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In a nested case–control study of 86 cases of gastric adenocarcinoma in relation to Helicobacter pylori infection in the Korean Multi-center Cancer Cohort, the H. pylori IgG seropositivity was 83.7% and that of the 344 matched controls was 80.8%, with a matched odds ratio for H. pylori infection of 1.06 (95% CI, 0.80–1.40).

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In 1994, the International Agency for Research on Cancer (IARC) classified Helicobacter pylori as a group 1 carcinogen (IARC, 1994), whereas that same year, a US body concluded that there was insufficient evidence for a causal association between H. pylori infection and gastric adenocarcinoma (NIH Consensus Development Panel, 1994). During the last decade, several nested case–control studies of H. pylori infection and gastric adenocarcinoma, including a meta-analysis (Huang et al, 1998; Danesh, 1999; Eslick et al, 1999; Helicobacter and Cancer Collaborative Group, 2001), were carried out. In high H. pylori infection areas, such as Eastern Asia and Africa, the findings from epidemiological studies have shown inconsistent results (Miwa et al, 2002; Tajima, 2002; Lunet and Barros, 2003).

Gastric cancer is the cancer with the most frequent incidence and is the second most common cause of cancer death in Korea (Korea Central Cancer Registry, 2002; National Statistical Office, 2002), where the prevalence of H. pylori infection is also high. In view of its potential importance, we carried out a nested case–control study of the subjects in a Korean cancer cohort.

MATERIALS AND METHODS

The Korean Multi-center Cancer Cohort (KMCC) consisted of male and female subjects aged over 30 years, who were voluntary participants in a cancer-screening survey in four geographically defined areas of Korea (Yoo et al, 2002). Each participant completed a detailed questionnaire administered by trained interviewers. In total, 10 ml of blood collected was fractionated and all the samples were stored at a temperature of −70°C. Informed consent was obtained from all the participants and the study protocol was approved by the Institutional Review Board of the Seoul National University Hospital and National Cancer Center.

Cases of cancer were identified through record linkage with the Korean Central Cancer Registry and the National Health Insurance Cooperation database. To validate the cancer diagnosis and obtain additional detailed clinical information, a medical record review was undertaken for potential gastric cancer patients. Among the 10927 participants recruited between 1993 and 1999, 228 participants who had cancer prior to recruitment were excluded from the study. Among the remaining 10699 potential study population, 86 incident gastric cancer cases were identified. The average time interval between the blood collection and the diagnosis of gastric cancer was 2.6 years. Four controls from the eligible cancer-free cohorts were matched to each cancer case by incidence density sampling based on their age within 5 years, gender, and the year and site of their recruitment. Thus, 86 newly diagnosed gastric adenocarcinoma patients and 344 matched controls were included in the final analysis.

A Genedia™ (Greencross Life Science) H. pylori IgG enzyme-linked immunosorbent assay (ELISA) kit, with a sensitivity of 100% and a specificity of 81.3% in the Korean population (Eom et al, 2001), was used to determine seropositivity of the cases and controls according to the manufacturer’s protocol.

A multivariate conditional logistic regression model was used to calculate the adjusted matched odds ratio (OR) and 95% confidence intervals. Statistical analysis was performed with the SAS v8.1 statistical package.

RESULTS

The demographic and clinical characteristics of the gastric adenocarcinoma cases are shown in Table 1; their mean age was 63 years at recruitment and 66% of the cases were male. Most of cases developed adenocarcinoma in the non-cardia region of the stomach (six cardia, 70 non-cardia, one both cardia and non-cardia, nine unspecified).
Cumulative smoking of more than 26 pack-years (OR, 1.22; 95% CI, 0.88–1.67) and a history of gastritis or gastric ulcer were not associated with increased risk (OR, 1.15; 95% CI, 0.80–1.67). Frequent consumption of yellow–green vegetables showed a decreased risk of gastric cancer, which was not significant (OR, 0.66; 95% CI, 0.35–1.27).

Table 1  Demographic and clinical characteristics of gastric adenocarcinoma cases in the nested case–control study

| Characteristics | Categories | Number | (%) |
|-----------------|------------|--------|-----|
| Age (years)     | 40–59      | 27     | (31.4) |
|                 | 60–69      | 41     | (47.7) |
|                 | 70–82      | 18     | (20.9) |
| Sex             | Male       | 57     | (66.3) |
|                 | Female     | 29     | (33.7) |
| Areas at recruitment | Haman county | 50     | (58.2) |
|                  | Choongju city | 26     | (30.2) |
|                  | Uljin county | 5      | (5.8)  |
|                  | Youngil county | 5      | (5.8)  |
| Tumour sites    | Cardia     | 6      | (7.0)  |
|                  | Non-cardia | 70     | (81.3) |
|                  | Both       | 1      | (1.2)  |
|                  | Unspecified | 9      | (10.5) |
| Follow-up duration | < 1 year | 24     | (27.9) |
|                  | 1–2 years  | 33     | (38.4) |
|                  | 3–5 years  | 16     | (18.6) |
|                  | > 5 years  | 13     | (15.1) |
| Total           |           | 86     | (100.0) |

DISCUSSION

The present study suggests that there might be no direct association between *H. pylori* infection and gastric adenocarcinoma risk in South Korea.

