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ORIGINAL ARTICLE

Incidence of Esophageal Carcinoma Among Malays in North-Eastern Peninsular Malaysia: An Area with an Exceptionally Low Prevalence of *Helicobacter pylori* Infection

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Abstract
Background Obesity, gastroesophageal reflux, and Barrett's esophagus have all been linked to esophageal adenocarcinoma. In addition, the decline in *Helicobacter pylori* (*H. pylori*) infection in affluent societies has also been suggested to be a major factor in the recent rise in the incidence of esophageal adenocarcinoma. If *H. pylori* infection has a protective role, populations with a naturally low prevalence of *H. pylori* infection such as the ethnic Malays of Northeastern Peninsular Malaysia should have high rates of esophageal adenocarcinoma.
Aim To test this hypothesis, we investigated the incidence of esophageal carcinoma among the ethnic Malays of the state of Kelantan in Northeastern Peninsular Malaysia.
Methods The pathology services in the state of Kelantan are provided by two main hospitals. The histopathological records of both hospitals were systematically examined to retrieve all cases of esophageal carcinoma diagnosed between 2004 and 2008. Incidence rates were determined based on the most recent population census.
Results The age-standardized incidence rates (per 100,000 population) of esophageal adenocarcinoma among Malay men and women were 0.75 and 0.69, respectively. The corresponding rates for squamous cell carcinoma of the esophagus were 0.66 and 1.34, respectively.
Conclusions The low rates of adenocarcinoma and squamous cell carcinoma of the esophagus in the study area, despite the fact that *H. pylori* infection is virtually absent, does not support the hypothesis that the absence of *H. pylori* infection is a pivotal factor in the pathogenesis of these cancers.

Keywords Esophageal cancer · *Helicobacter pylori* · Malaysia · Incidence

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Introduction

In recent years, a dramatic increase in the incidence of adenocarcinoma of the esophagus has been observed, particularly among male Caucasians [1]. This rise has been linked to the increasing prevalence of obesity, gastresophageal reflux, and Barrett's esophagus. It has also been suggested that the decline in the prevalence of

Helicobacter pylori (*H. pylori)* and the consequent changes in gastric acid homeostasis resulting in a higher esophageal acid load may be contributory [1–4]. Indeed an inverse relationship has been suggested between *H. pylori* infection and the risk of esophageal adenocarcinoma [5–8]. In the state of Kelantan in North-eastern Peninsular Malaysia, ethnic Malays constitute more than 90% of a population of 1.2 million. It is among the few geographical areas in the world with a natural exceptionally low prevalence rate of *H. pylori* infection [9, 10]. The *H. pylori* prevalence rate among ethnic Malay adults in the region is of the order of 4–5% [9] as a consequence of which the incidence of gastric cancer in Kelantan is among the lowest in the world [11]. The aim of this study was to test the hypothesis that the absence of *H. pylori* is associated with a high prevalence of esophageal adenocarcinoma.

Materials and Methods

The pathology services in the state of Kelantan are provided by two hospitals, one is the state Ministry of Health Hospital and the other a university teaching hospital. All endoscopic biopsy and surgical specimens in the state are processed and reported by the pathology departments of these two hospitals. The number of cases of esophageal carcinoma based on histology reports that are recorded in the pathology departments of these two hospitals would therefore provide an estimate of the true incidence of the disease in the state. All cases of esophageal carcinoma diagnosed over a 5-year period between 2004 and 2008 were retrieved by examining the histopathology records at both hospitals. Based on histology, most tumors were classified as squamous cell carcinoma or adenocarcinoma. Malignant tumors that did not conform to either of these histological patterns were classified as "others" and included adenosquamous carcinoma and sarcoma. Age-standardized incidence rates (ASR) were calculated based on the most recent population census statistics of Kelantan [12] and age-standardized to the "World Population" [13]. This study was approved by the human ethics committee of Universiti Sains Malaysia (USM).

