



H. pylori seroprevalence in patients with lung cancer

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Abstract

AIM: To assess *H. pylori* seroprevalence in lung cancer and determine whether there is a potential association between lung cancer and *H. pylori* infection.

METHODS: The study was conducted on forty consecutive patients with lung cancer, confirmed by pathology (32 men, 8 women; mean age 55.50 ± 11.91 years, range 16-77 years). Forty healthy subjects (25 men, 15 women; mean age 43.08 ± 12.60 years, range 20-79 years) from the patients' family members were matched to each case subject on the basis of age and socioeconomic status. *H. pylori* infection was detected with a commercially available immunoglobulin G (IgG) enzyme-linked immunosorbent assay (Trinity kit, Biotech co., USA), previously validated in adults (86% sensitivity, 96% specificity) against a gold standard of culture and histology.

RESULTS: *H. pylori* seropositivity was present in 52.5% of patients with lung cancer in comparison to 45.0% of healthy control subjects. Although *H. pylori* seropositivity was more frequent in lung cancer patients than in controls, the difference did not reach statistical significance (OR = 1.35, 95% CI = 0.56-3.25; $P = 0.65$). In addition, there was no significant difference between cases and controls in terms of gastrointestinal symptoms.

CONCLUSION: The earlier described association between *H. pylori* infection and lung cancer was not supported in this study. Further studies with larger sample sizes should be undertaken to assess the frequency of *H. pylori* infection in patients with lung cancer and their potential association.

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Key words: Lung neoplasm; *H. pylori*; Helicobacter infections/complications; Carcinoma/Non-small cell; Carcinoma/Squamous cell; Case-control studies

INTRODUCTION

Lung cancer remains the leading cause of cancer death, both in the United States and worldwide even though an extensive list of risk factors has been well-characterized^[1,2]. Without the development of efficacious primary prevention, the number of people diagnosed with lung cancer is expected to double in the next 50 years^[3]. Its high mortality rate results from both a high incidence rate and a low survival rate, with only 15.0% of US lung cancer patients surviving 5 years after diagnosis^[4,5].

The combination of exposure to new etiologic agents and an increasing lifespan make lung cancer a scourge of the 20th century. Identification of numerous exposures that are causally associated with lung cancer is critical in developing new preventive strategies. By reducing the population's exposure or interrupting the pathogenic chain leading to the development of lung cancer, we would expect to reduce the population's risk and subsequently the global burden of its mortality.

Recently a number of studies have reported an association between *H. pylori* infection and a variety of extra digestive disorders such as respiratory diseases. Moreover, lung cancer in peptic ulcer patients has been found to be 2-3 times more prevalent than in healthy subjects^[6-8].

These findings led to the hypothesis that: "*H. pylori* might be associated with lung cancer and play a role in developing the disease". Because of the conflicting reported results, we have performed this study to investigate the *H. pylori* seroprevalence in lung cancer patients and their potential association.

MATERIALS AND METHODS

Subjects

The study was conducted on forty consecutive patients with lung cancer, confirmed by pathology. The patients were selected from the outpatient clinic of Dr Masih Daneshvari Hospital, Tehran, Iran. Forty healthy subjects from the patients' family members were matched to each case subject on the basis of age. We used family members to control for socioeconomic status. The study was approved by the local ethics committee and informed

Table 1 Mean (SD) characteristics of the study cases and controls

Variables	Cases (n = 40)	Controls (n = 40)	P ¹
Sex (M/F)	32/8	25/15	0.03
Age (yr)	55.50 (11.91)	43.08 (12.60)	> 0.05
<i>H. pylori</i> IgG level (U/mL)	1.37 (0.74)	1.07 (0.44)	> 0.05
<i>H. pylori</i> serology ²			0.65
Positive for IgG antibodies to <i>H. pylori</i>	21 (52.5)	18 (45.0)	
Negative for IgG antibodies to <i>H. pylori</i>	13 (32.5)	17 (42.5)	

¹All *P* values are for 2-tailed *t* tests. ²Six case subjects and 5 control subjects had borderline results and were excluded from the study.

consent was obtained from each participant.

Measurements

H. pylori infection was detected with a commercially available immunoglobulin G (IgG) enzyme-linked immunosorbent assay (Trinity kit, Biotech Co., USA), previously validated in adults (86% sensitivity, 96% specificity) against a gold standard of culture and histology.

All serum samples from case and control subjects were coded, and assessed, in a blinded fashion, in the laboratory centre of the hospital. Briefly, serum samples were diluted 1:20, and 10-μL aliquots were plated. Plates were coated with purified *H. pylori* group specific antigens. Next, a 1:1000 dilution of anti-human IgG monoclonal antibodies conjugated to alkaline phosphatase was applied. A 1-mg/mL solution of p-nitrophenylphosphate was used as a substrate, and absorbance was read at 450 nm. The result for each serum sample was expressed as the ratio of the optical density value of the sample to the threshold value and was expressed in ELISA units.

As determined by a previous validation study, serum samples with an ELISA unit of greater than 1.10 U/mL, between 0.90-1.10 and less than 0.90 were considered positive, borderline and negative, respectively.

Borderline results were omitted from further analysis. All the subjects were questioned on educational level, number of person living in the same household, gastrointestinal symptoms, and history of respiratory diseases and proven peptic ulcer disease.

Statistical analysis

All data were expressed as mean ± SD. Parameter differences between groups were evaluated using Student's *t*-test for continuous variables and a chi-square test for proportions. The relationship between variables was analyzed by the Pearson correlation coefficient. The analyses were performed using SPSS software (SPSS 13.0 for Windows).

