

## Transnasal and standard transoral endoscopies in the screening of gastric mucosal neoplasias

Hiroya Nakata, Shotaro Enomoto, Takao Maekita, Izumi Inoue, Kazuki Ueda, Hisanobu Deguchi, Naoki Shingaki, Kosaku Moribata, Yoshimasa Maeda, Yoshiyuki Mori, Mikitaka Iguchi, Hideyuki Tamai, Nobutake Yamamichi, Mitsuhiro Fujishiro, Jun Kato, Masao Ichinose

Hiroya Nakata, Shotaro Enomoto, Takao Maekita, Izumi Inoue, Kazuki Ueda, Hisanobu Deguchi, Naoki Shingaki, Kosaku Moribata, Yoshimasa Maeda, Yoshiyuki Mori, Mikitaka Iguchi, Hideyuki Tamai, Jun Kato, Masao Ichinose, Department of Gastroenterology, School of Medicine, Wakayama Medical University, Wakayama City, Wakayama 641-0012, Japan  
Hiroya Nakata, Nakata Medical Clinic, Wakayama 641-0006, Japan

Nobutake Yamamichi, Mitsuhiro Fujishiro, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan

**Author contributions:** Nakata H and Ichinose M contributed equally to the conception and design of the study, performed the data analyses and drafted the manuscript; Enomoto S, Maekita T, Inoue I, Ueda K, Deguchi H, Shingaki N, Moribata K, Maeda Y, Mori Y, Iguchi M and Tamai H contributed to data acquisition; Yamamichi N, Fujishiro M and Kato J contributed to the analysis, interpretation of the data and critical revision of the manuscript for important intellectual content; all authors read and approved the final manuscript.

**Supported by** (in part) A Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan

**Correspondence to:** Masao Ichinose, MD, PhD, Department of Gastroenterology, School of Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan. [ichinose@wakayama-med.ac.jp](mailto:ichinose@wakayama-med.ac.jp)

Telephone: +81-73-4472300 Fax: +81-73-4453616

Received: December 24, 2010 Revised: May 6, 2011

Accepted: June 20, 2011

Published online: August 16, 2011

### Abstract

**AIM:** To compare the diagnostic performances of transnasal and standard transoral esophagogastroduodenoscopy (EGD) in gastric cancer screening of asymptomatic healthy subjects.

**METHODS:** Between January 2006 and March 2010, a

total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of the screened subjects, detection rates of gastric neoplasia and histopathology of the detected neoplasias were compared between groups according to the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis.

**RESULTS:** Clinical profiles of subjects did not differ significantly between the two EGD groups, except that there were significantly more men in the transnasal EGD group. During the study period, 55 cases of gastric mucosal neoplasias were detected. Of these, 23 cases were detected by transnasal EGD and 32 cases by standard transoral EGD. The detection rate for gastric mucosal neoplasia in the transnasal EGD group was thus 1.66%, compared to 1.65% in the standard transoral EGD group, with no significant difference between the two groups. Detection rates using the two endoscopies were likewise comparable, regardless of *H. pylori* infection. However, detection rates when screening subjects without extensive chronic atrophic gastritis (CAG) were significantly higher with standard transoral EGD (0.70%) than with transnasal EGD (0.12%,  $P < 0.05$ ). In particular, standard transoral EGD was far better for detecting neoplasia in subjects with *H. pylori*-related non-atrophic gastritis, with a detection rate of 3.11% compared to 0.53% using transnasal EGD ( $P < 0.05$ ). In the screening of subjects with extensive CAG, no significant differences in detection of neoplasia were evident between the two endoscopies, although the mean size of detected cancers was significantly smaller and the percentage of early cancers was significantly higher with standard transoral EGD.

**CONCLUSION:** These results strongly suggest that the diagnostic performance of transnasal endoscopy is

suboptimal for cancer screening, particularly in subjects with *H. pylori*-related non-atrophic gastritis.

© 2011 Baishideng. All rights reserved.

**Key words:** Transnasal endoscopy; Gastric cancer; Gastric adenoma; Atrophic gastritis; *Helicobacter pylori*; Cancer screening

**Peer reviewers:** Koga Komatsu, MD, PhD, Chief of Gastroenterology, Department of Gastroenterology, Honjo Daiichi Hospital, 110 Iwabuchishita, Yurihonjo City, Akita 015-8563, Japan; Ichiro Oda, MD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; Toru Hiyama, MD, PhD, Assistant Professor, Health Service Center, Hiroshima University, 1-7-1 Kagamiyama, Higashihiroshima 739-8514, Japan; Perminder Singh Phull, MD, FRCP, FRCPE, Gastrointestinal & Liver Service, Room 2.58, Ashgrove House, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, United Kingdom

Nakata H, Enomoto S, Maekita T, Inoue I, Ueda K, Deguchi H, Shingaki N, Moribata K, Maeda Y, Mori Y, Iguchi M, Tamai H, Yamamichi N, Fujishiro M, Kato J, Ichinose M. Transnasal and standard transoral endoscopies in the screening of gastric mucosal neoplasias. *World J Gastrointest Endosc* 2011; 3(8): 162-170 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v3/i8/162.htm> DOI: <http://dx.doi.org/10.4253/wjge.v3.i8.162>