Results

A total of 44 esophageal carcinoma cases were detected over the 5-year period; 22 (50.0%) of which were adenocarcinoma, 17 (38.6%) were squamous cell carcinoma, and five (11.4%) were classified as "others". This represented an overall age-standardized incidence rate of 1.89/100,000. Only five cases were non-Malays consisting of three cases of adenocarcinoma and two case of squamous cell carcinoma. When the ethnic Malay majority was considered separately, the overall age-standardized incidence rate was 1.91/100,000. Among the Malays, the age standardized incidence rate for squamous cell carcinoma (1.02/100,000) was slightly higher than that of adenocarcinoma (0.72/100,000). Based on age-standardized incidence rates, adenocarcinoma was slightly more common than squamous cell carcinoma among Malay men but the reverse was true among Malay women (Table 1). Esophageal cancers on the whole were slightly more frequent among women, and this was mainly due to the higher incidence of squamous cell carcinoma. As shown in Fig. 1a and b, the incidence rates of both adenocarcinoma and squamous cell carcinoma were higher in older age groups.

Discussion

Comparison of the findings in this study with the rates in other populations (Table 2) enables some plausible inferences [14–19]. It is clear from the study that the incidence of esophageal adenocarcinoma in this low *H. pylori* prevalence population is considerably lower than the high rates observed among males in high-risk Caucasian populations. The *H. pylori*-adenocarcinoma hypothesis was initially proposed in an attempt to explain the observed increase in adenocarcinoma among white men in Western countries.

Table 1 Frequency and incidence of esophageal cancer among ethnic Malays in Kelantan

	All esophageal cancers ($n = 39$)		Adenocarcinoma ($n = 19$)		Squamous cell carcinoma ($n = 15$)	
	Crude	ASR	Crude	ASR	Crude	ASR
Total (95%CI)	1.14 (−0.64,0.76)	1.91 (−0.42,0.98)	0.56 (−1.26,0.75)	0.72 (−1.15,0.87)	0.44 (−1.49,0.77)	1.02 (−1.12,1.14)
Male (95% CI)	1.20 (−0.90,1.06)	1.63 (−0.77,1.19)	0.72 (−1.41,1.12)	0.75 (−1.39,1.14)	0.30 (−2.48,1.44)	0.66 (−2.14,1.78)
Female (95% CI)	1.08 (−0.97,1.04)	2.16 (−0.67,1.34)	0.40 (−2.06,1.26)	0.69 (−1.82,1.49)	0.57 (−1.63, 1.14)	1.34 (−1.26,1.51)

Crude = Crude incidence rate per 100,000 population

ASR = Age-standardized rate per 100,000 population

Table 2 A summary of oesophageal cancer incidence rates among ethnic Malays in Kelantan in comparison to that of a variety of other populations

Population	Time period	ASR (males)		ASR (females)	
		AC	SCC	AC	SCC
Mainly Chinese, Singapore [14]	1998–2002	0.5	3.8	0.1	0.8
Japanese [15]	2001	0.3	8.2	0.05	1.0
Asian/Pacific islanders, USA [16]	1996–2000	0.9	4.9	0.2	0.9
Caucasians, USA [16]	1996–2000	5.0	2.1	0.7	1.1
African Americans, USA [16]	1996–2000	1.2	10.5	0.3	3.3
Hispanics, USA [17]	1998–2002	2.42	2.94	0.52	0.86
Mainly Caucasian, England/Wales [18]	1996–2001	4.5	–	0.9	–
Egypt [19]	1999–2001	0.44	1.04	0.1	0.79
Jordan [19]	1996–2001	0.57	0.84	0.09	0.53
Current study	2004–2008	0.75	0.66	0.69	1.34

AC Adenocarcinoma, *SCC* Squamous cell carcinoma, *ASR* Age-standarized rate per 100,000 population, *USA* United States of America

