The epidemiology of stomach cancer in Oman

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ABSTRACT

Background

Stomach cancer is the fourth most common cancer in the world, but the second most frequent cause of cancer deaths. In Oman, stomach cancer is the most common cancer among males and existing data suggest that the age-standardised incidence rate of stomach cancer in Oman for both sexes is higher than the rates in many neighbouring Arab and Gulf Cooperation Council (GCC) countries. Possible reasons for this have not been explored. Population-based cancer research has only recently become possible in Oman, with the introduction of mandatory cancer registration and the establishment of a national death registration system (The Directorate General of Civil Status, DGCS).

Aims

The main aims of the research described in this thesis were:

- To describe the incidence of stomach cancer in Oman and to compare it to the incidence in surrounding GCC countries.
- To compare the prevalences of known risk factors for stomach cancer in Oman and other GCC countries.
- To provide population-based estimates of mortality, and median and relative survival of stomach cancer patients in Oman.
- To assess the feasibility of routinely undertaking linkage between the NCR and DGCS to monitor cancer survival.

Methods

Incidence data in Oman and the GCC countries were obtained from NCR and the Gulf Centre for Cancer Registration reports. The health literature and key websites were searched for information about the prevalence of risk factors in the GCC countries. To identify deaths, NCR records were linked with the DGCS and a parallel mortality database (PMD).
Results

The incidence of stomach cancer in Oman differed by sex, age and region, and showed a decline over time. The age-standardised incidence rate in Oman was higher than in most of the GCC countries, with some variation by age and sex. However, bias from incomplete registration was possible.

Smoking, BMI and fruit and vegetable intake were unlikely to explain the apparent between-country differences in stomach cancer incidence, but the lower socioeconomic status in Oman might contribute. Information regarding the prevalence of \textit{H. pylori} infection and salt intake was lacking.

Because a unique identifier was missing from most NCR records, name, sex, address, and year of birth were used to search for death records in the DGCS and PMD. Matches were classified either as definite or possible. For definite matches, the median survival for males and females combined was 30 months (95% CI 16.3–--) and the one- and three-year relative survival rates were 0.70 (95% CI 0.62–0.78) and 0.58 (95% CI 0.49–0.67) respectively. When possible matches were included, the corresponding results were 14.7 months (95% CI 9.9–23.9), 0.60 (95% CI 0.52–0.68) and 0.44 (95% CI 0.36–0.53). There was evidence of incomplete death registration in both the DGCS and PMD. Mortality rates could not be estimated because of missing cause-of-death data.

Conclusions

The unavailability of comparable data on the prevalence of risk factors hinders the ability to identify possible reasons for the apparently higher risk of stomach cancer in Oman. Survival of stomach cancer patients in Oman seems to be poor. To better characterise the problem, the NCR and DGCS should continue improving the quality and completeness of their data, and ongoing monitoring of the burden of the disease seems desirable.
ACKNOWLEDGEMENTS

I wish to thank my wonderful supervisors, Dr Lianne Parkin and Dr Katrina Sharples from the Department of Preventive and Social Medicine, for their invaluable support throughout the whole period of the thesis. Supervising a project based on a country about which they have little background was not an easy task. Dr Lianne Parkin was very kind to visit me in Oman which greatly helped in putting the project in context.

I would also like to thank the staff at the Department of Preventive and Social Medicine for making me feel welcome and helping me in the technical issues. I am very grateful to Dr Mary Jane Sneyd for her help in calculating the relative survival rates.

I am extremely thankful to many people in Oman who made my project successful: the Scholarships committee at the Ministry of Higher Education in Oman for approving the project; Dr Jawad Al-Lawati and Mr Nabil Al-Siyabi from the Omani National Cancer Registry for providing and helping me with the cancer statistics; Mr Salah Al-Muzahmi from the Department of Health Information Services at the Ministry of Health for linking the cancer records with the Parallel Mortality Database; Mr Moheydin Al-Busaidi, Mr Saad Al-Hajri, Miss Wafa Al-Hilali, Miss Maimuna Al-Ismaili, and Miss Arwa Al-Kalbani from the Directorate General of Civil status (DGCS) for their work in linking cancer records to the DGCS database.

Lastly, I would like to thank all my family for their support while in Oman. This thesis is for you and for a better Oman.
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DCO</td>
<td>Death certificate only</td>
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<tr>
<td>DGCS</td>
<td>Directorate General of Civil Status</td>
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<tr>
<td>GCC</td>
<td>Gulf Cooperation Council</td>
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<tr>
<td>GCCR</td>
<td>Gulf Centre for Cancer Registration</td>
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<tr>
<td>GORD</td>
<td>Gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NCR</td>
<td>National Cancer Registry</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PMD</td>
<td>Parallel Mortality Database</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardised morbidity ratio</td>
</tr>
<tr>
<td>UAE</td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
</tr>
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<td>WHO</td>
<td>World Health Organization</td>
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1. CHAPTER ONE – INTRODUCTION AND LITERATURE REVIEW

1.1. Introduction

About eight decades ago stomach cancer was the most common cancer, at least in Europe and the United States (Crew and Neugut, 2006). However, over the past 80 years, a clear decline in incidence has been noted in many parts of the world (Ferlay et al. 2004) without the institution of any preventive policies (Howson et al. 1986). Now, stomach cancer is the fourth most common cancer worldwide, but due to its poor prognosis, it is the second most common cause of cancer deaths worldwide. Both incidence and mortality of stomach cancer show substantial variation globally (Ferlay et al. 2004).

In Oman in 2006, stomach cancer was the most common cancer in men and the fourth most common cancer in women (Mohammad et al. 2008), and the incidence has shown no apparent decline over the last decade. With improved longevity in Oman (Al-Lawati et al. 2008), the absolute burden of stomach cancer may become even greater in the future.

At the time the present study was initiated, the existing data suggested that Oman had a higher incidence of stomach cancer than the surrounding Gulf Cooperation Council (GCC)1 countries (Mohammad et al. 2008), despite the similar culture and lifestyle. However, these comparisons were based on data which were collected before several of the GCC countries had introduced mandatory notification of cancer diagnoses, nor had there been any comparative evaluation of the quality and completeness of the cancer registration practices in the GCC countries. Hence, while the differences in rates could be real, they might also be an artefact of incomplete reporting. As yet, the possible explanations for these differences have not been explored.

Mortality figures are important when it comes to understanding the burden of diseases and improving health care standards. While mortality data are available in Oman, these figures are based solely on people who died in hospitals. Since many people die at home, rates based on inpatients will inevitably underestimate the true mortality. Similarly,

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1 Includes Oman, Saudi Arabia, UAE, Qatar, Bahrain and Kuwait.
the only data available about the median and five-year survival of people with stomach cancer come from a hospital-based study (Al-Moundhri et al. 2006). In 2004, a vital registration system, the Directorate General of Civil Status (DGCS), was established where population-based deaths are recorded. Despite the establishment of the DGCS, no data on population-based mortality or survival from stomach cancer were available when this project was commenced.

This thesis aims to examine three epidemiological aspects of stomach cancer in Oman, namely, incidence, risk factors and survival. These three aspects are explored using three small studies. Each study is presented in a separate chapter.

1.2. **Overview of the thesis**

The organization of the chapters is as follows.

- Chapter one provides an overview of the thesis and a literature review regarding the clinical features, pathology, descriptive epidemiology, risk factors and prevention of stomach cancer.
- Chapter two explores the incidence of stomach cancer in Oman and compares that to the GCC countries, with some focus on the quality and completeness of cancer registration practices in the GCC countries.
- Chapter three investigates the prevalence of known risk factors for stomach cancer in the GCC countries in order to explore whether certain risk factors might explain the differences in the incidence of stomach cancer between Oman and the other GCC countries.
- After describing mortality registration in Oman, chapter four presents a study on finding the median and relative survival of stomach cancer patients in Oman using record linkage between the National Cancer Registry (NCR) and the mortality databases. The feasibility of routinely linking the NCR records to the records in the mortality databases to obtain survival data is also discussed.
- Finally, in chapter five, the main findings, limitations and strengths of this project are summarised. Also implications of the findings are discussed.
1.3. **Search strategy for the literature review**

A search strategy to review a topic is important because a systematic approach reduces the possibility of missing any pertinent papers. It also helps in replicating the work done. For my literature review on the epidemiology of stomach cancer I have pursued the following sequential search strategy.

**Review articles:** Reading a few review articles on the topic at the start gave me a sense of what my literature review would include. It also served as a good starting point for listing relevant keywords on the topic.

**References and keywords:** Important references from the review articles were sought to learn more about the topic and to refine and identify other keywords. This included articles, books, and databases (for example, of the World Health Organization and International Agency for Research on Cancer). The initial list of keywords included: “epidemiology”, “stomach”, “gastric”, “cancer”, “incidence”, “mortality”, “survival”, “survival analysis”, “geographical variation”, “time trends”, “ethnicity”, “aetiology”, “cause”, “risk factors”, “nutrition”, “Helicobacter pylori”, “Body Mass Index”, “smoking”, “socioeconomic status”, “pathology”, “pathogenesis”, “histology”, “histopathology”, “treatment”, “therapy”, “clinical features”, “signs”, “symptoms”, “prevention”, and “screening”. Each heading in the thesis was searched using the initial list of keywords and repeated if new terms were found and added to the list.

**Limits:** Limits were set to have a precise search. Some of the important limits were:

- Since adenocarcinoma accounts for more than 95% of all stomach cancer (Rubin et al. 2005), it should be the histological subtype focus.
- There should be *brief* sections on pathology/pathogenesis, treatment and clinical features.
- Detailed molecular genetics would be beyond the scope of the thesis.
- Due to the huge amount of information on diet and stomach cancer, the report “Food, Nutrition, Physical Activity and the Prevention of Cancer” (World Cancer Research Fund, 2007) would be used to assess the relationship between stomach cancer and relevant foods.

**Search/Read/Write:** Searching was performed using Ovid via the Medline database.
Reading started with the most recent review articles, and then sought out the important referenced sources either from the review article or the articles referenced. Finally, relevant articles that were captured by the Medline database search but had not been identified through the readings were reviewed. Four important sources that were invaluable to my literature review other than journal articles were the CANCERMondial database (http://www-dep.iarc.fr/), the World Health Organization Statistical Information System database (http://www.who.int/whosis/en/), the International Agency for Research on Cancer (IARC) monographs on the evaluation of carcinogenic risks to humans, and the report “Food, Nutrition, Physical Activity and the Prevention of Cancer” (World Cancer Research Fund, 2007). Concurrently, all applicable information to the literature review or to later chapters was noted in Microsoft Office OneNote program. Subsequently, notes gathered in the latter were refined and organized for write-up.

1.4. Cancer burden

The burden of cancer worldwide is substantial. In 2002, excluding non-melanoma skin cancers, it is estimated that there were 10.9 million new cases and 6.7 million deaths from cancer (Ferlay et al. 2004). Between 1990 and 2000, statistics showed a worrying trend. There was approximately a 20% increase in both crude incidence and mortality from cancer worldwide (Stewart and Kleihues, 2003), a phenomenon which might arise partly from aging populations.

The incidence of cancer by site varies by sex and nation. Worldwide, lung and prostate are the most frequent cancers among males. Among females, breast and cervical cancer are the most common (Parkin et al. 2005a). When comparing more-developed to less-developed countries (Figure 1), breast cancer has the highest incidence in both more- and less-developed countries for females. Among males, prostate cancer comes first for more-developed countries and lung cancer for less-developed ones, although the incidence of lung cancer in more-developed countries is only marginally lower than the incidence of prostate cancer. An important point to mention here is that developing countries may be more susceptible to cancers considered to be caused mainly by infectious agents (cervical, liver and stomach cancer). Hence one would anticipate the occurrence of such cancers being higher in developing countries than developed ones. Indeed, the incidences of cervical cancer and liver cancer but not stomach cancer seem to be higher in less-developed countries than in developed countries. However, to explain the differences one
needs to consider variations in the completeness of the cancer incidence data and prevention programs (for example, hepatitis B vaccination, cervical screening).

