Cancer High-Risk Subjects Identified by Serum Pepsinogen Tests: Outcomes after 10-Year Follow-up in Asymptomatic Middle-Aged Males

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Abstract

Background: Gastric cancer screening using the pepsinogen filter test is receiving wide recognition in Japan owing to convenience, freedom from discomfort or risk, efficiency, and economy. Because the long-term outcomes of cancer development in extensive atrophic gastritis detected by pepsinogen test are unclear, test-positive and test-negative subjects were investigated in a longitudinal cohort study.

Methods: Subjects comprised 5,209 middle-aged men with measured serum pepsinogen levels who were followed for 10 years. Cancer development based on "atrophy-positive" and "atrophy-negative" criteria used for cancer screening was investigated.

Results: During the study, 63 cases of cancer developed in the cohort, representing an incidence rate of 125 per 100,000 person-years. Pepsinogen test screening using the most widely used atrophy-positive criterion (pepsinogen I, ≤70 ng/mL; pepsinogen I/II ratio, ≤3.0) displayed 58.7% sensitivity, 73.4% specificity, and 2.6% positive predictive value. Cancer incidence rate was 276 per 100,000 person-years for the atrophy-positive group and 70 per 100,000 person-years for the atrophy-negative group. Incidence rate was higher in groups fulfilling stricter positive criteria detecting more extensive atrophy, reaching 424 per 100,000 person-years. In addition, 9.2% of atrophy-negative subjects with pepsinogen I of >70 ng/mL and pepsinogen I/II ratio of ≤3.0 (reflecting putative inflammation-based high pepsinogen II level) are at high risk for cancer, particularly diffuse-type cancer, with a cancer incidence rate comparable with atrophy-positive subjects (216 per 100,000 person-years).

Conclusion: Atrophy-positive subjects by pepsinogen filter test, particularly those fulfilling stricter criteria, and atrophy-negative subjects with low pepsinogen I/II ratio reflecting putative extensive active inflammation constitute populations at high risk for gastric cancer, requiring thorough endoscopic examination. (Cancer Epidemiol Biomarkers Prev 2008;17(4):838–45)

Introduction

Gastric cancer, despite a recent decline in incidence, is still one of the most common malignancies worldwide and remains a leading cause of cancer death not only in Japan but also in China, Korea, Central and Southern America, and some European countries (1-5). To reduce high mortality and morbidity rates in Japan, mass screening for gastric cancer has been conducted as a public health service since the mid-1960s. The screening program is currently done throughout the country, and ~6 million people annually undergo screening provided by either a community health service or the workplace (6-8). Thousands of stomach cancer cases are detected each year, with 5,859,697 people undergoing screening and 5,529 cancers detected in 2004 (detection rate, 0.094%; ref. 8). Cancer screening has thus greatly contributed to reductions in cancer mortality rates in our country (9-13). Although nationwide stomach cancer screening has achieved unparalleled success, the number of people screened has not increased in recent years, with the same people appearing to receive gastric cancer screenings each year; in 2004, the cancer screening covered only 12.9% of the cancer-prone aged population throughout Japan. In addition, cancer screening programs have most commonly adopted gastrophotofluorography with an image intensifier as a filter test. The low resolution of this test is considered problematic because gastrophotofluorography is usually only indicative of abnormalities in the gastric mucosa. More than half of early cancer cases go undiagnosed; whereas sensitivity for advanced cancer is 92%, that for early-stage cancer is as low as 39% (14). Furthermore, gastrophotofluorography is expensive and requires...
technical skills on the part of the radiographic technicians and expert diagnostic abilities on the part of the radiologist. Although the incidence of leukemia has reportedly not increased among participants in the screening program, the risks of X-ray exposure are considered to represent another problem (15, 16). A more efficient screening system is thus sorely needed.