## INTRODUCTION

To address the high mortality rate associated with gastric cancer, a nationwide program of gastric cancer screening has been introduced throughout Japan as a public service sponsored by local governments. In 2007, a total of 6 385 118 individuals underwent these screenings, resulting in the detection of 5606 cases of gastric cancer<sup>[1]</sup>. This screening program utilizes barium x-ray with photofluorography as a standard screening test and is considered effective in reducing the cancer mortality rate<sup>[2-5]</sup>. However, the sensitivity of barium X-ray is by no means high, reaching only 39% for early cancer<sup>[6]</sup>. To cope with this problem and improve the quality of screening, esophagogastroduodenoscopy (EGD) has gradually been adopted in several workplaces, local communities for organized screening and in health check-up institutions, including private health assessment clinics for opportunistic screening. A total of 211 821 subjects underwent cancer screening using EGD in 2007, according to the annual report of the Japanese Society of Gastroenterological Screening<sup>[1]</sup>. Since EGD is an unpleasant examination for subjects, evoking anxiety, pharyngeal discomfort, nausea, the gag-reflex and choking, and has been associated with adverse effects such as cardiovascular accidents<sup>[7-9]</sup>, this screening method is highly dependent on the skill of the endoscopist. The limited number of highly experienced endoscopists thus represents a major limitation to the feasibility of widespread cancer screening using EGD. Transnasal EGD using a small-diameter endoscope is

more patient-friendly than standard transoral EGD, is safer, with little impact on the cardiopulmonary and autonomic nerve systems<sup>[10-13]</sup>, and provides good operability. Transnasal EGD is thus more acceptable for patients and appears to be better suited to endoscopic cancer screening. However, because the luminous intensity and quality of endoscopic images varies greatly depending on differences in endoscope diameter, the screening performance of transnasal EGD for gastric cancer, particularly with regard to early cancer, must be determined carefully in the setting of cancer screening. The present study compared screening performance for gastric mucosal neoplasia (adenoma or cancer) between transnasal EGD and standard transoral EGD. In addition, the morphological and biological characteristics of gastric mucosal neoplasia are influenced by the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis<sup>[14-18]</sup>, which thus seems likely to influence the diagnostic ability of these two EGDs. We therefore compared screening by transnasal and standard transoral EGDs according to the stage of *H. pylori*-related chronic gastritis.

## MATERIALS AND METHODS

Subjects comprised 3324 patients [1442 men, 1882 women; mean (SD) age, 53.4 (15.4) years] who underwent EGD for screening of the upper gastrointestinal tract in our health assessment clinic between January 2006 and March 2010. All subjects were essentially symptom-free and each was free to choose between transnasal and standard transoral EGD. The transnasal EGD group included 1382 subjects [684 men, 698 women; mean (SD) age, 53.4 (15.4) years] and the standard transoral EGD group included 1942 subjects [758 men, 1184 women; mean (SD) age, 53.5 (15.4) years]. Standard transoral EGD was performed using a GIF-Q260 or prototype GIF-Y0004 endoscope (Olympus, Tokyo, Japan), whereas transnasal EGD was performed using a GIF-N260 or prototype GIF-Y0022 endoscope (Olympus) or an EG-530N2 endoscope (Fuji Film Medical, Tokyo, Japan). Outer diameters of the standard endoscopes were larger than those of transnasal endoscopes: GIF-Q260, 9.2 mm; GIF-Y0004, 7.7 mm; GIF-N260, 4.9 mm; GIF-Y0022, 5.4 mm; and EG-530N2, 5.9 mm. Sizes of the charge-coupled device for the two standard endoscopes were the same and about 30% larger than those of the GIF-N260 and GIF-Y0022 transnasal endoscopes. The optical system in EG-530N2 differs from those of the other endoscopes but image quality for the EG-530N2 was equivalent to that with the other two transnasal endoscopes. Standard endoscopes were equipped with two light guides, while transnasal endoscopes were equipped with either single (GIF-N260) or double light guides (GIF-Y0022 and EG-530N2); the visual field of the transnasal endoscopes were dark compared with the standard endoscopes, due to the smaller number of light guide fibers. Viewing angles of all standard and transnasal EGDs were 140° and 120°, respectively. The tip flexion capability of en-

**Table 1 Clinical profiles of the subjects screened by transnasal or transoral endoscopy and clinicopathological characteristics of detected gastric mucosal neoplasia (mean  $\pm$  SD) *n* (%)**

	Total subjects	Subject screened	
		By transnasal EGD	By transoral EGD
No. of screened subjects	3324	1382	1942
Age (yr)	53.4 $\pm$ 15.4	53.4 $\pm$ 15.4	53.5 $\pm$ 15.4
Males	1442 (43.4)	684 (49.4) <sup>a</sup>	758 (39.0)
Smokers	678 (20.4)	267 (19.3)	411 (21.1)
<i>Helicobacter pylori</i> -infected subjects	1202 (40.2)	510 (39.8)	692 (40.5)
CAG-positive subjects	1360 (40.9)	560 (40.5)	800 (41.2)
No. of subjects with gastric neoplasia/DR	55/0.0165	23/0.0166	32/0.0165
Location of neoplasia (U/M/L)	20/15/20	8/7/8	12/8/12
Adenoma cases/DR	12/0.0036	3/0.0022	9/0.0046
Location of adenoma (U/M/L)	2/4/6	0/2/1	2/2/5
Size of adenoma (mm)	10.5 $\pm$ 7.0	9.7 $\pm$ 4.0	10.8 $\pm$ 7.9
Cancer cases/DR	43/0.0129	20/0.0145	23/0.0118
Location of cancer (U/M/L)	18/11/14	8/5/7	10/6/7
Size of cancer (mm)	27.3 $\pm$ 16.7	32.6 $\pm$ 19.5 <sup>a</sup>	22.3 $\pm$ 12.8
Morphological cancer type (I - II a/ II b/ II c-III / Ad)	12/1/15/13	6/1/5/8	6/0/12/5
With intestinal-type cancer	33 (76.7)	18 (90.0) <sup>a</sup>	15 (65.2)
Depth of invasion (m/sm/pm-)	20/10/13	5/7/8	15/3/5
With early cancer	30 (69.7)	12 (60.0)	18 (78.3)

<sup>a</sup>*P* < 0.05 vs transoral esophagoduodenoscopy (EGD). CAG: Chronic atrophic gastritis; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach.

doscopes was 210° up, 90° down and 100° right and left, with the exception of GIF N260, a two-way angulation transnasal endoscope, which showed flexion capability of 210° up and 120° down in a single plane. All endoscopes used in the present study were equipped with a forceps channel (diameter, 2 mm).