Figure 1: Estimated age-standardised annual incidence (per 100,000) of cancer by site in both more- and less-developed countries*, 2002
Note: Data obtained from Ferlay et al. (2004)
*Less-developed: Average rates of nations excluding more-developed
More-developed: Average rates of New Zealand, Australia, Japan, Europe and North America

There are differences in survival from cancer between more- and less-developed countries. The differences observed depend on the cancer type. Although crude incidence rates from all types of cancer are generally higher in more-developed countries, the incidence rates of cancers with less favourable prognosis (liver and oesophagus) are higher in less-developed countries (Figure 1). The latter, together with the relatively lower standards of cancer clinical management, make survival rates worse than in more-
developed countries (Parkin et al. 2005a). Similarly, despite the fact that the worldwide male-to-female age-standardised incidence rate ratio from all cancers (except non-melanoma skin cancer) is 1.3, the corresponding age-standardised mortality rate ratio from all cancers (except non-melanoma skin cancer) is even higher at 1.5. The higher mortality rate ratio is due to the higher incidence among males of cancers with poor prognosis (lung, stomach, liver and oesophagus), an observation which applies in both more- and less-developed countries.

Focusing on the main topic of this thesis, stomach cancer is a major problem globally with about 933,000 new cases per annum estimated worldwide (Ferlay et al. 2004). Although stomach cancer is the third most common cancer among males, it is only the fourth most common cancer when both sexes are combined, but the burden of stomach cancer is augmented by its poor prognosis: it is the second most common cause of cancer deaths in the world.

1.5. **Pathology of stomach cancer**

1.5.1. *Classification by histology and anatomic site*

The histopathology of stomach cancer is pertinent for understanding its epidemiology and possible aetiology. The most common type of stomach cancer is adenocarcinoma which is responsible for more than 95% of cases (Rubin et al. 2005). However, regarding stomach adenocarcinoma as one entity is considered misleading as two main types have been recognised which exhibit different histopathological, clinical and epidemiological features (Vauhkonen et al. 2006). The two histological types of stomach adenocarcinoma, *diffuse* and *intestinal*, were first identified by Lauren (Lauren, 1965). The two types are morphologically different and distinguishable under the microscope. The intestinal type is well differentiated, but the diffuse type is poorly differentiated. The World Health Organization has also developed a classification of gastrointestinal tumours which is becoming increasingly popular (Hamilton and Aaltonen, 2000), but this is still not widely used when exploring the descriptive epidemiology and aetiology of stomach cancer.

Tumours of the stomach are often classified as *proximal* (cardia) or *distal* (non-cardia) according to their anatomical site. The epidemiology of the two sub-sites suggests that they are two distinct diseases with different aetiologies (Crew and Neugut, 2006). What is important to understand is that the two anatomical sites can have any histology
type. Histology and site classifications are both important in exploring aetiology, although site has the most impact on clinical management and outcome.

As the differences between the tumours classified by histology and site emerge through studying their epidemiology, aetiology and clinical features later in the literature review, a more comprehensive picture starts to take shape. The main differences are summarised in Tables 1 and 2.

**Table 1**: The differences between non-cardia and cardia stomach cancer

<table>
<thead>
<tr>
<th></th>
<th>Non-cardia stomach cancer</th>
<th>Cardia stomach cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socioeconomic status (SES)</strong></td>
<td>More frequent among lower SES groups</td>
<td>More frequent among higher SES groups</td>
</tr>
<tr>
<td><strong>Geography</strong></td>
<td>More common in high incidence areas</td>
<td>More common in lower incidence areas</td>
</tr>
<tr>
<td><strong>Male: Female ratio</strong></td>
<td>2: 1</td>
<td>3–7: 1</td>
</tr>
<tr>
<td><strong>Trend in incidence over time</strong></td>
<td>Decreasing</td>
<td>Increasing</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Better</td>
<td>Worse</td>
</tr>
</tbody>
</table>

References:
1(Terry et al. 2002, Wu et al. 2007); 2(Curado et al. 2007); 3(Schouten and Kiemeney, 1997); 4(Crew and Neugut, 2006); 5(Doglietto et al. 2000)

**Table 2**: The differences between intestinal and diffuse stomach cancer

<table>
<thead>
<tr>
<th></th>
<th>Intestinal type</th>
<th>Diffuse type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Well-differentiated; resembles colonic adenocarcinoma with glands</td>
<td>Poorly differentiated; resembles gastric mucous cells with no glands</td>
</tr>
<tr>
<td><strong>Precursor lesions</strong></td>
<td>Develops in parallel to precursor lesions (e.g. atrophy and dysplasia)</td>
<td>Develops spontaneously (i.e. metaplasia not prerequisite)</td>
</tr>
<tr>
<td><strong>Mean age of diagnosis (years)</strong></td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td><strong>Male: Female ratio</strong></td>
<td>2: 1</td>
<td>1: 1</td>
</tr>
<tr>
<td><strong>Trend in incidence over time</strong></td>
<td>Decreasing</td>
<td>Increasing</td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td>Higher Environmental: Genetic ratio</td>
<td>Lower Environmental: Genetic ratio</td>
</tr>
</tbody>
</table>

References:
1(Kumar et al. 2005); 2(Kaneko and Yoshimura, 2001, Henson et al. 2004); 3(Yamaguchi and Kakizoe, 2001)
1.5.2. *Potential histopathological misclassifications and implications for studying the epidemiology of stomach cancer*

Since cancer is primarily diagnosed by histopathology, a consensus about diagnostic criteria is important when making inter-country comparisons or examining time trends, both in terms of whether a specimen is cancerous and, if so, which type. However, it appears that such consensus has been lacking. For example, in diagnosing whether a particular specimen is cancer or not, Schlemper et al. (1997) assessed the criteria used by Western and Japanese pathologists in diagnosing carcinoma of the stomach. Four pathologists from different Western countries (USA, Canada, Finland and Germany) and another four from Japan were asked to evaluate a series of biopsies and endoscopically resected specimens of the stomach mucosa. All specimens were of the intestinal type (because of the absence of precursor lesions\(^1\), the diagnosis of diffuse stomach cancer was not contentious). Results demonstrated interesting differences. Whereas invasion was regarded as highly demonstrative of cancer from the Western pathologists’ point of view, the Japanese based their conclusions of cancer on nuclear features and glandular structures. Thus, many of the specimens diagnosed as benign adenoma or dysplasia (which may become invasive) by the Western pathologists were diagnosed as carcinoma by the Japanese pathologists. This could well be one explanation for the high incidence of stomach cancer (especially early stage stomach cancer) and the high survival rates in Japan (see Figure 4). In the year 2000, the Vienna classification of gastrointestinal epithelial neoplasia (Schlemper et al. 2000) was released in an attempt to ensure consistency in diagnostic criteria. However, the impact of the new classification system on the diagnosis of stomach cancer in Japan is still uncertain (de Vries and Kuipers, 2007).

A second histological misclassification can occur when assigning Lauren’s histology types (intestinal or diffuse). For example, Palli et al. (1991) examined the concordance between six pathologists from different departments (all Italians) of 100 stomach cancer specimens. The agreement between any two pathologists on Lauren’s histology type ranged from 68–83% (median kappa coefficient=0.48). A similar percentage of agreement (77%; kappa coefficient=0.59) was found when two pathologists

\(^1\) See Table 2.
examined 95 specimens in the USA (Shibata et al. 2001). To my knowledge subjectivity still persists in diagnosing Lauren’s two histology types.

Finally, the distinction between cardia cancers and those originating from the gastro-oesophageal junction or distal oesophagus is still contentious and definitions vary (Dawsey et al. 2002, Chandrasoma, 2008). According to the International Classification of Diseases for Oncology (Fritz et al. 2000), stomach cancer of the cardia should refer to tumours originating from the stomach cardia and gastro-oesophageal junction. However, in practice it is often difficult to identify the site of origin given the very small area of the stomach cardia (Young and Heath, 2000) and the fact that tumours originating in this region often extend out from their original site (Crane et al. 2008). Moreover, it may be incorrect to group cancers of the stomach cardia and distal oesophagus together since descriptive epidemiological studies show marked variation in the incidence of the two sites, thus arguing for distinct diseases (Corley and Buffler, 2001).

For the present thesis, when studying the clinical, epidemiological and preventive aspects of stomach cancer, other than acknowledging potential issues of misclassification, there is little if anything that can be done about verifying the validity and concordance of histological and sub-site diagnosis. This is because data come from various sources and are all dependent on the pathologist or pathologists involved. These issues of potential misclassification must be borne in mind when making inter-country comparisons.

1.6. Clinical aspects of stomach cancer

1.6.1. Symptoms/signs

The most frequent symptom reported by stomach cancer patients is epigastric pain, which is not dissimilar to the pain caused by peptic ulcer disease (Kumar and Clark, 2005). The pain can be relieved by food and antacids. Other symptoms include dyspepsia, if the tumour is close to the fundus, and vomiting, especially with tumours in the pyloris. These non-specific symptoms often accompany many gastrointestinal diseases and no pattern is suggestive of early stages of stomach cancer (Lochhead and El-Omar, 2008). However, advanced stages often present with loss of weight, loss of appetite, and anaemia.
1.6.2. **Diagnosis**

Stomach cancer is diagnosed by histological examination of biopsies taken during endoscopy (Kumar and Clark, 2005). Often multiple biopsies are taken from the lesion to increase the chance of making a correct diagnosis (Master, 2004).

1.6.3. **Treatment**

The main treatment of stomach cancer is surgery. Early stomach cancer is usually resected endoscopically (Lochhead and El-Omar, 2008). Patients with advanced disease which is still localised undergo partial or total gastrectomy with adjacent lymph node removal (Master, 2004). Usually, total gastrectomy is warranted for upper one third stomach tumours, regardless of histology type, and distal cancers with diffuse histology. Distal cancers of intestinal type usually undergo partial gastrectomy. Whether gastrectomy is partial or total, “curative” resection (a clear margin specimen) is the important prognostic factor (Kim et al. 1998, Siewert et al. 1998).

Whether regional or extended lymphoadenectomy should be undertaken is still debated (Khan and Shukla, 2006), but there appears to be little, if any, survival benefit. After curative resection, a randomised controlled trial (Macdonald et al. 2001) found a statistically significant improvement in median survival (36 months vs. 27 months) with chemoradiation compared with surgery alone. In advanced metastatic disease, chemotherapy gives an extra four to five months on the median survival of three to five months without chemotherapy (Khan and Shukla, 2006).

1.6.4. **Prognosis**

The prognosis of stomach cancer depends on several independent factors.

Firstly, surgery with “curative” intent (clear margins of specimen) has a better prognosis than incomplete resection of the primary tumour (Kim et al. 1998, Siewert et al. 1998). Whereas patients undergoing curative resection have about a 50–60% five-year survival rate, patients with incomplete resection of the tumour have about a 10% five-year survival rate.

Secondly, stage is the most important prognostic factor (Rubin et al. 2005). Of all surgically treated gastric cancers, early gastric cancer (confined to the mucosa or submucosa, regardless of lymph node invasion) is estimated to have a 95% ten-year
survival rate. However, even with surgical resection, for late-stage gastric cancer the five-year survival rate is only 20%.

