ORIGINAL ARTICLE

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Prevalence of Subjects at a High or Very High Risk of Gastric Cancer in Japan

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Background/Aims: The presence of *Helicobacter pylori* (*H. pylori*) infection represents a high-risk state of gastric cancer, but the risk is even higher in gastric atrophy. *H. pylori* stool antigen (HpSA) and serum pepsinogen (PG) tests are useful tools for screening present infection and gastric atrophy, respectively. To determine the prevalence of subjects at a high risk (HpSA+ or PG+) or very high risk (PG+) of gastric cancer in Japan, we applied the two tests to a general population. **Methods:** The subjects included 311 volunteers. We used Meridian HpSA ELISA for the HpSA test and Pepsinogen RIA Beads for the PG test. PG I at ≤70 μg/L and I/II ratio of ≤3.0 were used as cutoffs for PG-test positivity. **Results:** Positivity rates in HpSA and PG tests significantly increased with age in those younger than 60 years and in all age groups, respectively. The proportions of HpSA−/PG− and HpSA+/PG+ subjects decreased and increased with age, respectively. A small proportion of HpSA−/PG+ subjects were older than 40 years. The prevalence of subjects who were either HpSA+ or PG+ increased with age (>50% of those older than 40 years). Half of the subjects older than 60 years were PG+. **Conclusions:** In Japan, more than 50% of general population aged ≥40 years is at a high risk of gastric cancer, and half of the population aged ≥60 years is at a very high risk. **(Gut and Liver 2009;3:95-100)**

Key Words: *Helicobacter pylori*; Stool antigen; Pepsinogen; Gastric cancer screening; Epidemiology

INTRODUCTION

It is established that *Helicobacter pylori* (*H. pylori*) infection is a high-risk state of gastric cancer,[1,2] and it is important to screen high risk subjects for gastric cancer in general population by using a certain *H. pylori* test. Anti-*H.pylori* antibody test is widely used to screen *H. pylori* infection, but it demonstrates past infection as well as present infection. On the other hand, *H. pylori* stool antigen (HpSA) test predicts only present infection, and the test has a high sensitivity and specificity to screen present *H. pylori* infection.[3]

It is also established that gastric atrophy is a high risk state or a precursor lesion of gastric cancer.[4,5] Serum pepsinogen (PG) test is a useful tool to screen gastric atrophy with or without endoscopic examination.[6]

Therefore, high-risk subjects for gastric cancer are recognized as those who have present *H. pylori* infection or gastric atrophy (HpSA+ or PG+), and very high risk subjects as those who have atrophy irrespective of present *H. pylori* infection (PG+).[2]

To make a good strategy to screen high-risk subjects for gastric cancer in a population which has a high prevalence of gastric cancer such as Japanese or Korean, we examined sex and age distributions of HpSA and PG tests in a Japanese population.

MATERIALS AND METHODS

1. Subjects

The subjects were 333 volunteers who visited Healthcare Center of Social Insurance Shiga Hospital to undergo both HpSA and PG tests at annual health check in 2004. Twenty-two volunteers, who had undergone *H. pylori* eradication, are under treatment for peptic ulcer, had undergone surgical operation for stomach, or had unknown

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medical history were excluded from the study.

2. HpSA and PG tests

We used Meridian HpSA ELISA (TFB Inc., Tokyo, Japan/ Meridian Bioscience Inc., Cincinnati, OH, USA) to measure HpSA. Absorption was measured at 450/630 nm, and the results were evaluated as the followings. When ELISA value was 0.120 or above, the case was evaluated as HpSA-positive (HpSA+). When ELISA value was below 0.100, the case was evaluated as HpSA-negative (HpSA−). In case with intermediate result, the case was considered as indeterminate, and excluded from the study.

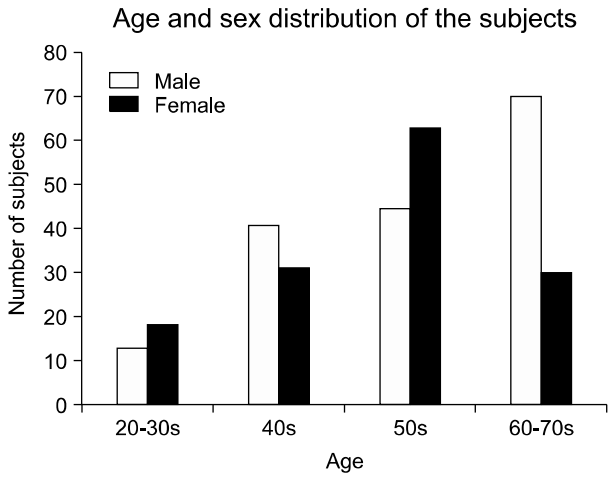

Fig. 1. Age and sex distributions of the study subjects. Age distribution of the study subjects differed significantly with sex (chi-square test, p=0.000274).