As a trial to improve the screening system, we recently introduced a serum pepsinogen test into gastric cancer screening as an alternative to gastrophotofluorography (17-19). This screening system is based on the hypothesis that chronic atrophic gastritis, including intestinal metaplasia, is a preneoplastic lesion of the stomach (20), together with the results of previous studies indicating that low serum pepsinogen levels reflect the extent of chronic atrophic gastritis (21, 22). In the screening system, individuals positive for extensive atrophic gastritis based on serum pepsinogen levels are further screened by endoscopy. Since 1992, when pepsinogen assay kits became commercially available, a number of screening services provided by work places or by community health services have adopted this serum test as a filter test (23-28). The results of the screening for the past 15 years have shown that addition of the serum test to the screening strategy has markedly increased the number of subjects undergoing screening and has also significantly improved detection rates of gastric cancer and early cancer, in particular, compared with conventional screening using gastrophotofluorography.

The effectiveness of the pepsinogen filter test is thus receiving wide recognition, and the observed high efficiency of the serum test in cancer detection strongly indicates that gastric cancer tends to develop from the atrophic stomach as detected by low serum pepsinogen. However, the long-term prognosis of subjects with extensive chronic atrophic gastritis identified by pepsinogen filter test is not fully known, including cancer incidence rates. In addition, various studies on cancer screening with the pepsinogen filter test have reported a nonnegligible number of test-negative cancers (17-19, 23-28), and the risk for cancer development among pepsinogen test-negative subjects has likewise not been fully elucidated. The present study investigated long-term outcomes of gastric cancer development among pepsinogen test-positive and test-negative subjects based on a 10-year follow-up study.

Subjects and Methods

Study Subjects. Subjects comprised 5,706 male employees ages 40-60 years (mean ± SD, 49.2 ± 4.7 years) who participated in an annual multiphasic health screening program in Wakayama City, Japan, between April 1994 and the end of March 1995. This type of screening program is generally done by various work places throughout Japan to detect incident diseases in the early stages. Subjects with specific symptoms were thus guided to receive medical attention and were excluded from screening. Subjects who had previously undergone gastric resection were also excluded and were examined separately. Symptom-free subjects underwent a series of screening tests and procedures: an interview to ascertain general state of health, physical examination, chest radiography, electrocardiography, blood laboratory tests, urinalysis, and fecal occult blood test. Some of these subjects had been investigated in a previous cohort study (28).

All subjects were followed for the study period of 10 years, from April 1994 to the end of March 2004. Subjects underwent the aforementioned health screening program annually and were also screened to identify incident gastric cancer, as described in the following Gastric Cancer Screening section. The incident day of gastric cancer was defined as the day of the health checkup when the cancer was detected. Duration of the observation period was calculated for each subject from the time of the baseline survey to the diagnosis of gastric cancer.

Analysis of Serum Pepsinogen Levels. Aliquots of separated sera from fasting blood samples collected as routine laboratory tests for general health checkup were stored below −20°C until measurement of serum pepsinogen levels. Serum pepsinogen levels (pepsinogens I and II) were measured using a modification (RIA beads kit, Dainabott) of our previously reported RIA (29). Subjects with renal failure were excluded from analyses of the results of serum pepsinogen levels. Subjects who had been prescribed medication that might affect gastrointestinal function, such as proton pump inhibitors or nonsteroidal anti-inflammatory drugs, before examination and subjects who had undergone eradication therapy for Helicobacter pylori were also excluded.

Gastric Cancer Screening. Cancer screening was done by double-contrast barium X-ray with digital radiography and by serum pepsinogen as filter tests. For upper gastrointestinal barium X-ray, a remote controlled X-ray fluoroscope (TU-230XB, Hitachi Medical Corp.) and real-time digital radiography (DR-2000H; Hitachi Medical) were used. The double-contrast upper gastrointestinal X-ray series used 150 mL of high-concentration barium at 200%, and 11 films were taken for each subject as described previously (28). Subjects were also screened using the serum pepsinogen filter test. Among several test-positive criteria of the pepsinogen filter test used for cancer screening in our country, the criterion of pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0 is the most widely applied, with atrophy-positive defined when the criterion is fulfilled and atrophy-negative defined when the criterion is not fulfilled (19, 30-33). Additional and stricter criteria of pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤3.0 or pepsinogen I of ≤30 ng/mL and pepsinogen I/II ratio of ≤2.0 are also used to detect subjects with more extensive atrophy (18, 23, 24). The latter two criteria are used variously, independently or in combination with the aforementioned atrophy-positive criteria, depending on the purpose of screening. When used in combination, each criterion constitutes pepsinogen index 1+ to 3+ within the atrophy-positive group according to the first criterion of pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0.

