ORIGINAL ARTICLE

Four Year Analysis of *Helicobacter pylori* Infection among Patients with Dyspepsia at Universiti Kebangsaan Malaysia Medical Centre

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ABSTRAK

Helicobacter pylori merupakan agen etiologik gastritis kronik jenis B, ulser peptik dan kanser gaster. Jangkitan *H. pylori* adalah lazim di dunia dengan anggaran 50% populasi dijangkiti. Majoriti individu yang dijangkiti bersifat asimptomatik, dan sebahagian daripada mereka akan mengalami gastrititis. Walaubagaimanapun, jangkitan kronik *H. pylori* tanpa rawatan antibiotik mendedahkan individu dijangkiti kepada perkembangan kanser. Tujuan kajian ini adalah untuk menentukan jangkitan aktif *H. pylori* di kalangan pesakit dengan simptom dispepsia menggunakan kombinasi 3 kaedah ujian. Dalam laporan ini, kami mengkaji 1376 pesakit secara konsekutif yang menjalani prosedur endoskopi di Pusat Perubatan Universiti Kebangsaan Malaysia dari Januari 1999 hingga Disember 2002. Klasifikasi diagnosis pesakit ditentukan melalui pemeriksaan endoskopi dan histologi. Status jangkitan *H. pylori* ditentukan dengan ujian pantas urease, pemeriksaan histologi atau kultur *H. pylori*. Jangkitan *H. pylori* dikesan pada 30.8% pesakit dengan dispepsia. Jangkitan *H. pylori* ini adalah lebih prevalen pada pesakit dengan usia yang lebih tua dan lebih tinggi pada pesakit lelaki berbanding wanita. Pesakit dengan penyakit gastroduodenum parah adalah lebih prevalen dijangkiti *H. pylori*. Jangkitan *H. pylori* juga menunjukkan perbezaan yang signifikan di kalangan kumpulan etnik berbeza. Kaum India menunjukkan kadar jangkitan yang paling tinggi iaitu 45.4%, diikuti kaum Cina (36.8%) dan paling rendah pada kaum Melayu (18.3%). Hasil kajian ini yang menentukan jangkitan aktif *H. pylori* di kalangan pesakit dengan simptom dispepsia adalah selaras dengan kajian serologi terdahulu yang menunjukkan terdapat perbezaan etnik pada prevalen jangkitan *H. pylori*. Walaubagaimanapun, corak jangkitan *H. pylori* ini tidak selari dengan prevalen penyakit gastroduodenum parah di kalangan kumpulan etnik.

Kata kunci: *Helicobacter pylori*, prevalen, etnik, penyakit gastroduodenum

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ABSTRACT

Helicobacter pylori has been implicated as an aetiologic agent for type B chronic gastritis, peptic ulcer and gastric cancer. It is considered the most common bacterial infection in the world with approximately 50% of the population being infected. The majority of infected individuals are asymptomatic, with some developing gastritis only. However, chronic infection with *H. pylori* without antibiotic treatment predisposes infected individuals to the development of gastric cancer. The aim of this study is to determine active *H. pylori* infection among patients with symptoms of dyspepsia using three combinations of diagnostic methods. In this report, we studied 1,376 consecutive patients who underwent upper gastrointestinal endoscopy at Universiti Kebangsaan Malaysia Medical Center (UKMMC) for dyspepsia from the period January 1999 to December 2002. The classification of patient's diagnosis was assessed by endoscopic and histological examination. The *H. pylori* status was determined by rapid urease test, histological examination or *H. pylori* culture. Presence of *H. pylori* infection was confirmed in 30.8% of patients with dyspepsia. *H. pylori* infection was more prevalent in older patients and in males compared to females. Patients with severe gastroduodenal diseases were more commonly infected with *H. pylori*. There was a significant difference in *H. pylori* prevalence among the different ethnic groups. Indians had the highest infection rate (45.4%), followed by Chinese (36.8%) and the lowest were seen in Malays (18.3%). This finding on determination of active *H. pylori* infection among patients with dyspepsia is consistent with serological studies that showed racial differences in *H. pylori* prevalence. However, the pattern of *H. pylori* infection does not reflect the prevalence of severe gastroduodenal diseases among different ethnic groups.

