Effect of *Helicobacter pylori* Infection Combined with CagA and Pepsinogen Status on Gastric Cancer Development among Japanese Men and Women: A Nested Case-Control Study

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Abstract

Background: Although accumulating evidence suggests that *Helicobacter pylori* plays a role in gastric carcinogenesis (1), Estimates of risk range considerably between studies and the magnitude of the risk remains uncertain.

Aim: We aimed to estimate the magnitude of the risk of gastric cancer associated with *H. pylori* infection by a large case-control study nested within a prospective cohort. Possible effect modification by CagA status, and serum pepsinogen status, as a marker of atrophic gastritis, was also considered to see its effect on developing gastric cancer.

Subjects and Methods: Subjects (n = 123,576) were followed up from 1990 to 2004; 511 gastric cancer cases matched to 511 controls were used in the analysis. Plasma immunoglobulin G antibody to *H. pylori*, CagA, and pepsinogen I and II were measured.

Introduction

Accumulating evidence suggests that infection with *Helicobacter pylori* plays a role in gastric carcinogenesis (1). Estimates of risk range considerably between studies and the magnitude of the risk remains uncertain. The variation in the results may be explained by different distribution of gender, age, cardia and noncardia cancers, and study design. In retrospective case-control studies, *H. pylori* infection is, by necessity, assessed after the development of cancer in patients. For some years before cancer diagnosis, many of the patients likely would have had severe atrophic gastritis and intestinal metaplasia, conditions that favor the loss of *H. pylori* colonization and a subsequent loss of seropositivity (2). Because this result will not occur to the same extent in controls, such differential misclassification leads to underestimation of the risk of *H. pylori* infection. However, few studies have attempted to correct the underdetection of *H. pylori*, and more epidemiologic studies with precise analyses are needed.

Results: The adjusted odds ratio (95% confidence interval) of gastric cancer associated with *H. pylori* infection was 5.1 (3.2-8.0). Assuming all CagA-positive subjects are true *H. pylori* positives doubled this risk. Atrophic gastritis was also associated with an elevated risk of gastric cancer and the risk increased further with pepsinogen levels.

Conclusions: Subjects with pepsinogen levels indicative of severe atrophic gastritis may need careful examination regularly regardless of *H. pylori* infection. Those who have other pepsinogen levels but who are *H. pylori* seropositive are likely to benefit from *H. pylori* eradication therapy. Considering both the cost and the potential for misclassification that may occur using multiple serologic tests, caution is needed in interpreting or extrapolating these findings into a screening strategy. (Cancer Epidemiol Biomarkers Prev 2006;15(7):1341–7)

Materials and Methods

Study Population. The Japan Public Health Center (JPHC)–based prospective study on cancer and cardiovascular diseases (JPHC Study) was established in 1990 for cohort I and in 1993 for cohort II; part of the study was reported elsewhere (12-14). The JPHC Study was approved by the institutional review board of the National Cancer Center (Tokyo, Japan).
Diseases for Oncology

Cases of gastric cancer were extracted from the cancer registry when the date of birth and name, address, and date of birth and entered in the cancer registry for the JPHC Study when the date of birth and name, address, and date of birth and entered in the cancer registry (usually prefecture-wide). Candidate patients were linked by cancer were collected through two data sources, one from local within the study period.