For serum PG I and II, we used Pepsinogen RIA Beads I and II (Abbott Japan Co. Ltd., Tokyo, Japan). The result of PG test was interpreted by the value of PG I and the ratio of PG I/II. The criteria for positive PG test were defined as the followings: both PG I was 70 μg/L or below, and PG I/II ratio was 3.0 or below.

3. Statistical analyses

Statistical analysis was performed using ystat2004.xls for Windows/Macintosh (Igaku Tosho Shuppan Co., Ltd, Tokyo, Japan). The Chi square test or Yates corrected Chi square test were used to compare the difference between sexes or age groups. Spearman's correlation test was used to evaluate correlations between age groups and positive rates of HpSA or PG tests. Significance was evaluated with p value below 0.05 in two-tailed examination.

4. Ethics

The study was approved by the Ethical Committee of Social Insurance Shiga Hospital.

RESULTS

After exclusion of the subjects, 311 volunteers were included in the study. The study population is shown in Fig. 1. The age distribution of the study subjects was significantly different between sexes. Therefore the results were analyzed in each sex.

The results of HpSA test are shown in Fig. 2. There was significant difference in HpSA positivity between sexes in only 50s, but no difference in the other age groups.

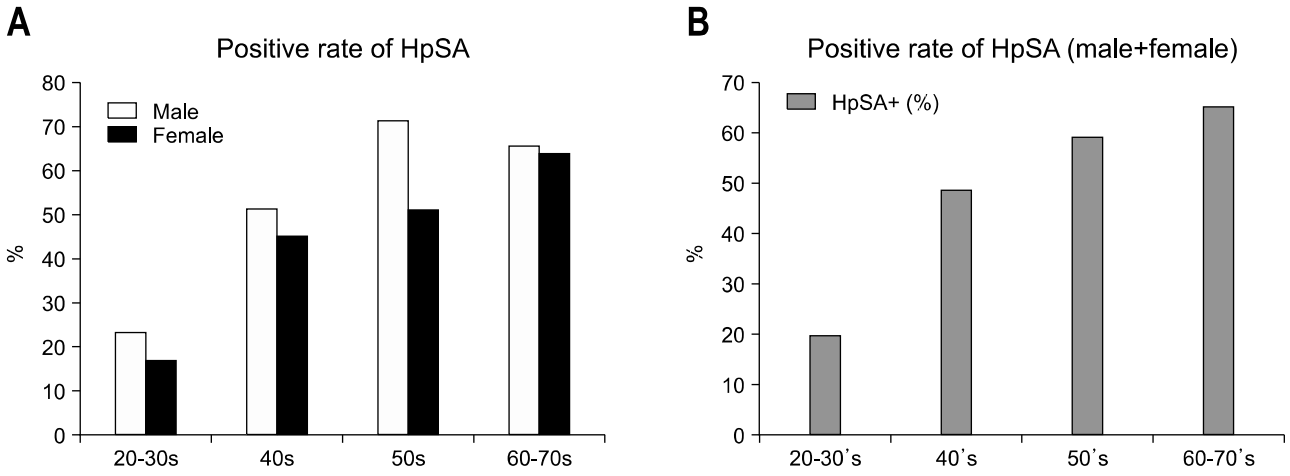

Fig. 2. Positive rate in the HpSA test for each sex (A) and across all subjects (B) according to age groups. HpSA positivity differed significantly with sex only in those aged 50-59 years (Yates' corrected chi-square test, p=0.034). The positive rate in the HpSA test was significantly correlated with age in males <60 years old and in all age groups in females (Spearman's correlation test: r_s=1, p<0.0001). The positive rate in the HpSA test was significantly correlated with age in combined males and females younger than 60 years (Spearman's correlation test: r_s=1, p<0.0001).