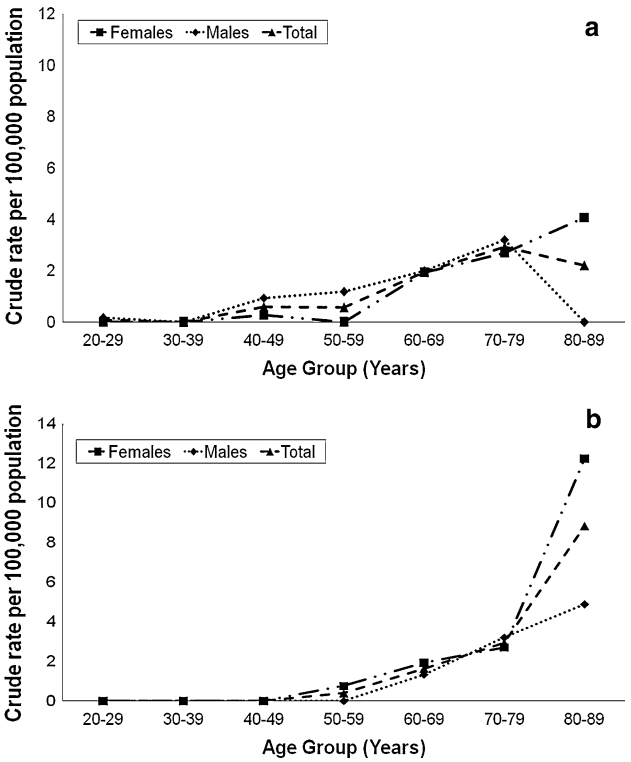

Fig. 1 **a** Graph showing 5-year age-specific rates for adenocarcinoma of esophagus among ethnic Malays. **b** Graph showing 5-year age-specific rates for squamous cell carcinoma of esophagus among ethnic Malays

This hypothesis was then extended to suggest that eradication of *H. pylori* would likely lead to an "epidemic" of adenocarcinoma such that general eradication strategies should be reconsidered [20].

This study suggests that a low presence of *H. pylori* infection alone is unlikely to be the pivotal factor accounting for the recently observed rise in esophageal adenocarcinoma in some populations. Although, one may argue that the change in the prevalence of *H. pylori* is the critical factor and that populations "starting" with a low prevalence of *H. pylori* may behave differently from populations with "declining" prevalence; gastric cancer in this region is among the lowest reported in the world, a finding that is expected independent of whether one starts with a "starting low" or "declining" prevalence of *H. pylori* [11]. While the current study does not address the question of whether it is the eradication of *H. pylori* in previously infected individuals that predisposes to esophageal adenocarcinoma, [21] direct evidence for this phenomenon is lacking. Indeed a meta-analysis showed no convincing association between *H. pylori* eradication and the development of GERD; a potential precursor of Barrett's and esophageal adenocarcinoma [22]. Furthermore, the rise in the incidence of esophageal adenocarcinoma in high-incidence populations was observed before *H. pylori* eradication became widespread.

Of interest, the incidence of esophageal adenocarcinoma among women was similar to that reported in Caucasians and somewhat greater than that observed among East Asians, African Americans and Pacific Islanders as well as in the Middle East [14–19]. It is equally notable that the ratio of squamous cell carcinoma to adenocarcinoma in this study was lower than in most non-Caucasian populations.

It has been proposed that gastric atrophy induced by chronic *H. pylori* infection results in hypoacidity and in turn reduces the tendency for chronic gastresophageal reflux, Barrett's and esophageal carcinoma [4]. Absence of *H. pylori* would thus enhance the esophageal acid load for those who experienced gastresophageal reflux leading to more severe clinical disease, a higher incidence of Barrett's esophagus, and subsequently adenocarcinoma of the esophagus. The key differences between populations in

terms of esophageal adenocarcinoma could therefore be related to differences in factors that predisposed to gastresophageal reflux such as the parietal cell mass, the intrinsic ability of the squamous mucosa to withstand acid reflux, and obesity. The results from this unique population support the notion that the absence of *H. pylori* infection plays at best a relatively minor role in promoting adenocarcinoma and argues the case for more attention to be directed towards factors that correlate with race, gender, and obesity as risk factors for chronic gastresophageal reflux. Kelantan has not escaped the recent global epidemic of obesity. The combined prevalence of overweight and obesity in the local population is just under 50% [23]; a figure lower than that of the US, England, and Australia, but higher than that of France and Switzerland [24]. However, the prevalence of esophagitis and Barrett's esophagus among endoscoped patients in the area was rather low at 5.5 and 0.8%, respectively [25]. The inherent limitations of endoscopically derived prevalence data notwithstanding, the findings are concordant with the low incidence of esophageal adenocarcinoma in the area.

