vegetables, and fruit more frequently than the controls.

Table 2 shows the RR and its CI for stomach cancer according to green tea consumption. The age/sex-adjusted RRs associated with drinking one or two, three or four, five to nine, and 10 or more cups of green tea per day, relative to those of drinking less than one cup per day, were 1.2 (95% CI: 0.5–2.9), 0.9 (95% CI: 0.4–1.9), 0.7 (95% CI: 0.3–1.5), and 1.0 (95% CI: 0.4–2.4), respectively. Multivariate RRs were similar to age/sex-adjusted and age/sex- and *H. pylori* infection-adjusted RRs.

Table 1 Characteristics of cases and controls

	Case	Control
No	**151**	**265**
Age (years)	61.7	61.5
Green tea (cups per day)		
<1	18	31
1 or 2	19	23
3 or 4	41	73
5–9	50	105
⩾10	23	33
H. pyroli infection (%)	88.7	77.7
History of peptic ulcer (%)	19.7	18.2
Family history of stomach cancer (%)[a]	20.5	16.2
⩽9 years of schooling (%)[b]	37.1	32.0
Smoking (%)		
Current	32.2	28.7
Past	18.5	18.0
Daily dietary consumption (%)		
Rice (⩾4 bowls day^{-1})	36.5	31.8
Miso soup (⩾1 cup day^{-1})	83.7	77.9
Preference for salty foods (yes)	33.8	29.6
Green-yellow vegetables (⩾1 day^{-1})	46.7	42.3
White vegetables (⩾1 day^{-1})	38.6	40.5
Fruits (⩾3 week^{-1})	44.4	39.3

[a]We defined a positive family history of stomach cancer as when the subject had a least one first-degree relative (parents or siblings) with a history of stomach cancer. [b]Information on educational level was measured as the age of formal schooling completed and was classified into two categories: ⩽15 years old (corresponds to ⩽9 years of schooling) and ⩾16 years old (corresponds to ⩾10 years of schooling).

Table 2 Relative risk of stomach cancer according to green tea consumption

	Green tea consumption (cups day^{-1})					
	<1	1 or 2	3 or 4	5–9	⩾10	*P* for trend
Case/controls	18/31	19/23	41/73	50/105	23/33	
Age/sex-adjusted RR	1.0	1.2 (0.5–2.9)	0.9 (0.4–1.9)	0.7 (0.3–1.5)	1.0 (0.4–2.4)	0.515
Age/sex- and *H. pylori*-adjusted RR	1.0	1.1 (0.4–2.9)	0.9 (0.4–1.9)	0.7 (0.3–1.5)	1.1 (0.4–2.5)	0.628
Multivariate RR[a]	1.0	1.3 (0.6–2.8)	1.0 (0.5–1.9)	0.8 (0.4–1.6)	1.2 (0.6–2.5)	0.899

[a]Adjusted for age (four classes), smoking status (never, past, current), sex, *H. pylori* infection, history of peptic ulcer, family history of stomach cancer, educational level (two levels), consumption of rice, miso soup, green–yellow vegetables, white vegetables, fruits, and preference for salty foods (two categories). Values in parantheses are 95% confidence intervals. RR = relative risk.

Table 3 Relative risk of *H. pylori* infection positive according to green tea consumption among controls

	Green tea (cups day^{-1})					
	<1	1 or 2	3 or 4	5–9	⩾10	P for trend
Age–sex-adjusted RR of *H. pylori* infection positive	1.0	1.0 (0.2–3.8)	1.0 (0.3–2.8)	1.1 (0.4–3.1)	0.7 (0.2–2.5)	0.901

Table 3 shows the age/sex-adjusted RRs of *H. pylori* infection positivity according to green tea consumption. *H. pylori* infection did not differ with the consumption of green tea.

DISCUSSION

This nested case–control study is the first study to investigate any association between green tea consumption and the risk of stomach cancer while controlling *H. pylori* infection. Among the possible limitations of the present study was incomplete data. About 10% of subjects were excluded from the analysis because they had not provided information concerning their daily consumption of green tea. We could not fully evaluate the effects of the exclusion of these data. Nevertheless, there was no difference between the percentages of smokers in the whole data (53.1% of men and 2.9% of women) and those in the included data (51.9% and 3.7%, respectively), as examined by the Cochran–Mantel–Haenszel χ^2 test ($P = 1.000$ and 0.843, respectively). The missing information therefore seemed to occur randomly.

The second possible problem with the present study was in the questionnaire. The original words of the question on green tea were: Do you drink Japanese tea (green tea)? There are various kinds of Japanese tea, although for Japanese people green tea is the one that most often comes to mind. About 89% of the total production of Japanese tea in 1999 was ordinary green tea (The Ministry of Agriculture, Forestry, and Fisheries, 1999). We believe that a slight misclassification could have derived from the idiosyncrasy of our questionnaire pertaining to Japanese tea (green tea).