Key words: *Helicobacter pylori*, prevalence, ethnicity, gastroduodenal diseases

INTRODUCTION

Helicobacter pylori is a microaerophilic, gram-negative, slow-growing, spiral-shaped and flagellated bacterium that infects more than 50% of the human population. It resides in gastric-type epithelium within the overlying mucous gel and in gastric glands. Invasion of the gastric mucosa by this organism is rarely demonstrated (Chen et al. 1986). It has been identified as the cause of acute and chronic gastritis, peptic ulcer disease (Nomura et al. 1994) and atrophic gastritis (Kuipers et al. 1995). The bacterium is also involved in the genesis of gastric adenocarcinoma (Parsonnet et al. 1991) and mucosa-associated lymphoid tissue lymphoma (Wotherspoon 1998). Infection usually occurs early in life and if untreated persists forever (Blaser 1990). Most people infected with *H. pylori* essentially develop chronic superficial gastritis, with only a few patients develop clinical sequelae of infection such as duodenal and gastric ulceration, gastric adenocarcinoma and gastric lymphoma (Marshall 2002). Difference in the consequences of colonization could depend on variation among colonizing *H. pylori* strains, environmental cofactors or host genetics.

Numerous reports from different parts of the world demonstrated that the prevalence of *H. pylori* strongly varies between developing and developed countries with

high prevalence rates in developing countries (80-90%) and lower rates in developed countries (<40%). Furthermore, modes and risk factors of transmission, as well as reinfection rates are likely to vary between developing and developed countries (Frenck & Clemens 2003; Rothenbacher & Brenner 2003). Within a particular country, marked differences of *H. pylori* prevalence have been observed between different ethnic groups. The data suggested that certain ethnic groups are more susceptible to infection with *H. pylori* than other ethnic groups (Dehesa & Dooley 1991; Goh & Parasakthi 2001). The trend of *H. pylori* infection in Malaysia has been studied previously (Goh 1997; Goh & Parasakhti 2001; Kaur & Naing 2003). Overall *H. pylori* prevalence was identified between 13.5 to 55%. However, in these studies, only one method of detection was used, which is serology or histology. *H. pylori* infection can be determined by various methods such as the urea breath test, rapid urease test, histology, culture, serology or fecal antigen test. Each method has its pros and cons. Furthermore, previous reports examined *H. pylori* prevalence in small numbers of patients with dyspepsia, and recruitment of patients was done in a short period of time. In this study, we attempt to determine the prevalence of *H. pylori* infection in a larger numbers of patients with symptoms of dyspepsia using a combination of three methods that detect active *H. pylori* infection.

MATERIALS AND METHODS

Patients' population

This is a prospective study on consecutive patients who underwent upper gastrointestinal endoscopy at the Endoscopy Unit, UKMMC from January 1999 to December 2002. Only patients with clear signs of reflux or dyspepsia were included in the study. Patients who are pregnant, under the age of 10 years old and those with a history of recent antibiotics use or proton pump inhibitors were excluded from the study. This study has been approved by the UKM Medical Ethics Committee and informed consent was taken from the patients before endoscopy. Demographic data (age, sex and ethnic group), endoscopic findings and histological diagnoses of all patients were recorded.

Patients were classified based on endoscopic and histological findings into four groups:

i) Non-ulcer dyspepsia (NUD); when no disease was found after endoscopy, but presenting with upper abdominal pain or epigastric pain, symptoms related to meals or heartburn, nausea or vomiting, gastritis and/or duodenitis.
ii) Peptic ulcer disease (PUD); when active peptic ulceration (gastric ulcer and/or duodenal ulcer) was detected after the endoscopic analysis with a mucosal break of at least 0.5 mm in one dimension, with depth or a diagnosis of peptic ulceration made at a previous endoscopy of upper gastrointestinal series. Past ulcers also included because *H. pylori*-associated peptic ulcer disease is regarded as a relapsing and remitting condition that may not be detected at a single endoscopy.
iii) Precancerous and cancerous lesions (PCL); includes intestinal metaplasia, atrophy, dysplasia and gastric carcinoma which is determined by histopathological examination.
iv) Other diseases; includes gastro-oesophageal reflux disease, Barret's oesophagus, gastric polyp, oesophageal ulcer and hiatus hernia which is detected after endoscopy with no other disease found by histopathological examination.