In both groups, a sedative (midazolam, 2.5-5 mg/body) was provided for subjects who desired it. All endoscopic examinations were performed by a single endoscopist with 20 years' experience in gastrointestinal endoscopy. Narrow-band imaging, flexible spectral imaging color enhancement or indigo carmine spraying was applied for full observation when considered necessary. Chronic atrophic gastritis (CAG), defined as chronic gastritis with open-type atrophy in the background gastric mucosa according to the definitions of Kimura *et al.*<sup>[19]</sup>, was diagnosed by endoscopic observation, whereas *H. pylori* infection was diagnosed by histopathological analysis using Giemsa staining of endoscopically biopsied mucosal samples obtained from the greater curvature of the gastric body and antrum. Furthermore, on the basis of previous reports<sup>[20,21]</sup>, subjects with *H. pylori*-related chronic gastritis were examined after being divided into the following 4 groups according to the stage of *H. pylori*-related chronic gastritis: Group A, *H. pylori*-negative and CAG-negative; Group B, *H. pylori*-positive and CAG-negative; Group C, *H. pylori*-positive and CAG-positive; and Group D, *H. pylori*-negative and CAG-positive. Among the subjects screened, the status of *H. pylori*-related chronic gastritis in the background stomach was able to be analyzed in 2987 subjects.

Histopathological assessment of gastric mucosal neoplasias, adenoma and cancer was performed on resected specimens obtained by endoscopy or surgery. Early gas-

tric cancers were defined as those confined to the mucosa or submucosa. Advanced cancers were defined as those invading into the muscularis propria or beyond. Pathologically, gastric cancer cases were classified into intestinal type or diffuse type, according to Lauren's classification<sup>[22]</sup>. The ethics committee of Wakayama Medical University approved the protocol of the present study and informed consent was obtained from all subjects prior to participation.

### Statistical analysis

Data were analyzed using SPSS version 11.0 (SPSS, Chicago, IL, USA) and STATA (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons between groups and Scheffe's LSD test for comparisons between pairs of groups. The  $\chi^2$  test and Fisher's exact test were used to compare categorical variables. For all comparisons, values of *P* < 0.05 were considered statistically significant.

## RESULTS

Between January 2006 and March 2010, a total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of subjects in the two endoscopy groups are shown in Table 1. Although significantly more men were included in the transnasal EGD group than in the standard transoral EGD group, no significant differences in age, smoking habits, *H. pylori* infection or extent of concomitant CAG were seen between groups. Endoscopy screening identified 55 cases of gastric mucosal

**Table 2** Screening performance of the two esophagogastroduodenoscopies in subjects with or without *Helicobacter pylori* infection (mean  $\pm$  SD) *n* (%)

	Total subjects ( <i>H. pylori</i> analyzed)	<i>H. pylori</i>	
		Positive	Negative
Screened by transnasal EGD			
Screened subjects	1280	510	770
Age (yr)	53.4 ± 15.4	56.8 ± 13.6 <sup>c</sup>	50.2 ± 14.3
Males	623 (48.7) <sup>a</sup>	268 (52.5) <sup>a</sup>	355 (46.1) <sup>a</sup>
Smokers	247 (19.3)	118 (23.1) <sup>c</sup>	129 (16.7) <sup>a</sup>
Subjects with gastric neoplasia/DR	21/0.0164	16/0.0314 <sup>c</sup>	5/0.00649
Location of neoplasia (U/M/L)	7/6/8	4/6/6	3/0/2
Adenoma cases/DR	3/0.0023	3/0.00589	0/0
Size of adenoma (mm)	9.7 ± 4.0	9.7 ± 4.0	0
Cancer cases/DR	18/0.0141	13/0.0255 <sup>c</sup>	5/0.00649
Size of cancer (mm)	31.2 ± 19.5	25.5 ± 13.3	46.0 ± 28.2
Morphological cancer type ( I - II a/ II b/ II c-III/Ad)	6/1/4/7	5/0/4/4	1/1/0/3
With intestinal-type cancer	16 (88.9)	12 (92.3)	4 (80)
Depth of invasion (m/sm/pm-)	5/6/7	4/5/4	1/1/3
With early cancer	12 (66.7)	10 (76.9)	2 (40)
Screened by transoral EGD			
Screened subjects	1707	692	1015
Age (yr)	53.5 ± 15.4	56.3 ± 14.7 <sup>c</sup>	51.8 ± 14.8
Males	655 (38.4)	298 (43.1)	357 (35.2)
Smokers	354 (20.7)	141 (20.3)	213 (21.0)
Subjects with gastric neoplasia/DR	33/0.0193	26/0.0376 <sup>c</sup>	6/0.00591
Location of neoplasia (U/M/L)	12/8/12	10/8/9	2/0/3
Adenoma cases/DR	9/0.0052	5/0.00722	4/0.00394
Size of adenoma (mm)	10.8 ± 7.9	13 ± 11.5	10 ± 4.08
Cancer cases/DR	23/0.0135	21/0.0303 <sup>c</sup>	2/0.00197
Size of cancer (mm)	22.3 ± 12.8	23.2 ± 13.4	20 ± 0
Morphological cancer type ( I - II a/ II b/ II c-III/Ad)	6/0/12/5	6/0/10/5	0/0/2/0
With intestinal-type cancer	15 (65.2)	14 (66.7)	1 (50)
Depth of invasion (m/sm/pm-)	15/3/5	13/3/5	2/0/0
With early cancer	18 (78.3)	14 (76.2)	2 (100)

<sup>a</sup>*P* < 0.05 vs transoral, <sup>c</sup>*P* < 0.05 vs *Helicobacter pylori* (*H. pylori*)-negative. DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy.

neoplasia (detection rate, 1.65%), with gastric cancers in 43 subjects (detection rate, 1.29%) and adenomas in 12 subjects (detection rate, 0.36%). Of these, 23 cases were detected by transnasal EGD (detection rate, 1.66%) and 32 cases by standard transoral EGD (detection rate, 1.65%). Detection rates for screening using the two different types of endoscopes were thus almost equivalent (Table 1). The detection rate of adenoma was higher in the standard transoral EGD group (0.46%) than in the transnasal EGD group (0.22%), but no significant differences in detection rate, size or location of adenoma were evident between groups. The detection rate of gastric cancer likewise did not differ significantly between groups, at 1.45% for transnasal EGD and 1.18% for standard transoral EGD. However, mean size of detected lesions was significantly smaller with standard transoral EGD. The percentage of early cancers tended to be higher for standard transoral EGD (78.3%) than for transnasal EGD (60%), although no significant difference was apparent. Locations and morphological types of detected cancers did not differ significantly between groups, although standard transoral EGD detected depressed-type cancers located in the upper third of the stomach more frequently. With regard to the histopathological type of

detected cancers, standard transoral EGD detected significantly more non-intestinal-type cancers (i.e. diffuse-type cancers) than transnasal EGD.