Green tea is widely consumed in Japan and other Asian countries. If drinking green tea protects against stomach cancer, it would be an inexpensive and convenient method of primary prevention. Tsubono *et al* reported that there was no association between green tea consumption and the risk of stomach cancer, consistent with the finding of this prospective study. Little other evidence is available from prospective studies (Galanis *et al*, 1998; Tsubono *et al*, 2001). Past studies did not consider the influence of *H. pylori* infection. Subjects with chronic gastritis caused by *H. pylori* infection might have limited their consumption of green tea. If so, the prevalence of infection would have been lower in the subjects with higher intakes of green tea. If not, the prevalence of infection would have been higher among the subjects with higher intakes of green tea. This condition would have masked an inverse association between the risk of stomach cancer and green tea consumption. We examined the association of *H. pylori* infection and green tea consumption, and found that *H. pylori* infection did not differ with the consumption of green tea (see Table 3).

Our findings are in general agreement with those of four prospective studies which found no inverse association between green tea consumption and the risk of stomach cancer (Galanis *et al*, 1998; Nakachi *et al*, 2000; Nagao *et al*, 2001; Tsubono *et al*, 2001). The number of cases of stomach cancer was relatively large in three studies. Recently, another prospective study was conducted in Shanghai, China. Urinary EGC positivity showed a statistically significant inverse association with stomach cancer (OR = 0.52, 95% CI = 0.28–0.97) after adjustment for *H. pylori* seropositivity, smoking, alcohol drinking, and the level of serum carotenes (Sun *et al*, 2002). Cumulative excretion of EGC increased with increasing green tea consumption in human subjects (Yang *et al*, 1998). It might be important to evaluate biomarkers of tea polyphenol exposure.

In summary, we found no inverse association between the consumption of green tea and the risk of stomach cancer in Japan in a nested case–control study.

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Appendix

JAPAN COLLABORATIVE COHORT STUDY GROUP

The investigators involved in the present JACC study and their affiliations are as follows: Dr Yoshiyuki Ohno, (the present chairman of the Monbusho ECC), Dr Akiko Tamakoshi (Secretary General of the Monbusho ECC), and Dr Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr Mitsuru Mori, Sapporo Medical University School of Medicine; Dr Yutaka Motohashi, Akita University School of Medicine; Dr Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr Yosikazu Nakamura, Jichi Medical School; Dr Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr Haruo Mikami, Chiba Cancer Center; Dr Shuji Hashimoto, School of Health Sciences and Nursing, University of Tokyo; Dr Yutaka Inaba, Juntendo University School of Medicine; Dr Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr Yoshiharu Hoshiyama, Showa University School of Medicine; Dr Hiroshi Suzuki, Niigata University School of Medicine; Dr Hiroyuki Shimizu, Gifu University School of Medicine; Dr Shinkan Tokudome, Nagoya City University Medical School; Dr Yoshinori Ito, Fujita Health University School of Health Sciences; Dr Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr Takashi Kawamura, Kyoto University Center for Student Health; Dr Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine, Research Institute for Neurological Diseases Geriatrics; Dr Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr Tsutomu Hashimoto, Wakayama Medical University; Dr Takayuki Nose, Tottori University Faculty of Medicine; Dr Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr Katsuhiro Fukuda, Kurume University School of Medicine; Dr Tomoyuki Kitagawa, Cancer Institute of Japanese Foundation for Cancer Research; Dr Toshio Kuroki, Institute of Molecular Oncology, Showa University; Dr Naoyuki Okamoto, Kanagawa Cancer Center; Dr Teruo Ishibashi, Asama General Hospital; Dr Hideo Shio, Shiga Medical Center and Dr Kazuo Tajima, Aichi Cancer Center Research Institute.