Biopsy materials and H. pylori culture

During oesophagogastroduodenoscopy (OGDS), biopsies were taken from an intact antral gastric mucosa using the endoscope (Olympus, Japan) by gastroenterologists and surgeons for rapid urease test, histological examination and culture. Biopsy for rapid urease test was inoculated into urea medium and incubated aerobically at room temperature, and results were obtained within 24 hours. Biopsy for histopathological examination was fixed in buffered formalin and sent to the Histopathology Unit to look for any pathological changes including presence of *H. pylori*. Biopsy for *H. pylori* culture was placed immediately into a transport medium at 4°C and sent to the Microbiology laboratory for culture within six hours after the endoscopy procedure. For *H. pylori* culture, biopsy was inoculated onto Columbia agar containing 7% ox blood, 10 mg/l vancomycin, 5 mg/l trimethoprim, 5 mg/l cefsulodin and 5 mg/l amphotericin B. Plates were incubated in a microaerophilic condition obtained by using an anaerobic jar with a gas-generating kit (Campy GasPak, Oxoid) for microaerophilic atmosphere (10% CO_2, 6% O_2, 0% H_2, 84% N_2) and incubated at 37°C for 5 to 7 days. *H. pylori* isolates were confirmed by colony morphology, Gram staining and positivity for urease, catalase and oxidase tests.

Statistical analysis

Data were analyzed using independent t-test, one way ANOVA and Pearson chi-square, and *p* value less than 0.05 were considered significant.

RESULTS

Study population demography

A total of 1376 patients were recruited in this study. Of these, 670 were male and 706 were female, with age ranges from 13 to 99 years (mean age 52.6, standard deviation 15.5). Patients were from three major ethnic groups comprising 541 Malays, 630 Chinese and 205 Indians. The distribution of mean age, gender and gastroduodenal diseases in the study population are shown in Table 1. Data showed that the mean age was higher in patients with severe diseases such as peptic ulcer disease and precancerous and cancerous lesions compared to patients with non-ulcer dyspepsia. More male patients had peptic ulcer compared to female patients, whereas non-ulcer dyspepsia were high in female patients.

Table 1: Demographic data of total population recruited in the study with respect to gender and mean age in each disease group.

Disease group	Gender		Age (year)	
	Male	Female	Mean	Range
NUD (n= 949)	428 (45.1%)	521 (54.9%)	49.2	13-99
PUD (n = 264)	162 (61.4%)	102 (38.6%)	57.8	19-96
PCL (n = 121)	53 (43.8%)	68 (56.2%)	62.1	22-89
Others (n = 42)	27 (64.3%)	15 (35.7%)	58.4	25-75

Pearson Chi-square for NUD *vs.* PUD (gender), $\chi^2 = 21.869$, $p < 0.0005$

Table 2 showed the distribution of disease groups among patients of three different ethnic groups. Patients with non-ulcer dyspepsia were high in Malays and Indians compared to Chinese. Peptic ulcer disease and precancerous and cancerous lesions were high in Chinese patients compared to Malays and Indians.

H. pylori infection

Specimens were considered to be *H. pylori* positive if either rapid urease test

Table 2: Demographic data of total population recruited in the study with respect to patients' ethnic in each disease group.

Disease group	Ethnic group		
	Malay (n = 541)	Chinese (n = 630)	Indian (n = 205)
NUD (n = 949)	418 (44%)	382 (40.3%)	149 (15.7%)
PUD (n = 264)	84 (31.8%)	152 (57.6%)	28 (10.6%)
PCL (n = 121)	20 (16.5%)	82 (67.8%)	19 (15.7%)
Others (n = 42)	19 (45.2%)	14 (33.3%)	9 (21.4%)

Pearson Chi-square, $\chi^2 = 59.014$, $p < 0.0005$

Table 3: Characteristics of the patients with and without *H. pylori* infection.

Characteristics	*H. pylori* status	
	Positive (n=424)	Negative (n=952)
[a]**Age**		
Mean (± s.d)	53.99±14.74	51.99±15.82
Range	15 - 98	13 - 99
[b]**Gender**		
Male	225 (33.6%)	445 (66.4%)
Female	199 (28.2%)	507 (71.8%)
[c]**Ethnic**		
Malays	99 (18.3%)	442 (81.7%)
Chinese	232 (36.8%)	398 (63.2%)
Indian	93 (45.4%)	112 (54.6%)
[d]**Disease group**		
NUD (n = 949)	239 (25.2%)	710 (74.8%)
PUD (n = 264)	122 (46.2%)	142 (53.8%)
PCL (n = 121)	56 (46.3%)	65 (53.7%)
Others (n = 42)	7 (16.7%)	35 (83.3%)

a: t = -2.209, $p = 0.027$, b: $\chi^2 = 4.694$, $p = 0.03$, c: $\chi^2 = 70.784$, $p < 0.0005$, d: $\chi^2 = 60.990$, $p < 0.0005$

