SOME OBSERVATIONS ON THE EPIDEMIOLOGY OF PEPTIC ULCER DISEASE IN SINGAPORE

J Y Kang

ABSTRACT
Several lines of evidence suggest that, of the three main races of Singapore, peptic ulcers are more common among the Chinese and Indians when compared to the the Malays. These include studies on hospital series of patients with or without appropriate control groups, studies on the incidence of surgery for perforated ulcer as well as mortality statistics. A reduction in the Chinese : Malay difference in the incidence of perforated ulcer over three decades suggests that environmental factors are involved in producing these racial differences. However, we have to date been unable to determine the factor(s) responsible. The incidence of perforated ulcer in Singapore is increasing while ulcer mortality is declining. This is similar to the situation in Hong Kong but different from that in the western countries.

Keywords: race, perforation, surgery, Helicobacter, acid

INTRODUCTION
Epidemiology is concerned with the patterns of disease occurrence in human populations and of factors which influence these patterns. Such studies may provide useful insight into disease aetiology and pathogenesis. The epidemiology of peptic ulcer disease in Singapore is of particular interest because: (1) the three main racial groups ie Chinese, Malays and Indians have different frequencies of peptic ulcer. This provides an opportunity to study the factors which underlie these racial differences and (2) a small number of hospitals with a high standard of record keeping serving a well defined population enable studies of disease frequency to be carried out over time.

ASSESSMENT OF PEPTIC ULCER FREQUENCY
Disease frequency is usually expressed in terms of prevalence or incidence. The prevalence of a disease is the proportion of subjects affected at one point in time. The incidence of a disease is the proportion of subjects developing that disease over a given period.

Several special problems exist in the assessment of peptic ulcer frequency:

1. The basis of diagnosis
Symptoms of peptic ulcer disease are neither sensitive nor specific and there are no pathognomonic physical signs. Diagnosis therefore depends either on specialised investigations ie barium meal or endoscopy, or on findings at surgery or autopsy.

2. Varying severity of symptoms
Some ulcer patients have little or no symptoms and do not come to medical attention. They can only be picked up from population-based studies. Other patients may receive treatment from general practitioners and not be referred to hospital. Such patients will be missed if only hospital patients were studied.

3. Non-uniformity of treatment
Treatment for peptic ulcer is variable and there is no uniformity in the criteria for patient selection regarding par-

Division of Gastroenterology
Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

J Y Kang, MD, FRCP, FRCP(Edin), FRACP, FAMS
Associate Professor

SINGAPORE MED J 1992; Vol 33: 468-471

4. Low fatality rate
Because ulcer disease is seldom a cause of death, mortality statistics would be as dependent on the efficacy of medical treatment as on the frequency of ulcer disease.

5. Gastric ulcer and duodenal ulcer
These are probably two separate diseases. However, they are often considered together in statistics obtained in earlier years.

METHODS USED TO ASSESS PEPTIC ULCER FREQUENCY
The following methods have been used to assess the frequency of peptic ulcer disease:

1. Hospital records
Records of the number of hospital admissions and ulcer operations are, like mortality statistics, readily available. Disadvantages in their use as indices of ulcer frequency include variability in their accuracy and completeness. The catchment population from which a hospital draws its patients is often poorly defined. Criteria for hospital admission or surgery for peptic ulcer vary from place to place, and from time to time. However, the frequency of surgery for perforated ulcer has been regarded as one of the best indices of ulcer frequency. This is because most patients with perforated ulcer will get admitted to hospital and be operated upon. It is assumed that the proportion of peptic ulcers which perforate remains constant. This assumption is, however, unproven.

2. Mortality statistics
Mortality statistics are available for many countries over long periods of time. They have therefore been used to assess chronological changes in ulcer frequency. The diagnostic accuracy in death certification may, however, be low. Because peptic ulcer is seldom fatal, changes in mortality rates will reflect the efficacy of treatment as much as the frequency of disease.

3. Necropsy studies
A good estimate of ulcer frequency can be obtained by necropsy findings in patients dying from miscellaneous causes. However, ulcer scars are liable to be missed unless the autopsies are carried out prospectively by an interested
4. Prospective surveys of peptic ulcer

A prospective survey of ulcer disease in a given town or country would be one of the best ways of assessing ulcer frequency. The whole population, or a random sample of it, may be used. However, surveys which are based on hospital records would encounter problems in diagnostic accuracy, whereas a survey of peptic ulcers as routinely diagnosed in medical practice would miss patients who have mild symptoms and who do not come to medical attention. Last but not least is the large amount of work involved in such a project.

5. Sickness benefit records

Sickness benefit records have been used as an index of peptic ulcer frequency in a community. This method only covers subjects in employment. Diagnostic accuracy may be a problem. Patients who have symptoms and who continue to work will not be included.