The former investigators involved in the JACC study and their affiliations are as follows: Dr Kunio Aoki, Aichi Cancer Center; Dr Suketami Tominaga, Aichi Cancer Center Research Institute; Dr Sadamu Anzai, Dr Takeshi Kawaguchi, Dr Kenichi Nakamura, Dr Motofumi Masaki, Showa University School of Medicine; Dr Shuugo Kanamori, Dr Masachika Morimoto, Dr Seishi Yoshimura, Shiga Medical Center for Adults; Dr Sigetosi Kamiyama, Dr Yukio Takizawa, Dr Noriyuki Hachiya, Akita University School of Medicine; Dr Keiichi Kawai, Dr Shuichi Nakagawa, Dr Hiroki Watanabe, Kyoto Prefectural University of Medicine; Dr Minoru Kurihara, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr Yoshio Komachi, Institute of Community Medicine, University of Tsukuba; Dr Ruichiro Sasaki, Aichi Medical University; Dr Minoru Sugita, Toho University School of Medicine; Dr Iwao Sugimura, Asahikawa Kosei Hospital; Dr Toshihiko Tanaka, Chigasaki Public Health Center; Dr Tomio Hirohata, Kyushu University School of Medicine; Dr Isaburo Fujimoto, Center for Adult Diseases, Osaka; Dr Minoru Matsuzaki, Chigasaki Public Health and Welfare Center; Dr Hirotsugu Miyake, Sapporo Medical University School of Medicine; Dr Motoi Murata, Chiba Cancer Center; Dr Shinsuke Morio, Kanagawa Cancer Center; Dr Hiroshi Yanagawa, Jichi Medical School and, Dr Shaw Watanabe, Tokyo University of Agriculture.

Serum midkine concentrations and gastric cancer

Yuki Obata,[1] Shogo Kikuchi,[1,4] Yingsong Lin,[1] Kiyoko Yagyu,[1] Takashi Muramatsu,[2] Hideshi Kumai[3] and Tokyo Research Group on Prevention of Gastric Cancer

[1]Department of Public Health, Aichi Medical University, School of Medicine, 21 Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan; [2]Department of Health Science, Faculty of Psychological and Physical Sciences, Arichi Gakuin University, 12 Araike, Iwasaki-cho, Nisshin, Aichi 470-0915, Japan; and [3]Meiji Dairies Corporation, 540 Naruda, Odawara, Kanagawa 250-0862, Japan

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Midkine (MK) is one of a family of heparin-binding growth factors, and increased MK expression is reported in various types of human carcinomas. To clarify the association between serum MK (S-MK) concentrations and gastric cancer, we examined S-MK concentrations of gastric cancer patients (n = 275) and healthy controls (n = 275). S-MK concentrations of all subjects were measured by enzyme-linked immunosorbent assay (ELISA). The medians (25th and 75th percentiles) of S-MK were 192 (123 and 314) pg/mL in the cases and 170 (81 and 273) pg/mL in the controls ($P < 0.01$). We also compared S-MK concentrations in each group divided by the progression stage or histological type of cancer. A difference was observed in the median S-MK concentrations between early and advanced cancers [182 (105 and 301) pg/mL *vs* 203 (139 and 331) pg/mL, $P = 0.07$], but not between intestinal and diffuse type cancers [185 (121 and 306) pg/mL *vs* 198 (127 and 323) pg/mL, $P = 0.51$]. We found that those progression stages affect S-MK concentration more strongly than the histological types in gastric cancer patients. Because S-MK seems to reflect the progression stage of gastric cancer, it may serve as a useful marker in the clinical follow-up of gastric cancer patients. (*Cancer Sci* 2005; 96: 54–56)

Midkine (MK) is a heparin-binding growth factor which is the product of a retinoic acid-responsive gene whose expression increases during the early differentiation stage in embryonal carcinoma cells.[1–3] MK exhibits various activities such as vascularization, promoting the growth of fibroblast, suppressing apoptosis, and inducing cell migration, and is considered to be involved in carcinogenesis and tumor progression.[4–9] Increased MK mRNA and protein expressions are reported in many human carcinomas such as gastric, pancreatic, bile duct, colorectal, hepatocellular, esophageal cancers, and in lung, breast, bladder, ovarian, and prostate carcinomas as well as in Wilms' tumors and neuroblastomas.[10–20] As it is a secreted protein, MK can be detected in the blood. Increased concentrations of blood MK have been reported in esophageal cancer and neuroblastoma.[21,22] Although there are several reports indicating that serum MK (S-MK) is elevated in other cancers, those studies involved only a few subjects.[23–25] To gain a better understanding of S-MK concentrations in gastric cancer, we investigated S-MK concentrations in each group divided by the progression stage or histological type of gastric cancer.

Materials and methods

Subjects. The case subjects were patients who were newly diagnosed as having gastric cancer at one of nine hospitals in the Tokyo Metropolitan Area between 1993 and 1995. Patients who had undergone treatment for gastric cancer were excluded at entry. An endoscopy was performed on all eligible cases, and the diagnosis was confirmed by an examination of resection or biopsy specimens. Data on pathological findings, including the type and stage of the cancer, were then recorded. Gastric cancer was subdivided by progression stage (early or advanced) and histological type (intestinal or diffuse) based on the criteria proposed by the Japanese Research Society for Gastric Cancer (JRSGC). The control subjects were recruited from a group of apparently healthy people who underwent medical checkups at a health promotion center in the same area. The cases and the controls were asked to provide sera, and written informed consent was obtained from all subjects. All sera of the cases were provided within 2 months from diagnosis; and before surgery between 1993 and 1995 we enrolled 788 gastric cancer patients and 1007 apparently healthy controls. From this group, we randomly selected 275 cases considering sex and age. Between case and control subjects, sex and age (±2 years) were matched. From the control subjects with the same age and sex, one whose date of phlebotomy was the nearest to that of each case subject was selected.