The third criterion, pepsinogen I of ≤30 ng/mL and pepsinogen I/II ratio of ≤2.0, is defined as pepsinogen index 3+. The second criterion, pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤3.0 but not meeting the criterion for pepsinogen index 3+, is defined
as pepsinogen index 2+. The first criterion, but not meeting the criteria for pepsinogen index 2+ or 3+, is defined as pepsinogen index 1+ (ref. 34; Fig. 1A). In the present study, data on serum pepsinogen levels of subjects were classified basically using the atrophy-positive criterion and pepsinogen index. If a subject was identified as test-positive by serum pepsinogen test, fulfilling the atrophy-positive criterion, that is, pepsinogen index 1+ to 3+, or by barium digital radiography, further examination was conducted by upper gastrointestinal endoscopy (XQ-200, Olympus).

Resected specimens of gastric cancer obtained by endoscopy or surgery were assessed histopathologically and classified according to the classification of Lauren (34) as intestinal or diffuse type. Location of the cancer in the stomach was classified as cardia or noncardia based on clinical or histopathologic records. The ethics committee of Wakayama Medical University approved the study protocols, and informed consent was obtained from all participating subjects.

**Statistical Analysis.** Data were analyzed using SPSS 11.0 (SPSS) and STATA (STATA Corp.). Differences were tested for significance using the t test for comparisons between two groups, ANOVA for comparisons among multiple groups, and Scheffe’s least significant difference test for comparisons of pairs of groups. The $\chi^2$ test was used to compare categorical variables. Long-term effects of pepsinogen test-positive or test-negative criteria on gastric cancer development were evaluated using Cox proportional hazards models.

**Results**

A total of 5,706 eligible subjects were examined. Of these, 489 subjects who declined to participate in the study program or who met the exclusion criteria described were excluded from the study. In addition, eight cases of gastric cancer that developed within the 1st year of the study were also excluded. The remaining 5,209 subjects...
Among 37 cancers developed from atrophy-positive subjects, 16.2% (n = 6) were from the pepsinogen index 1+ group, 37.8% (n = 14) from the pepsinogen index 2+ group, and 46.0% (n = 17) from the pepsinogen index 3+ group (Table 2). Kaplan-Meier analysis showed that after 6 years of follow-up, cancer development occurred in the order of pepsinogen index and was highest in the 3+ group, followed by the 2+, 1+, and atrophy-negative group.

Among subjects, irrespective of test positivity or differences in pepsinogen index. Of 63 cases of gastric cancer that developed during the study period, 58.7% (n = 37) developed in the atrophy-positive group and the remaining 41.3% (n = 26) developed in the atrophy-negative group. With the second and third criteria, 49.2% (n = 31) and 27.0% (n = 17) of cancer cases were test-positive, respectively (Table 1). The accuracy of cancer screening by each of the three criteria was thus as follows: for pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0, 58.7% sensitivity [95% confidence interval (95% CI), 45.6-70.8%], 73.4% specificity (95% CI, 72.1-74.6%), and 2.6% positive predictive value (95% CI, 1.9-3.6%); for pepsinogen I of ≤72.1 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL, that is atrophy positive. Likewise, 19.8% (n = 1,033) and 8.2% (n = 427) were positive by the second criterion, pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL and pepsinogen I/II ratio of ≤50 ng/mL, respectively (Table 1). Among the atrophy-positive group, 27.0% (n = 374) were categorized as pepsinogen index 1+, 43.0% (n = 606) as pepsinogen index 2+, and 30.0% (n = 427) as pepsinogen index 3+ (Table 2). Mean age was significantly higher in test-positive subjects than in test-negative subjects in each of the three criteria and increased in a stepwise manner with increasing pepsinogen index, whereas no significant difference was seen in mean follow-up period