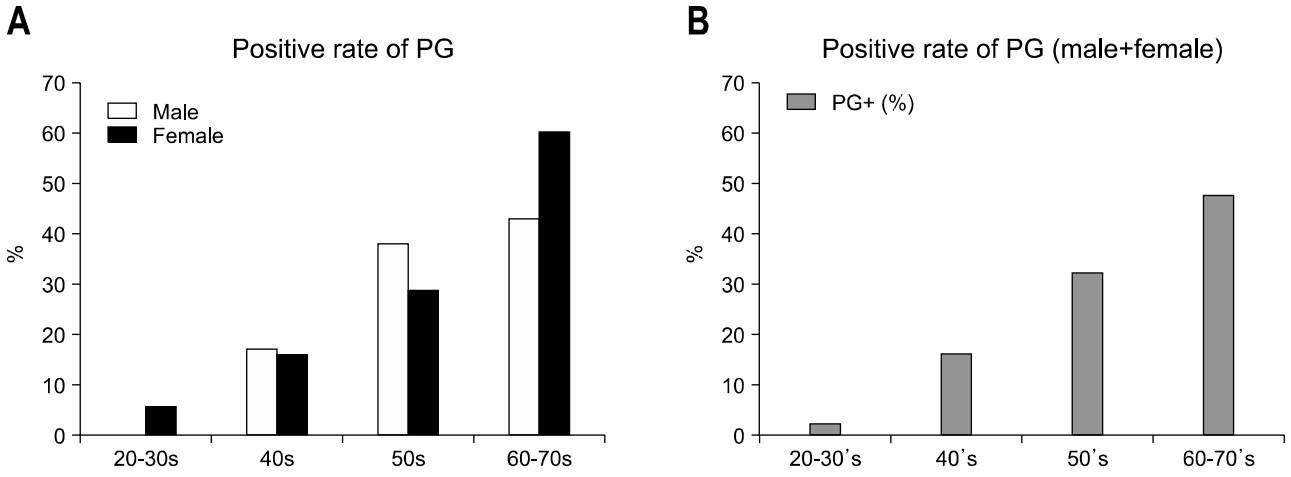

Fig. 3. Positive rate in the PG test for each sex (A) and across all subjects (B) according to age groups. PG positivity did not differ significantly with sex (Yates' corrected chi-square test). PG positivity was significantly correlated with age for each sex (A) and across all subjects (B) (Spearman's correlation test: $r_s=1$, $p<0.0001$).