Serum samples of the subjects were collected using the same methods and frozen at −80°C until analysis.

ELISA assay. Serum *Helicobacter pylori* IgG antibodies were measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (J-HM-CAP; Kyowa Medex, Japan). Intra-assay coefficient of variation in J-HM-CAP (three different concentration samples in eight intra-assays) was 5.7% (range, 1.2–14.3%). Inter-assay coefficient of variation in J-HM-CAP (10 different concentration samples in three interassays) was 0.5% (range, 0.0–2.0%). The assay was performed according to the manufacturer's instructions. The *H. pylori* IgG level of ≥2.7 EV (the appropriate cut-off value of this kit established in our previous study) was determined as positive.[26] S-MK concentrations were measured with solid-phase human MK immunoassay ELISA kit systems as previously described.[25] Intra-assay coefficient of variation in S-MK kit (5 different concentration samples in 2 intra-assays) was 3.1% (range, 0.0–8.6%). Inter-assay coefficient of variation in S-MK kit (5 different concentration samples in 5 interassays) was 16.5% (range, 11.0–24.5%). During the measurements, serum samples were analyzed in randomly ordered duplicates in order to reduce systematic and interassay errors. All assays were performed by laboratory personnel who were blinded to each case/control status.

Statistics analysis. Because skewness and kurtosis of the distribution in S-MK concentrations was not improved though logarithmic transformation of S-MK concentrations was performed, we used non-parametric analysis. A comparison of the median S-MK concentrations between different groups was made using the Mann–Whitney U-test. The other characteristics were compared between cases and controls by using the χ^2 test. Cut-off points of the quartiles for smoking and drinking doses were described in our previous study.[27] All analyses were carried out using HALWIN (Gendaisugakusha, Kyoto, Japan).

Results

The age distribution of the cases was as follows: 20–29 years, 4 cases (1.4%); 30–39, 36 (13.1%); 40–49, 47 (17.1%); 50–59,

[4]To whom correspondence should be addressed. E-mail: kikuchis@aichi-med-u.ac.jp

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Table 1. Characteristics of cases and controls

	Cases (n = 275)		Controls (n = 275)		P for difference
	N	%	N	%	
Sex					
Male	142	51.6	142	51.6	
Female	133	48.4	133	48.4	
Mean age ± SD	53.5 ± 10.5		53.6 ± 10.5		
Mean S-MK ± SD (pg/mL)	265 ± 367		190 ± 146		$P < 0.01$
H. pylori infection					$P < 0.01$
No	18	6.5	105	38.2	
Yes	257	93.5	170	61.8	
Smoking dose (cigarette-years†)					$P = 0.31$
0 (Never-smoker)	127	46.2	141	51.3	
1–399	39	14.2	44	16.0	
400–799	52	18.9	42	15.3	
800+	51	18.5	35	12.7	
unknown	6	2.2	13	4.7	
Drinking dose (alcohol-years‡)					$P < 0.05$
0 (Never-drinker)	92	33.5	74	26.9	
Occasional and 0.1–134.9	46	16.7	63	22.9	
135.0–1349.9	51	18.5	57	20.7	
1350.0+	68	24.7	45	16.4	
unknown	18	6.6	36	13.1	

†Cigarettes/day multiplied by years of smoking. ‡Pure alcohol intake (ml)/day multiplied by years of drinking.

Table 2. S-MK concentrations in cases and controls

	N	Median of S-MK† (pg/ml)	P‡
Controls	275	170 (81 and 273)	<0.01
Cases	275	192 (123 and 314)	
Progression stage§			
Ealy	123	182 (105 and 301)	0.07
Advanced	151	203 (139 and 331)	
Histological type			
Intestinal	120	185 (121 and 306)	0.51
Diffuse	155	198 (127 and 323)	

†The numbers in parentheses indicate 25th and 75th percentiles.
‡The Mann-Whitney U test was used for group comparison.
§One case lacked data on the progression stage for cancer.

94 (34.2%); 60–69, 94 (34.2%). The cases included 142 males (51.6%) and 133 females (48.4%).