Every method of assessing ulcer frequency has advantages and disadvantages. Generally, the more accurate a method is, the more laborious it is to carry out. When records are required over a long period eg for chronological studies, less satisfactory indices will have to be used. In practice, several indices of ulcer disease are often taken together to give an overall picture.

In the rest of this review, I shall summarise all published studies from Singapore relating to peptic ulcer epidemiology with regards to (1) racial differences in frequency, (2) chronological trends in ulcer frequency and (3) studies on pathophysiology which may help to explain the observed racial differences in ulcer frequency.

Racial Differences

Studies based on hospital records

Most of the data on peptic ulcer epidemiology in Singapore are based on hospital series of patients. In 1961 Yeh reported on patients undergoing peptic ulcer surgery in one unit49. Ong and Yong50 studied patients operated on for bleeding peptic ulcer in the same unit, but one decade later. Chua and Seah51 reported on all peptic ulcer patients diagnosed at one medical unit and subsequently all bleeding peptic ulcer seen at the same unit. Ho and Kho52 studied patients diagnosed endoscopically to have peptic ulcer in one medical unit. We performed a survey of patients presenting with upper gastrointestinal haemorrhage in all the medical and surgical units of one hospital over a six-month period89.

In all the above studies the proportions of Chinese were increased while that of Malays were decreased when compared to the racial composition of the general population of Singapore (Chinese 75%, Malays 15%). The proportion of Indians amongst ulcer patients was variable but approximated to that of the general population.

These studies do not definitely establish racial differences in peptic ulcer frequency because (1) Malays are known to undergo hospital services. Malay ulcer patients may therefore be under-represented in hospital series merely because they are less likely to seek hospital treatment and (2) each study was based on one hospital or unit. The catchment populations from which patients were drawn were not well defined and their racial population may differ from that of the general population.

In order to overcome these two problems we studied the racial composition of a consecutive series of patients with peptic ulcer seen at two medical units of a general hospital, and compared this with a series of general medical in- and out-patients seen at the same units. Both general medical patients as well as ulcer patients should be equally subjected to racial differences in the use of hospital services and the two series of patients would have been drawn from the same catchment population89.

The results are shown in Tables I and II. Chinese were over-represented amongst both gastric ulcer and duodenal ulcer patients. Malays were under-represented amongst the gastric and especially duodenal ulcer patients. Indians were under-represented amongst gastric ulcer patients but not duodenal ulcer patients. This study therefore provided good evidence for genuine racial differences in peptic ulcer frequency. These differences could not be accounted for by different usages of tobacco, alcohol and analgesics.

Amongst his Chinese patients, Yeoh noticed an excess of Cantonese women compared to women of other dialect groups89. In the same hospital, three decades later, we also noticed an excess of female Cantonese ulcer patients when compared to the dialect composition of the Chinese population of Singapore. Chinese of different dialect groups vary in their dietary and other habits, and dialect differences in ulcer frequency would be of interest since it would provide an opportunity to study underlying aetiological factors49. However, when the dialect composition of our Chinese ulcer patients was compared to that of our general medical patients, no major differences emerged.49. We felt that the initial impression of an increased prevalence of ulcer disease amongst Cantonese women was artefactual, due to an excess of elderly Cantonese women in the Chinatown area served by the Singapore General Hospital. This study emphasizes the importance of having valid control groups in epidemiological studies if correct conclusions are to be drawn.

Studies on hospital records for all hospitals in Singapore

Operating theatre records of all Singapore hospitals were available from 1951 onwards. We have studied the incidence of surgery for perforated and non-perforated ulcer in Singapore from 1951-8019. Since hospital services are readily available in Singapore we may expect that any patient, irrespective of race, is likely to seek hospital care for a painful condition like perforated ulcer. As the vast majority of ulcer perforations are treated surgically the incidence of surgery for perforated ulcer should give a good indication of the frequency of ulcer disease over time. The same cannot be said of the incidence of surgery for non-perforated ulcer, which would be influenced by varying fashions in ulcer treatment and personal preferences of the surgeons involved. Another weakness in this study is that ulcer site, whether gastric or duodenal, was frequently not indicated in the theatre record books.

Significant racial differences were seen in the incidence of operations for both perforated ulcer as well as all ulcer operations. The incidence was highest amongst Chinese followed by Malays and Indians. Of particular importance was the finding that Chinese/Malay ratio for perforated ulcer surgery declined over the three decades of study, in contrast to the Chinese/Malay ratio for all ulcer operations and for surgery for gastric carcinoma49, or the Chinese/Indian ratios for all ulcer operations or those for perforated ulcer in particular.