### Table 1. Gastric cancer incidence rate by various criteria of pepsinogen filter test

<table>
<thead>
<tr>
<th>Screening criteria</th>
<th>PG I ≤70 and PG I/II ≤3.0</th>
<th>PG I ≤70 and PG I/II ≤3.0</th>
<th>PG I ≤30 and PG I/II ≤2.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>3,802</td>
<td>1,407</td>
<td>4,176</td>
<td>1,033</td>
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<tr>
<td>Person-years</td>
<td>37,010.0</td>
<td>13,416.0</td>
<td>40,626.5</td>
<td>9,799.5</td>
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<tr>
<td>Age [mean (SD)]</td>
<td>48.8 (4.8)</td>
<td>50.3 (4.4)*</td>
<td>48.9 (4.7)</td>
<td>50.6 (4.3)*</td>
</tr>
<tr>
<td>Follow-up years</td>
<td>9.7 (0.8)</td>
<td>9.5 (1.1)</td>
<td>9.7 (0.8)</td>
<td>9.5 (1.2)</td>
</tr>
<tr>
<td>Total gastric cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>50.7 (4.3)</td>
<td>50.9 (3.4)</td>
<td>50.3 (4.2)</td>
<td>51.4 (3.2)</td>
</tr>
<tr>
<td>Follow-up years</td>
<td>6.3 (2.6)</td>
<td>5.9 (2.6)</td>
<td>6.5 (2.5)</td>
<td>5.6 (2.6)</td>
</tr>
<tr>
<td>Cases/ incidence rate</td>
<td>26/70</td>
<td>37/276</td>
<td>32/79</td>
<td>31/316</td>
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<tr>
<td>Intestinal gastric cancer</td>
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<td></td>
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<tr>
<td>Age [mean (SD)]</td>
<td>51.1 (4.0)</td>
<td>51.4 (3.4)</td>
<td>50.6 (3.6)</td>
<td>51.6 (3.4)</td>
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<tr>
<td>Follow-up years</td>
<td>6.0 (2.7)</td>
<td>5.7 (2.5)</td>
<td>6.2 (2.6)</td>
<td>5.7 (2.4)</td>
</tr>
<tr>
<td>Cases/ incidence rate</td>
<td>16/41</td>
<td>26/194</td>
<td>18/44</td>
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<tr>
<td>Diffuse gastric cancer</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>50.2 (4.8)</td>
<td>49.7 (3.2)</td>
<td>50.0 (5.0)</td>
<td>50.6 (2.0)</td>
</tr>
<tr>
<td>Follow-up years</td>
<td>6.8 (2.5)</td>
<td>6.2 (2.8)</td>
<td>6.7 (2.4)</td>
<td>5.4 (3.3)</td>
</tr>
<tr>
<td>Cases/ incidence rate</td>
<td>10/30</td>
<td>11/82</td>
<td>14/35</td>
<td>7/71</td>
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<td>Accuracy of screening criteria</td>
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<tr>
<td>Sensitivity (95% CI)</td>
<td>58.7% (45.6-70.8)</td>
<td>49.2% (36.5-62.0)</td>
<td>37.0% (22.4-52.6)</td>
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<tr>
<td>Specificity (95% CI)</td>
<td>73.4% (72.1-74.6)</td>
<td>80.5% (79.4-81.6)</td>
<td>72.1% (69.9-74.4)</td>
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<tr>
<td>Positive predictive value (95% CI)</td>
<td>2.6% (1.9-3.6)</td>
<td>3.0% (2.1-4.3)</td>
<td>4.0% (2.4-6.4)</td>
<td></td>
</tr>
<tr>
<td>Negative predictive value (95% CI)</td>
<td>99.3% (99.0-99.5)</td>
<td>99.2% (98.9-99.5)</td>
<td>99.0% (98.7-99.3)</td>
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<tr>
<td>Likelihood ratio of a positive test (95% CI)</td>
<td>2.21% (1.78-2.73)</td>
<td>2.53% (1.95-3.27)</td>
<td>3.39% (2.23-5.14)</td>
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<tr>
<td>Likelihood ratio of a negative test (95% CI)</td>
<td>0.56% (0.42-0.76)</td>
<td>0.63% (0.49-0.80)</td>
<td>0.79% (0.68-0.92)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** PG, pepsinogen.