The characteristics of the cases and controls are shown in Table 1. The differences were observed in the distribution of *H. pylori* infection and drinking dose between cases and controls, but we found that these factors didn't affect S-MK values significantly for multiple regression analysis with log-transformation of S-MK values (data not shown). The distributions of all characteristics between early and advanced cases, and between intestinal and diffuse type cancer cases were not significantly different (data not shown). The medians (25th and 75th percentiles) of S-MK were 192 (123 and 314) pg/mL in the cases and 170 (81 and 273) pg/mL in the controls (Table 2). We also calculated the median S-MK concentrations of each group divided by the progression stage or histological type of cancer (Table 2). A difference was observed in the median (25th and 75th percentiles) S-MK concentrations between early and advanced cancers [182 (105 and 301) pg/mL *vs* 203 (139 and 331) pg/mL, $P = 0.07$], but not between intestinal and diffuse type cancers [185 (121 and 306) pg/mL *vs* 198 (127 and 323) pg/mL, $P = 0.51$].

Discussion

Increased MK expression has been reported in various human carcinomas.[10–20] Our study showed that the S-MK levels in gastric cancer patients were significantly higher than those in age- and gender-matched control subjects. A recent study has also reported that the S-MK levels in esophageal cancer patients were elevated.[21] Given the inherent limitations of any case-control study, it is not clear whether the high S-MK levels in their case subjects were the cause or the result of gastric cancer. Previous studies have demonstrated that S-MK levels decreased after surgical resection of the tumor in several carcinomas, including gastric cancer.[24] This indicates that the high level of S-MK in our case subjects may be the result rather than the cause of their gastric cancer. MK protein overexpressed in carcinoma tissue may be secreted into the circulation, thus inducing those S-MK high levels. However, there still remains the possibility that up-regulated MK accelerates tumor progression. A prospective study will be needed to clarify whether MK produces such an effect.

The median S-MK concentrations in the advanced cancer group was higher than that in the early cancer group, but there was no significant difference in S-MK concentrations between the intestinal and diffuse types. Therefore, it would seem that the progression stage of cancer rather than the histological type of cancer affects S-MK concentrations more strongly. In neuroblastoma patients, plasma MK levels were found to be higher among patients in the more advanced stages of the disease.[22] Those results suggested that the amount of MK produced may increase with advancing cancer stages. We also analyzed the association between tumor volume and gastric cancer, but could find no clear association between the two (data not shown).

In conclusion, S-MK may be more useful as a marker in the clinical follow-up of patients rather than in the early diagnosis of gastric cancer.

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The members (names and affiliations) of the Tokyo Research Group on Prevention of Gastric Cancer are: Toshifusa Nakajima, Department of Surgery, Cancer Institute Hospital, Tokyo; Osamu Kobayashi, Department of Surgery, Kanagawa Cancer Center Hospital; Tatsuo Yamazaki, 1st Department of Surgery, Saitama Medical School (now Maruyama Memorial Hospital); Masahiro Kikuichi, Department of Surgery, Mitsui Memorial Hospital; Kiyoshi Mori, 2nd Department of Surgery, Graduate School of Medicine, University of Tokyo (now department of Surgery, Sanikukai Hospital); Shinsuke Oura, 2nd Department of Surgery, Juntendo University School of Medicine (now Department of Surgery, Yanagibashi Hospital); Hideaki Watanabe, 1st Department of Surgery, Juntendo University School of Medicine; Hirokazu Nagawa, Department of Surgical Oncology, Graduate School of Medicine, University of Tokyo; Reiji Otani, Sempo Tokyo Takanawa Hospital (now Sempo Shibaura Clinic); Naoyuki Okamoto, Department of Epidemiology, Kanagawa Cancer Research Institute; Michiko Kurosawa, Department of Epidemiology and Environmental Health, Juntendo University School of Medicine; Haruyuki Anzai, 1st Department of Surgery, Saitama Medical School; Toshiro Konishi, 2nd Department of Surgery, Graduate School of Medicine, University of Tokyo (now Department of Surgery, Kanto Medical Center NTT EC); Shunji Futagawa, 2nd Department of Surgery, Juntendo University School of Medicine; Noboru Mizobuchi, 1st Department of Surgery, Juntendo University School of Medicine; Oichiro Kobori, International Medical Center; Ruriko Kaise, Sempo Tokyo Takanawa Hospital; Yutaka Inaba, Department of Epidemiology and Environmental Health, Juntendo University School of Medicine; Osamu Wada, Department of Hygiene and Preventive Medicine, Graduate School of Medicine, University of Tokyo (now Professor Emeritus, University of Tokyo).

