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, 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.

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.

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.

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 for the JPHC Study when the date of birth and major hospitals and the other from population-based registries. Cancer were collected through two data sources, one from local within the study period. Subcohort in Suita City that was set up by the National Cardiovascular Center was also added. As a whole, a population-based cohort of 61,009 men (27,062 in cohort I and 33,947 in cohort II) and 62,567 women (27,436 in cohort I and 35,131 in cohort II) was established.

Baseline Survey. In 1990 for cohort I and in 1993 to 1994 for cohort II, subjects were asked to reply to a lifestyle questionnaire covering sociodemographic characteristics, medical history, smoking and drinking habits, and diet. A total of 99,808 (81%) subjects, 47,525 men and 52,283 women, responded to the questionnaires.

A total of 10 mL blood was provided voluntarily by subjects during their health checkups. The plasma and buffy layer were divided into four tubes each holding 1.0 mL (three tubes for plasma and one tube for the buffy layer) and stored at −80°C. The blood was collected from 1990 to 1992 in cohort I and from 1993 to 1995 in cohort II.

We excluded subjects with a self-reported cancer at baseline (n = 2,136), subjects who were not Japanese (n = 18), and subjects who had already moved away at baseline (n = 11), which left 46,803 eligible men and 50,841 women. Among them, 13,467 (29%) men and 23,278 (46%) women donated their blood samples at baseline and were included in the study.

Follow-up and Identification of Gastric Cancer

Death and Relocation. Subjects were followed from January 1, 1990 to December 31, 2004 for cohort I and from January 1, 1993 (1994 for Tomobe Town) to December 31, 2004 for cohort II. In Japan, all death certificates are submitted to a local government office and forwarded to the PHC in the area of residence. The changes in residency status, including death, were identified annually through the residential registry in each area. Among study subjects, 6,133 (6.3%) had relocated, 13,467 (29%) men and 23,278 (46%) women donated their blood samples at baseline and were included in the study.

Cancer Registry for JPHC Study. Newly diagnosed cases of cancer were collected through two data sources, one from local major hospitals and the other from population-based registries (usually prefecture-wide). Candidate patients were linked by name, address, and date of birth and entered in the cancer registry for the JPHC Study when the date of birth and residence fulfilled cohort inclusion criteria.

Identification of Gastric Cancer and Selection of Control Subjects. Cases of gastric cancer were extracted from the cancer registry for the JPHC Study based on site [International Classification of Diseases for Oncology (ICD-O) code C160-169; ref. 15]. Among 1,681 cases with a histologically proven diagnosis made from 1990 to 2004 for cohort I and from 1993 to 2004 for cohort II, as of July 2004, plasma at baseline had been obtained from 512 cases.

Until quite recently in Japan, the upper third of the stomach has been called the “cardia” based on the guidelines for gastric cancer classification (16). Because it seemed difficult to distinguish a so-called cardia, which is located mainly in the esophagogastric junction, from the upper third of the stomach, we combined tumors at these sites into one group for analysis in this study (ICD-O code C160-161). A tumor located on the lower side of the stomach was classified as distal gastric cancer (ICD-O code C162-167). Those subsites that could not be classified because of a diffuse lesion (ICD-O code C168) or those with no information (ICD-O code C169) were categorized as an unclassified subsite. Histologic classification was based on one of the author’s (S.S.) review, in consultation with a pathologist, of the record reported by each hospital. The subdivisions were made based on a classification derived by Lauren (17).

For each case, we selected one control matched for gender, age (±3 years), study area, blood donation date (±2 months), and fasting time at blood donation (±5 hours). The final analysis included 511 sets each of 511 cases and 511 controls, excluding 1 case with biological evidence for H. pylori antibody measurement and the matched control.