*Significantly different from each counterpart (P < 0.05).

1 Per 100,000 person-years.

(mean age, 49.2 ± 4.7 years) were followed for 10 years and investigated for gastric cancer development. During 50,426 person-years of follow-up, 63 cases of cancer developed, representing an incidence rate of 125 of 100,000 person-years in the cohort (Table 1). Histopathologic features of the detected cancer revealed intestinal type in 42 cases (65%) and diffuse type in 21 cases (35%).

Most cases (61 cases, 96.8%) were noncardia cancer, and only 2 cases (3.2%) were located in the gastric cardia. Fifty-four cases (86%) were in the early stage and confined to the mucosa or submucosa. The remaining nine cases were in the advanced stage. Mucosal cancers comprised 74% (40 of 54) of early cancers and were treated by endoscopic resection. The remaining 14 early cancers and 9 advanced cancers underwent surgical resection, and all cases were successfully treated.

Of 5,209 study subjects, 27.0% (n = 1,407) were positive according to the first criterion, pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0, that is atrophy positive. Likewise, 19.8% (n = 1,033) and 8.2% (n = 427) were positive by the second criterion, pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤3.0, and third criterion, pepsinogen I of ≤30 ng/mL and pepsinogen I/II ratio of ≤2.0, respectively (Table 1). Among the atrophy-positive group, 27.0% (n = 374) were categorized as pepsinogen index 1+, 43.0% (n = 606) as pepsinogen index 2+, and 30.0% (n = 427) as pepsinogen index 3+ (Table 2). Mean age was significantly higher in test-positive subjects than in test-negative subjects in each of the three criteria and increased in a stepwise manner with increasing pepsinogen index, whereas no significant difference was seen in mean follow-up period.
groups (Fig. 1B). A significant stepwise increase in cancer incidence rate was seen with increases in pepsinogen index among the atrophy-positive group from 166 to 424 per 100,000 person-years, and hazard ratio also increased significantly and in a stepwise manner from atrophy-negative to pepsinogen index 3+, reaching 5.16 (95% CI, 2.77-9.51); \( P < 0.01 \); Table 2. Of the two histologic types of cancer, a significant positive correlation between cancer incidence rate and pepsinogen index was observed only for intestinal-type cancer.

As described previously, 41.3% (26 of 63) of detected cancers developed from the atrophy-negative group. Of the two histopathologic types of cancer, 10 cancers (38.5%) derived from this group were diffuse-type, meaning that nearly half (47.6%) of the 21 diffuse-type cancers detected during the study period developed from nonatrophic stomachs. Whereas the atrophy-positive group comprised subjects with low values for both serum pepsinogen I and pepsinogen I/II ratio, the negative group was composed of not only subjects with high serum pepsinogen I and pepsinogen I/II ratio but also subjects with low serum pepsinogen I or low pepsinogen I/II ratio. The atrophy-negative group can thus be further classified into the following three groups: group \( \alpha \) with pepsinogen I of \( \leq 70 \) ng/mL and pepsinogen I/II ratio of \( >3.0 \); group \( \beta \), with pepsinogen I of \( >70 \) ng/mL and pepsinogen I/II ratio of \( >3.0 \); and group \( \gamma \) with pepsinogen I of \( >70 \) ng/mL and pepsinogen I/II ratio of \( \leq 3.0 \).