Next, we compared detection rates of gastric mucosal neoplasia using the two different EGDs according to the status of *H. pylori* infection (Table 2) and the extent of CAG (Table 3). Mean age of screened subjects was significantly higher in the *H. pylori*-positive group and in the CAG-positive group than in their respective negative counterparts, and no significant differences in mean age of screened subjects were seen between the two EGD groups when stratified into subgroups according to positivity for *H. pylori* infection or the extent of CAG. However, the percentage of men was significantly higher in the transnasal EGD group irrespective of *H. pylori* status or the extent of CAG. In the *H. pylori*-negative group, the percentage of smokers was significantly higher among subjects screened by standard transoral EGD than by transnasal EGD, while the *H. pylori*-positive group showed no significant difference in the percentage of smokers between EGD groups. No significant difference in the percentage of smokers was seen between EGD groups, regardless of CAG status.

Detection rates of gastric mucosal neoplasia using



**Table 3** Screening performance of the two esophagogastroduodenoscopies in subjects with or without chronic atrophic gastritis (mean  $\pm$  SD) *n* (%)

	Total subjects	CAG	
		Positive	Negative
Screened by transnasal EGD			
Screened subjects	1382	560	822
Age (yr)	53.4 ± 15.4	60.3 ± 11.8 <sup>c</sup>	47.0 ± 14.5
Males	684 (49.4) <sup>a</sup>	316 (56.4) <sup>a</sup>	368 (44.8) <sup>a</sup>
Smokers	267 (19.3)	121 (21.6)	146 (17.8)
Subjects with gastric neoplasia/DR	23/0.0166	22/0.0286 <sup>c</sup>	1/0.00122 <sup>a</sup>
Location of neoplasia (U/M/L)	8/7/8	8/6/8	0/1/0
Adenoma cases/DR	3/0.0022	3/0.00536	0/0
Size of adenoma (mm)	9.7 ± 4.0	9.7 ± 4.0	0
Cancer cases/DR	20/0.0145	19/0.0315 <sup>c</sup>	1/0.00122
Size of cancer (mm)	32.6 ± 19.5 <sup>a</sup>	34.1 ± 18.8 <sup>a</sup>	5 ± 0
Morphological cancer type ( I - II a/ II b/ II c-III /Ad)	6/1/5/8	6/1/4/8	0/0/1/0
With intestinal-type cancer	18 (90.0)	18 (94.7)	0 (0)
Depth of invasion (m/sm/pm-)	5/7/8	4/7/8	1/0/0
With early cancer	12 (60.0)	11 (57.9) <sup>a</sup>	1 (100)
Screened by transoral EGD			
Screened subjects	1942	800	1142
Age (yr)	53.5 ± 15.6	62.3 ± 11.4 <sup>c</sup>	47.3 ± 14.2
Males	758 (39.0)	363 (45.3)	395 (34.6)
Smokers	411 (21.2)	165 (20.6)	246 (21.6)
Subjects with gastric neoplasia/DR	32/0.0164	24/0.0300 <sup>c</sup>	8/0.0070
Location of neoplasia (U/M/L)	12/8/12	8/7/9	4/1/3
Adenoma cases/DR	9/0.0046	7/0.00875 <sup>c</sup>	2/0.00175
Size of adenoma (mm)	10.8 ± 7.9	11.7 ± 8.8	7.5 ± 3.5
Cancer cases/DR	23/0.0118	17/0.0213 <sup>c</sup>	6/0.00525
Size of cancer (mm)	22.3 ± 12.8	19.4 ± 11.7	31.4 ± 12.1
Morphological cancer type ( I - II a/ II b/ II c-III /Ad)	6/0/12/5	6/0/9/2	0/0/3/3
With intestinal-type cancer	15 (65.2)	12 (70.6) <sup>c</sup>	2 (33.3)
Depth of invasion (m/sm/pm-)	15/3/5	13/2/2	2/1/3
With early cancer	8 (78.3)	15 (88.2)	3 (50.0)

<sup>a</sup>*P* < 0.05 vs transoral; <sup>c</sup>*P* < 0.05 vs CAG-negative. CAG: Chronic atrophic gastritis; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy.

each of the two EGDs were significantly higher in the *H. pylori*-positive group than in the negative group (Table 2). No significant differences in the detection rate of neoplasia, as either adenoma or cancer, or in the size or percentage of early cancers were found between the two EGDs, irrespective of *H. pylori* infection. The percentage of morphologically depressed and histologically diffuse-type cancer tended to be higher among cancers detected by standard transoral EGD than by transnasal EGD, irrespective of *H. pylori* infection, but no significant differences were evident. Table 3 shows the results of screening by the two EGDs according to CAG status. The detection rate for gastric mucosal neoplasia was significantly higher among CAG-positive subjects than among negative subjects, regardless of the type of endoscope. In CAG-positive subjects, 65% (30/46) of detected neoplasias were located in the lower two-thirds of the stomach, 50% (23/46) showed an elevated-type morphology and 87% (40/46) displayed intestinal-type histology. No significant differences in the detection rate of neoplasia, morphological or histological types or location were noted between the two EGD groups. However, mean size of the cancer detected was significantly smaller and the percentage of early cancers was higher with stan-

dard transoral EGD than with transnasal EGD. Among CAG-negative subjects, 44.4% (4/9) of detected neoplasias were located in the upper third of the stomach and all cancers detected showed depressed- or ulcerated-type morphology. Seventy-one percent (5/7) displayed diffuse-type histology and 42.9% of cases (3/7) showed complications of nodular gastritis. Detection rates of neoplasia were significantly higher in the standard transoral EGD group (0.70%) than in the transnasal EGD group (0.12%, *P* < 0.05). This reflects the high rate of cancer detection for standard transoral EGD in the CAG-negative stomach.