Thirdly, tumours in the upper third of the stomach have a worse prognosis than tumours in the middle and lower thirds for patients who undergo curative resection. In a study testing prognostic factors, the five-year survival rate was only 37% for the upper third, compared to 64% and 57% for the middle and lower thirds respectively (Doglietto et al. 2000). But location was not found to be an independent prognostic factor for advanced stomach cancer patients undergoing palliative therapy only.

Finally, in a large Korean retrospective case-control study which included more than 10,000 stomach cancer patients treated surgically, young patients (less than 40 years old), females, and people with intestinal stomach cancer were found to have a better prognosis than, respectively, older patients (more than 40 years old), males, and people with diffuse type stomach cancer (Kim et al. 1998). However, when included in a multivariate analysis for independent prognostic factors (such as age, sex, site, stage, histology and treatment), sex, age, and histological type differences did not show statistically significant results.

1.7. Descriptive epidemiology of stomach cancer

1.7.1. By person

When studying the epidemiology of stomach cancer, it is important to consider personal factors such as age, sex and ethnicity. As with many other cancers, stomach cancer incidence increases with age. The median age of stomach cancer diagnosis is estimated to be about 71 years in the United States (Rebecca et al. 1995). Stomach cancer occurring in people aged 45 years and younger is often called early onset gastric cancer (Milne et al. 2007). It is estimated that less than 10% of all stomach cancer occurs in this age group. Histopathologically, young patients (less than 40 years) are more likely to be diagnosed with diffuse type stomach cancer than older patients (40 years and above) (Katai et al. 1996, Kulig et al. 2008). However, no difference is found between the two age groups in terms of stomach cancer site.

Stomach cancer exhibits some sex differences. The incidence rate in males is twice that of females (Ferlay et al. 2004), although the male-to-female ratio (M:F) is closer to one among young patients (less than 40 years) than the old (40 years and above) (Kaneko

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1 Includes cardia and some non-cardia (for example, the fundus) regions.
and Yoshimura, 2001, Katai et al. 1996, Kulig et al. 2008). The M:F also differs according to site. For adenocarcinoma of the stomach cardia, the estimated M:F is between three and seven, and tends towards the higher end of the range in younger age groups (Schouten and Kiemeney, 1997). In contrast, the M:F is about two for non-cardia stomach cancer. In terms of Lauren’s histological types, only the intestinal type shows a difference by sex. The M:F for the intestinal type is about two. The observed differences between the sexes are thought to be due mainly to the variation in the degree of exposure to causative factors1 rather than any sex-based differences in susceptibility (Stewart and Kleihues, 2003).

The epidemiology of stomach cancer demonstrates interesting within-country ethnic differences. For example, the age-adjusted total stomach cancer incidence rates are higher among minority groups in the USA (African, Asian, Indian and Hispanic Americans) than Whites, an observation which holds for both sexes (Jemal et al. 2008). But African and Hispanic Americans have lower incidence rates of cardia stomach cancer than Whites in the USA (Wu et al. 2007). This observation is more evident in males than in females (Yao et al. 2002). However, the incidence of non-cardia stomach cancer is much higher in minority groups than Whites, resulting in the higher total stomach cancer incidence. Similarly, African Americans have a higher incidence of intestinal type stomach cancer than Whites (Henson et al. 2004). Elsewhere, a case-control study in Malaysia found Chinese ethnicity compared to Malay was an independent risk factor for stomach cancer (Goh et al. 2007). The result was obtained from multivariate analysis adjusted for level of education, fruit and vegetable intake, salted food intake and \textit{H. pylori} seropositivity. Although, the result was statistically significant, the 95% CI was wide (OR 10 [95% CI 3–36]). Maori in New Zealand are also at higher risk of developing stomach cancer than non-Maori. Compared with cancers at other sites, stomach cancer in New Zealand shows one of the highest ethnic inequalities: the Maori incidence rate is triple that of non-Maori (New Zealand Health Information Service, 2002). In short, biological differences reflected by racial differences may play a role in the development of stomach cancer.

Personal characteristics seem to play a minor role in terms of survival from stomach cancer. Whereas the differences seen with age and sex may be important in exploring aetiology and host exposure to causative factors, age and sex alone do not appear to affect survival from stomach cancer (Park et al. 2009). Likewise, Jemal et al. (2008)

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1 Causative factors are discussed in more detail beginning on p.24.
reported that the five-year relative survival rates were not dissimilar, for a particular stage at diagnosis, among African Americans, White Americans and all ethnicities (grouped together) in the USA. However, a case-control study in the USA found that Asians living in the USA are more likely to be diagnosed with localised disease and non-cardia stomach cancer than other racial groups (grouped as non-Asians) and hence have a higher five-year survival rate (Theuer et al. 2000). The authors excluded any differences in diagnostic criteria and treatment that might have affected the given survival outcome. The authors attributed the findings to biological differences, rather than the early seeking of medical attention or diagnostic tools, as minority groups in the USA generally have poorer access to health care.

1.7.2. By place

The incidence of stomach cancer shows wide geographic variation. It is highest in Western South America, Eastern Europe and Russia, and Asia (Figure 2). Within these regions, the incidence is quite similar in neighbouring countries, although countries within the African continent show a wide variation in the incidence of the disease. This could be attributed to the incomplete registration of cancer in Africa (Parkin et al. 2003) or, more speculatively, to differences in susceptibility to causative factors.

Figure 2: Age-standardised annual incidence rate (per 100,000) for females (right) and males (left) worldwide, 2002
Note: Figure adopted from Ferlay et al. (2004)
Figure 3 shows the age-standardised incidence for males and females in a number of selected cancer registry populations. Korea has the highest stomach cancer incidence (66 and 26 per 100,000 per annum for males and females respectively) followed by Japan (51 and 20 per 100,000 per annum for males and females respectively). Other than Japan, more-developed countries like New Zealand, Australia (Queensland) and Canada have a generally lower incidence (less than 10 per 100,000). Others like Oman and Singapore have rates somewhat in-between. As the figures demonstrate, stomach cancer is an important issue in Asia. It is the most common cancer in Japan and the second most common in China and Korea. It is also one of the top five cancers in terms of frequency in Singapore, the Philippines and Taiwan (Leung et al. 2008). China accounts for about 40% of the cases worldwide, because of its large population (Ferlay et al. 2004), although the crude and age-standardised incidence rates are comparable to other Asian countries.

Epidemiological studies have identified interesting information on which histological type or sub-site could account for the majority of the geographical variation. There is a suggestion that the observed international variation in incidence is mostly due to the differing incidence of the intestinal histological type rather than the diffuse type (Parkin, 2004, Crew and Neugut, 2006, Lochhead and El-Omar, 2008). If this is truly the case, then one might expect the incidence of the diffuse type to be similar in both high and
low incidence areas and conversely, the incidence of intestinal type to be much higher in high incidence areas than in low incidence areas. Unfortunately stomach cancer incidence rates for various countries stratified by histological type and age-standardised to the same population are lacking in the literature. This merits further research.

Most stomach malignancies are of non-cardia type in the majority of countries. Countries with a high stomach cancer incidence rate generally tend to have a lower percentage of stomach cardia cancer (Table 3). In contrast, in areas like Canada, USA, and the UK where stomach cancer incidence rates are lower, the percentage of cardia stomach cancer is greater. Nevertheless, the age-standardised incidence rate for cardia stomach cancer does not differ greatly between the high incidence and the low incidence areas. Therefore, most of the disparity in percentage seems to result from the higher frequency of non-cardia stomach cancer in countries with a high incidence of total stomach cancer compared to countries with a low incidence. This disparity in the incidence of non-cardia stomach cancer certainly affects the overall survival from total stomach cancer (Hundahl et al. 2000).

Table 3: Age-standardised average annual incidence rates (per 100,000) and percentage of site-specific gastric cancer for selected countries, 1998-2002

<table>
<thead>
<tr>
<th>Country/Locality</th>
<th>Cardia ASR (%)</th>
<th>Fundus ASR (%)</th>
<th>Body ASR (%)</th>
<th>Pyloric ASR (%)</th>
<th>Lesser Curve ASR (%)</th>
<th>Greater Curve ASR (%)</th>
<th>Other* ASR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada (Ontario)</td>
<td>2.6 (31.8)</td>
<td>0.3 (3.6)</td>
<td>0.5 (6.6)</td>
<td>1.3 (16.7)</td>
<td>0.2 (3.0)</td>
<td>0.6 (7.8)</td>
<td>0.2 (3.0)</td>
</tr>
<tr>
<td>Japan (Osaka Prefecture)</td>
<td>2.0 (3.8)</td>
<td>0.1 (0.3)</td>
<td>6.3 (12.1)</td>
<td>4.4 (8.5)</td>
<td>0.4 (0.7)</td>
<td>0.3 (0.5)</td>
<td>0.2 (0.3)</td>
</tr>
<tr>
<td>Australia (Queensland)</td>
<td>0.5 (14.9)</td>
<td>0.1 (1.0)</td>
<td>0.2 (4.6)</td>
<td>0.4 (11.3)</td>
<td>0.2 (5.7)</td>
<td>0.4 (11.3)</td>
<td>0.2 (5.7)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>0.7 (16.4)</td>
<td>0.1 (2.8)</td>
<td>0.5 (10.4)</td>
<td>0.5 (12.9)</td>
<td>0.2 (5.1)</td>
<td>0.5 (10.4)</td>
<td>0.3 (5.8)</td>
</tr>
<tr>
<td>Brazil (Brasilia)</td>
<td>0.8 (3.0)</td>
<td>0.2 (0.7)</td>
<td>0.6 (1.9)</td>
<td>1.6 (5.7)</td>
<td>0.3 (1.0)</td>
<td>0.1 (0.5)</td>
<td>0.0 (0.2)</td>
</tr>
<tr>
<td>Egypt (Gharbiah)</td>
<td>0.6 (17.7)</td>
<td>0.1 (1.4)</td>
<td>0.1 (4.8)</td>
<td>0.3 (11.6)</td>
<td>0.2 (6.1)</td>
<td>0.1 (4.8)</td>
<td>0.1 (3.4)</td>
</tr>
<tr>
<td>UK (Oxford region)</td>
<td>0.5 (13.7)</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.8)</td>
<td>0.3 (7.5)</td>
<td>0.1 (2.6)</td>
<td>0.2 (4.2)</td>
<td>0.1 (1.8)</td>
</tr>
<tr>
<td>USA (14 Registries): Non-Hispanic White</td>
<td>2.7 (43.3)</td>
<td>0.3 (4.6)</td>
<td>0.3 (6.1)</td>
<td>0.7 (12.3)</td>
<td>0.1 (2.0)</td>
<td>0.4 (6.4)</td>
<td>0.2 (3.7)</td>
</tr>
<tr>
<td>Korea</td>
<td>2.5 (3.7)</td>
<td>0.5 (0.7)</td>
<td>13.0 (20.3)</td>
<td>21.1 (32.3)</td>
<td>0.9 (1.4)</td>
<td>1.8 (2.7)</td>
<td>0.2 (0.3)</td>
</tr>
<tr>
<td>France (Bas-Rhin)</td>
<td>3.3 (30.5)</td>
<td>0.4 (3.9)</td>
<td>0.1 (0.8)</td>
<td>1.2 (11.3)</td>
<td>0.1 (0.5)</td>
<td>0.8 (7.9)</td>
<td>0.4 (3.7)</td>
</tr>
<tr>
<td>Oman†</td>
<td>0.4 (3.2)</td>
<td>-</td>
<td>0.1 (0.9)</td>
<td>0.6 (4.1)</td>
<td>0.1 (0.9)</td>
<td>0.1 (0.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Refers to overlapping lesions and those which are not specified
† Denotes limitation in interpreting data (for further information refer to the reference)
Note: Data obtained from Curado et al. (2007)
Note: Fundus, body, pyloric, lesser curve and greater curve collectively make up non-cardia stomach cancer.
Overall, the prognosis for stomach cancer is poor. The mortality-to-incidence ratio can be as high as 0.8 to 0.9 in Europe, America, Australia and the less-developed countries (Pisani et al. 1999). However, in places like Japan the mortality rate is less than half of the incidence rate and the estimated age-adjusted five-year survival exceeds 50% (Figure 4). The lower mortality rates and better survival in Japan are thought to be partly attributable to stomach cancer screening (Lee et al. 2006). Although, this preventive measure is theoretically radical, its success is still debated (Suzuki et al. 2006). In Japan, stomach cancer surgical resections have demonstrated a consistent trend towards early stage over the past four decades. In 1995, early gastric/stomach cancer patients comprised 59% of the total patients who underwent surgery for stomach cancer (Maehara et al. 2000). But in places like the UK and USA, early gastric cancer accounts for only about 10–20% of total resected stomach cancer (Everett and Axon, 1997). Because of the excellent prognosis for early gastric cancer, and probably the lower percentage of cardia stomach cancer, survival is higher in Japan than in the other nations.