## Table 2. Gastric cancer incidence rate in atrophy-negative and atrophy-positive groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Atrophy-negative group</th>
<th>Atrophy-positive group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Subject</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Subjects</td>
<td>3,802</td>
<td>2,219</td>
</tr>
<tr>
<td>Person-years</td>
<td>37,010.0</td>
<td>21,702.5</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>9.7 (0.8)</td>
<td>9.8 (0.7)</td>
</tr>
<tr>
<td>Follow-up years</td>
<td>PG I [mean (SD)]</td>
<td>69.3 (29.6)</td>
</tr>
<tr>
<td></td>
<td>PG I/II [mean (SD)]</td>
<td>5.1 (1.8)</td>
</tr>
<tr>
<td>Total gastric cancer</td>
<td>Age [mean (SD)]</td>
<td>50.7 (4.3)</td>
</tr>
<tr>
<td></td>
<td>Follow-up years</td>
<td>6.3 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Cases/incidence rate</td>
<td>26/70</td>
</tr>
<tr>
<td>Intestinal gastric cancer</td>
<td>Age [mean (SD)]</td>
<td>51.1 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Follow-up years</td>
<td>6.0 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Cases/incidence rate</td>
<td>16/41</td>
</tr>
<tr>
<td>Diffuse gastric cancer</td>
<td>Age [mean (SD)]</td>
<td>50.2 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Follow-up years</td>
<td>6.8 (2.5)</td>
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<tr>
<td></td>
<td>Cases/incidence rate</td>
<td>10/29</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

1 Significantly different from group \( \alpha \) subjects (\( P < 0.05 \)).
2 Significantly different from pepsinogen index 1+ subjects (\( P < 0.05 \)).
3 Per 100,000 person-years.

In the atrophy-positive group, hazards ratio was calculated in comparison with cancer incidence rate of the atrophy-negative group (total) and, in the atrophy-negative group, was calculated in comparison with that of group \( \alpha \).
cancer but not that of intestinal-type cancer (Table 2). Kaplan-Meier analysis revealed that after 5 years of follow-up, cumulative incidence of diffuse-type cancer was in the order of groups γ, β, and α (Fig. 1C), with an incidence rate of 120 per 100,000 person-years for group γ and significantly increased hazard ratio compared with that in group α (hazard ratio, 8.04; 95% CI, 1.78-36.25).

Discussion

In the present study, 5,209 middle-aged male subjects with measured serum pepsinogen levels were followed for 10 years, and gastric cancer development was investigated based on the criteria of the pepsinogen filter test widely used for gastric cancer screening in Japan. For cancer screening in our country, the following pepsinogen test-positive criteria have been used depending on differences in target population and the purpose of screening: pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0; pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤3.0; or pepsinogen I of ≤30 ng/mL and pepsinogen I/II ratio of ≤2.0.

Among these, the first criterion (pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0) is considered both the most efficient for identifying extensive atrophic gastritis and the best cancer screening criterion based on the results of previous studies (19, 26, 30-33). In addition, the results of a recent meta-analysis of seven studies analyzing organized population-based cancer screening indicated that pooled sensitivity and specificity of the criterion were 77.3% and 73.2%, offering a better sensitivity/specificity balance than any other criteria and also providing strong support for the use of pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0 (37). In our observation over 10 years, pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0 was considered the best among the criteria currently used for cancer screening, showing 58.7% sensitivity (95% CI, 45.6-70.8%) and 73.4% specificity (95% CI, 72.1-74.6%).