or culture or histopathological examination methods gave positive results. Of 1376 patients, 424 (30.8%) were positive for *H. pylori*. Ninety nine were Malays, 232 were Chinese and 93 were Indians. Of these, 225 patients were male and 199 were female. The mean age was 54 (age range: 15 – 98) with standard deviation of 14.7. Table 3 shows the characteristics of patients with and without *H. pylori* infection. There was a significant difference in mean age between *H. pylori*-positive and *H. pylori*-negative patients ($p = 0.027$). *H. pylori*-positive infection was more prevalent among males compared to females ($p = 0.03$). There was a significant difference in *H. pylori* infection between the different ethnic groups, Indians had the highest infection rate of 45.4% (93/205), followed by Chinese with 36.8% (232/630) and Malays 18.3% (99/541). There was also a significant difference between *H. pylori* infection and severity of gastroduodenal diseases. *H. pylori*-positive infection was high in patients with severe gastroduodenal diseases (peptic ulcer disease and precancerous and cancerous lesions) compared to patients with non-ulcer dyspepsia and other disease groups.

Table 4 showed the characteristics of *H. pylori*-positive patients from the different ethnic groups. Chinese patients at older age were more prevalent to be infected compared to Indians and Malays. In all ethnic groups, *H. pylori* prevalence was similar in males and females. Significant difference was seen between disease groups and patients' ethnicity. In Malays and Indians, the prevalence rate of non-ulcer dyspepsia was high compared to Chinese, whereas peptic ulcer disease and precancerous and cancerous lesions were seen more in Chinese patients compared to Malays and Indians.

DISCUSSION

Gastric ulcer, duodenal ulcer and gastric cancer are common and serious gastroduodenal disease but occur in only a minority of people. Non-ulcer dyspepsia is one of the most frequently encountered

Table 4: Characteristics of *H. pylori*-positive patients from different ethnic groups with various diseases.

Characteristics	Ethnic groups		
	Malay (n = 99)	Chinese (n = 232)	Indian (n = 93)
[a]Mean age ± s.d	52.18 ±14.54	56.26 ± 14.54	50.27 ± 14.55
[b]Gender (Male:Female)	46 : 53	132 : 100	47 : 46
[c]Disease groups:			
NUD	65 (65.7%)	110 (47.4%)	64 (68.8%)
PUD	23 (23.2%)	85 (36.6%)	14 (15.0%)
PCL	9 (9.1%)	35 (15.1%)	12 (12.9%)
Others	2	2	3

a; Malays *vs.* Chinese: t = -2.334, $p = 0.02$, Malays *vs.* Indians: t = 0.911, $p = 0.364$, Chinese *vs.* Indians: t = 3.354, $p = 0.001$
b; $\chi^2 = 3.338$, $p = 0.188$
c; $\chi^2 = 21.441$, $p < 0.0005$

disorders in gastroenterology clinics worldwide (Talley et al. 1992). Previous studies showed that the cumulative risk of ulcer development in non-ulcer dyspepsia patients ranged from 1% to 21% during a follow up period of 1 – 10 years (Hsu et al. 2002). However, the risk factors influencing the subsequent development of peptic ulcer in non-ulcer dyspepsia patients remain unclear. In the present study, the non-ulcer dyspepsia group constituted the largest of patients (69%), whereas 19.2% patients had peptic ulcer disease. A small proportion of patients (8.3%) had precancerous lesions and 0.5% of patients were diagnosed with gastric carcinoma. Patients were from a single center i.e., from the Endoscopy Unit of UKMMC which is a tertiary and referral center for the country. This offers uniformity in standards for endoscopy, definitions of dyspepsia and histology.

The important variables for increased prevalence of severe gastroduodenal diseases were age and male patients. The mean age of patients was higher in those with severe gastroduodenal diseases and more male patients had gastric or duodenal ulcer. This could be explained by the presence of age related changes in the gastric mucosal defense in the elderly (Hsu et al. 2002). A study in humans (Cryer et al. 1992) demonstrated that gastric mucosal prostaglandin content declines with age. Feldman and Cryer (1998) also showed that advanced age is associated with a significant decline in gastric bicarbonate, sodium ions and non-parietal fluid secretion. Thus aging is associated with selective as well as specific changes in the gastric mucosal defenses that may predispose to the development of severe disease.