6,035 (6.2%) had died, and 82 (0.08%) were lost to follow-up within the study period. The changes in residency status, including death, were identified annually through the residential registry in Japan, all death certificates are submitted to a local code C160-169; ref. 15]. Among those measured by RIA (pepsinogen I/II RIA-BEAD, Dinabot kit, Fujioka and Tokieda reported the sensitivity and specificity of the kit with respect to cell culture and rapid urease test in 70 Japanese subjects and the value was 100% and 80.0%, respectively (18). These values were highest among other commercially available kits. Furthermore, the values reported by the assay supplier was 100% and 93.8%, respectively. Assays of CagA were done with the use of an ELISA kit, in which horseradish peroxidase was used as enzyme tracer (CagA IgG EIA, Sctei Co. Ltd., Tokyo, Italy). During the first incubation, the sample anti-CagA IgG antibodies, if any, are bound to the CagA antigen-coated wells. A second antibody (anti-human IgG conjugated with peroxidase) will bind to the CagA-antigen-antibody complex. The specificity and sensitivity were reported in the protocol of the kit by the assay supplier with respect to a Western blot assay, and the result was 100% and 93.7%, respectively. Serum levels of pepsinogen I and II were measured by two-step enzyme immunoassay by using commercial kits (E Plate “Eiken” Pepsinogen I, Eiken Kagaku) and (E Plate “Eiken” Pepsinogen II, Eiken Kagaku). Results were defined as “atrophic” when the criteria of both pepsinogen I levels ≤70 ng/mL and pepsinogen I/II ratio ≤3.0 were fulfilled (pepsinogen index +, ~3+). Miki et al. (19) reported that the values measured by the same kit showed a good correlation (correlation coefficient 0.983 for pepsinogen I, 0.991 for pepsinogen II, and 0.935 for pepsinogen I/II) with those measured by RIA (pepsinogen I/II RIA-BEAD, Dinabot Co. Ltd., Tokyo, Japan), in which a sensitivity of 70.5% and a specificity of 97.0% for atrophic gastritis, compared with histology, have been reported (20). These criteria have been applied widely to mass screening for gastric cancer in Japan (18). Among atrophic cases, more severe cases with a pepsinogen I level ≤30 ng/mL and pepsinogen I/II ratio ≤2.0 were defined as pepsinogen index 3+, whereas cases with a pepsinogen I level ≤50 ng/mL and pepsinogen I/II ratio ≤3.0 but excluding pepsinogen 3+ cases were defined as pepsinogen index 2+. Pepsinogen I level ≤70 ng/mL and pepsinogen I/II ratio ≤3.0 but excluding pepsinogen index 2+ and 3+ cases were defined as pepsinogen index +. All measurements were conducted by a person blinded to the case-control situation.

Statistical Analysis. χ² test or one-way ANOVA were used to calculate the P for difference between cases and controls (Table 1). Matched odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to indicate the relationship between H. pylori infection or pepsinogen index and the risk of gastric cancer. Multiple conditional logistic regression analysis was conducted to control for potential confounding factors, such as smoking status, consumption of fish gut, green-yellow vegetables, other vegetables, fruit, green tea, body mass index, and family history of gastric cancer. Smoking status was applied widely to mass screening for gastric cancer in Japan (18). Among atrophic cases, more severe cases with a pepsinogen I level ≤30 ng/mL and pepsinogen I/II ratio ≤2.0 were defined as pepsinogen index 3+, whereas cases with a pepsinogen I level ≤50 ng/mL and pepsinogen I/II ratio ≤3.0 but excluding pepsinogen 3+ cases were defined as pepsinogen index 2+. Pepsinogen I level ≤70 ng/mL and pepsinogen I/II ratio ≤3.0 but excluding pepsinogen index 2+ and 3+ cases were defined as pepsinogen index +. All measurements were conducted by a person blinded to the case-control situation.

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Table 1. Baseline characteristics of cases and control subjects

|                          | Cases (n = 511) | Controls (n = 511) | P for difference*
|--------------------------|-----------------|-------------------|----------------
| Age (matching factor)    | 57.4 (0.32)     | 57.4 (0.32)       | 1.00           
| Male (matching factor; %)| 66.8            | 66.8              | 1.00           
| Current smoker (%)       | 35.7            | 30.3              | 0.06           
| Alcohol drinking, 1+ d/wk (%) | 50.8 | 50.2              | 0.85           
| Body mass index          | 23.0 (0.13)     | 23.4 (0.13)       | 0.02           
| Family history of gastric cancer (%) | 11.9 | 7.8              | 0.03           

NOTE: Numbers are mean (SE) unless specified otherwise.

*×2 test or one-way ANOVA.

Table 2. Adjusted ORs (95% CIs) of developing gastric cancer for all subjects with H. pylori IgG seropositivity and with stratification by several factors