Laboratory Analysis. IgG antibodies to H. pylori were measured with a direct ELISA kit (E Plate “Eiken” H. pylori Antibody, Eiken Kagaku Co. Ltd., Tokyo, Japan). Levels of IgG were categorized as seropositive and seronegative for H. pylori according to a selective cutoff value (492 nm). Using the same kit, Fujisawa 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, Sceti Co. Ltd., Rome, 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 ≤30 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...
Table 1. Baseline characteristics of cases and control subjects

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

NOTE: Numbers are mean (SE) unless specified otherwise.
* t-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>40-49 (77 pairs)</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>4-8 (205 pairs)</td>
</tr>
<tr>
<td></td>
<td>6-8 (181 pairs)</td>
</tr>
<tr>
<td></td>
<td>8-12.5 (125 pairs)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper third of stomach, including cardiac (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, meat, green vegetables, other vegetables, fruit, tea, green tea, body mass index, and family history of gastric cancer.
**Table 3. Matched ORs (95% CIs) for association of gastric cancer with CagA strains and pepsinogen index alone and in combination with *H. pylori* IgG**

<table>
<thead>
<tr>
<th>CagA status</th>
<th>No. cases/controls</th>
<th>Adjusted OR* (95% CI)</th>
<th>PAF (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CagA (−)</td>
<td>121/153</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>CagA (+)</td>
<td>390/358</td>
<td>1.5 (1.1-2.1)</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> (IgG) and CagA combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (−) and CagA (−)</td>
<td>6/51</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>IgG (−) and CagA (+)</td>
<td>27/77</td>
<td>3.2 (1.1-9.0)</td>
<td>3.6 (1.1-6.1)</td>
</tr>
<tr>
<td>IgG (+)</td>
<td>478/383</td>
<td>11.4 (4.4-29.2)</td>
<td></td>
</tr>
<tr>
<td>IgG (+) and CagA (−)</td>
<td>115/102</td>
<td>9.5 (3.6-25.0)</td>
<td>20.1 (15.7-24.4)</td>
</tr>
<tr>
<td>IgG (+) and CagA (+)</td>
<td>363/281</td>
<td>12.5 (4.8-32.5)</td>
<td>65.4 (57.5-71.6)</td>
</tr>
<tr>
<td>IgG (−) and/or CagA (+)</td>
<td>505/460</td>
<td>10.2 (4.0-25.9)</td>
<td>89.1 (73.4-95.6)</td>
</tr>
<tr>
<td>Pepsinogen status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepsinogen index (−)</td>
<td>92/216</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Pepsinogen index (+)</td>
<td>21/18</td>
<td>3.2 (1.5-7.0)</td>
<td></td>
</tr>
<tr>
<td>Pepsinogen index (2+)</td>
<td>171/141</td>
<td>3.3 (2.2-4.8)</td>
<td></td>
</tr>
<tr>
<td>Pepsinogen index (3+)</td>
<td>227/136</td>
<td>4.6 (3.1-6.9)</td>
<td></td>
</tr>
<tr>
<td>Pepsinogen index (+, −3+)</td>
<td>419/295</td>
<td>3.8 (2.7-5.4)</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> (IgG) and pepsinogen index combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (−) and pepsinogen index (−)</td>
<td>16/108</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>IgG (−) and pepsinogen index (+, −3+)</td>
<td>17/20</td>
<td>4.9 (2.0-12.1)</td>
<td>2.6 (1.0-4.3)</td>
</tr>
<tr>
<td>IgG (+)</td>
<td>478/383</td>
<td>7.9 (4.5-14.0)</td>
<td></td>
</tr>
<tr>
<td>IgG (+) and pepsinogen index (−)</td>
<td>76/108</td>
<td>4.2 (2.2-8.0)</td>
<td>11.3 (7.4-15.1)</td>
</tr>
<tr>
<td>IgG (+) and pepsinogen index (+, −3+)</td>
<td>402/275</td>
<td>10.1 (5.6-18.2)</td>
<td>70.9 (63.6-76.7)</td>
</tr>
<tr>
<td>IgG (+) and/or pepsinogen index (+, −3+)</td>
<td>495/403</td>
<td>7.6 (4.3-13.4)</td>
<td>84.1 (73.1-90.6)</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 ≤50 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* trend < 0.0001.