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【原 著】

葛飾区におけるペプシノゲン2段階法による住民胃がん検診3年間の評価

Evaluation of Two-step Gastric Cancer Detecting Program Using Serum Protein Test for People in Katsushika Ward in Tokyo from 2000 to 2003

伊藤史子・鈴木祐子

Fumiko Ito, Yuko Suzuki

葛飾区保健所

Katsushika Ward Public Health Center

要 旨

葛飾区では、節目年齢（40，45，50，55歳）の住民を対象に平成12年度からペプシノゲン2段階法胃がん検診を実施してきた。これまでの3年間の成績をまとめ検討する。本検診の受診者総数は13,705人で、全体の胃がん発見率は13人0.095％で、早期胃がんは11人で早期胃がん率は84.6％と高かった。このうちペプシノゲン（以下PG）陽性がんは11人、PG陰性がんは2人であった。本検診におけるPG陰性がんの発見率はX線検査受診者（6,483人）の0.031％で、陽性反応適中度は0.33％であった。地域住民の胃がん検診においてもPG2段階法は、PG法とX線法を相補って胃がん発見に寄与していると思われる。一人当たり1次検診コストはX線単独法の比して低いが、それほど太きな差はなかった。老人保健法対象人口に対する受診率は28.9％であった。

キーワード：胃がん検診 ペプシノゲン法 2段階法

Key Words：Gastric cancer screening pepsinogen test two-step program

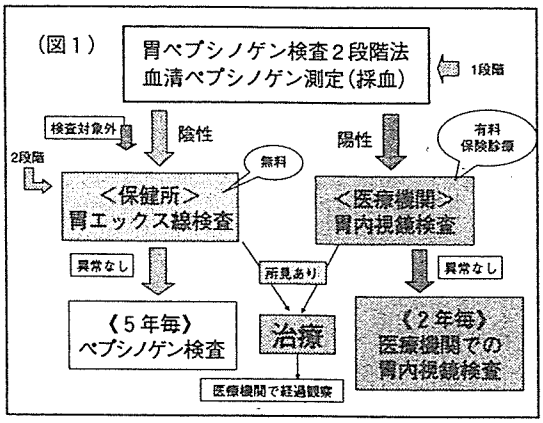
[目 的]

総人口約43万の葛飾区では、平成12年度から、壮年者の節目健診に併せてペプシノゲン2段階法による胃がん検診を実施してきた。平成14年度まで3年間の成績をまとめ、胃がん発見状況、現時点での本法の検診コスト、対象者に対する検診カバー率及び課題等について検討する。

[対象と方法]

検診の対象と方法は、既に詳細に述べている[1]のでその要旨を記載する。節目健診においては、40歳、45歳、50歳及び55歳の節目年令の区民全員に健診通知を発送する。健診希望者は保健所に申し込み、保健所及び保健センター(計6ヵ所)で健診を受ける。この際採取した血液サンプルは民間の検査機関に送付しエンザイムイムノアッセイ(EIA)法により血清ペプシノゲン(以下PG)の測定を行う。PG値の判定基準はPGⅠ値70ng／ml以下且つⅠ／Ⅱ比3.0以下を陽性とし、PG陽性者には医療機関で胃内視鏡検査を勧め、PG陰性者には保健所直営の胃X線間接撮影を勧める。さらにPG陽性者には、2年後に管理健診の通知を発送し、受診勧奨を行っている(図1)。検診コストについては、区職員人件費を除いた胃がん検診に要する総コスト(胃がん検診車の維持管理費、X線撮影に要するフィルム、造影剤等消耗品費、葛飾区医師会への撮影フィルム読影委託、PG検査委託料、返信料を含む諸通信費及び臨時職員の人件費)を積算し、1人当たりの経費及び1次検診での1胃がん発見費用を算出した。検診カバー率は、平成12年度に東京都が行った検診対象人口の調査[2]をもとに算出した。

（図１）



[結　果]

平成12年度から３年間の胃がんの発見状況は、PG検査受診総数13,705人中発見数13人、内早期胃がん11人で発見率は0.095％（早期胃がん率84.6％）であった（表１）。これをPG陽性群とPG陰性群別に見ると、陽性群では胃がん11（内早期胃がん9）、陰性群では2（内早期胃がん２）であった（表２）。PG陽性者の精検受診率は４年齢平均67.8％（66.0～70.1％）で、胃がん発見率は0.08％、陽性反応適中率は0.53％であった。一方PG陰性者の胃X線検査実施状況は、要精検率は14.9％、受診率57.2％、医療機関での精検受診率は62.6％であった。なお、12年度受診者のフォローの管理検診を14年度に実施したが、受診率はPG陽性者の22.3%で、胃がん発見はなかった。発見された胃がんの自覚症状、手術所見、治療法、術前術後の病期比較を一覧表に示した（表３）。本検診で発見されたPG陰性胃がんは２例とも未分化型早期がんであった。胃がん検診に要する費用では、平成12,13,14年３年間の一般公募による胃X線 単独法と２段階PG法に要したそれぞれの総コストを算出し、検診受診者１人当たりの１次検診コストを見ると、X線単独法では2,680円、２