<table>
<thead>
<tr>
<th>No. H. pylori–positive cases/controls</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (511 pairs)</td>
<td>478/383</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Men (342 pairs)</td>
<td>327/259</td>
</tr>
<tr>
<td>Women (169 pairs)</td>
<td>151/124</td>
</tr>
<tr>
<td>Age at baseline (y)</td>
<td></td>
</tr>
<tr>
<td>40-49 (77 pairs)</td>
<td>72/52</td>
</tr>
<tr>
<td>50-59 (235 pairs)</td>
<td>220/180</td>
</tr>
<tr>
<td>60-69 (199 pairs)</td>
<td>186/151</td>
</tr>
<tr>
<td>Duration between blood donation and cancer diagnosis (y)</td>
<td></td>
</tr>
<tr>
<td>0-4 (205 pairs)</td>
<td>190/144</td>
</tr>
<tr>
<td>4-8 (181 pairs)</td>
<td>170/141</td>
</tr>
<tr>
<td>≥8 (125 pairs)</td>
<td>118/98</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper third of stomach, including cardia (39 pairs)</td>
<td>37/33</td>
</tr>
<tr>
<td>Distal portion of stomach (368 pairs)</td>
<td>344/274</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Differentiated type</td>
<td>281/223</td>
</tr>
<tr>
<td>Undifferentiated type</td>
<td>149/122</td>
</tr>
</tbody>
</table>

*Matched for age, gender, resident area, blood donation date, and fasting times at blood donation. Adjusted for smoking status, consumption of fish gut, green yellow vegetables, other vegetables, fruit, green tea, body mass index, and family history of gastric cancer.

divided into current or noncurrent smokers. The frequencies of consumption of each food and body mass index were categorized into three groups so that each category included an equal number as possible of controls. Family history of gastric cancer was regarded positive if at least one of their parents or siblings had gastric cancer. Because adjustment for confounding factors did not alter the results essentially, only adjusted ORs are listed in the tables. Trend was assessed by assigning ordinal values for categorical variables. To express the effect of the combination of H. pylori infection with either CagA or pepsinogen status on occurrence of gastric cancer among this population, we estimated the population attributable fraction (PAF; %) as follows: Pr(OR – 1) / OR, where Pr is the proportion of cases exposed to the factor and OR is the adjusted OR (21). The PAF (95% CI) was estimated by the formula of Greenland (22). Reported Ps were two-sided, and all statistical analyses were done with the use of the SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics are shown in Table 1. Cases had a lower body mass index and more family history of gastric cancer than controls. In addition, these differences were statistically significant. Other variables, including matching variables, did not significantly differ between cases and controls.

Adjusted OR of gastric cancer associated with H. pylori IgG seropositivity was shown for all subjects and by stratification with gender, age at baseline, duration between blood donation and cancer diagnosis, tumor location, and histologic type (Table 2). H. pylori IgG seropositivity was significantly associated with an increased risk of gastric cancer; adjusted ORs and 95% CIs were calculated as 5.1 (3.2-8.0), PAF (95% CI) for H. pylori IgG seropositivity was calculated as 75.2% (63.3-83.2%). The OR for H. pylori infection was large in men compared with women; however, the 95% CIs overlapped widely. H. pylori infection seemed to be more important in young subjects (40-49 years) than in older subjects (≥50 years). OR tended to decrease for gastric cancer when the duration between blood donation and cancer diagnosis became longer; the matched ORs (95% CIs) of H. pylori infection for the duration 0 to 4, 4 to 8, and ≥8 years were 7.4 (3.4-16.2), 4.9 (2.2-10.9), and 4.5 (1.8-11.4). This result did not differ when the tumor was restricted to the distal part of the stomach. H. pylori infection was associated with the development of gastric cancer located in the distal portion of the stomach, whereas a statistically significant association was not observed for cancer in the upper third of the stomach. Some 104 cases, which correspond to 20% of the total number of cases, could not be classified by subsite because of diffuse lesion (n = 16) or no information (n = 88) and further analysis was not restricted to distal gastric cancer. When the cases were separated by histologic type, the association was statistically significant for both differentiated-type and undifferentiated-type gastric cancers. Although the 95% CIs greatly overlapped, the ORs were larger in the differentiated type than in the undifferentiated type.

Table 3 shows the proportion of cases and controls defined as positive for H. pylori CagA seropositivity or pepsinogen index alone and their combination with H. pylori IgG antibody together with the matched ORs (95% CIs). PAF also was calculated for each combination group of CagA, pepsinogen, and H. pylori IgG. CagA seropositivity was associated with a statistically significant increased risk of gastric cancer as well as H. pylori IgG seropositivity, although the magnitude was different; adjusted OR (95% CI) was calculated as 1.5 (1.1-2.1). When IgG-based H. pylori and CagA were combined, a statistically significant 3-fold risk was observed among those who were H. pylori IgG negative but CagA positive. However, PAF (95% CI) for this group was calculated as only 3.6% (1.1-6.1%). When this group was excluded from the H. pylori–seronegative group, the OR (95% CI) for H. pylori infection was calculated as 11.4 (4.4-29.2). Among the H. pylori–seropositive group, the OR for CagA-negative group was 9.5, whereas the value for CagA positive was 12.5. When the H. pylori IgG-seronegative and CagA-positive group was included in the H. pylori–seropositive group, the OR (95% CI) for H. pylori–positive and/or CagA-positive group to develop gastric cancer was calculated as 10.2 (4.0-25.9).