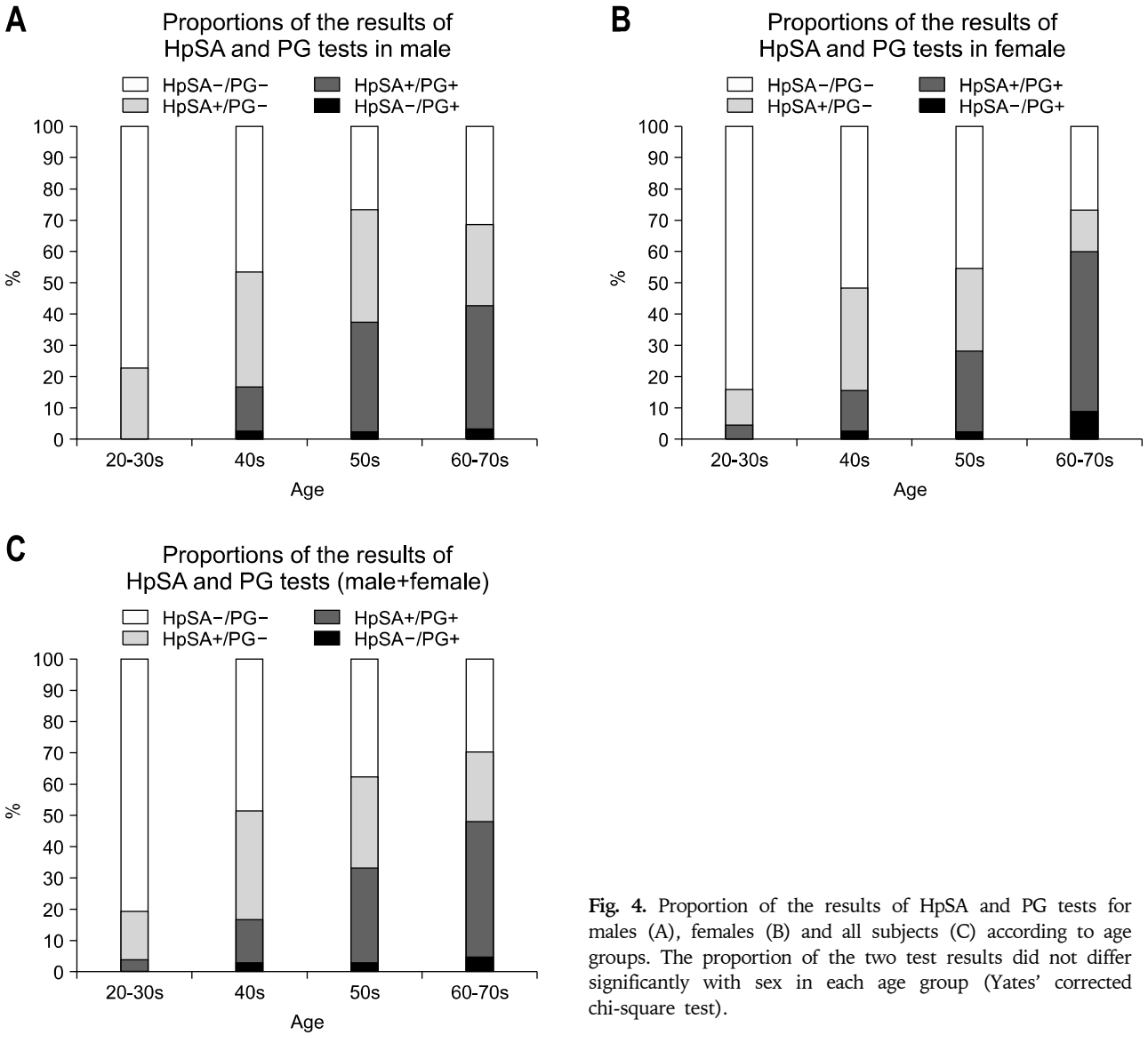

Fig. 4. Proportion of the results of HpSA and PG tests for males (A), females (B) and all subjects (C) according to age groups. The proportion of the two test results did not differ significantly with sex in each age group (Yates' corrected chi-square test).

Positive rate of HpSA test increased with age in both sexes under 60s, but decreased in the older age in male whereas increased in female. Combined with both sexes, the positive rate of HpSA test significantly increased with age under 60s.

The results of PG test are shown in Fig. 3. The positive rate of PG test significantly increased with age in all age groups in both sexes. There was no significant difference in PG positivity between sexes. Combined with both sexes, the positive rate of PG test significantly increased with age in all age groups.

The results of combination with HpSA and PG tests are shown in Fig. 4. There was no significant difference in the proportion of the two test results between sexes in each age group. Combined with both sexes, the proportion of HpSA−/PG− subjects decreased with age. On the other hand, the proportion of HpSA+/PG+ subjects increased with age, whereas that of HpSA+/PG− subjects increased until 40s, but then decreased in 50s and older. A small proportion of HpSA−/PG+ subjects were detected in 40s and older. The prevalence of either HpSA+ or PG+ subjects increased with age. More than 50% subjects aged 40 or older are either HpSA+ or PG+, and nearly 50% subjects in 60-70s were PG+ (Fig. 4).

DISCUSSION

The present study showed that the positive rate of HpSA test increased with age in both male and female, except for 60-70s in male. This age-dependent increase of HpSA positive rate was similar to the tendency of the positive rate of serum anti-*H. pylori* antibody in a Japanese population reported by Asaka *et al.*[7] in 1992. There was a small difference in HpSA positive rate between sexes in only 50s in our study. We can not evaluate if it is meaningful or not in the present study. It may be related to the male predominance of gastric diseases in 50s in Japanese.[8] The fact that the rate of HpSA-positive test did not increase in 60-70s in male may be the similar tendency in Asaka's study in which the rate of antibody-positive subjects born before 1950 did not increase. Combined with both sexes, the positive rate of HpSA test significantly increased with age under 60s in our study. The positive rate of HpSA test in our study was approximately 60% in the subjects born before 1954 (50s or older), whereas the positive rate of *H. pylori* antibody in Asaka's study was 70-80% in the subjects born before 1950. Because serum antibody is detected in the subjects who have been eradicated, the rate of positive antibody test may be greater than that of positive HpSA test which shows present infection of *H. pylori* in the stomach. Thus our study indicated that the rate of present *H. pylori* infection increased with age and the rate of present infection in the subjects born before 1954 was approximately 60%. Although HpSA test shows present infection of *H. pylori* in the stomach, the test needs a measurable amount of *H. pylori* antigens in the stool. If there are only small amount of the bacteria in the stomach, the test could show a negative result. Therefore our results with HpSA test may be underestimated. This is one of the reasons why the positive rate of HpSA test in our study was lower than that of antibody test in Asaka's study.