Figure 4: Estimated age-adjusted five-year survival (%) for stomach cancer for males and females in different regions
Note: Data obtained from Parkin et al. (2005a)
*More developed: Average rates of New Zealand, Australia, Japan, Europe and North America
†Less Developed: Average rates of nations excluding more-developed

1 Screening is discussed in more detail on p.54.
1.7.3. **By time**

The burden of stomach cancer has been decreasing in the past several decades. Incidence rates have shown a steadily declining trend (Figure 5). Mortality from stomach cancer has also decreased correspondingly (Figure 6). Although the figures show the trend for males, the trend for females is similar. The findings of a study by Lambert et al. (2002), comparing trends in the USA, Slovenia and Japan, showed a decline in risk of stomach cancer in successive birth cohorts born in Japan after 1900. The relative risk in reference to 1914 has shown a decreasing trend; similarly for mortality. By contrast, in the USA and Slovenia, the decrease in stomach cancer was more of a period-specific effect (“secular change in risk”) than a cohort effect. The findings reflect the importance of current and childhood factors in the development of stomach cancer.

**Figure 5**: Trend in age-standardised annual incidence rate (per 100,000) of stomach cancer for males of selected cancer registry populations

Note: Figure adopted from Parkin et al. (2005b)
Most of the decrease in the incidence of stomach cancer has been observed in non-cardia stomach cancer anatomically, and intestinal type histologically. In Japan, while there was a large decrease in the intestinal type, the diffuse type has remained stable over the past four decades (Kaneko and Yoshimura, 2001). Similarly, Henson et al. (2004) showed a declining trend in the incidence of intestinal type stomach cancer in the USA. Although the authors also reported a small increase in the diffuse type in the USA, the magnitude of decrease in the intestinal type (age-standardised incidence rate dropped from 11 to 5 per 100,000 over 27 years) was much larger than the increase in the diffuse type (age-standardised incidence rate increased from close to 0 to 2 per 100,000 over 27 years). Ekstrom et al. (2000) found that the majority of the decrease in the intestinal type in Sweden was confined to the non-cardia region. Stomach cancer in this region also showed a declining trend, but this was attributable to decreases in both histological types. However, stomach cancer of the cardia showed an increase in Japan (Liu et al. 2004), and a more marked increase in the USA (Pohl and Welch, 2005), European countries (Botterweck et al. 2000) and among non-Maori in New Zealand (Armstrong and Borman, 1996). As one might anticipate from the previous points, there was a tendency for the diffuse histological type to account for the increase in cardia stomach cancer (Miyahara et

Figure 6: Trend in age-standardised annual mortality rates (per 100,000) of stomach cancer for males of selected populations
Note: Figure adopted from Ferlay (2008)
al. 2007). Miyahara et al. (2007) predict that Japan will follow the USA and European countries in a more marked increasing incidence of cancer at this site.

Lastly, Forman and Burley (2006) anticipate that while a decrease in cancer registrations and deaths will be observed in the next several decades among the more-developed countries, there will be a higher, non-balancing, increase in both new cases and deaths among less-developed ones. Consequently, the global burden of stomach cancer will likely show a rise. Forman and Burley attribute this trend to the increase in the world’s population and improved longevity.

1.8. Seeking causes

Simply listing risk factors gives an inadequate sense of the overall process by which a disease develops (McDowell, 2008). For instance, upstream causes of the risk factors may not be considered. Conversely, downstream factors, such as host factors and pathology are missed. Although the bacterium *Helicobacter pylori* plays almost a necessary causal role in the development of non-cardia stomach cancer, animal studies show that stomach cancer can develop in the absence of the infection.¹ Hence, it may be misleading to categorise stomach cancer as an infectious disease. Accordingly, using the approach of host, agent and environment to elucidate possible causes is not appropriate. Therefore, after reviewing the importance of environmental factors compared to genetic factors, through migrant studies, I have categorised the causes into environmental and genetic/host factors. Before reviewing environmental risk factors, I briefly discuss the health determinants/environmental forces (upstream causes; causal role of risk factors). The fine pathology (downstream) will be discussed on p.38.

1.8.1. Migrant studies

Migrant studies are often good indicators of the relative importance of the environment or genetics in the development of a disease. Migrant studies show that the risk of stomach cancer alters to approach the risk of the hosting country. For example, Swerdlow et.al (1995) compared the incidence of stomach cancer in non-Maori who were born in New Zealand with the incidence in English and Welsh born in England and Wales respectively. Their findings showed that New Zealanders born in New Zealand had a lower risk of stomach cancer than the English and Welsh despite many New Zealanders having

¹ See the section on *H. pylori*, p. 22
English or Welsh ancestry. Likewise, a study showed that Japanese migrants in the USA had a lower incidence of stomach cancer than Japanese living in Japan (Kamineni et al. 1999). The incidence decreased gradually over generations. The second generation (born in USA) had a lower incidence of stomach cancer than the first generation (born in Japan), though still higher than the USA-born Whites. The same study found a similar pattern of reduction in incidence of stomach cancer in Chinese migrants.

The reduction of stomach cancer observed in migrant studies has primarily been in the intestinal type (Correa et al. 1973) and non-cardia stomach cancer (Kamineni et al. 1999). Having established that there ought to be an environmental component to the reductions seen, a study examining the factors which might account for the observed reduction in risk among migrants from Japan to Hawaii attributed the fall in risk partly to the decrease in consumption of salted dried fish and pickled vegetables. This in turn, decreased the amount of salt and nitrosamines consumed. Although this association did not show a dose-response relationship (Haenszel et al. 1972), environmental factors seem to play a major role in the development of stomach cancer.

1.8.2. Environmental risk factors

- Health determinants and environmental forces

Although environmental forces include place, politics and climate (McDowell, 2008), information about the effect of such factors on the development of stomach cancer is scarce in the literature. This is not true of another factor of importance for stomach cancer, socioeconomic status (SES). Many studies have assessed the effect of socioeconomic status on stomach cancer. The link is likely to be indirect via risk factors associated with socioeconomic status, such as smoking, diet and H. pylori infection (see following sections). With retrospective or cross-sectional studies one should be cautious about “reverse causation”, that is, a health outcome affecting occupation, income or education. However, because stomach cancer occurs mainly at older ages and has a poor prognosis overall, retrospective studies using educational status and, to a lesser extent, occupation may be reasonable measures of SES as these are present before the diagnosis of stomach cancer.

One interesting study was conducted in Scotland of all registered cancers of the stomach and oesophagus from 1977–1996 (Brewster et al. 2000). It was found that there was a clear association between higher deprivation (which encompassed social class, male
unemployment, overcrowding and car ownership) and the risk of non-cardia stomach cancer and non-adenocarcinoma oesophageal cancer. However, adenocarcinoma of the oesophagus and the stomach cardia exhibited no clear association with socioeconomic status, though stomach cardia adenocarcinoma alone exhibited a weak association, being lower in more deprived areas. A similar measure of deprivation, called the deprivation index, is used in New Zealand. Stomach cancer demonstrates a very clear association with deprivation index: the risk is higher in most deprived areas (New Zealand Health Information Service, 2002). In fact, it exhibits a clear dose-response relation, especially for males. However, deprivation indices are used for areas rather than individuals and hence are prone to the ecological fallacy: that is, what applies to areas may not necessarily apply to individuals with the disease of interest.

Whether socioeconomic status per se is a risk factor for stomach cancer has not been determined. A retrospective case-control study which assessed smoking, drinking, socioeconomic status and stomach and oesophageal cancer showed that college education, compared with less than 12 years of school education, seemed to be protective against non-cardia, but not cardia, stomach cancer (Gammon et al. 1997). However, this study did not examine the effect of risk factors such as *H. pylori* infection or diet which may be associated with socioeconomic status and could explain the underlying link. A nested case-control study from a prospective large cohort study assessed the relationship between socioeconomic status and stomach cancer after adjusting for age, sex, smoking, fruit and vegetable intake, alcohol consumption, body mass index, physical activity and *H. pylori* infection (Nagel et al. 2007). Results showed that people with a university degree were 88% (OR 0.12 [95% CI 0.02–0.85]) and 94% (OR 0.06 [95% CI 0.01–0.63]) less likely to develop cardia or intestinal type stomach cancer respectively than those who had only completed primary school. There was no significant association between education and total stomach cancer, or with non-cardia or diffuse types. Interestingly, removing *H. pylori* infection from the adjustment gave a statistically significant protective result for overall stomach cancer, but not for the non-cardia or diffuse types. The link between socioeconomic status and stomach cancer may be indirect, but *H. pylori* infection seems to be important.

While occupation is an important SES measure, some occupations predispose to carcinogenesis. The International Agency for Research on Cancer (IARC) classified industries manufacturing art glass, glass containers and pressed ware as probably carcinogenic to humans. Suspected sites include stomach and lung cancer. Both Raj et al.
(2003) and Cocco et al. (1996) have reviewed the relationship between occupation and stomach cancer. The reviews acknowledged that many studies’ findings were probably confounded by socioeconomic status, H. pylori infection or dietary factors, but occupations that expose workers to known carcinogens, such as N-nitroso compounds or polycyclic aromatic hydrocarbons, may be associated with a real increased risk of stomach cancer. One such occupation is farming.

Blair et al. (1992) conducted a meta-analysis on the risk of farming to various cancers. The overall result showed that farming was a risk factor for stomach cancer. However, Blair et al. did not define what was included as farming. A more recent meta-analysis that included the studies reviewed by Blair et al. and more recent studies suggested that farming may not be a risk factor (Acquavella et al. 1998). Both meta-analyses, by Blair et al. and Acquavella et al. did not restrict their criteria to a specific type of farming because this was not defined in most studies. This limited the interpretation of the findings. Both the above meta-analyses showed significant heterogeneity, which was not unexpected given the disparity in type of farming, time and geographic area.

- Helicobacter pylori

H. pylori is the most important risk factor for non-cardia stomach cancer and gastric mucosal associated lymphatic tissue (MALT) lymphoma (Moss and Malfertheiner, 2007). In 1994, IARC classified H. pylori as a group 1 carcinogen. This conclusion was reached following substantial evaluation of both human and animal studies. Although the evidence from animal studies was inadequate, sufficient evidence existed from human studies (International Agency for Research on Cancer, 1994). The World Cancer Research Fund (WCRF) regards H. pylori as a necessary cause for non-cardia stomach cancer (World Cancer Research Fund, 2007).