Finally, screening for gastric mucosal neoplasias using the two different EGDs was analyzed according to the stages of *H. pylori*-related chronic gastritis. Mean age in each stage group increased in a stepwise manner with the progression of *H. pylori*-related chronic gastritis from Group A to Group D, and no significant differences were found between the two EGD groups in any stage. The transnasal EGD group showed a higher proportion of men than the transoral group throughout all stages, with significant differences in Groups A and C. In Group A, the standard transoral EGD group included significantly more smokers than the transnasal EGD group,

**Table 4** Screening performance of the two esophagogastroduodenoscopies according to the stages of *Helicobacter pylori*-related chronic gastritis (mean  $\pm$  SD) *n* (%)

	Group A	Group B	Group C	Group D	Total subjects ( <i>H. pylori</i> analyzed)
Screened by transnasal EGD					
Screened subjects	572	189	321	198	1280
Age (yr)	45.3 $\pm$ 13.8	49.2 $\pm$ 14.6 <sup>c</sup>	59.8 $\pm$ 12.1 <sup>c</sup>	63.4 $\pm$ 12.8 <sup>c</sup>	53.4 $\pm$ 15.4
Males	257 (44.9) <sup>a</sup>	74 (39.3)	194 (60.2) <sup>a</sup>	98 (49.4)	623 (48.7) <sup>a</sup>
Smokers	89 (15.6) <sup>a</sup>	43 (22.8) <sup>a</sup>	75 (23.3)	40 (20.2)	247 (19.2)
Subjects with gastric neoplasia/DR	0/0	1/0.0053 <sup>a,c</sup>	15/0.0466 <sup>c</sup>	5/0.0253	21/0.0164
Location of neoplasia (U/M/L)	0	0/1/0	4/5/6	3/0/2	7/6/8
Adenoma cases/DR	0/0	0/0	3/0.0093	0/0	3/0.0023
Size of adenoma (mm)	0	0	9.7 $\pm$ 4.0	0	9.7 $\pm$ 4.0
Cancer cases/DR	0/0	1/0.00532	12/0.0373	5/0.0253	18/0.0141
Size of cancer (mm)	0	5 $\pm$ 0	27.3 $\pm$ 12.3	46.0 $\pm$ 28.2	31.2 $\pm$ 19.5
Morphological cancer type (I-II a/II b/II c-III/Ad)	0	0/0/1/0	5/0/3/4	1/1/0/3	6/1/4/7
With intestinal-type cancer	0 (0)	0/1 (0)	12/12 (100)	4/5 (80)	16/18 (88.9)
Depth of invasion (m/sm/pm-)	0	1/0/0	3/5/4	1/1/3	5/6/7
With early cancer	-	1 (100)	8 (66.7)	2 (40)	12 (66.7)
Screened by transoral EGD					
Screened subjects	751	257	435	264	1707
Age (yr)	46.0 $\pm$ 12.6	46.6 $\pm$ 15.4	60.9 $\pm$ 11.8 <sup>c</sup>	64.0 $\pm$ 11.4 <sup>c</sup>	53.5 $\pm$ 15.4
Males	247 (32.9)	95 (37.0)	203 (46.7)	110 (41.7)	655 (38.4)
Smokers	167 (22.2)	39 (15.2)	102 (23.4)	46 (17.4)	354 (20.7)
Subjects with gastric neoplasia/DR	0/0	8/0.0311 <sup>c</sup>	18/0.0414 <sup>c</sup>	6/0.0227	32/0.0187
Location of neoplasia (U/M/L)	0	4/1/3	6/7/5	2/0/4	12/8/12
Adenoma cases/DR	0/0	2/0.00778	3/0.00689	4/0.0152	9/0.0052
Size of adenoma (mm)	0	7.5 $\pm$ 3.53	8.0 $\pm$ 13.9	10 $\pm$ 4.08	10.8 $\pm$ 7.9
Cancer cases/DR	0/0	6/0.0233	15/0.0345	2/0.00758	23/0.0134
Size of cancer (mm)	0	31.4 $\pm$ 12.1	19.4 $\pm$ 12.5	20 $\pm$ 0	22.3 $\pm$ 12.8
Morphological cancer type (I-II a/II b/II c-III/Ad)	0	0/0/3/3	6/0/7/2	0/0/2/0	6/0/12/5
With intestinal-type cancer	0 (0)	2/6 (33.3)	12/15 (80)	1/2 (50)	16/24 (66.7)
Depth of invasion (m/sm/pm-)	0	2/1/3	11/2/2	2/0/0	15/3/5
With early cancer	-	3 (50)	13 (86.7)	2 (100)	18 (78.3)

<sup>a</sup>*P* < 0.05 vs transoral; <sup>c</sup>*P* < 0.05 vs previous stage. *H. pylori*: *Helicobacter pylori*; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy. Group A: *H. pylori* (-), chronic atrophic gastritis (CAG) (-); Group B: *H. pylori* (+), CAG (-); Group C: *H. pylori* (+), CAG (+); Group D: *H. pylori* (-), CAG (+).

while Group B included significantly more smokers in the transnasal EGD group than in the standard transoral EGD group. No neoplasias were detected in Group A (*H. pylori*- and CAG-negative), which comprised of subjects with an infection-free healthy stomach (Table 4). In Group B (*H. pylori*-positive, CAG-negative), representing subjects with an *H. pylori*-infected non-atrophic stomach, the detection rate of gastric mucosal neoplasia was significantly higher in the standard transoral EGD group (3.11%) than in the transnasal EGD group (0.53%, *P* < 0.05). In Group C (*H. pylori*- and CAG-positive) and Group D (*H. pylori*-negative, CAG-positive), no significant differences in detection rates were found between endoscopy groups. Mean size of the detected cancer was smaller and the proportion of early cancers was higher in the standard transoral EGD group, although the difference was not significant. Furthermore, no significant differences in location, morphological type or histopathological type of detected cancers were seen, irrespective of differences in the endoscope used.