Our study also showed that the positive rate of PG test increased with age in both male and female. There was no significant difference between sexes. The rate of positive PG test in male did increase in 60-70s, indicating that increasing PG positive tendency continued over 50s in spite that the rate of present *H. pylori* infection did not increase. In female the positive rates of HpSA and PG tests increased with age. Combined with both sexes, the positive rate of PG test increased with age. The positive rate of PG test increased later than the increase of the positive rate of HpSA test. Because PG test demonstrates gastric atrophy[6] and atrophy develops in subjects who have long-term infection of *H. pylori* in the stomach,[9-11] our results of HpSA and PG test are consistent with the facts.

In combination with both HpSA and PG tests, there was no significant difference between sexes in the proportion of the results of the two tests in each age group. Thus, combined with both sexes, the proportion of HpSA−/PG− subjects decreased with age. This compartment of the subjects reflects *H. pylori*-virgin subjects, indicating that younger people have less possibility of *H. pylori* infection in Japan. On the other hand the proportion of HpSA+/PG+ subjects increased with age. This compartment reflects *H. pylori*-infected subjects with gastric atrophy, indicating that gastric atrophy increased with age. HpSA+/PG− subjects increased until 40s, but then decreased in 50s and older. These tendencies of the two HpSA+ compartments reflect that gastric atrophy developed from HpSA+/PG− subjects to HpSA+/PG+ subjects, and a half of the 50s and the majority of the 60-70s subjects with *H. pylori* infection had gotten atrophy, respectively. A small proportion of HpSA−/PG+ subjects were detected in 40s and older. It is reported that long-term *H. pylori* infection causes gastric atrophy and intestinal metaplasia,[12] and the amount of the bacteria decreases in the individuals who have a large amount of intestinal metaplasia in the stomach.[13] Because intestinal metaplasia develops in parallel to the development of gastric atrophy,[9] the appearance of HpSA−/PG+ subjects reflects that *H.*

pylori had been rejected from the stomach or decreased below the measurable amount in some subjects in older ages due to progressed intestinal metaplasia with atrophy. It is reported that this compartment is the group that has the highest risk for gastric cancer,[2] so that we should not neglect the individuals in this compartment. In screening high risk subjects for gastric cancer with only HpSA test, the individuals with the highest risk could not be trapped. Thus PG test should be combined with HpSA test for screening high risk subjects for gastric cancer.

If we classified either HpSA+ or PG+ subjects as high-risk subjects for gastric cancer, the prevalence of high-risk subjects increased with age, and more than 50% subjects aged 40s or older are at high risk in Japan. If we classified PG+ subjects as very high-risk subjects for gastric cancer, nearly 50% subjects in 60-70s are at very high-risk in Japan. The combination of HpSA and PG test is one of the choices for screening and classifying high risk subjects for gastric cancer.

However, in countries where the prevalence of *H. pylori* infection and gastric atrophy is high, such as in Japan, majority of the subjects in middle and high-aged populations show positive results by screening with the two tests. It may not be cost-effective to examine all the positive subjects with endoscopy. Therefore one more examination such as barium X-ray examination may be added for screening subjects who really need endoscopy.

Recently, four methods for gastric cancer screening, barium X-ray examination, endoscopy, serum pepsinogen testing and *Helicobacter pylori* antibody testing, were evaluated by a systematic review in Japan.[14] According to the report, gastric cancer screening using barium X-ray examination is recommended for population-based screening, but the other methods were not recommended due to insufficient evidence. However, the report also suggested that the high-risk subjects for gastric cancer could be identified with combination of *H. pylori* antibody and serum PG tests.[14] From the present study, by using HpSA and PG tests, we can also screen and identify those who are in high risk and very high risk for gastric cancer. Because eradication therapy is effective for prevention of gastric cancer in those who have atrophy in the stomach,[15] and because HpSA test predicts current infection of *H. pylori*, this combination of HpSA and PG tests may give valuable information for eradication therapy to prevent gastric cancer.

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