Helicobacter pylori infection appears essential for stomach carcinogenesis: Observations in Semarang, Indonesia

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The gastric cancer incidence in Semarang, Indonesia, is exceedingly low: only approximately 1/100th of the level in Japan. To elucidate the reason, we carried out an ecological study recruiting 69 male and 102 female participants from the general populace in January 2005. Positive urea breath tests were 0% for both men and women, and Helicobacter pylori (H. pylori) IgG antibodies were found in 2% (0–5, 95% confidence interval) of men and 2% (0–4) of women, significantly lower than the 62% (58–65) and 57% (53–60), respectively, in Japan. Furthermore, there were no positive findings with the pepsinogen tests in Semarang, again significant in comparison with the 23% (22–25) and 22% (20–23) in Japan. Variation in smoking levels and consumption of NaCl, vegetables and fruit were found, but not to an extent that would allow explanation of the major differences in gastric cancer incidence. We may conclude that the very low prevalence of H. pylori infection and thus chronic atrophic gastritis account for the rarity of stomach cancer in Semarang, Indonesia. (Cancer Sci 2005; 96: 873–875)

Since 2002, we have been conducting a collaborative epidemiologic appraisal of host and environmental factors for stomach and colorectal cancer in several South-east Asian countries. Ecological and case-control studies are now being carried out in Hanoi and Ho Chi Minh City, Vietnam; Khon Kaen, Thailand; and Yogyakarta and Semarang, Indonesia, in order to take advantage of the major variation in cancer incidence among these geographical areas and also with data for Japan. Stomach cancer incidence rates in Hanoi, Ho Chi Minh City, Khon Kaen, Yogyakarta and Semarang are approximately 1/2, 1/4, 1/10, 1/50 and 1/100 those prevailing in Japan. Variation in smoking levels and consumption of NaCl, vegetables and fruit were found, but not to an extent that would allow explanation of the major differences in gastric cancer incidence. We may conclude that the very low prevalence of H. pylori infection and thus chronic atrophic gastritis account for the rarity of stomach cancer in Semarang, Indonesia. (Cancer Sci 2005; 96: 873–875)

Subjects and Methods

In January 2005, we randomly recruited 69 male and 102 female participants from the general populace, mostly Javanese, in the city of Semarang. Mean ages were 57.4 ± 10.9 (SD) for men and 49.2 ± 9.8 for women. Written informed consent was obtained from the study participants and the protocol was approved by the Internal Review Boards of Nagoya City University, Japan, and Diponegoro University and Tugurejo Hospital, Semarang, Indonesia. The subjects were requested to respond to lifestyle questions, including smoking habits, and food frequency questionnaires, and were interviewed by health nurses at a local hospital. Bodyweight and height were measured, and oral mucous membranes, overnight-fasting blood, breath, second morning voiding urine and feces were sampled from each participant.

For the urea breath test (UBT), UBit-IR300 kits (Otsuka Pharmaceutical, Tokyo, Japan) were used with ≥ 2.5‰ as positive. Serum antibodies for H. pylori were examined by enzyme immunoassay (Kyowa Medics, Tokyo, Japan) and...
ELISA values ≥ 2.3 were defined as positive. Serum pepsinogen (PG) I and PGII were measured by chemical luminescence enzyme immunoassay (Eiken Chemicals, Tokyo, Japan) with cut off points of PGI ≤ 70 ng/mL and PGII ≤ 3.0.\(^{11}\) as a non-invasive surrogate for the Sydney classification of CAG.\(^{10}\) For all of these parameters, age-adjustment was made adopting the world population,\(^{1}\) as standard, for comparison with Japanese figures.

Second morning voiding urine excretions of sodium, as a marker of intake of salt or salty foods, and potassium, as a marker of consumption of vegetables and fruit, were analyzed by electrode assays, and creatinine was analyzed by an enzymatic method. The daily levels were then estimated with adjustment for creatinine,\(^{13}\) and compared with the consumption values of Japanese people.\(^{13}\)

### Results

As shown in Table 1, age-adjusted positive rates for UBT were 0% for both men and women in Semarang. \textit{H. pylori} IgG antibodies were found in only 2% (0–5) of men and 2% (0–4) of women, and were significantly lower than the 62% (58–65) and 57% (53–60), respectively, in Japan.\(^{17}\) Positive findings for the PG tests were 0% in both sexes, again significantly lower than the 23% (22–25) and 22% (20–23) reported for Japanese people.\(^{12}\)

Smoking rates were rather higher for men in Semarang than in Japan but lower for women (Table 2).\(^{18}\) Salt excretions were calculated to be 11.1 g/day (9.8–12.5 g/day) for men and 10.4 g/day (9.9–11.0 g/day) for women in Semarang, and only slightly lower than the consumption of 12.9 g/day (12.7–13.1 g/day) for men and 11.2 g/day (11.1–11.4 g/day) for women in Japan.\(^{13}\) Values for potassium excretions were 2.3 g/day (2.2–2.5 g/day) for men and 2.1 g/day (2.1–2.2 g/day) for women, again close to the consumption of 2.5 g/day (2.5–2.5 g/day) and 2.4 g/day (2.3–2.4 g/day) in Japan.