Before establishing the association between H. pylori and stomach cancer, an important point should be noted. Many studies use serology as a test for H. pylori infection. However, the bacterium may spontaneously be lost in the event of atrophic gastritis, metaplasia or stomach cancer, because of their resistant nature to H. pylori colonisation (Karnes et al. 1991) so that antibody titres attenuate. Thus, prospective studies

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1 The agent is carcinogenic to humans.
2 The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.
3 A causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer.
may be more accurate than retrospective ones, as serology testing precedes the development of the disease.

Although the strength of association of *H. pylori* with stomach cancer is relatively small, it is statistically significant. A meta-analysis of case-control studies nested in prospective cohort studies has shown that overall there is about a two-fold increase (OR 2.36 [95% CI 1.98–2.81]) in the risk of developing stomach cancer among individuals infected with *H. pylori* than among those not infected (Helicobacter Cancer Collaborative Group, 2001).

It is estimated that among 100 individuals who are infected by *H. pylori* (see Figure 7 for estimated prevalence of *H. pylori* infection in asymptomatic individuals) and who develop chronic active gastritis, 50 will develop atrophy, and of those 50, 40 will develop metaplasia, and of those 40, 8 will develop dysplasia, but only 1 will eventually develop stomach cancer of the intestinal type.

The risk of cancer from *H. pylori* infection varies for different stomach (and probably oesophageal) sub-sites. *H. pylori* infection increases the risk of non-cardia stomach cancer (Helicobacter Cancer Collaborative Group, 2001). There is also a suggestion that it is inversely associated with oesophageal adenocarcinoma (Islami and Kamangar, 2008). The association is higher for cytotoxin associated gene A (cagA) positive strains of *H. pylori*. Whereas the increase in risk of distal (non-cardia) stomach cancer caused by *H. pylori* infection is well established, the association of *H. pylori* with cardia stomach cancer is still controversial. Kamangar et al. (2006) and Hansen et al. (1999) conducted nested case-control studies, to find the risk of stomach cancer from *H. pylori* infection, in Finland and Norway respectively. *H. pylori* infection was found to be protective against cancer of the stomach cardia (OR 0.3 [95% CI 0.1–0.9] and 0.4 [95% CI 0.2–0.8] respectively). However, two separate nested case-control studies, by Limburg et al. (2001) and Kamangar et al. (2007) in China, showed that *H. pylori* infection increased the risk of cardia stomach cancer (OR 1.9 [95% CI 1.1–3.2] and 1.6 [95% CI 1.3–2.1] respectively).

Some differences between the two European studies and the two Chinese studies exist. Firstly, the European studies relied on their respective cancer registries for diagnosis of stomach cancer and cancer sub-type, whereas the Chinese studies had a more consistent approach to confirming diagnosis using a panel of experts to review the pathologic slides. Secondly, the Chinese studies adjusted ORs only for age and sex whereas the European studies adjusted, at a minimum, for sex, smoking and socioeconomic status. The
differences observed by the four studies could be due to variation in the definition of stomach cardia, or to the different OR adjustments, or to differences in the study populations. As to which studies are more accurate is still unclear. Nyren and Blot (2006) think that in the studies which showed a protective effect, oesophageal adenocarcinoma may have been over-represented, whence the decrease in risk. Integrating the findings, Dawsey et.al (2002) believe that gastro-oesophageal reflux disease (GORD) accounts for most of the oesophageal adenocarcinoma and some stomach cardia cancers. In contrast, most non-cardia, and some cardia, stomach cancers are associated with *H. pylori* infection. The whole conundrum has led some researchers (Hansen et al. 2007, Derakhshan et al. 2008) to hypothesise that stomach cardia adenocarcinoma may be caused by two discrete mechanisms, one associated with *H. pylori* infection and the other with GORD (see section on BMI, p. 32).

The relationship of *H. pylori* infection to the different histology types is still argued. There are suggestions from a meta-analysis of 34 case-control studies and eight cohort studies that *H. pylori* infection is more associated with intestinal type stomach cancer than the diffuse type (Eslick et al. 1999). However, the meta-analysis included many retrospective studies and overall there was much heterogeneity. A meta-analysis of prospective studies showed that the increased risk of stomach cancer associated with *H. pylori* infection is not confined to a specific histology type (Helicobacter Cancer Collaborative Group, 2001). Possibly, *H. pylori* acts as a causal agent in both histological types.

Most of the evidence about the mechanism of *H. pylori* carcinogenesis relates to stomach acid. Acute infection is accompanied by a decrease in acid secretion (hypochlorohydria). A similar picture is seen in the majority (85%) of chronically infected individuals (Schubert and Peura, 2008). The decrease in acid secretion is thought to help the bacterium survive in the stomach environment (Meyer-Rosberg et al. 1996). Thus, the altered acid secretion alters the stomach microflora with an increase in anaerobic bacterial colonisation. These bacteria metabolise nitrates to nitrites, which form a carcinogenic group of compounds called N-nitroso compounds (Stewart and Kleihues, 2003, p.60).

In a review of experimental evidence for *H. pylori* carcinogenesis, the majority of studies showed that *H. pylori* is a promoter rather than an initiator of stomach cancer development (Tsukamoto et al. 2007). The promoting effect of *H. pylori* is further enhanced by salt, the two acting synergistically (Nozaki et al. 2002) in a dose-response manner (Kato et al. 2006).
The mechanism behind the protective effect of *H. pylori* infection on stomach cardia/oesophageal adenocarcinoma is also related to acid of the stomach. A meta-analysis found that GORD symptoms were associated with absence of *H. pylori* infection (Cremonini et al. 2003). Indeed, anti-*H. pylori* treatment triggers both de novo and rebound symptoms of GORD. Thus the reduced acid from *H. pylori* infection may protect against the development of Barrett’s oesophagus and hence oesophageal adenocarcinoma. Another possible mechanism suggested for the decrease in oesophageal adenocarcinoma and stomach cardia is the decrease in ghrelin, a hormone which stimulates appetite (Wren and Bloom, 2007). The reduction of ghrelin reduces the possibility of being obese and hence lowers gastro-oesophageal reflux.\(^1\)

Acquisition of *H. pylori* infection depends on several factors. *H. pylori* infection is more prevalent in lower socioeconomic groups, especially during childhood. Moayyedi et al. (2002) found that having a higher number of siblings and being a male were independent risk factors for acquiring *H. pylori* infection. The authors acknowledged vagueness regarding the reason for the sex difference in the acquisition of *H. pylori*, but suggested it might be behavioural, resulting from the poorer childhood hygiene of boys than girls. The prevalence of *H. pylori* infection increases with increasing age (Rothenbacher and Brenner, 2003). This increase is thought to be a cohort effect (Parkin et al. 2001) as most infections occur at a young age (Malaty et al. 2002). A Russian study which evaluated the prevalence of *H. pylori* in two successive birth cohorts (2–19 years old), a decade apart showed that there had been a dramatic decrease (about 70%) in the prevalence of *H. pylori* infection (Tkachenko et al. 2007). This decrease was attributed to an improved standard of living. The results match the observed data that stomach cancer risk in Japan exhibits a cohort effect (Lambert et al. 2002). Lastly, evidence shows that person-to-person is the most likely mode of transmission of *H. pylori* infection. The role of the faecal-oral pathway is probably greater than the oral-oral (Delport and van der Merwe, 2007).

Although, the prevalence of *H. pylori* infection in the world is variable (Figure 7), it is substantial. About half of the world’s population is infected, although the prevalence of *H. pylori* infection in more-developed countries is lower than in less-developed ones. Figure 7 matches Figure 2 to some extent: the higher the prevalence of *H. pylori* infection, the higher the incidence of stomach cancer, but caution should be paid when interpreting

\(^*\) Obesity is discussed in more detail on p. 30.
this result due to the ecological fallacy. Although half of the world’s population is infected with \textit{H. pylori}, only 2\% develop stomach cancer (McColl, 2005).

\textbf{Figure 7:} The estimated prevalence of \textit{H. pylori} infection in asymptomatic adults by worldwide area

\textit{Note:} Figure adopted from Parkin (2004)

The \textit{African enigma} denotes the high prevalence of \textit{H. pylori} infection accompanied by low prevalence of \textit{H. pylori}-related medical conditions such as peptic ulcers and stomach cancer (Agha and Graham, 2005). One can speculate about the appropriateness of this term with its generalising connotation, since stomach cancer rates show a wide range of variation among African countries (see Figure 2), but it is still often used in the literature and, for a number of African countries, the phenomenon still exists. Several explanations are discussed in the literature.

An immunology-based study showed that mice co-infected with a helminth had a different immunology profile (Th-2 instead of Th-1) and less gastric atrophy than uninfected mice (Fox et al. 2000). Th-1 reaction (cell-mediated immunity) fails to eradicate the infection which persists throughout life leading to harmful changes to the stomach wall. Conversely, Th-2 reaction (antibody-mediated immunity) is accompanied by minimal damage to body tissues. Testing the IgG sub-class in Australian, German and African groups suggests that in comparison with the African cohort, the Australian and German groups show a predominantly Th-1 reaction (Segal et al. 2001). Parasitic infections are known to be ubiquitous in Africa (World Health Organization, 2008a).

Since stomach cancer is a multifactorial disease, another possible explanation is differences in lifestyle, such as diet (Segal et al. 2001) and smoking (Lunet and Barros, 2003), between African countries and the richer countries. Also, CagA positive stains of \textit{H. pylori} were found to be more common among groups at high risk of stomach cancer (Bravo et al. 2002). Above all, because of limited resources data from Africa on cancer
incidence may be inadequate or inaccurate so that making comparisons can be misleading (Parkin et al. 2003). Recently, the African enigma was refuted by a study which aimed to assess the prevalence of medical conditions related to *H. pylori* infection in Africa, using endoscopy (Agha and Graham, 2005). The authors concluded that the observed rates of medical conditions related to *H. pylori* infection were comparable to those seen in developed countries. They attributed the so-called African enigma firstly to limited access to health care and secondly to lower life expectancy in Africa, as ulcers and cancers are usually conditions of old age.

- **Diet**

An extensive list of foods that could increase or decrease the risk of stomach cancer has been proposed in the literature. Some of these foods have been researched comprehensively, others tested only in single studies. Recently, the World Cancer Research Fund (WCRF) published a report called “Food, Nutrition, Physical Activity and the Prevention of Cancer” (World Cancer Research Fund, 2007). This report is the result of a multi-national, five-year project to systematically review available literature on food and various cancers of the body. It is the most extensive and up-to-date review so far. Therefore, this report is used, with some elaboration, to assess the dietary factors which might be linked to stomach cancer.

It is worth mentioning that the reviewers acknowledge the different aetiologies of cardia and non-cardia stomach cancers. However, many studies have not stratified their results according to sub-site. The reviewers’ conclusion is that most of the evidence collected relates mainly to non-cardia stomach cancer. Nevertheless, because cardia stomach cancer has been increasing, some of the recent studies reviewed may pertain to a combination of the two sub-sites and hence the results may be less conclusive.