## DISCUSSION

Previous studies have reported that the diagnostic accu-

racy of transnasal EGD is equivalent to that of standard transoral EGD for the detection of esophagogastric lesions, including gastric cancer<sup>[23-30]</sup>. However, despite recent advances in endoscopic technologies, small-diameter endoscopes used for transnasal EGD still show disadvantages when compared to standard endoscopes, due to lower luminous intensity, lower resolution of endoscopic images, a narrow field of view, low maneuverability and low biopsy performance, all of which are attributable to the small diameter of the endoscope<sup>[31]</sup>. Yoshida *et al.*<sup>[30]</sup> found no significant differences in detection rates of early gastric cancer and adenoma between transnasal and standard transoral EGD, but also noted that gastric cancers may be overlooked by transnasal EGD when performed by less-experienced endoscopists. Furthermore, Hayashi *et al.*<sup>[32]</sup> investigated the detection of early gastric cancer  $\leq$  2 cm in diameter using the two different EGDs and indicated that transnasal EGD offers inadequate diagnostic yield compared with standard transoral EGD. Supporting those findings, the present results strongly suggest that, although detection rates of gastric mucosal neoplasia might not differ significantly between transnasal and standard transoral EGDs, mean sizes of the detected cancers were significantly larger with transnasal EGD. In addi-

tion, percentages of early or diffuse-type cancers, which require higher resolution for detection, were lower among cancers detected by transnasal EGD. Of note, the difference in detection rates of diffuse-type cancer between the two EGDs was significant. Hayashi *et al.*<sup>[32]</sup> also reported that ultra thin endoscopes were less efficient in screening for lesions located in the upper third of the stomach, due to the narrower field of view and low luminous intensity. Diffuse-type cancer tends to develop from fundic gland mucosa located mainly in the gastric body<sup>[14,15,17]</sup>, providing a possible explanation for the low diagnostic performance of transnasal EGD in detecting diffuse-type cancer. However, the present study found no significant differences in the locations of detected neoplasias between the two EGDs. Screening performance of transnasal EGD thus seems to remain suboptimal compared with standard transoral EGD, at least in the detection of subtle mucosal changes presented by small-sized cancers or by diffuse-type cancers with biologically infiltrating characteristics.

The proliferation and growth of neoplastic cells derived from the stomach mucosa is widely accepted to be regulated by the acidic environment in the gastric lumen. The morphological and biological characteristics of gastric mucosal neoplasia are under the influence of the stage of *H. pylori*-related chronic gastritis<sup>[14-16]</sup>. With the development of gastric atrophy together with intestinal metaplasia, intra-luminal pH in the stomach becomes less acidic and mucosal neoplasia with an elevated or protruding morphological type and intestinal histological type tends to become more prevalent<sup>[14-17]</sup>. Conversely, chronic active inflammation of the stomach, regardless of the existence of gastric atrophy, directly induces histologically diffuse-type cancer, which tends to develop in the non-atrophic stomach and is thus usually morphologically depressed or ulcerated<sup>[14,15,17,18]</sup>. The natural history of *H. pylori*-related chronic gastritis can be classified into four stages (Groups A-D), based on the establishment of *H. pylori* infection or CAG<sup>[20,21]</sup>. In the present study, the screening performance of transnasal EGD according to each of the four stages of *H. pylori*-related chronic gastritis was also investigated in comparison with standard transoral EGD. No gastric cancers were detected among subjects with an *H. pylori*-negative healthy stomach (Group A), while establishment of *H. pylori* infection (Group B) was associated with the development of gastric mucosal neoplasias. The incidence of gastric mucosal neoplasias increased significantly as the extent of CAG increased from Group B to Group C. In Group B (subjects with *H. pylori*-infected non-atrophic stomach), the detection rate of gastric mucosal neoplasia was significantly lower with transnasal EGD than with standard transoral EGD, representing the detection rate of gastric cancer. Types of cancers detected in Group B were predominantly depressed or ulcerated type morphologically and diffuse type histologically, supporting the reported clinicopathological characteristics of cancers developing from a non-atrophic stomach<sup>[14,15,17]</sup>. The present results clearly indi-

cate that the screening performance of transnasal EGD is low for detecting the above-mentioned types of cancer developing against a background of the non-atrophic stomach. Meanwhile, in Groups C and D, comprising subjects with extensive CAG, no significant differences in detection rates of gastric mucosal neoplasia were seen between the two EGDs. As postulated in the multistep model of stomach carcinogenesis, a major proportion of cancers develop from the stomach mucosa with extensive CAG together with intestinal metaplasia in regions with a high risk for cancer, including Japan<sup>[14,15,17,18]</sup>. Consistent with this, 83.0% of gastric mucosal neoplasias (82.9% of cancers) developed in Groups C and D. In these groups, intestinal-type cancer predominated histopathologically and 50% of detected neoplasias were morphologically elevated or protruding, compatible with clinicopathological findings of cancer developing from extensive CAG<sup>[14-17]</sup>. Based on the observed detection rates for the two EGDs, screening performance of transnasal EGD appears comparable to that of standard transoral EGD in detecting this major type of cancer. However, the significantly smaller size of detected cancers and the significantly higher percentage of early cancers among cancers detected by standard transoral EGD suggest great room for improvement in the diagnostic performance of transnasal EGD for cancer screening in subjects with extensive CAG. Meanwhile, the present study has some limitations. Firstly, in our country gastric cancer screening is being carried out as a public health service and a non-negligible number of people underwent the screening by endoscopy. Thus, the detection rate of gastric mucosal neoplasia is to some extent under the influence of the time intervals between the previous EGD and the EGD performed in the present study. In both groups of the two EGDs, around 55% of the study subjects underwent the cancer screening by EGD in the previous year. The proportion of the subjects who underwent EGD within the last 3 years was 11% and 18% in transnasal and standard transoral EGD, respectively. As for the remaining subjects, no information about the previous EGD is available. Secondly, in general the incidence of gastric neoplasia is higher in males compared to females. In the present study, the number of male subjects included in the transnasal EGD group was significantly higher than in the transoral EGD group. Thus, the screening performance of transnasal EGD might have been overestimated, although it still remains suboptimal compared with that of standard transoral EGD. Since tolerability, acceptability and safety of transnasal EGD with a small-diameter endoscope are better than standard transoral EGD, transnasal EGD has been increasingly used for gastric cancer screening<sup>[30-32]</sup>. However, the present results indicate that the screening performance of transnasal EGD remains suboptimal, even in subjects with extensive CAG, which represents a key route of stomach carcinogenesis in Japan. Furthermore, in screening for the small proportion of cancers developing from the *H. pylori*-infected non-atrophic stomach, small-diameter endoscopes are clearly