The overall risk (95% CI) of having a pepsinogen value indicative of atrophy was calculated as 3.9 (2.7-5.4). ORs were shown by pepsinogen index (≥1) (≥2+) according to the severity of atrophic gastritis and the risk increased further with pepsinogen levels, reflecting more severe gastritis (P < 0.0001). When H. pylori infection and pepsinogen status were combined, H. pylori–negative subjects with pepsinogen status indicative of the atrophic gastritis group showed a statistically significant association with gastric cancer; the adjusted OR (95% CI) was 4.9 (2.0-12.1). However, the PAF (95% CI) was
To our knowledge, this is the largest nested case-control study, with >500 gastric cancer cases, to investigate the relationship between \textit{H. pylori} infection and the subsequent risk of gastric cancer. The largest previous investigation of the kind was a Norwegian study that included only 208 gastric cancer cases (22). Including the Norwegian study, 12 studies were needed to pool 1,228 gastric cancer cases and to estimate the pooled OR of \textit{H. pylori} infection for developing gastric cancer (1). Although the interpretation of a pooled analysis of several studies from different countries with different study methods may be limited, a carefully designed, single, large study may contribute significantly to solving the question of whether \textit{H. pylori} infection to develop gastric cancer became 7.6 (4.3-13.4).

### Discussion

To our knowledge, this is the largest nested case-control study, with >500 gastric cancer cases, to investigate the relationship between \textit{H. pylori} infection and the subsequent risk of gastric cancer. The largest previous investigation of the kind was a Norwegian study that included only 208 gastric cancer cases (22). Including the Norwegian study, 12 studies were needed to pool 1,228 gastric cancer cases and to estimate the pooled OR of \textit{H. pylori} infection for developing gastric cancer (1). Although the interpretation of a pooled analysis of several studies from different countries with different study methods may be limited, a carefully designed, single, large study may contribute significantly to solving the question of whether \textit{H. pylori} infection induces gastric cancer. Our study showed a 5-fold elevated risk of gastric cancer for \textit{H. pylori} infection when IgG antibody was seropositive in spite of the presence of atrophic gastritis group was added to the \textit{H. pylori} positive group, the OR (95% CI) for \textit{H. pylori} positive and/or pepsinogen-positive group to develop gastric cancer became 7.6 (4.3-13.4).

### Table 3. Matched ORs (95% CIs) for association of gastric cancer with CagA strains and pepsinogen index alone and in combination with \textit{H. pylori} IgG

<table>
<thead>
<tr>
<th>Pepsinogen status</th>
<th>No. cases/controls</th>
<th>Adjusted OR* (95% CI)</th>
<th>PAF (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepsinogen index (+)</td>
<td>37/20</td>
<td>2.1 (1.1-4.0)</td>
<td>1.4 (0.4-5.0)</td>
</tr>
<tr>
<td>Pepsinogen index (+, -3+)</td>
<td>478/383</td>
<td>7.9 (4.5-14.0)</td>
<td>4.5 (1.3-15.0)</td>
</tr>
<tr>
<td>Pepsinogen index (+) and pepsinogen index (+, -3+)</td>
<td>16/108</td>
<td>1.0</td>
<td>0.0 (0.0-0.0)</td>
</tr>
<tr>
<td>IgG (+) and pepsinogen index (+, -3+)</td>
<td>17/20</td>
<td>2.0 (1.0-4.0)</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td>IgG (+) and pepsinogen index (+)</td>
<td>478/383</td>
<td>7.9 (4.5-14.0)</td>
<td>4.5 (1.3-15.0)</td>
</tr>
<tr>
<td>IgG (+) and IgG (+)</td>
<td>76/108</td>
<td>4.2 (2.2-8.0)</td>
<td>2.1 (0.6-6.0)</td>
</tr>
<tr>
<td>IgG (+) and IgG (+) and pepsinogen index (+, -3+)</td>
<td>402/275</td>
<td>10.1 (5.6-18.2)</td>
<td>5.5 (2.0-14.0)</td>
</tr>
<tr>
<td>IgG (+) and pepsinogen index (+, -3+)</td>
<td>495/403</td>
<td>7.6 (4.3-13.4)</td>
<td>4.1 (1.0-15.0)</td>
</tr>
</tbody>
</table>