Table 4 has been adapted from the WCRF’s final conclusion on stomach cancer. Each food item reviewed by the panel is classified according to the evidence available. While there is no convincing evidence about any type of food being a risk factor for stomach cancer, fruit and non-starchy and allium vegetables are probable protectors against stomach cancer while high salt intake is a probable risk factor. Limited but suggestive evidence exists that pulses and foods containing selenium reduce the risk of stomach cancer. Likewise, limited but suggestive evidence exists that chilli, processed meat, smoked food and grilled or barbecued food increase the risk of stomach cancer.
Reviewers of the WCRF report caution that *H. pylori* infection may be a confounder in the relationship between food types and stomach cancer. Only recent studies have adjusted for the infection. However, the European Prospective Investigation into Cancer and Nutrition group (EPIC) found that *H. pylori* infection does not alter the effect of fruit and vegetable intake on stomach cancer (Gonzalez et al. 2006). Another pertinent point is that diet differs with socioeconomic status. Generally, consumption of healthier food is greater among higher socioeconomic status (SES) groups. This certainly applies to

**Table 4: Food, nutrition and stomach cancer**

*Note: Table adapted from World Cancer Research Fund (2007)*

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Decreased risk</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convincing</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-starchy vegetables(^1)</td>
<td>Salt</td>
</tr>
<tr>
<td></td>
<td>Allium vegetables(^1)</td>
<td>Salted and salty food(^2)</td>
</tr>
<tr>
<td></td>
<td>Fruit(^1)</td>
<td></td>
</tr>
<tr>
<td><strong>Probable</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulses (legumes)(^3)</td>
<td>Chilli</td>
</tr>
<tr>
<td></td>
<td>Food containing Selenium(^4)</td>
<td>Processed meat(^5)</td>
</tr>
<tr>
<td><strong>Limited-suggestive</strong></td>
<td></td>
<td>Smoked food(^6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grilled (broiled) or barbecued (charbroiled) meat(^6)</td>
</tr>
<tr>
<td><strong>Limited-not conclusive</strong></td>
<td></td>
<td>Cereals (grains) and their products; dietary fiber; potatoes; starchy roots, tubers, and plantains; nuts and seeds; herbs, spices and condiments; meat (unprocessed); poultry; eggs; milk and dairy products; fat and oils; total fat; fatty acid composition; cholesterol; sugars; sugar(sucrose); fruit juices; coffee; tea; alcohol; dietary nitrate nitrite; N-nitrosodimethylamine; drying or dried food; protein; thiamine; riboflavin; vitamin C; vitamin D; multivitamins; mineral supplements; calcium; iron; selenium supplements; carotenoids; culturally defined diets; meal frequency; eating speed; body fatness; energy intake</td>
</tr>
</tbody>
</table>

1. Judgments on vegetables and fruits do not include those preserved by salting and/or pickling.
2. “Salt” here means total salt consumption, from processed food, including salty and salted food and also salt added in cooking or at the table.
3. Including soya and soya products.
4. Includes both foods naturally containing the constituent and foods which have the constituent added.
5. The term “processed meat” refers to meats preserved by smoking, curing, salting, or addition of chemical preservatives.
6. The evidence is mostly from meats preserved or cooked in these ways.

* Enough evidence exists to make policy recommendations for prevention.

** Evidence is too limited to conclude a causal relationship.
fruits and vegetables which are consumed at lesser rates among lower socioeconomic status groups (Ministry of Health, 2008b, Galobardes et al. 2001). Reviewers of the WCRF report have adjusted for SES before drawing conclusions.

The biological plausibility behind the carcinogenic/protective effect of food is important in appreciating the full picture of the causes of stomach cancer. Table 5 summarises the mechanisms for each food item. Anti-oxidants seem to underlie the protective effect of foods that are thought to decrease the risk of developing stomach cancer (World Cancer Research Fund, 2007, p.265-270). Conversely, a wide variety of different compounds may explain the mechanism of stomach carcinogenesis. In particular, alcohol is known to be a risk factor for several cancers and may increase the risk of stomach cancer, but the IARC Cancer Monograph Working Group recently concluded that potential confounders such as smoking and dietary factors cannot be ruled out (Baan et al. 2007). Since there may also have been misclassification of cardia stomach cancer with distal adenocarcinoma of the oesophagus, the evidence for alcohol causing adenocarcinoma of the oesophagus is also weak.
Table 5: Biological mechanisms behind the carcinogenic/protective effects of food associated with stomach cancer

<table>
<thead>
<tr>
<th>Food</th>
<th>Biological plausibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase risk</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Salt, salted and salty food</strong></td>
<td>When given alone it does not cause neoplasia (Nozaki et al., 2002, Tatematsu et al., 1975). However, salt was found to be a promoter of stomach carcinogenesis when given with a nitro-carcinogenic compound and the carcinogenesis promoting effect of <em>H pylori</em> is enhanced by salt: <em>H pylori</em> and salt act synergistically (Nozaki et al., 2002) in a dose-response manner (Kato et al., 2006). Further, impure salt may contain nitrate, nitrite and <em>N</em>-nitroso compounds. In countries where impure salt is used, higher levels of <em>N</em>-nitroso compounds are found (Cohen and Roe, 1997).</td>
</tr>
<tr>
<td><strong>Chilli</strong></td>
<td>Some constituents of chilli are irritants to the stomach, but chilli can also disguise off flavours. The reviewers at the WCRF (World Cancer Research Fund, 2007) acknowledge that the data could be confounded by socioeconomic status or availability of refrigeration.</td>
</tr>
<tr>
<td><strong>Processed meat</strong></td>
<td>There are several possible mechanisms. Nitrites and nitrates are added to processed meat (Eichholzer and Gutzwiller, 1998). These could react in the stomach to form <em>N</em>-nitroso compounds which are carcinogenic (International Agency for Research on Cancer, 1987) (see Box 1). Processed food often contains a considerable amount of salt (World Cancer Research Fund, 2007, p.265-270). Also, iron in the haem may facilitate free radical formation (McCord, 2004). Finally, haem may promote production of <em>N</em>-nitroso compounds in the stomach (Lunn et al.).</td>
</tr>
<tr>
<td><strong>Smoked, grilled and barbecued food</strong></td>
<td>Smoking, grilling and barbecuing food generates high levels of heterocyclic amines and polycyclic aromatic hydrocarbons (World Cancer Research Fund, 2007, p.265-270). Many of these compounds are known to be carcinogenic (Sugimura, 1997).</td>
</tr>
<tr>
<td><strong>Decrease risk</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-starchy vegetables</strong></td>
<td>The anti-cancer effect of non-starchy vegetables is thought to be complex. Vegetables contain considerable anti-oxidants, vitamins and phytochemicals which, it is supposed, act synergistically to protect against malignancy (World Cancer Research Fund, 2007, p.265-270).</td>
</tr>
<tr>
<td><strong>Alliums vegetables</strong></td>
<td>Allium vegetables contain flavonols which are anti-oxidants (Bohm et al., 1998). Also, garlic has been found to have antibiotic properties and thus may protect against <em>H pylori</em> colonisation (Sivam et al., 1997).</td>
</tr>
<tr>
<td><strong>Fruit</strong></td>
<td>A mixture of phytochemicals and especially vitamins play a role in the protection against cancer (World Cancer Research Fund, 2007, p.265-270).</td>
</tr>
<tr>
<td><strong>Pulses (legumes)</strong></td>
<td>Soya contains considerable amounts of saponins which have been shown to possess anti-carcinogenic effects (Rao and Sung, 1995). Other constituents are isoflavones, which also show anti-tumour activity (Yanagihara et al., 1993).</td>
</tr>
<tr>
<td><strong>Foods containing selenium</strong></td>
<td>Many different mechanisms have been proposed for selenium protection against cancer development. Some of the mechanisms are: antioxidation, up-regulation of the immune system, inhibition of angiogenesis and effects on the cell cycle (Gromadzinska et al., 2008).</td>
</tr>
</tbody>
</table>
Nitrogen-based compounds:

The IARC concluded recently that ingested nitrates and nitrites are probable carcinogens (International Agency for Research on Cancer, 2006). Nitrates are converted to nitrites in saliva and, subsequently in the stomach, nitrites react with amino acids to form N-nitroso compounds (NOC). Although the IARC working group concluded that the evidence from human studies for the risk of stomach cancer from ingested nitrite is still limited, the evidence from animal experiments is sufficient to show the carcinogenicity of nitrite in combination with amines and amides (N-nitroso compounds). Endogenous NOC are formed by two major pathways, one acid-catalysed, the other bacterially catalysed. The two pathways are influenced by many factors like diet, pH and microflora (Hill, 1996). In particular, during chronic inflammation induced by H. pylori, hypochlorohydria develops (Schubert and Peura, 2008). This slows the acid-catalysed reaction but speeds the bacterial. Hence, the latter may play the more relevant role in gastric carcinogenesis. Additionally, the reaction for the formation of NOC is particularly potent when vitamin C intake is low (Grosse et al. 2006) and, again, H. pylori infection is found to reduce the bioavailability of vitamin C (World Cancer Research Fund, 2007).

The source of nitrates and nitrites is primarily food. Vegetables may account for more than 70% of the dietary intake of nitrate (Eichholzer and Gutzwiller, 1998). Some nitrate also comes from water. Because of nitrate leeching from fertilisers into groundwater (Galloway et al. 2008), many studies have assessed the role of nitrate in drinking water in causing stomach cancer, but no clear conclusion can be drawn as yet (International Agency for Research on Cancer, 2006). Similarly nitrites are found in vegetables. In fact in a New Zealand-based report (Thomson, 2004) potatoes were found to contribute about a third of the nitrite dietary intake; another third came from preserved meats. While human exposure to nitrate is primarily exogenous (i.e. through diet), nitrite exposure is principally endogenous (International Agency for Research on Cancer, 2006).

As mentioned briefly above, many factors influence the process of nitrosation in vivo including bacteria and diet. Thus assessing dietary nitrate and nitrite intake is regarded insufficient to appraise the extent of the risk from the formation of NOC. A test which better estimates both endogenous and exogenous N-nitroso compounds is N-nitroproline test (measurement of N-nitroproline in urine). Interestingly, the total exposure of NOC was found to be greater in high risk population of stomach cancer (Bartsch, 1991).

Over the years, there has been a major achievement in the reduction of nitrite use in preserving foods including fish and meat, some of which was regulated by governments (Lijinsky, 1999). This together with refrigeration may have contributed in the reduction of stomach cancer.
Body mass index and physical activity

Body mass index (BMI) is an important factor when considering stomach cancer, although the results from retrospective studies should be interpreted with caution as weight loss accompanies cancer. The relationship of BMI to stomach cancer varies with the sub-site. Accordingly, most studies stratify stomach cancer by sub-site. In contrast, there is a paucity of information on the relationship of BMI to stomach cancer stratified by histology type.

BMI seems to be more related to cardia stomach cancer than non-cardia stomach cancer. High BMI (BMI > 25) have been shown in two meta-analyses (Kubo and Corley, 2006, Hampel et al. 2005) to increase the risk of oesophageal adenocarcinoma, which usually occurs in the lower third of the oesophagus, in close proximity to the stomach cardia. The two meta-analyses also found an increased risk of cardia stomach cancer with high BMI (BMI > 25). Although both meta-analyses found considerable heterogeneity among the studies included, it was in the magnitude of the association rather than direction. Kubo and Corley (2006) explored possible sources of heterogeneity but found stratification by BMI, adjustment for confounders, differences in study design and exposure measurement did not influence the initial heterogeneity. What did have an influence was stratification by country of origin and source of population (hospital vs. population-based). Stratification using only European and American studies (the majority of studies included) still found that there is a 50% increase in risk of developing cardia stomach cancer in people with high BMI (BMI > 25) compared to those of normal weight [OR 1.5 (95% CI 1.3–1.8)] (Kubo and Corley, 2006). In contrast, BMI does not appear to be closely related to non-cardia stomach cancer (Whiteman et al. 2008, Sjodahl et al. 2008, Merry et al. 2007).