inadequate compared with standard endoscopes. Evaluation of the accuracy of transnasal EGDs in cancer screening must await the results of long-term follow-up studies. However, the present findings offer compelling evidence that the introduction of small-diameter endoscopes into cancer screening first requires improvements in the low image quality of transnasal EGD due to low resolution, low luminous intensity and narrow angle of view.

Special attention should be paid to the screening of individuals with *H. pylori* infection of the non-atrophic stomach. This group of subjects as a whole is not considered to be at high risk of cancer, with an annual incidence rate of around 0.1% in Japan<sup>[20,21,33]</sup>. However, considering the rapid growth and high malignant potential of the diffuse-type cancer that tends to arise in this group, together with the subtle endoscopic findings present in the early stage, use of high-performance endoscopy is strongly recommended. We have recently reported that a group of subjects with non-atrophic stomach at high risk for diffuse-type cancer can be identified using serum pepsinogen (PG) levels (PG I > 70 ng/mL; PG I / II ratio  $\leq 3.0$ )<sup>[33]</sup>. We believe that cancer screening in such individuals should be performed cautiously using standard transoral EGD. In the near future, high-performance, small-diameter endoscopes will surely be developed and are likely to contribute greatly to the establishment of highly efficient cancer screening programs. However, with the currently available small-diameter endoscopes, cancer screening should be performed meticulously based on ample experience with standard transoral EGD and also with full knowledge of the limitations and characteristics of small-diameter endoscopes.

## ACKNOWLEDGMENTS

The authors would like to express their deepest thanks to Ms. Kazu Konishi for her excellent secretarial assistance.

## COMMENTS

### Background

Transnasal esophagogastroduodenoscopy (EGD) is more acceptable for patients and has been increasingly applied for gastric cancer screening. Previous studies showed that the diagnostic accuracy of transnasal EGD was equivalent to that of standard transoral EGD for the detection of esophagogastric lesions. However, the screening performance of transnasal EGD for gastric mucosal neoplasias must be determined carefully because of its lower luminous intensity and lower quality of endoscopic images.

### Research frontiers

In the present study, the diagnostic ability of transnasal and standard transoral EGD for gastric cancer screening has been evaluated from various points of view. Especially, the screening performance of both EGDs has been investigated according to the stages of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis.

### Innovations and breakthroughs

The results have clearly demonstrated that the diagnostic performance of transnasal EGD remains suboptimal for cancer screening, particularly in subjects with *H. pylori*-infected non-atrophic stomach.

### Applications

Based on the present results, special attention should be paid to the cancer screening of the subjects with *H. pylori*-infected non-atrophic stomach, who are

at high risk for diffuse-type cancer, and transoral EGD is strongly recommended for such individuals. The results of the authors' previous study have already revealed that such individuals can be identified using serum pepsinogen levels.

### Peer review

Nakata *et al* compared the diagnostic performances of transnasal and standard transoral EGD in gastric cancer screening of asymptomatic healthy subjects. A total of 3324 subjects including 1382 screened by transnasal EGD and 1942 screened by standard transoral EGD were enrolled. They concluded that the diagnostic performance of transnasal endoscopy is suboptimal for cancer screening, particularly in subjects with *H. pylori*-related atrophic gastritis. This is a well-written paper describing an extensive experience in the use of transnasal endoscopy for gastric cancer screening.

## REFERENCES

- 1 Committee of National Statistics. The 2007 annual report of mass screening for digestive organs (in Japanese). *J Gastroenterol Cancer Screening* 2009; 47: 69-92
- 2 Oshima A, Hirata N, Ubukata T, Umeda K, Fujimoto I. Evaluation of a mass screening program for stomach cancer with a case-control study design. *Int J Cancer* 1986; 38: 829-833
- 3 Fukao A, Tsubono Y, Tsuji I, Hisamichi S, Sugahara N, Takano A. The evaluation of screening for gastric cancer in Miyagi Prefecture, Japan: a population-based case-control study. *Int J Cancer* 1995; 60: 45-48
- 4 Abe Y, Mitsushima T, Nagatani K, Ikuma H, Minamihara Y. Epidemiological evaluation of the protective effect for dying of stomach cancer by screening programme for stomach cancer with applying a method of case-control study - a study of an efficient screening programme for stomach cancer (in Japanese). *Nihon Shokakibyo Gakkai Zasshi* 1995; 92: 836-845
- 5 Tsubono Y, Hisamichi S. Case control studies of screening for gastric cancer in Japan. *J Gastroenterol Mass Surv* 1999; 37: 182-185
- 6 Nishizawa M. Present status and prospect for cancer screening. *J Gastroenterol Mass Surv* 1993; 78: 100-103
- 7 Brandt LJ. Patients' attitudes and apprehensions about endoscopy: how to calm troubled waters. *Am J Gastroenterol* 2001; 96: 280-284
- 8 Hart R, Classen M. Complications of diagnostic gastrointestinal endoscopy. *Endoscopy* 1990; 22: 229-233
- 9 Bough EW, Meyers S. Cardiovascular responses to upper gastrointestinal endoscopy. *Am J Gastroenterol* 1978; 69: 655-661
- 10 Zaman A, Hahn M, Hapke R, Knigge K, Fennerty MB, Katon RM. A randomized trial of peroral versus transnasal unsedated endoscopy using an ultrathin videoendoscope. *Gastrointest Endosc* 1999; 49: 279-284
- 11 Yagi J, Adachi K, Arima N, Tanaka S, Ose T, Azumi T, Sasaki H, Sato M, Kinoshita Y. A prospective randomized comparative study on the safety and tolerability of transnasal esophagogastroduodenoscopy. *Endoscopy* 2005; 37: 1226-1231
- 12 Nakata H, Oka M, Magari H, Inoue I, Iguchi M, Yanaoka K, Tamai H, Arii K, Ichinose M. Prospective study comparing transoral and transnasal upper gastrointestinal endoscopy on the cardiorespiratory parameter and tolerability (in Japanese). *Gastroenterol Endosc* 2007; 49: 2684-2689
- 13 Kawai T, Miyazaki I, Yagi K, Kataoka M, Kawakami K, Yamagishi T, Sofuni A, Itoi T, Moriyasu F, Osaka Y, Takagi Y, Aoki T. Comparison of the effects on cardiopulmonary function of ultrathin transnasal versus normal diameter transoral esophagogastroduodenoscopy in Japan. *Hepatogastroenterology* 2007; 54: 770-774
- 14 Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; 52: 6735-6740
- 15 Sipponen P, Kosunen TU, Valle J, Riihelä M, Seppälä K. *Helicobacter pylori* infection and chronic gastritis in gastric