calculated as only 2.6% (1.0-4.3%). When this group was excluded from the *H. pylori*—seronegative group, the OR (95% CI) for *H. pylori* infection to develop gastric cancer became 7.9 (4.5-14.0). When this type of *H. pylori*—negative subjects with pepsinogen status indicative of atrophic gastritis group was added to the *H. pylori*—positive group, the OR (95% CI) for *H. pylori*—positive and/or pepsinogen-positive group 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 *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 (23), including the Norwegian study, 12 studies were needed to pool 1,228 gastric cancer cases and to estimate the pooled OR of *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 *H. pylori* infection induces gastric cancer. Our study showed a 5-fold elevated risk of gastric cancer for *H. pylori* infection determined by IgG antibody. According to the 12 case-control studies nested within prospective cohorts, the OR (95% CI) of *H. pylori* infection ranged from 1.50 (0.70-3.22) to 6.0 (2.1-17.3) and the pooled OR (95% CI) of these estimates was calculated as 2.36 (1.98-2.81; ref. 1). The largest OR among these studies was 6.0 in a study of Japanese American men living in Hawaii (24). In our study, the OR (95% CI) for men [6.8 (3.6-12.6)] was larger than even the Japanese American study. Only a few prospective studies have shown an association between *H. pylori* infection and gastric cancer for men and women separately. During 9-year follow-up in a prospective cohort study conducted in Japan, 67 gastric cancer cases were identified and the adjusted relative risks (95% CI) for *H. pylori* infection were calculated as 2.90 (1.14-7.38) for men and 1.01 (0.34-2.97) for women (25). On the other hand, Parsonnet et al. (26) showed that the OR (95% CI) of *H. pylori* infection was 2.0 (0.9-4.5) for men among 76 pairs and 18.0 (2.4-134.8) for women among 33 pairs. However, the 95% CIs are large because of the small numbers of subjects, making it difficult to interpret the results precisely. The different ORs of different age groups were in line with previous studies, which showed higher OR for the young subjects (23-25, 27-30). The effect is reduced in older subjects presumably because of increased seroprevalence among the older controls and little change in the seroprevalence among cases with age. In our study, ORs for *H. pylori* infection decreased as the follow-up time increased. Previous pooled analysis showed an association between an increasing time interval between sample collection and cancer diagnosis and a higher OR (1), although this association has not been seen in some individual studies (27, 28, 31). If gastric cancer is diagnosed only a short time after blood donation, it is hypothesized that the disease already would be in an advanced stage with gastric atrophy, which favors the loss of *H. pylori* infection and would lower the association between *H. pylori* infection and gastric cancer (32). However, several studies indicate that many subjects may still be seropositive in spite of the presence of atrophic gastritis (33-35). The OR for pepsinogen index also declined as the duration between the blood donation and cancer diagnosis increased (data not shown). The stronger association at relatively short follow-up times of pepsinogen index as a sign of atrophic gastritis can be understood on the basis that advanced atrophic gastritis is closely associated with gastric cancer. Previous studies have shown an increased risk of distal gastric cancer for *H. pylori* seropositive subjects compared with seronegative subjects, whereas no association was observed among upper third gastric cancer (25-27) but not all (23, 36, 37). The discrepancy in results between studies may, to some extent, be due to different levels of misclassification of cardia cancers, such as the recent introduction of a separate diagnostic code, the lack of consensus for a definition of cardia, and an increased interest in cardia cancers (38, 39). The definition of cardia cancer (upper third) was more inclusive than most definitions used outside Japan and would include...
an unknown proportion of what others would categorize as noncardia cancers. This will dilute any cardiaca-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 Scett. 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+, 3+, and 4+ 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

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References


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