The mechanism behind the proposed increased risk of oesophageal and stomach cardia adenocarcinoma is contentious. A meta-analysis aiming to determine whether the risk of Barrett’s oesophagus (precursor lesion to oesophageal adenocarcinoma) was increased by high BMI found that high BMI did not confer additional risk on top of what was expected from gastro-oesophageal reflux disease (GORD) (Cook et al. 2008). It can be concluded that the association of BMI to adenocarcinoma of the oesophagus is indirect, through GORD, leading to Barrett’s oesophagus. The researchers also mentioned that BMI alone could not account for the high male-to-female ratio observed for stomach cancer, given that obesity is more common among females.
However, others have suggested that obesity could be a risk factor for oesophageal adenocarcinoma independent of GORD (Mayne and Navarro, 2002). The proposed mechanism is through a hormonal effect. This possibility is supported by a recent case-control study in Australia which showed that when controlling for potential confounders (age, sex, income, smoking, alcohol), the risk of adenocarcinoma of the gastro-oesophageal junction increased in a dose-dependent manner with increasing BMI for the same level of frequency of GORD symptoms, although the results were statistically significant only for GORD symptoms occurring at least weekly (Whiteman et al. 2008). Further, for the same BMI, there was an increasing risk of oesophageal adenocarcinoma with increasing frequency of GORD reported. This suggests that BMI may be an independent risk factor. In any case, the parallel increases in cancer of the cardia and obesity suggest that obesity may contribute to some of the observed increase in the incidence of this type of cancer (Mayne and Navarro, 2002).

Information about physical activity and stomach cancer is sparse in the literature. Two studies found that physical activity is not associated with stomach cancer (Pukkala et al. 1993, Severson et al. 1989). While these two studies were not specific to stomach cancer, a more recent cohort study conducted in Norway showed that moderate to high physical activity reduced both overall stomach cancer and specifically non-cardia cancer by 50% (Sjodahl et al. 2008). This area warrants further research.

- **Cigarette smoking**

The contribution of smoking to malignancy is substantial. The IARC has classified tobacco smoke as a Type 1 carcinogen (International Agency for Research on Cancer, 2004). The IARC group concluded in 2004 that there was sufficient evidence that tobacco smoking causes stomach cancer, besides 14 other cancers in different sites of the body. In assessing the evidence behind smoking and stomach cancer, the IARC reviewing panel observed that most of the case-control studies and many cohort studies showed a dose-response relationship which was statistically significant for both the intensity and duration (years since starting) of smoking.

Additionally, smoking seems to be related to both cardia and non-cardia cancers. A large cohort study, by the EPIC group, showed that current, but not former, smokers were at a higher risk of developing stomach cancer than those who had never smoked (González et al. 2003). Current smokers had a two-fold increased risk for total stomach cancer over the never-smokers group. Although results were inconsistent for a dose-response
relationship in current smokers, the risk was increased only if smoking for more than 40 years. Also, the relative risk for stomach cancer of the cardia (RR 4.1 [95% CI 1.8–9.6]) was higher than for non-cardia cancers (RR 1.9 [95% CI 1.1–3.6]). Adjustment of the relative risk included sex, BMI, education level, and consumption of fruit, vegetables and alcohol. The EPIC group estimated that about 17% of all stomach cancers could be attributed to smoking. Nonetheless, one should be cautious before accepting the results of this study, as the results may be confounded by H. pylori infection. Some studies have shown that H. pylori infection is more prevalent among smokers (Kanbay et al. 2005, Cardenas et al. 2005). Others have shown no link between smoking and H. pylori infection (Limburg et al. 2001, The EUROGAST Study Group, 1993). Overall the IARC group (International Agency for Research on Cancer, 2004) conclude that there is no association between H. pylori infection and smoking, so that its relevance as a potential confounder is questionable. However, there may still be an imbalance in H. pylori infection rates between current smokers and those who have never smoked since smoking is linked to socioeconomic status (Salmond and Crampton, 2000, Brewster et al. 2000), which could therefore be a confounder when relating H. pylori infection to smoking. The EPIC study did adjust for education.

Lastly, evidence from animal studies shows that smoking both initiates and promotes carcinogenesis. Tobacco smoke contains many compounds which are carcinogenic, but the major carcinogens in tobacco smoke are N-nitroso compounds (Box 1).

- **Medical conditions and pharmaceuticals**

Pernicious anaemia has been identified as a precursor condition to the development of stomach cancer and carcinoid tumours (Sjoblom et al. 1993, Hsing et al. 1993). The risk seems to be mostly related to non-cardia cancers (Ye and Nyren, 2003). Although many studies in the past explored this association, few incorporated H. pylori infection in their analysis, probably because of the unknown carcinogenicity of H. pylori for the stomach at the time. However, studies show that the prevalence of H. pylori infection in pernicious anaemia patients is low (Perez-Perez, 1997). This may be due simply to the resistant nature of atrophic gastritis to colonisation by H. pylori. Although chronic atrophic gastritis is a common presentation of both H. pylori infection and pernicious anaemia, evidence from histological sub-sites suggests this stage is reached by distinct pathways for H. pylori infection and pernicious anaemia. Thus, H. pylori infection may not be a risk factor for
pernicious anaemia. Prospective studies are warranted to elucidate whether there is any relationship between pernicious anaemia and *H. pylori* infection and subsequent development of stomach cancer.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in medicine is substantial, and the balance between their benefits and side-effects is important in clinical practice. A meta-analysis of case-control studies showed that NSAIDs are protective against non-cardia stomach cancer in a dose-response manner (Wang et al. 2003). Although this meta-analysis concluded that there was no association between NSAID use and cardia stomach cancer, a more recent nested case-control study found that the use of NSAIDs was protective against adenocarcinoma of the oesophagus and cardia stomach cancer combined, and against Barrett’s oesophagus (Anderson et al. 2006). It has been suggested that the protective role of NSAIDs lies on their inhibitory effect on prostaglandin synthesis (Zaridze et al. 1999). Prostaglandins alter many tumour specific characteristics including proliferation and apoptosis. Here again, studies such as the above may be confounded by *H. pylori* infection, smoking, or even BMI. But the use of NSAIDs as a preventive measure against stomach cancer is questionable since they possess their own stomach-related side-effects such as peptic ulceration (Rubin et al. 2005). Interestingly, *H. pylori* eradication prior to short to medium term use of NSAIDs was found to be protective against the development of peptic ulcer disease (Vergara et al. 2005), an effect more pronounced in naïve NSAID users. It would be more sensible, therefore, to administer *H. pylori* eradication therapy, which would prevent both peptic ulcer disease and stomach cancer.

Several suspicions have led researchers to study the link between the use of acid-secretion-reducing drugs and stomach cancer. Evidence shows that previous stomach surgery to reduce acid or to treat ulcer disease predisposes to stomach cancer (Elder and Knight, 1991). The mechanism behind this phenomenon is thought to be the growth of nitrate-reducing bacteria, due to hypochlorohydria. This finding raises the question of whether proton pump inhibitors or H2 blockers given for dyspepsia possess any risk for the development of stomach cancer. One animal study found that H2 blockers might be linked to the development of this cancer (Fossmark et al. 2004). A case-control study nested in a huge cohort study that involved 4.3 million people aged 40–84 years in the UK, found that proton pump inhibitors, and H2 blockers alone, increase the risk of stomach cancer (both cardia and non-cardia) in analyses stratified by duration of use and adjusted for known confounders (Rodriguez et al. 2006). However, when the results were adjusted
for the conditions for which the drugs were prescribed, the ORs included unity. Therefore, the risk of cancer seems to be more dependent on the conditions (for example, GORD and peptic ulcers) for which the drugs were prescribed rather than the drugs themselves. Moreover, *H. pylori* may be a strong confounder given that colonisation can result in dyspepsia so that people with the infection are more likely to be prescribed proton pump inhibitors or H2 blockers.

- **Others**

Several studies documented in the IARC monograph relating to Epstein-Barr virus (International Agency for Research on Cancer, 1997) suggested that this virus might be associated with stomach cancers, particularly stomach lymphoepithelial carcinomas. However, in the overall evaluation, sufficient evidence did not exist to regard Epstein-Barr virus as a carcinogenic agent for stomach cancers.

### 1.8.3. Host factors/Genes

Cancer which occurs at a young age is often suggestive of genetic causes. Early onset stomach/gastric cancer (EOGC) is defined as stomach cancer occurring in people aged 45 years and younger (Milne et al. 2007). It is estimated that EOGC accounts for about 10% of stomach cancer cases, although the percentage varies between 3% and 15% depending on the study population. Of this 10%, it is postulated that a tenth have a positive family history (Kokkola and Sipponen, 2001); the remaining 90% of EOGC remains unexplained. A well-known cancer type which exhibits a strong family history is hereditary diffuse stomach cancer. This is an autosomal dominant disease associated with E-cadherin gene mutations (Kaurah et al. 2007).

EOGC is generally of the diffuse type and occurs more frequently in females (Katai et al. 1996, Kokkola and Sipponen, 2001). Some have attributed the female predominance to hormonal differences (Maeta et al. 1995). The Shanghai Women’s Health Study investigated the association between women’s menstrual and reproductive factors and stomach cancer (Freedman et al. 2007). After controlling for many potential confounders, including *H. pylori* infection, it was found that a longer period of fertility and delayed age of menopause were protective against stomach cancer. It is postulated that *H. pylori* may still play a role in EOGC, but to a lesser extent than for stomach cancer in older age groups (>45 years old) (Milne et al. 2007).
Lewis blood groups have been implicated in the development of stomach cancer. Ired et al. (1953), more than five decades ago, first showed that the frequency of Lewis blood group type A was higher among stomach cancer patients than patients without stomach cancer. Conversely, the frequency of the O blood group was low. Subsequently, a Finnish study showed similar results (Turunen and Pasila, 1957). However, this study further noted that the difference was pronounced in non-cardia stomach cancer and among males. Exploring the biological pathway, it was found that tumour cells produce a glycoprotein similar to the glycoprotein on blood group A erythrocytes (Hakomori et al. 1967). Thus, because individuals with blood group O have antibodies against antigens A and B, they provide some protection against tumour development. It follows that one might expect survival from stomach cancer of people with blood group O to be better than those with blood group A. However, survival adjusted for possible prognostic factors suggested no difference according to blood groups (Viste et al. 1986). Other observational studies show no association between stomach cancer and blood groups (Pocard et al. 1998, Umlauft et al. 1996).

Because the frequencies of blood groups do not differ substantially between countries (Editorial, 1953), the effect of blood grouping on stomach cancer, if it exists, is likely to be minimal for explaining the differences in incidence between different countries.

1.8.4. Integrating Causes together

- From an epidemiological perspective

The environmental risk factors discussed can be fitted into a single model (Figure 8), although there may still be risk factors which are not yet known. Forman and Pisani (2008) developed a model which assumes that there is a background risk of stomach cancer from *H. pylori* and possibly genetic factors. The remaining risk (or proportion) is caused by *H. pylori* interacting with other co-factors. The background risk is based on regions (for example, Gharbiah in Egypt) in which the prevalence of *H. pylori* infection is high but the stomach cancer rates are low. Adopting this model, each population has an avoidable proportion of stomach cancer. Subsequently, the authors have calculated the relative risk a co-factor would need to exhibit in order to account for the excess stomach cancer cases in that particular place. Taking Japan as an example, for a single co-factor that is present in 30% of the population, it needs to exhibit a relative risk of more than 50
to account for the excess stomach cancer cases. Even if the prevalence of a co-factor was 90%, it would still need to have a relative risk of about 10. This demonstrates that stomach cancer might certainly be a multi-factorial disease.