As for the other two criteria, pepsinogen I of ≤50 ng/mL and pepsinogen I/II ratio of ≤3.0 or pepsinogen I of ≤30 ng/mL and pepsinogen I/II ratio of ≤2.0, the sensitivity of screening is <50%, at 49.2% (95% CI, 36.5-62.0%) and 27.0% (95% CI, 16.9-39.9%), respectively. Cancer screening using either of these criteria as an independent criterion for the filter test thus does not seem feasible. As a whole, the sensitivity of these criteria analyzed in the present study was considerably lower than that reported in other studies (37). This is probably due to the fact that previous studies analyzed an initial phase of screening when the pepsinogen filter test was newly applied, in cross-sectional evaluations, whereas the present study analyzed the subsequent phase of screening by prospective evaluation, with eight cases of cancer detected during the 1st year of investigation excluded from the analysis.

The present results strongly indicate that the sensitivity of pepsinogen filter test, which is high on initial prevalent screening, is not equally high for noninitial incident screenings in subsequent years. The reported high sensitivity in these studies was likely caused by overestimating the accuracy of the pepsinogen filter test. Nonetheless, the present results clearly show that the atrophy-positive criterion of pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0 detects 58.7% of cancers developing over 10 years and also identifies a group of subjects susceptible for gastric cancer. The incidence rate of gastric cancer in the group defined by this criterion was 276 per 100,000 person-years and increased in a stepwise to a maximum level of 424 per 100,000 person-years with an increase in pepsinogen index from 1+ to 3+. The observed correlation between incidence rate of gastric cancer and grade of atrophy as indicated by pepsinogen index verifies the hypothesis that risk for cancer increases with progression of chronic atrophic gastritis (20) and that serum pepsinogen level offers a reliable marker for cancer development and coexisting atrophic gastritis.

Meanwhile, a nonnegligible proportion (41.3%) of gastric cancers developed in the atrophy-negative group during the study period. In this group, the percentage of diffuse-type cancers (38.5%) was significantly higher than that in the atrophy-positive group (29.7%), and nearly half of diffuse-type cancers (47.6%) developed in this group during the study period, in good accordance with the hypothesis that this type of cancer develops in the stomach following chronic inflammation without passing through an intermediate step of atrophic gastritis together with intestinal metaplasia (38-40).

Unlike the atrophy-positive group, this group displays heterogeneous serum pepsinogen levels, containing subjects with both high and low levels of serum pepsinogen I and pepsinogen I/II ratio, and can be classified into three subgroups: group α, with pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of >3.0; group β, with pepsinogen I of >70 ng/mL and pepsinogen I/II ratio of >3.0; and group γ, with pepsinogen I of >70 ng/mL and pepsinogen I/II ratio of ≤3.0. Among these subgroups, cancer incidence rate was highest in group γ at 216 per 100,000 person-years, comparable with that in the atrophy-positive group and even higher than that for pepsinogen index 1+ (166 per 100,000 person-years). Establishment of H. pylori infection results in increased serum pepsinogen levels, and this elevated pepsinogen level (particularly pepsinogen II in the nonatrophic stomach) is considered to reflect the severity of gastritis (41, 42). Gastric inflammation is thus likely to be increasingly severe in groups α, β, and γ, in that order, as revealed by respective pepsinogen levels. In addition, the mean age in each of the three subgroups increased in the order of groups α, β, and γ, and the number of subjects in these subgroups decreased in the same order.

Furthermore, the proportion of H. pylori–negative subjects was larger in the order of group α (33%; 733 of 2,219), group β (19%; 229 of 1,234), and group γ (1%; 4 of 349). The process of gastritis thus seems to advance from group α through group β and finally to group γ after the establishment of H. pylori infection. These results strongly indicate that a group of subjects with putative extensive active gastritis in the nonatrophic stomach are at high risk for cancer comparable with that in subjects with extensive atrophy. These subjects comprised 9.2% (349 of 3,802) of the atrophy-negative group and can be identified using a criterion of pepsinogen I of >70 ng/mL and pepsinogen I/II ratio of ≤3.0.
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However, this criterion detects only about one quarter of cancers (26.7%) developing in the nonatrophic stomach. This is probably because serum pepsinogen level, especially pepsinogen II, does not show marked elevation in most *H. pylori*-related multifocal gastritis unless *H. pylori*-induced active inflammation becomes widespread, and we cannot detect subjects in whom the active inflammatory process is focally severe enough to commit epithelial cells to neoplastic transformation.