### Discussion

Our findings of negative or very low prevalence of UBT and \textit{H. pylori} IgG antibodies in both men and women in Semarang, Indonesia are in clear contrast to the case in Japan and, presumably, are directly related to the null PG testing. Smoking was found to be more common for men in Semarang than in Japan, but less common for women. There were only minor differences in estimated intake values for salt, and for vegetables and fruit between people in Semarang and Japan. No evidence was obtained that the marked variation in cancer incidence could be explained on the basis of low consumption of salt or salty foods, or far greater vegetable and fruit consumption. We can assume that refrigeration is less prevalent in Semarang than in Japan. Whether host genetic polymorphisms associated with cellular immunity for chronic inflammation,\(^{19}\) or differences in \textit{H. pylori} strains regarding infectivity, virulence or inflammatory potency,\(^{5,20}\) may be important factors in Semarang remains to be clarified. However, the most plausible interpretation of our results is that the rarity of gastric cancer in Semarang is attributable to a low prevalence of \textit{H. pylori} infection along with the non-existence of CAG, the well-established precursor for stomach cancer.\(^{5,7-10}\)

The precise reason why \textit{H. pylori} prevalence is very low in Javanese people in Semarang and Yogyakarta is unknown.\(^{21}\) It seems paradoxical given the fact that \textit{H. pylori} is transmitted via fecal–oral, oral–oral or water-borne routes, because most people in Semarang still use well water and the sanitary environment conditions remain basic.\(^{5}\) The low positivity in Javanese people is, however, compatible with the low prevalence reported for Malay people in Malaysia who share ethnic traits.\(^{22}\) We should scrutinize whether genetic polymorphisms of Javanese people might confer immunity against \textit{H. pylori} infection. It is also conceivable that specific environmental factors on Java island, including dietary habits, may be effective in preventing \textit{H. pylori} infection.

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**Table 1. Helicobacter pylori-related markers and pepsinogen (PG) tests in the populace in Semarang compared with Japan**

<table>
<thead>
<tr>
<th>Test</th>
<th>Semarang (Men (n = 69)</th>
<th>Women (n = 102)</th>
<th>Japan (Men)</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive urea breath test (%)(^a)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Positive serum \textit{H. pylori} IgG (%)(^b)</td>
<td>2 (0–5)</td>
<td>2 (0–4)</td>
<td>62 (58–65)</td>
<td>57 (53–60)</td>
</tr>
<tr>
<td>Positive pepsinogen test (%)(^c)</td>
<td>0</td>
<td>0</td>
<td>23 (22–25)</td>
<td>22 (20–23)</td>
</tr>
</tbody>
</table>

\(^a\)Positive test was defined as ≥ 2.5% by UBT-IR300 kits. \(^b\)Positive test was defined as ELISA value ≥ 2.3 by enzyme immunoassay. \(^c\)Age-adjusted prevalence (95% confidence interval).

**Table 2. Smoking rates and urinary excretion of salt and potassium in the populace in Semarang compared with Japan**

<table>
<thead>
<tr>
<th></th>
<th>Semarang</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking rate (%)</td>
<td>55.0 (22.3–87.8)(^d)</td>
<td>49.5 (47.2–51.7)</td>
</tr>
<tr>
<td>Salt (g/day)</td>
<td>11.1 (9.8–12.5)</td>
<td>12.9 (12.7–13.1)</td>
</tr>
<tr>
<td>Potassium (g/day)</td>
<td>2.3 (2.2–2.5)</td>
<td>2.5 (2.5–2.5)</td>
</tr>
</tbody>
</table>

\(^d\)Age-adjusted mean (95% confidence interval).
While ecological studies are generally regarded as providing low-rank evidence, and the number of recruited subjects was not, strictly speaking, randomly selected and not sufficiently large to be representative of the Semarang populace, our data do provide simple and compelling evidence that the low stomach cancer incidence in Semarang is due to the very low prevalence of \textit{H. pylori} infection and CAG, suggesting that \textit{H. pylori} is a definite and essential factor for the onset of stomach cancer. Further, large scale studies taking into account local medical practice, such as gastric cancer screening and cancer registration, including its completeness and accuracy, now need to be carried out for confirmation.

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References