**NOTE:** Pepsinogen index (+), pepsinogen I >70 or pepsinogen I/II ratio >3; (+), pepsinogen I >70 and pepsinogen I/II ratio >3, excluding pepsinogen index 2+ and 3+; (2+), pepsinogen I ≤70 and pepsinogen I/II ratio ≤3, excluding pepsinogen index 3+; (3+), pepsinogen I ≤30 and pepsinogen I/II ratio ≤2.

*See footnote in Table 2.

†P<0.001 calculated as only 2.6% (1.0-4.3%). When this group was excluded from the \textit{H. pylori} seronegative group, the OR (95% CI) for \textit{H. pylori} infection to develop gastric cancer became 7.9 (4.5-14.0). When this type of \textit{H. pylori} negative subjects with pepsinogen status indicative of atrophic gastritis group was added to the \textit{H. pylori} positive group, the OR (95% CI) for \textit{H. pylori} positive and/or pepsinogen-positive group to develop gastric cancer became 7.6 (4.3-13.4).
an unknown proportion of what others would categorize as noncardia cancers. This will dilute any cardia-specific risk associations. The similar estimated risk by histologic type is in line with most of the previous studies.

Antibodies to CagA remain longer after H. pylori eradication than surface antibodies detected by conventional IgG ELISA (7). Thus, several studies recommend using both H. pylori IgG antibody test and CagA seropositivity to define H. pylori infection appropriately (36, 40-44). H. pylori—seronegative group with CagA positivity showed a statistically significant 3-fold risk of gastric cancer. When subjects in this group were further divided by pepsinogen status, the OR (95% CI) for those having a pepsinogen index indicative of atrophic gastritis was elevated to 10.2 (2.8-37.5), whereas the value for those having a pepsinogen index indicative of normal mucosa was 2.0 (0.7-6.2). This indicates that among this group those with developed atrophic gastritis are strongly associated with gastric cancer development. In dealing with the false-negatives for H. pylori status, we excluded the H. pylori IgG-seronegative and CagA-positive group from the H. pylori—seronegative group or added this group to the H. pylori—seropositive group. Then, the OR of H. pylori infection to develop gastric cancer was doubled to ~10 by either approach. This means that, even in a prospective study followed for >10 years like this, the effect of H. pylori infection might be underestimated by a single test of H. pylori IgG.

Although CagA was effective to define the false-negative group of H. pylori infection, its effect modification among the H. pylori—positive group was not as marked as expected. Accumulating evidence indicates there is an association between clinical outcome and genotype of the CagA pathogenicity island as well as CagA serology in Western patients but not in Japanese patients (45-47). However, a recent case-control study (48) conducted in Japan showed a >13-fold risk of noncardia gastric cancer for both H. pylori IgG- and CagA-positive subjects compared with subjects who are negative for both. Furthermore, Tatemichi et al. (49) investigated ethnic differences of CagA serology in two sets of case-control subjects, Japanese Brazilians and non-Japanese Brazilians; the CagA antibody also was found to be a useful marker for gastric cancer in Japanese subjects. Nevertheless, numerical results from studies using different antigens and different protocols may not be comparable, and Yamaoka and Graham pointed out that serologic tests yield a lower estimate of CagA status than PCR or immunoblotting of H. pylori isolates (50). They also examined the reliability of the serum anti-CagA antibody assay using four different tests and concluded that none could be recommended for determining the CagA status (51). Our measurement of CagA status was based on ELISA kit from Sceti. Misclassification due to measurement tool and assay performance may be inevitable. Thus, much caution may be needed in interpreting the results regarding CagA status.