（表1）　胃がん発見状況

葛飾区

平成年度	PG法受診者数	胃がん（早期）人		
		PG陽性	PG陰性	計
12	4,577	6(5)	1(1)	7(6)
13	4,476	4(3)	0(0)	4(3)
14	4,652	1(1)	1(1)	2(2)
計	13,705	11(9)	2(2)	13(11)

胃がん発見率　0.095%

（表２）胃がん検診３年間の成績

（葛飾区・平成12,13,14年度）

ペプシノゲン法（PG法）陽性者

年齢	健診対象者（人）	PG法受診者（人）	PG法陽性者（人）	PG法陽性率（%）	精検受診者（人）	精検受診率（%）	がん（早期）（人）
40	17,388	4,156	524	12.6	358	68.3	2 (2)
45	15,346	2,704	526	19.5	369	70.1	1 (0)
50	18,368	3,493	898	25.7	615	68.5	2 (2)
55	17,921	3,352	1,103	32.9	728	66.0	6 (5)
計	69,022	13,705	3,051	22.3	2,070	67.8	11 (9)

発見率：0.08%　陽性反応適中度0.53%

ペプシノゲン法（PG法）陰性者

年齢	PG法受診者（人）	X線対象者（PG陽性者）（人）	胃X線受診者（人）	X線受診率（%）	精検対象者（人）	精検受診者（人）	精検受診率（%）	がん（早期）（人）
40	4,156	3,975	2,231	56.1	303	193	63.7	0 (0)
45	2,704	2,245	1,310	58.4	197	126	64.0	0 (0)
50	3,493	2,771	1,490	53.8	240	153	63.8	0 (0)
55	3,352	2,341	1,452	62.0	216	126	58.3	2 (2)
計	13,705	11,332	6,483	57.2	956	598	62.6	2 (2)

発見率：0.03%　陽性反応適中度 0.33%

（表３）　発見胃がん一覧

平成年度	No	年齢	性別	PG法判定	自覚症状	手術所見 肉眼型	組織型	深達度	占拠部位	治療法	病期 内視鏡	病期 手術後
12	1	40	F	陽性	なし	IIc+IIa	por	sm	幽門部小弯	胃切除	早期	早期
	2	45	F	陽性	あり	IIc+III	sig por	mp	体上部前壁	胃切除	早期	進行
	3	50	M	陽性	なし	IIc	tub2	m	幽門部小弯	胃切除	早期	早期
	4	55	M	陽性	なし	(A)IIc (B)I	tub1	sm	(A)幽門部前壁 (B)体上部後壁	胃切除	早期	早期
	5	55	M	陽性	なし	IIc	tub2	m	幽門部大弯	胃切除	早期	早期
	6	55	M	陽性	なし	(A)IIc (B)IIc	(A)tub1 (B)por	(A)m (B)sm2	(A)体部前壁 (B)体部後壁	胃切除	早期	早期
	7	55	F	陰性	あり	IIc	sig por	m	幽門部大弯	胃切除	進行	早期
13	8	40	F	陽性	なし	IIa	tub2 tub1	m	胃角部前壁	胃切除	早期	早期
	9	50	F	陽性	なし	IIb+IIc	tub2	sm2	幽門部大弯	胃切除	早期	早期
	10	55	M	陽性	あり	Borr3	por	se	体部前庭部	胃切除	進行	進行
	11	55	F	陽性	なし	IIc	tub2	m	体中部前壁	胃切除	早期	早期
14	12	55	M	陽性	なし	IIc	tub2	m	小弯前壁	胃切除	早期	早期
	13	55	M	陰性	なし	V	sig por	sm	体中部後壁	胃切除	早期	早期

段階PG法では2,070円であった。1胃がん発見コストは、PG法導入前の3年間の同節目年令のX線単独法による胃がん発見数を用いて比較すると、271万円(X線)、218万円(PG)、1早期胃がん当りそれぞれ301万円、258万円であった(表4)。当区における検診対象人口に対する胃がん検診のカバー率は、平成14年度において、PG法及び一般公募によるX線法胃がん検診受診者の合計で見ると40歳以上の老健法対象人口の5.1％で、PG法では、4区分の節目年令では対象者の28.9％を占めていた。