Taken together, the present results clearly indicate that the atrophy-metaplasia-dysplasia-cancer sequence described by Correa (20) represents the main route of stomach carcinogenesis in Japan, and the pepsinogen filter test using a criterion of pepsinogen I of ≤70 ng/mL and pepsinogen I/II ratio of ≤3.0 offers a reliable method for identifying individuals at high risk for the sequence-derived cancer, with an incidence rate of 276 per 100,000 person-years. In addition, we have revealed another group at high risk for cancer without gastric atrophy, identified by a criterion of pepsinogen I of >70 ng/mL and pepsinogen I/II ratio of ≤3.0. The characteristics of this minor group are that it comprises only 6.7% (349 of 5,209) of total cancer-prone aged subjects, shows a high cancer incidence rate comparable with that in subjects with extensive atrophy (216 per 100,000 person-years), and tends to develop diffuse-type cancers with higher malignant potential. Based on the present results, screening targeting both of these high-risk groups would provide 69.8% sensitivity (95% CI, 56.8-80.4%), 66.7% specificity (95% CI, 65.4-68.0%), and 2.5% positive predictive value (95% CI, 1.3-5.1%).

The major aim of cancer screening is to detect treatable early-stage cancer in asymptomatic individuals. For early detection of premalignant or malignant lesions, endoscopic visualization is considered the best method. Endoscopy is invasive, uncomfortable, and expensive and is thus only offered to subjects with positive results on a filter test in cancer screening. In Japan, mass screening for gastric cancer has primarily adopted gastrophotofluorography as a filter test. Compared with this traditional filter test, serum pepsinogen test is easier to perform, provides quicker results, and produces no patient discomfort (17, 19).

Furthermore, the test is inexpensive; the cost for detection of a single cancer was much less than that for conventional screening, comparable with that for surgical resection of a single cancer case (19, 28). Gastrophotofluorography reportedly offers 57% to 90% sensitivity, 77% to 91% specificity, and 9.9% to 2.0% positive predictive value (43). The present results indicate that specificity of the pepsinogen filter test using the criterion of pepsinogen I of ≥70 ng/mL and pepsinogen I/II ratio of ≤3.0 as a cutoff is slightly lower (73.4%), representing a higher false-positive rate than reported for gastrophotofluorography.

However, as clearly indicated in the present study, pepsinogen test-positive subjects are at high risk for cancer, and this low specificity (high false-positive rate) may be partly attributable to the relatively long latency between initiation of the carcinogenic step and clinically established cancer development. The incidence rate of cancer in pepsinogen test-positive subjects is 276 per 100,000 person-years, meaning that one cancer develops in about every 36 subjects during the 10-year period. Regular and strict long-term endoscopic surveillance of this group thus seems warranted. Whether eradication of *H. pylori* is effective for preventing cancer development in these pepsinogen test-positive subjects warrants further investigation.

In conclusion, atrophy-positive subjects and atrophy-negative subjects with putative extensive active inflammation as defined by pepsinogen test criteria constitute populations at high risk for gastric cancer and need thorough examination by endoscopy. Because the results of previous studies have clearly indicated that use of the same cutoff for pepsinogen test results in comparable outcomes in different sets of individuals and in different countries for the detection of preneoplastic or neoplastic lesions (37), the present data are probably useful not only for subjects in high-risk areas of gastric cancer outside Japan but also for subjects in low-risk areas. Mass cancer-screening programs may not be feasible, but strict follow-up of high-risk subjects will probably be effective even in Western countries (44). Further studies are necessary, particularly analyzing follow-up programs of subjects identified by pepsinogen tests and including examination of cost-effectiveness.

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