- cancer. *J Clin Pathol* 1992; **45**: 319-323
- 16 **Nardone G**, Rocco A, Malfertheiner P. Review article: helicobacter pylori and molecular events in precancerous gastric lesions. *Aliment Pharmacol Ther* 2004; **20**: 261-270
- 17 **Laurén P**. Histogenesis of intestinal and diffuse types of gastric carcinoma. *Scand J Gastroenterol Suppl* 1991; **180**: 160-164
- 18 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362
- 19 **Kimura K**, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1969; **3**: 87-97
- 20 **Ohata H**, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H, Shimizu Y, Takeshita T, Mohara O, Ichinose M. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. *Int J Cancer* 2004; **109**: 138-143
- 21 **Watabe H**, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, Doi H, Yoshida H, Kawabe T, Omata M. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut* 2005; **54**: 764-768
- 22 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49
- 23 **Sorbi D**, Gostout CJ, Henry J, Lindor KD. Unsedated small-caliber esophagogastroduodenoscopy (EGD) versus conventional EGD: a comparative study. *Gastroenterology* 1999; **117**: 1301-1307
- 24 **Saeian K**, Staff D, Knox J, Binion D, Townsend W, Dua K, Shaker R. Unsedated transnasal endoscopy: a new technique for accurately detecting and grading esophageal varices in cirrhotic patients. *Am J Gastroenterol* 2002; **97**: 2246-2249
- 25 **Saeian K**, Staff DM, Vasilopoulos S, Townsend WF, Almagro UA, Komorowski RA, Choi H, Shaker R. Unsedated transnasal endoscopy accurately detects Barrett's metaplasia and dysplasia. *Gastrointest Endosc* 2002; **56**: 472-478
- 26 **Catanzaro A**, Faulx A, Isenberg GA, Wong RC, Cooper G, Sivak MV, Chak A. Prospective evaluation of 4-mm diameter endoscopes for esophagoscopy in sedated and unsedated patients. *Gastrointest Endosc* 2003; **57**: 300-304
- 27 **Thota PN**, Zuccaro G, Vargo JJ, Conwell DL, Dumot JA, Xu M. A randomized prospective trial comparing unsedated esophagoscopy via transnasal and transoral routes using a 4-mm video endoscope with conventional endoscopy with sedation. *Endoscopy* 2005; **37**: 559-565
- 28 **Jobe BA**, Hunter JG, Chang EY, Kim CY, Eisen GM, Robinson JD, Diggs BS, O'Rourke RW, Rader AE, Schipper P, Sauer DA, Peters JH, Lieberman DA, Morris CD. Office-based unsedated small-caliber endoscopy is equivalent to conventional sedated endoscopy in screening and surveillance for Barrett's esophagus: a randomized and blinded comparison. *Am J Gastroenterol* 2006; **101**: 2693-2703
- 29 **Murata A**, Akahoshi K, Sumida Y, Yamamoto H, Nakamura K, Nawata H. Prospective randomized trial of transnasal versus peroral endoscopy using an ultrathin videoendoscope in unsedated patients. *J Gastroenterol Hepatol* 2007; **22**: 482-485
- 30 **Yoshida Y**, Hayami Y, Matuoka M, Nakayama S. Comparison of endoscopic detection rate of early gastric cancer and gastric adenoma using transnasal EGD with that of transoral EGD. *Dig Endosc* 2008; **20**: 184-189
- 31 **Tatsumi Y**, Harada A, Matsumoto T, Tani T, Nishida H. Current status and evaluation of transnasal esophagogastroduodenoscopy. *Dig Endosc* 2009; **21**: 141-146
- 32 **Hayashi Y**, Yamamoto Y, Suganuma T, Okada K, Nego M, Imada S, Imai M, Yoshimoto K, Ueki N, Hirasawa T, Uragami N, Tsuchida T, Fujisaki J, Hoshino E, Takahashi H, Igarashi M. Comparison of the diagnostic utility of the ultrathin endoscope and the conventional endoscope in early gastric cancer screening. *Dig Endosc* 2009; **21**: 116-121
- 33 **Yanaoka K**, Oka M, Mukoubayashi C, Yoshimura N, Enomoto S, Iguchi M, Magari H, Utsunomiya H, Tamai H, Arii K, Ohata H, Fujishiro M, Takeshita T, Mohara O, Ichinose M. Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 838-845

S- Editor Wang JL L- Editor Roemmele A E- Editor Zheng XM