(表4)　胃がん検診の費用

■検診単価（平成12,13,14年度）

2段階PG法　2,070円／人　節目年齢13,705人受診　PG検査委託
X線単独法　2,680円／人　一般公募7,774人受診　読影委託

■1胃がん発見コスト（節目年齢）

	受診数（人） 胃がん（早期）	1次検診費用（万円） 胃がん（早期）
X線単独法 (平成9,10,11)	12,571 10 (9)	271 (301)
2段階PG法 (平成12,13,14)	13,705 13 (11)	218 (258)

[考　察]

本検診では、40歳から55歳までの各節目年令において胃がんが発見されている。ペプシノゲン法による胃検診は、早期胃がんの発見を目的として行われるが、葛飾区における3年間の成績でも、PG陽性胃がんでは早期がんが81.8％と高率であった。一方、進行胃がんがPG陰性を示す場合が多いことから、PG陰性者には胃X線検査を行うことが推奨されている[3]。本区で実施した2段階の胃X線撮影では2例のPG陰性がんが発見された。これらは、肉眼的に進行がん様であったが、1例は無症状、1例は胃部痛を訴えていた。病理組織学的所見ではいずれも未分化型早期胃がんで、早期がんの拾いあげにも有効であった。このように住民検診における2段階PG法による胃がん検診は、現時点ではPG法とX線法の限界を相補い合い胃がんの発見効率を高めていると思われる。次に、PG法を導入した平成12年度から年次ごとの胃がん発見数を見ると、順に7(内PG陰性がん1名)、4名、2(内PG陰性がん1名)とPG陽性がんの発見が減少傾向にある。我が国の胃がん罹患率は減少しつつあることが示されているが[4]、地域で短期間に同様な傾向をとるとするのは無理があると思われる。しかし、検診の対象集団の質、検診方法、受診率等に変更がないので、この減少傾向は一過性のものか、あるいは胃がん罹患数の減少傾向の影響を受けているのか、内視鏡読影上の精度管理を進めつつ、今後の推移をみて検討が必要と思われる。また、X線検査における要精検率が14.9％と高く、15年度より高濃度低粘張性バリウムを使用した新撮影法を[5]導入し、要精検者の絞込みを図ることとした。次に、検診コストであるが、行政としては、先ず1人当たりの所要経費が問題となる。葛飾区においては、2段階PG胃がん検診の他に30歳以上の区民を対象とした公募方式によるX線単独法による胃がん検診を実施している。両方式の胃がん検診の一人当りの経費は2段階法が低額であるが差はそれ程大きくなかった。さらに、他地域(足立区、高崎市及び熊本県)の例にならって[6]、1胃がん当たりの1次検診コストを、PG検査導入前の平成9,10,11年に同じ節目年令対象者に実施していたX線単独法による胃がん検診の成績を用いて算出し比較すると、2段階PG法が低コストであった。この値はPG単独法を採用している他地域より2.5～4.5高い。しかし、1胃がん発見に要する経費は、検診方法あるいは発見胃がん数に大きく左右され、さらに、発見胃がん数は集団の年令構成、男女比、内視鏡の検出力等に大きく影響される。上記の3地域においては、対象者に60歳節目、あるいはより高齢者群を含んでいるので、55歳以下を対象とする葛飾区との比較は困難である。1胃がん発見コストは、当該地域で採用した検診方法が従来法のX線単独法に比してどの程度かを知る目安を意味するものであろう。とは言え、行政検診においては1人でも多くの早期がんを発見し、1人当たりのコストを下げることは重要である。葛飾区においては検診対象を胃がん罹患率がより高い60歳節目へと拡大することも必要と思われた。最後に、検診対象のカバー率であるが、東京都は区部を含めた全都の調査を昭和60年から5年ごとに実施し、平成13年2月に4回目を実施している。この調査から得られた胃がん検診の対象人口率は40歳以上人口の68.9％であった。対象人口率で補正した検診対象者を真の検診対象者とするならば、葛飾区における2段階胃がん検診受診者の真の対象者に対する受診率は28.9％であった。40歳以上の検診カバー率については、PG陽性者のフォロー検診実施者は2年間、PG陰性者で胃X線検査受診者は5年間継続受診者とみなすことが可能なので、実体的にはさらに高いものと考えられる。一般に、対象集団の30％以上が受診するとがん死亡の減少が期待できるとされているので、受診率をさらに上げることにより当該年令の胃がん死亡の減

少が期待できる。

[結 語]

1 地域住民を対象とした2段階ペプシノゲン胃がん検診においてもPG陰性がんが発見され、胃がん検診としての見逃しを最小限におさえている。
2 ペプシノゲン陰性がんの発見率は胃X線検査受診者(6,483人)の0.031％であった。
3 胃がん発見効率を高めるため、60歳節目検診への2段階法導入が必要である。
4 胃がん検診の真の対象者に対する受診率(カバー率)は28.9％であった。

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