The study population comprised patients with symptoms of dyspepsia from three major ethnic groups; Malays, Chinese and Indians. Chinese formed the largest group of patients, followed by Malays and Indians, which is consistent with the high prevalence of gastroduodenal diseases in Chinese compared to

other ethnics. More Chinese patients were diagnosed with severe disease compared to other ethnics and the pattern has not change so much since 1994 (Haron et al. 1994; NCR 2003).

In this study, *H. pylori* infection status was determined by rapid urease test, culture or histological assessment on gastric biopsy. Urease test has been rendered a highly sensitive (90 – 93%) and specific (93 – 95%) diagnostic test (Laine et al. 1996). The test is fast and inexpensive for detecting *H. pylori* infection. Culture is the gold standard for identifying bacterial infection and culture of *H. pylori* provide the *H. pylori* isolate for further characterization. Histological examination does allow for definitive diagnosis of infection, the severity of gastritis as well as the presence of intestinal metaplasia, atrophy, dysplasia and gastric carcinoma to be assessed at the same time. In this study, an overall prevalence of *H. pylori*-infected patients with symptoms of dyspepsia was 30.8% and increased *H. pylori*-positive infection rates were observed with the increased severity of disease. Gender and age did prove to be significant risk factors for *H. pylori* infection in this study, and it is consistent with other studies which showed these variables to be independent risk factors as well (Goh 1997). The ethnic composition in both studies was almost similar in which the majority of patients were Chinese. In contrast, a study in North Eastern Peninsular Malaysia showed that gender and age were not significant risk factors for *H. pylori* infection. In the study, Malays constituted the majority of the study population with 64%, whereas Chinese were 28% and Indians were 5.2% (Kaur & Naing 2003). These results showed that the composition of the ethnic groups play a role in determining the risk factors for *H. pylori* infection.

The composition of ethnic groups recruited may also affect the overall prevalence rates of *H. pylori* infection. In the present study, the population comprised of 39.3% Malays, 45.8% Chinese and 14.9% Indians. Whereas, in the study which comprised of 17% Malays, 53% Chinese and 30% Indians, results showed more than 45% of *H. pylori* prevalence (Goh 1997). In the study in which *H. pylori* prevalence rates was less than 15%, the major study population comprised of Malays (64%), followed by Chinese (28%) and 5.2% Indians (Kaur & Naing 2003).

The differences in the prevalence of *H. pylori* between the ethnic groupswere consistent with the findings by other endoscopy-based and seroepidemiological studies (Goh 1997; Goh & Parasakthi 2001; Kaur & Naing 2003) previously reported in the region. Further observations revealed differences in the distribution of non-ulcer dyspepsia, peptic ulcer disease and precancerous and cancerous lesions in *H. pylori*-positive patients among various ethnic groups. Chinese shows consistently higher rates of severe disease compared to other ethnics. Although Indians have a higher prevalence of *H. pylori* infection, a lower frequency of peptic ulcer disease was observed compared to other ethnic groups. The difference in the prevalence of *H. pylori* and gastroduodenal diseases among patients of different ethnic groups living in the same country is interesting, and may provide valuable insights into the possible mode of pathogenesis of the infection. Pathogenic *H. pylori* strains, host genetics and environmental factors may account for the differences. This needs to be investigated.

There were some limitations in this study which should be taken into account. It is almost impossible to be completely certain of the clinical diagnosis. A definite diagnosis of non-ulcer is difficult. Patients with only gastritis at endoscopy may develop ulcer disease later in life and therefore may have been misclassi-

fied in the present study. Furthermore, our limitation is that different gastroenterologists or surgeons did the endoscopic observation on each patient, and different pathologists analyzed the biopsy specimens, although they used the same scale or scoring system. This may affect the clinical diagnosis of the patients and classification of our patients' disease group. Another important limitation in our study is that the number of patients in each disease group is not equal between different groups since peptic ulcer and precancerous and cancerous lesions constitute a small proportion of patients with dyspepsia.

In conclusion, results of this study showed that there was a significant difference in *H. pylori* infection among ethnic groups in which, Indians had the highest infection rate followed by Chinese and the lowest in Malays. *H. pylori* infection rates were high in patients with severe gastroduodenal diseases. However, the distribution of severe gastroduodenal diseases does not reflect the prevalence of *H. pylori* infection among different ethnic groups. The reasons for racial differences in *H. pylori* infection and distribution of severe gastroduodenal diseases cannot be explained. This may be related to the host or bacteria genetic factors, and sociocultural behavior of the particular ethnic and this needs further investigation.