The severity of atrophic gastritis indicated by the pepsinogen index was associated with gastric cancer with a significant trend. In addition, for the combination of H. pylori and pepsinogen status, subjects were further divided by the severity of atrophic gastritis among H. pylori—seronegative and pepsinogen-positive groups. More severe atrophy was associated with a higher OR of developing gastric cancer. The ORs for pepsinogen index 2+ and 3+ were 3.3 and 6.5, respectively. Likewise, the severity was associated with a high OR among H. pylori—seropositive subjects; the value for H. pylori seropositivity and pepsinogen index 2+, 2+, and 3+ were calculated as 7.8, 8.7, and 12.6, respectively.

A recent prospective endoscopic cohort study showed the combination of serum pepsinogen and anti-H. pylori antibody provides a good predictive marker for the development of gastric cancer (52). Compared with “normal” pepsinogen and negative H. pylori antibody group, the hazard ratios (95% CI) of developing gastric cancer for normal pepsinogen and positive H. pylori antibody group, atrophic pepsinogen and positive H. pylori antibody group, and atrophic pepsinogen and negative H. pylori antibody group were 1.1 (0.4-3.4), 6.0 (2.4-14.5), and 8.2 (3.2-21.5), respectively. In addition, a case-control study conducted in Japan showed the largest OR of gastric cancer in the positive pepsinogen and negative H. pylori infection group compared with other combination groups (53). In our study, although a statistically significant, ~5-fold risk of developing gastric cancer was observed among those who were H. pylori IgG-seronegative and pepsinogen-positive, the PAF (95% CI) was calculated as only 2.6% (1.0-4.5%)

One of the disadvantages of the present study is that the diagnosis of atrophic gastritis is based on a serologic rather than a pathologic test. The reported sensitivity was not high, so there may be misclassification of pepsinogen status.

Our study subjects are restricted to those who participated at the baseline health checkup survey. Among 97,644 eligible subjects of the JPHC Study cohort, 36,745 (38%) men and women participated in the survey and provided blood samples. As reported previously, when compared with nonparticipants, participants in the health checkup survey, especially women, had a different socioeconomic status and a favorable lifestyle profile, such as smoking less, participating in more physical exercise, and eating more green vegetables or fruits (54). This finding means that caution is needed in generalizing or interpreting the results in this report.

In our study, a 5-fold elevated risk of gastric cancer was observed for H. pylori infection determined by IgG antibody. Assuming all CagA-positive subjects are true H. pylori positives approximately doubled this risk. The large PAF relating H. pylori infection and gastric cancer also indicates that controlling infection might prevent gastric cancer. However, whether eradication of H. pylori is the best approach remains to be seen. The best timing for treatment is not known with certainty (55, 56), and as only a limited number of people with H. pylori infection develop gastric cancer, indiscriminate eradication may not be a practical, cost-effective approach. Subjects with pepsinogen levels indicative of severe atrophic gastritis may need careful examination regularly regardless of H. pylori infection. Those who have other pepsinogen levels but who test seropositive for H. pylori infection are likely to benefit from H. pylori eradication therapy. Considering both the cost and the potential for misclassification that may occur using multiple serologic tests, caution is needed in interpreting or extrapolating these findings into a screening strategy.

Appendix Notes

The members of the JPHC-based Prospective Study Group are S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka (National Cancer Center, Tokyo); J. Ogata, S. Baba, T. Mannami, and A. Okayama (National Cardiovascular Center, Suita); K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, and I. Hashimoto (Iwate Prefectural Ninohe PHC, Ninohe); Y. Miyajima, N. Suzuki, S. Nagasawa, and Y. Furusugi (Akiha Prefectural Yokote PHC, Yokote); H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, and Y. Miyagawa (Nagano Prefectural Saku PHC, Saku); Y. Kashimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irie, and H. Kishimoto (Okinawa Prefectural Chubu PHC, Okinawa); K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, and F. Shoji (Katsushika PHC, Tokyo); A. Murata, K. Minato, K. Motegi, and T. Fujieda (Ibaraki Prefectural Mitoh PHC, Mitoh); K. Matsui, T. Abe, M. Katagiri, and M. Suzuki (Niigata Prefectural Kashiwazaki and Nagaoaka PHC, Kashiwazaki and Nagaoaka);
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References


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Effect of *Helicobacter pylori* Infection Combined with CagA and Pepsinogen Status on Gastric Cancer Development among Japanese Men and Women: A Nested Case-Control Study

Shizuka Sasazuki, Manami Inoue, Motoki Iwasaki, et al.