Another notable finding is the relatively low incidence of squamous cell carcinoma among males in this study (Table 2). This is particularly noteworthy as squamous cell carcinoma of the esophagus is generally associated with lower socioeconomic status and yet the incidence in this study was lower than in most industrialized nations [26]. This may at least partly be attributed to the fact that the consumption of alcohol (an established risk factor for esophageal squamous cell carcinoma) in the predominantly Muslim population of Kelantan is very low. Cigarette smoking among males on the other hand is very prevalent [27]. It is interesting that the incidence rates of squamous cell carcinoma in Egypt and Jordan that have predominantly Muslim populations [19] are also relatively low whereas in those populations *H. pylori* prevalence is high [28, 29]. Recent studies have associated squamous cell carcinoma of the esophagus with the presence of achlorhydria suggesting a possible link between *H. pylori* (a common cause of achlorhydria) and squamous cell carcinoma [8, 30]. However, environmental factors appear responsible for the marked differences in atrophic gastritis among populations with *H. pylori* infections making the association actually one with *H. pylori* and co-existing achlorhydria rather than with *H. pylori* by itself. Thus, the general fall in the incidence of squamous cell carcinoma in Western populations may in part be due to the change in the pattern of gastritis that has been linked to diet as well as to the loss of *H. pylori*. At least one study has shown an association between *H. pylori* and squamous cell carcinoma [8] but other studies have not [5, 31]. The fact that the rates of squamous cell carcinoma among males in our study with a low *H. pylori* prevalence are of the same order as that of the mainly Muslim populations of Egypt and Jordan suggest that low alcohol consumption is more likely to be important than *H. pylori* infection in causing squamous cell carcinoma of the esophagus. It is intriguing that the incidence of squamous cell carcinoma in the area was slightly higher among women in contrast to most other parts of the world. It is tempting to speculate that this may be related to the not uncommon habits of smoking unfiltered tobacco and chewing betel quid among older women in the community. It is noteworthy that the divergence in the incidence of squamous cell carcinoma between men and women occurs after the age of 70 years (Fig. 1b).

There is some evidence that ethnic Malays who constitute the overwhelming majority of the population in Kelantan may have a generally lower propensity for cancer. Examination of the statistics from a comprehensive cancer registry of the neighboring city state of Singapore shows that the ethnic Malay minority of Singapore has a lower overall incidence of cancer than the ethnic Chinese but higher than that of ethnic Indians [32]. The incidence of lung, breast, and colorectal cancers among Singaporean Malays are considerably lower than that of Western Europe and North America but higher than in many other parts of the world [33]. In this context it is again notable that the incidence of both squamous cell carcinoma and adenocarcinoma of the esophagus among Malay women in the current study is of the same order as that of female Caucasians in the US, England, and Wales (Table 2).

Some limitations to the study were worth noting. Firstly, the relatively rural area in this region means that some patients with esophageal cancer may never have been seen at the hospitals which would underestimate the incidence of esophageal carcinoma. On the other hand, the data was taken from the only two hospitals serving the whole state and the data was part of national cancer registry of which the diagnosis and records are meticulous. Secondly, the incidence rates were calculated based on "world standard population" and may therefore not be entirely comparable to other populations using other standards. However, a study did not report any difference in relative risk estimation when comparing the WHO world standard population and other available standards especially the widely used Segi standard (1960) [34]. While not directly comparable, Table 2 provides an overview and differences on available esophageal carcinoma incidence rates across the globe. Finally, determining incidence rates in a population from an ecological area may increase risk of fallacy and therefore undermine the actual rates and study of individual risk factors. However, population level study may still be useful since it is increasingly recognized that some risk factors operate more genuinely at population level rather than individual level and also it is important in generating hypotheses to causes of public health problems [35].

In conclusion, the results of this study do not support the hypothesis that absence of *H. pylori* infection will likely result in a marked increase in the incidence of esophageal adenocarcinoma.

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Conflicts of interest David Y. Graham is a consultant for Novartis in relation to vaccine development for treatment or prevention of *H. pylori* infection. He is a also paid consultant for Otsuka Pharmaceuticals and until July 2007 was member of the Board of Directors of Meretek Diagnostics, the manufacturer of the 13C-urea breath test. He also receives royalties on the Baylor College of Medicine patent covering materials related to 13C-urea breath test. All other authors report no relevant conflicts.

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