The confidence intervals of our study (0.80–1.40) are exclusive of those in the meta-analysis from 12 nested case–control studies (Helicobacter and Cancer Collaborative Group, 2001). The major heterogeneity among the studies in the meta-analysis was from age and time interval between sample collection and cancer diagnosis. There was a 2.4-fold (95% CI, 1.82–3.12) increase in risk when samples were collected less than 10 years before the diagnosis of cancer, as were our own. A Taiwanese study, which had a median 2.0 years of follow-up showed 1.55-fold nonsignificantly increased risk (95% CI, 0.68–3.54), whereas a Japanese study and a Chinese study with median 3.6 years of follow-up showed 3.38 (95% CI, 1.15–9.90)- and 1.66 (95% CI, 1.08–2.54)-fold increased risk, respectively (Webb et al, 1996; Watanabe et al, 1997; Yuan et al, 2001).

Table 2  Seropositivity for *Helicobacter pylori* IgG antibody and adjusted matched odds ratios (ORs) for their relationship stratified by clinical characteristics and demographics

| Strata         | Cases Infected/total | *Hp* (+) (%) | Controls Infected/total | *Hp* (+) (%) | Adjusted matched OR (95% CI) |
|----------------|----------------------|--------------|-------------------------|--------------|-----------------------------|
| Overall        | 72/86 (83.7)         |              | 278/344 (80.8)          |              | 1.06 (0.80–1.40)            |
| Tumour sites   |                      |              |                         |              |                             |
| Cardia         | 4/6 (66.7)           |              | 20/24 (83.3)            |              | 0.88 (0.38–2.28)            |
| Non-cardia     | 60/70 (85.7)         |              | 231/280 (82.5)          |              | 1.07 (0.77–1.49)            |
| Follow-up duration | < 1 year | 21/24 (87.5) | 80/96 (83.3)            |              | 1.10 (0.63–1.92)            |
|                | 1–3 years            | 27/33 (81.8) | 109/132 (82.6)          |              | 1.02 (0.63–1.65)            |
|                | 3–5 years            | 12/16 (75.0) | 51/64 (79.7)            |              | 0.96 (0.51–1.81)            |
|                | > 5 years            | 12/13 (92.3) | 38/52 (73.1)            |              | 1.26 (0.64–2.48)            |
| Age (years)    |                      |              |                         |              |                             |
| 40–59          | 25/27 (92.6)         |              | 88/108 (81.5)           |              | 1.25 (0.73–2.14)            |
| 60–69          | 33/41 (80.5)         |              | 135/164 (82.3)          |              | 0.97 (0.64–1.47)            |
| 70–82          | 14/18 (77.8)         |              | 55/72 (76.4)            |              | 1.03 (0.59–1.77)            |
| Sex            |                      |              |                         |              |                             |
| Male           | 47/57 (82.5)         |              | 179/228 (78.5)          |              | 1.08 (0.78–1.50)            |
| Female         | 25/29 (86.2)         |              | 99/116 (85.3)           |              | 1.03 (0.60–1.77)            |
| Recruited areas |                    |              |                         |              |                             |
| Haman county   | 41/50 (82.0)         |              | 159/200 (79.5)          |              | 1.05 (0.74–1.49)            |
| Choongju city  | 22/26 (84.6)         |              | 85/104 (81.7)           |              | 1.06 (0.62–1.81)            |
| Uljin county   | 5/5 (100.0)          |              | 18/20 (90.0)            |              | 1.03 (0.18–6.02)            |
| Youngil county | 4/5 (80.0)           |              | 16/20 (80.0)            |              | 1.06 (0.29–3.84)            |

*Hp (+) = Helicobacter pylori seropositivity. Adjusted matched OR controlling for education, alcohol consumption, and cumulative dose of smoking.
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The major limitations of our study are its relatively small size of the cohort and short follow-up period, and a larger study with longer follow-up period will be needed to confirm its findings in this study region. The study participants were mostly farmers, so a generalisation with respect to the entire Korean population cannot be assumed. The disappearance of incidence of childhood infection may have introduced temporality bias (Ohata et al, 2004). The history of gastric ulcer or gastritis did not affect the association of H. pylori infection to gastric cancer in our data (data not shown). The use of serum pepsinogen as a marker of chronic gastritis could usefully be applied in a future study.

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