REFERENCES

Blaser, M.J. 1990. *Helicobacter pylori* and the pathogenesis of gastroduodenal inflammation. *J.Infect.Dis*. **161**: 626-633.

Chen, X.G., Correa, P., Offerhaus, J., Rodriguez, E., Janney, F., Hoffman, E., Fox, J., Hunter, F., & Diacolitsis, S. 1986. Ultrastructure of the gastric mucosa harboring Campylobacter-like organisms. *Am.J.Clin.Pathol*. **86**: 575-582.

Cryer, B., Redfern, J.S., Goldschmiedt, M., Lee, E. & Feldman, M. 1992. Effect of aging on gastric and duodenal mucosal prostaglandin concentration in humans. *Gastroenterology* **102**: 1118-1123.

Dehesa, M & Dooley, C.P. 1991. High prevalence of *Helicobacter pylori* infection and histology of gastritis in asymptomatic Hispanics. *J. Clin. Microbiol*. **29**: 1128-1131.

Feldman, M. & Cryer, B. 1998. Effects of age on gastric alkaline and nonparietal fluid secretion in humans. *Gerontology* **44:** 222-227.

Frenck, R.W. Jr & Clemens, J. 2003. *Helicobacter* in the developing world. *Microbes Infect.* **5**: 705-713.

Goh, K.L. 1997. Prevalence of & risk factors for *Helicobacter pylori* infection in a multi-racial dyspeptic Malaysian population undergoing endoscopy. *J. Gastroenterol. Hepatol.* **12:** S29-S35.

Goh, K.L. & Parasakthi, N. 2001. The racial cohort phenomenon: seroepidemiology of *Helicobacter pylori* infection in a multiracial South East Asian country. *Eur. J. Gastroenterol. Hepatol.* **13**: 177-183.

Haron, A., Mazlam, M.Z., Aminuddin, A., Isa, M,R., Madhav, V.K. & Che Ghani, S. 1994. Six year review of gastric carcinoma at the Universiti Kebangsaan Malaysia. *J. Perubatan UKM* **16**: 13-18.

Hsu, P.I., Lai, K.H., Lo, G.H., Tseng, H.H., Lo, C.C., Chen, H.C., Tsai, W.L., Jou, H.S., Peng, N.J., Chien, C.H., Chen, J.L. & Hsu, P.N. 2002. Risk factors for ulcer development in patients with non-ulcer dyspepsia: a prospective two years follow up study of 209 patients. *Gut* **51**: 15-20.

Kaur, G. & Naing, N.N. 2003. Prevalence and ethnic distribution of *Helicobacter pylori* infection among endoscoped patients in North Eastern Peninsular Malaysia. *Mal. J. Med. Sci.* **10**(2): 66-70.

Kuipers, E.J., Perez-Perez, G.I., Meuwissen, G.S. & Blaser, M.J. 1995. *Helicobacter pylori* and atrophic gastritis: importance of the *cagA* status. *J. National Cancer Inst*. **87**: 1777-1780.

Laine, L., Lewin, D., Naritoku, W., Estrada, R. & Cohen, H. 1996. Prospective comparison of commercially available rapid urease tests for the diagnosis of *Helicobacter pylori. Gastrointest. Endosc*. **44**: 523-526.

Marshall, B. 2002. *Helicobacter pylori*: 20 years on. *Clin. Med*. **2**: 147-152.

National Cancer Registry. 2003. edited. Chye, G.L.M. & Halimah, Y. 2nd report. *Cancer Incidence in Malaysia.* Ministry of Health Malaysia.

Nomura, A., Stemmermann, G.N., Chyou, P., Perez-Perez, G.I. & Blaser, M.J. 1994. *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. *Ann. Intern. Med.* **120**: 977-981.

Parsonnet, J., Friedman, G.D., Vandersteen, D.P., Chang, Y., Vogelman, J.H., Orentreich, N. & Sibley, R.K. 1991. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N. Eng. J. Med*. **325**: 1127-1131.

Rothenbacher, D. & Brenner, H. 2003. Burden of *Helicobacter pylori* and *H. pylori*-related diseases in developed countries: recent developments and future implications. *Microbes Infect*. **5**: 693-703.

Talley, N.J., Zinsmeister, A.R., Schleck, C.D. & Melton, L.J. 1992. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* **102:** 1259-1268.

Wotherspoon, A.C. 1998. *Helicobacter pylori* infection and gastric lymphoma. *Br. Med. Bull*. **54:** 79-85.