Racial differences in peptic ulcer frequency can theoretically be due to genetic or environmental differences since genetic influences are unlikely to have changed over a period of decades. It seemed likely that a significant part of the Chinese/Malay difference is due to environmental influences. If these factors could be identified new insights into the aetiology of peptic ulcer may be obtained.

Mortality statistics

Peptic ulcer is a disease with a low mortality rate and the use of mortality statistics as an index of peptic ulcer frequency is
therefore subject to many pitfalls. Nevertheless, over a thirty-year period consistent racial differences in peptic ulcer mortality were demonstrable for both sexes: Chinese having the highest mortality and Malays the lowest (69). The differences in the order of two to threefold approximated to that calculated from other indices of ulcer frequency.

**CHRONOLOGICAL TRENDS IN PEPTIC ULCER FREQUENCY**

In most western countries the frequencies of peptic ulcer disease as judged by hospital attendances, complications and mortality have declined in the last few decades (18). In Singapore, however, the incidence of surgery for perforated and non-perforated ulcer increased over the same period (19). Mortality from peptic ulcer has in contrast declined, presumably the result of improvement in medical care (19). The same phenomenon of declining ulcer mortality associated with an increased frequency of hospitalisation for ulcer disease is seen in Hong Kong (9). It may be relevant that both Singapore and Hong Kong are city states which have a predominantly Chinese population and that both cities have seen both rapid development and large-scale immigration over the last few decades.

A cohort phenomenon is demonstrable for peptic ulcer mortality in several European countries as well as in Japan. Persons born between 1890 and 1900 experienced higher mortality rates from peptic ulcer when compared to persons born before and after (17). A similar cohort phenomenon occurs for peptic ulcer mortality in Singapore (18). This suggests that some environmental factor was operative at the turn of the century which increased the susceptibility to ulcer disease of persons exposed to it. An infectious agent would be a plausible explanation for this phenomenon.

**FACTORS IMPLICATED IN THE PATHOGENESIS OF PEPTIC ULCER**

Peptic ulcer disease can be considered to arise from an imbalance between attacking forces, which tend to damage the gastroduodenal mucosa, on the one hand, and defensive forces tending to maintain mucosa integrity, on the other.

Attacking forces include:

1. **Gastric Acid and pepsin secretion**

As a group, patients with duodenal ulcer secrete more acid than normal subjects. Patients with gastric ulcer tend to produce less acid than controls but this is thought to be secondary to gastritis (69). Peptic ulcers are said not to occur in achlorhydric subjects.

2. **Gastritis**

Antral gastritis occurs in almost all patients with peptic ulcer but as it persists even after ulcer healing it may not be the cause of the ulcer. Helicobacter pylori is now thought to be a cause of antral gastritis and some feel that it may cause peptic ulcer also (20). Infection with H pylori increases meal stimulated gastric output and this has been postulated to be a pathogenetic mechanism for ulcer development (20). Formal studies of acid secretion, however, reveal no major differences between H pylori positive ulcer patients and those infected with the organism (20).

3. **Duodeno-gastric reflux**

Bile reflux has been postulated to cause gastric mucosal damage and hence predispose to gastric ulcer development.

Defending forces include gastroduodenal mucosal mucus and bicarbonate secretion, mucosal blood flow and epithelial restitution. Prostaglandins are involved in these protective mechanisms and non-steroidal anti-inflammatory drugs are thought to cause gastric damage by inhibiting prostaglandin synthesis.

4. **Possible aetiological factors for peptic ulcer disease**

There are rare syndromes where the propensity to ulcer development is inherited in a Mendelian fashion (23). In general, hereditary factors play a limited role in determining the likelihood of ulcer development.

Lam has divided duodenal ulcer patients into early-onset and late-onset groups who differ in their family history, blood group distribution and the course of ulcer disease (23). Hereditary factors may be relevant in determining the age of onset of disease.

Smoking is generally thought to predispose a person to ulcer development as well as aggravate the course of ulcer disease if already present. The role of anti-inflammatory drugs has already been mentioned. Dietary factors which have been postulated to favour ulcer development include reduced consumption of dietary fibre and polyunsaturated fatty acids.

Stress has long been implicated in ulcer pathogenesis but scientific proof is difficult to obtain. Under experimental conditions stress may affect gastric acid secretion (24). Suggestions that ulcer disease is more prevalent in stressful occupations have not been well substantiated.

**RACIAL DIFFERENCES IN VARIOUS FACTORS IMPLICATED IN THE AETIO-PATHOGENESIS OF PEPTIC ULCER**

The clinical features and response to treatment of peptic ulcer patients in Singapore are similar to those of patients elsewhere. There are no obvious racial differences either in the clinical behaviour of ulcer disease in Singapore. Several investigators have studied various factors implicated in the pathogenesis or aetiology of ulcer disease and their findings are summarised below.