A review of previous literature suggests that the prevalence of *H. pylori* infection is about 44.9% in the general population^[7]. Estimations from power calculations predicted that 40 cases and 40 controls would have 80% power to detect a minimal OR of 3.60 between the two groups, at α (two-sided) = 0.05.

RESULTS

From March 2003 to December 2003, 40 consecutive

Table 2 Frequency of gastrointestinal symptoms in patients and normal controls

Symptoms	Cases (n = 40)	Controls (n = 40)	P
Epigastric pain	8/40	10/40	NS
Heartburn	10/40	9/40	NS
Bloating	11/40	8/40	NS

NS: not significant.

patients with lung cancer were included in this study. Patients consisted of 32 men and 8 women with a mean age of 55.50. The control group consisted of 25 men and 15 women with a mean age of 43.08 (Table 1).

There were no significant differences between groups in terms of distribution of age, socioeconomic status, educational level and number of people living in the same household (*P* < 0.05).

Because 6 case subjects and 5 control subjects had borderline results when tested for IgG antibodies to *H. pylori*, they were excluded from the study, which left 34 case subjects and 35 control subjects in the analysis.

The values for *H. pylori* IgG serum level in the case and control groups were 1.37 ± 0.74 U/mL and 1.07 ± 0.44 U/mL, respectively (*P* > 0.05). *H. pylori* seropositivity was present in 52.5% of patients with lung cancer in comparison to 45.0% of healthy control subjects. Although *H. pylori* seropositivity was more frequent in lung cancer patients than in controls, the difference did not reach statistical significance (OR = 1.35, 95% CI = 0.56 – 3.25; *P* = 0.65). In addition, there was no significant difference between cases and controls in terms of gastrointestinal symptoms (Table 2).

DISCUSSION

We examined the hypothesis that “*H. pylori* seroprevalence is associated with lung cancer”. The *H. pylori* seroprevalence in our patients with lung cancer did not differ significantly from that of our healthy subjects.

Our results were in accordance with those of Philippou and colleagues^[8] which compared 55 men and 17 women who had lung cancer with an age and gender-matched control group of 68 healthy subjects. No significant difference in *H. pylori* seroprevalence between the two groups was observed in their study (61.1% vs 55.9%, *P* = 0.23).

In contrast to our results, in 2000, Gocyk *et al*^[9] published a preliminary report comparing 50 Polish patients who had lung cancer with 100 healthy subjects. They demonstrated a significantly higher *H. pylori* seroprevalence among patients with lung cancer in comparison with healthy subjects (89.5% vs 64% respectively, *P* < 0.05). Lung cancer patients were characterized by a significant increase of gastrin concentration in both serum and bronchoalveolar lavage (BAL). They also demonstrated that m-RNA expression for gastrin and its receptor, as well as for cyclooxygenase (COX)-2, is enhanced in the tumor tissue.

Similarly, Ece *et al*^[10] pointed out an association between *H. pylori* infection and the risk of lung cancer. By comparing 43 patients with non-small cell carcinoma of the lung and 28

healthy controls selected from the patients' family members, they found that *H pylori* seroprevalence was statistically higher in cancer patients than in the control group (93% *vs* 42%, $P < 0.05$). Moreover, both VacA and CagA seropositivity was higher in lung cancer patients. However, only VacA was statistically significant (81% *vs* 42%, $P < 0.05$).

It is important to note that the prevalence of *H pylori* infection in healthy subjects reported in this study is much lower than the prevalence expected in the population in which the study was carried out (42% *vs* 77.5%-90%)^[11-13]. Consequently, the observed difference in the prevalence of *H pylori* infection between lung cancer cases and controls-perhaps given the manner of selection-may have not necessarily been the result of higher prevalence of *H pylori* infection in cases, but rather of lower prevalence in controls that was expected.

Furthermore, the association between *H pylori* infection and lung cancer that was observed in these studies could be due to another factor strongly correlated with *H pylori* infection. For example, *H pylori* infection is closely linked to chronic bronchitis, and it is possible that a factor linked to chronic bronchitis is the true cause of the association observed^[12,13].

The mechanism underlying an association between *H pylori* and lung cancer is uncertain. It has been suggested that *H pylori* might indirectly induce increased mucosal cell proliferation of bronchial epithelium by the enhancement of gastrin and its receptor expression, as well as cyclooxygenase (COX)-2, in the tumor tissue.

Evidence for or against this hypothesis is limited and studies have shown conflicting results^[14-16].

Finally, it must be noted that the findings have not been entirely consistent with other data, although it would not completely rule out the hypothesis.

Lung cancer tends to be more common in the developed countries, particularly in North America and Europe and less common in the developing countries^[15]. On the other hand, the prevalence of *H pylori* infection is much higher in developing countries^[16].

Our study has had some limitations. First, we should have used a larger sample size to detect a lower effect size and to avoid a Type II error. Secondly, we did not perform a stratified analysis according to the smoking status of the subjects to remove the potential confounding effect of smoking. Despite the strong evidences of cigarette smoking as a causal factor of developing lung cancer, the association of *H pylori* infection and smoking has not yet been clear and recent studies provide conflicting results. (The prevalence of *H pylori* infection in smokers has been reported variously as low^[17], normal^[18], and high^[19].)

In conclusion, interpreting the meaning of the reported epidemiological association between *H pylori* infection and lung cancer on the basis of available data, which rest only on case-control studies with relatively small sample size, is difficult.

Further different types of studies with larger sample sizes are required to confirm that chronic *H pylori* infection is a risk factor for lung cancer and to clarify the underlying mechanisms.

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