1. **Gastric acid output**

Fung and Tye (25) measured gastric acid output in 60 male control Chinese, Malay and Indian subjects. Tp (25) investigated 61 male controls and 144 male duodenal ulcer subjects of different races. We have measured basal and pentagastrin-stimulated gastric acid output in 310 duodenal ulcer patients and 96 gastric ulcer patient of different races (69). No racial differences were demonstrable for gastric acid output in either ulcer patients or controls.

2. **Gastritis and Helicobacter pylori**

We investigated the prevalence of antral gastritis and Helicobacter pylori in 1,502 patients undergoing gastroduodenoscopy (25). Six hundred and forty-five had peptic ulcer (gastric ulcer 195, duodenal ulcer 422, combined gastric and duodenal ulcer, 28) while 729 had non-ulcer dyspepsia. The prevalence of both antral gastritis and Helicobacter varied depending upon the diagnosis. Thus gastritis was present in 96% of subjects with duodenal ulcer, 94% with gastric ulcer and 67% with non-ulcer dyspepsia while the proportions positive for Helicobacter were 86%, 66% and 47% respectively. There were no racial differences in the proportions of peptic ulcer patients with either antral gastritis or Helicobacter. Interestingly, Malay patients with non-ulcer dyspepsia were less likely to have antral gastritis or Helicobacter when compared to Chinese or Indian patients.

These studies on peptic ulcer patients do not exclude the possibility that racial differences in the prevalence of Helicobacter pylori infection could account for racial differences in peptic ulcer frequency. To study this further the prevalence of Helicobacter infection control subjects of different races have to be determined. A non-invasive method eg serology has to be used to diagnose Helicobacter infection in control subjects and we hope to embark upon such studies in the near future.
3. Age of onset of symptoms

Lam and others have proposed that duodenal ulcer subjects could be divided on the basis of age of onset of symptoms into two groups which differ in their clinical presentation, family history, sex and blood group distribution and acid secretory capacity. We have shown that duodenal ulcer patients in Singapore can also be divided into early-onset and late-onset groups. Genetic influences are likely to be important in determining which of these two groups each patient falls into.

We looked for racial differences in the age of onset of symptoms in duodenal ulcer. The onset age of Chinese (33.7 ±16.1: mean years ±SD) and Indian patients (38.4±16.5) were similar but that of Malay patients was higher (43.6±16.0: Malays vs Chinese p < 0.05). Therefore the difference in duodenal ulcer frequency between Chinese and Malays were greater for early-onset patients compared to late-onset ones. However, even among late-onset patients the ratio of Chinese to Malays was higher than that among the general population.

4. Antibody to Herpes simplex virus

Herpetic infection and duodenal ulcer disease share several common features. An association has been described between duodenal ulcer and titres of antibodies to Herpes simplex virus type 1 and the possibility of a causal relationship raised. We have therefore examined serum antibody titres of Herpes simplex virus type 1 in 163 patients with duodenal ulcer, 38 patients with gastric ulcer and sex-age-race matched controls. No difference in antibody titres were demonstrable between peptic ulcer patients and controls. Antibody titres were also comparable between subjects of different races. Our results therefore do not support a role for Herpes simplex virus in peptic ulcer disease.

5. Site of duodenal ulcer

We have demonstrated that posterior wall duodenal ulcers are more likely to present with haemorrhage when compared to those on the anterior wall. We have examined the distribution of duodenal ulcer site in patients of different races but found no difference.

6. Other factors

Racial differences in peptic ulcer frequency cannot be accounted for by differences in usage of tobacco or analgesics.

CONCLUSION

Our studies and those of others have clearly demonstrated significant racial difference in peptic ulcer frequency in Singapore. A reduction in the Chinese : Malay difference over the last three decades indicates that environmental factors are implicated in these racial differences. However, no racial differences have so far been demonstrated in any factor implicated in the aetiology or pathogenesis of ulcer disease.

We feel that two further lines of enquiry are worthwhile. Firstly, the prevalence of Helicobacter pylori infection in the general population should be investigated for possible racial differences which may explain the differences in ulcer frequency. Secondly, the influence of diet could be studied in greater detail. Chilli, for example, is consumed in greater amounts by the Malays and Indians when compared to the Chinese. Recently, capsaicin, the active ingredient of chilli, has been shown to have a protective effect on the gastric mucosa. It is therefore possible that the lower prevalence of ulcer disease in the Malays could be due to the protective effect of chilli.

ACKNOWLEDGEMENT

This review is dedicated to the late Professor Seah Chiang Sian.

REFERENCES

20. Shibahara YK, Dyer PO, Campbellbوج g pharloglycosidic g quarters: the past, the present and the perspectives of the future. Am J Gastroenterol 1987; 82: 283-6.