**Figure 8: Environmental causes of stomach cancer**

- **From a pathological perspective**

  The pathogenesis of stomach cancer is quite complicated. Known potential risk factors may affect the whole stomach or a sub-site. Additionally, risk factors have a tendency to be associated with a certain histology type. An ideal model for stomach cancer pathogenesis should incorporate the different sub-sites and histology types, albeit such a model would be very complex. A relatively simple pathogenesis model (Figure 9) was proposed by Yamaguchi and Kakizoe (2001). Although the model presents the pathogenesis pathways for the different histology types, it is assumed that the histology types can occur either in the cardia or the non-cardia regions. It should be noted that genetics governs most of the development of the diffuse type whereas the intestinal type is the culmination of a sequence of mainly environmental events. *H. pylori* seems to play a role in both. Note that the model does not incorporate obesity and smoking, possibly
because such a relationship was not convincing at the time, and it is still unclear as to where these two risk factors would fit.

1.9. Prevention

Efforts at prevention of any disease can be directed at different stages along the path of disease progression. Primary prevention is directed at risk factors to reduce the incidence of the disease. Secondary prevention is directed at early diagnosis of the disease to achieve better outcomes. Tertiary prevention is concerned with rehabilitation and reducing the impact of the disease after it has occurred. Although all levels of prevention are important in cancer epidemiology, here I discuss primary and secondary prevention, and their cost-effectiveness, because these two levels are often preferred in cancer prevention.
1.9.1. **Primary**

Most primary prevention is directed at curing *H. pylori* infection, although it is still uncertain whether curing a chronic *H. pylori* infection decreases the risk of subsequent development of stomach cancer. Nevertheless, curing the infection would achieve other favourable outcomes such as decreasing peptic ulcers and stomach lymphomas and, above all, preventing transmission of infection (Stewart and Kleihues, 2003). A prospective study enrolled 1342 patients with peptic ulcers on an *H. pylori* eradication regimen (Take et al. 2005). Results showed that patients that were cured by the eradication regimen were less likely to develop stomach cancer than treated patients in whom the infection persisted. However, the study did not control for confounders or imbalance in the distribution of risk factors that might have resulted in over- or under-estimating the true effect of *H. pylori* eradication on subsequent development of stomach cancer.

The best evidence comes from randomised controlled trials (RCT). A recent RCT (Fukase et al. 2008) enrolled 554 patients diagnosed with early gastric cancer. After endoscopic mucosal resection (EMR) for early gastric cancer, the patients were randomised to either have *H. pylori* eradication therapy or only standard care without the eradication therapy. Patients were followed endoscopically for three years. The primary outcome was recurrent cancer. Results showed that the group on eradication therapy had about a 70% risk reduction (RR 0.3 [95% CI 0.2–0.7]) in the development of stomach cancer compared with the standard care group, a statistically significant result. At the end of the trial, patients in the latter group were given eradication therapy at the request of the ethical committee. Although this study was not strictly primary prevention, it has implications for primary prevention of stomach cancer.

*H. pylori* infection may recur after eradication (Niv and Hazazi, 2008). The annual recurrence rate in more-developed countries is about 2.7%; in less-developed countries a rate about four-times greater is observed. Thus, chemoprevention is likely to be more effective in more-developed countries given the high re-infection rate in the less-developed nations. Even so, eradication of *H. pylori* infection seems to genuinely decrease the risk of developing stomach cancer. Conceivably, as evidence builds on this matter, future RCTs may no longer be ethical because of the lack of clinical equipoise.
1.9.2. **Secondary**

Secondary prevention is aimed at screening for early gastric cancer. Early gastric cancer is defined as a lesion confined to the mucosa or submucosa of the stomach regardless of whether lymph nodes are involved or not (Rubin et al. 2005). It has an excellent survival rate: the 10-year survival rate is estimated to be 85% (Degiuli and Calvo, 2006). A study of 71 patients in Japan for whom treatment was not carried out, or was delayed for more than six months, estimated that about 63% of patients with early gastric cancer have a risk of progressing to an advanced stage of the disease within five years of diagnosis (Tsukuma et al. 2000). Although this study involved a small number of participants, future studies with larger cohorts may no longer be ethical.

China, Korea and Taiwan all have some kind of screening for stomach cancer, although there is still a paucity of information regarding their progress. In contrast, Japan is a good country for evaluating a screening program for stomach cancer. During the 1960s stomach cancer accounted for more than half of all deaths in Japan for males, and more than a third for females (Hisamichi, 1989). Hence, screening programs were initiated in the 1960s and, later, in 1983, a nationwide screening program of photofluorography was introduced for individuals aged 40 years and above (Hamashima et al. 2008). Although opportunistic screening (screening conducted outside an organized screening program; for example, screening patients while visiting for a different complaint) includes several other techniques like endoscopy, serum pepsinogen and *H. pylori* serology, a recent systematic review of evidence by Hamashima et al. (2008) on the effectiveness of such screening programs recommended photofluorography for both population-based and opportunistic programs. In 2004, it is estimated that about 13% (4.4 million) of the Japanese target population underwent screening for stomach cancer (Hamashima et al. 2008).

The success and limitations of the Japanese population-based screening program are well documented in the literature. When evaluating a screening program, epidemiologists favour focusing on mortality as it is less prone to specific screening biases such as over-diagnosis and length bias. The signs of success in Japan are many. Firstly, there is a discrepancy in the decreasing rates of mortality and incidence: mortality from stomach cancer decreased at a higher rate than incidence (Hisamichi et al. 1988). This effect is pronounced in the targeted age groups. Secondly, studies show that unscreened individuals have a two-fold higher risk of dying from stomach cancer than screened ones (Hisamichi and Sugawara, 1984, Lee et al. 2006). And lastly, screened participants have
about a 25% risk reduction in incidence of advanced gastric cancer than unscreened ones (Lee et al. 2006).

However, whether the increase in early gastric detection in Japan over the past four decades is entirely due to the screening program or not is still debated (Maehara et al. 2000). A study by Suzuki et al. (2006) showed that the majority (>80%) of asymptomatic patients were detected at outpatient or private health clinics, which suggests that the increase in detection of early gastric cancer is primarily due to a greater awareness by the public and health professionals. In addition, the screening program in Japan has a sensitivity of 82.4%, a specificity of 77.2%, a positive predictive value of 1.8%, and a negative predictive value of almost 100%. The positive predictive value is certainly a drawback of this screening program.

1.9.3. Cost-effectiveness

Although primary prevention is still not widely practised, many studies have shown that it might be more efficient than secondary prevention. Lee et al. (2007) explored the cost-effectiveness of primary versus secondary prevention of stomach cancer using a simulation program. Primary prevention involved screening for *H. pylori* infection using a urea breath test and treating the infection. Secondary prevention used serum pepsinogen to identify individuals with atrophic gastritis, followed by surveillance endoscopy. It was found that primary prevention is more cost-effective than secondary prevention when reinfection is lower than 2.2% and the proportion of early gastric cancer is less than half of detected gastric cancer. Further, eradication of *H. pylori* infection at an early age was more cost-effective than later in life. The researchers attributed this finding to an early irreversible injury caused by the *H. pylori* infection, so that eradication was more effective prior to the “point of no return”. The authors did not incorporate other gastrointestinal diseases (for example, ulcers) which are caused by *H. pylori* in their analysis. If they had, this would have tipped the balance even more towards primary prevention. Another study, carried out in Singapore, found that population-based primary prevention of stomach cancer through screening and treating *H. pylori* infected individuals was cost-effective using serology but not a urea breath test (Xie et al. 2008). The study used a Markov model and involved about a quarter of a million Chinese males aged between 35 and 44 years. The implication of this for other population groups, perhaps with a lower incidence of stomach cancer, is unknown.
2. CHAPTER TWO – STOMACH CANCER IN OMAN AND THE GULF COOPERATION COUNCIL COUNTRIES (GCC): ANALYSIS OF THE INCIDENCE DATA

2.1. Introduction

Stomach cancer is estimated to be the eighth most common cancer among citizens in the Gulf Cooperation Council (GCC) countries (Al-Zahrani et al. 2006), but it is the most frequent neoplasm among Omani and Emirati males. Further, the estimated age-standardised incidence rate among Omani males is almost double that of Emirati males. Given that the GCC countries are believed to have similar customs and lifestyles, it may seem odd that stomach cancer is much higher among Omanis than citizens of the other GCC countries.

The research in this chapter was undertaken to determine whether the difference in the incidence of stomach cancer between Oman and the other GCC countries is real. The specific aims are listed below.

2.2. Aims

A) To describe the cancer registration systems in the GCC countries (Oman, Saudi Arabia, United Arab Emirates, Bahrain, Qatar and Kuwait).
B) To describe the incidence of stomach cancer in Oman by person, place and time.
C) To conduct a comparative analysis of the incidence of stomach cancer in the GCC countries taking into account the quality and completeness of cancer registration.

2.3. Cancer registration in the Gulf Cooperation Council (GCC) countries

The Gulf Cooperation Council, established in 1981, includes Oman, Saudi Arabia, United Arab Emirates (UAE), Bahrain, Qatar and Kuwait (GCC Secretariat General,
The Council was established in view of the geographic proximity, related customs, Islamic beliefs and political systems of the countries. The main goal of the Council is to strengthen unity among the six countries in all fields of concern such as politics, economics, health and social affairs. The GCC states are all within the Arabian Peninsula and most of the land belongs to Saudi Arabia. More than three quarters of the GCC states’ population are Saudis (Table 6). The population structures of the GCC states are fairly similar, being young populations.

Cancer is a notifiable disease in all the GCC countries. Because of their similarities, it may seem desirable to compare cancer incidence data among the countries. To obtain accurate and unbiased cancer incidence rates requires data of high quality. Therefore, it is pertinent to review the completeness and quality of the datasets before making any cancer incidence comparisons. Apart from Kuwait, national cancer registries in the Gulf countries are quite recent. National registries covering the whole population started only in the 1990s (Mohammad et al. 2008, Bener et al. 2007, Al-Eid and Arteh, 2008, Curado et al. 2007, Tadmouri and Al-Sharhan, 2004), with Bahrain and UAE achieving whole population coverage most recently, in 1998 (Table 7). Although mandatory reporting started in 1998 or earlier in Kuwait, Bahrain, Saudi Arabia and Qatar, it was only around the beginning of 2001 that it started in Oman (Mohammad et al. 2008) and UAE (Tadmouri and Al-Sharhan, 2004).

Table 6: Population of GCC countries, 2003*

<table>
<thead>
<tr>
<th>Country</th>
<th>Population in 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oman</td>
<td>1,781,558</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>16,109,197</td>
</tr>
<tr>
<td>UAE</td>
<td>858,710</td>
</tr>
<tr>
<td>Qatar</td>
<td>196,229</td>
</tr>
<tr>
<td>Bahrain</td>
<td>427,954</td>
</tr>
<tr>
<td>Kuwait</td>
<td>913,500</td>
</tr>
</tbody>
</table>

*Data obtained from Al-Zahrani et al. (2008)
Table 7: Date at which cancer notification attained total population coverage and compulsory notification in the GCC countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Population coverage</th>
<th>Compulsory notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oman</td>
<td>1996</td>
<td>2001</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1994</td>
<td>1994</td>
</tr>
<tr>
<td>UAE</td>
<td>1998</td>
<td>2001</td>
</tr>
<tr>
<td>Qatar</td>
<td>1990</td>
<td>1990</td>
</tr>
<tr>
<td>Bahrain</td>
<td>1998</td>
<td>1998</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1974</td>
<td>1974</td>
</tr>
</tbody>
</table>

Rigorous technical evaluation of the completeness and quality of the GCC countries’ cancer registries is beyond the capabilities of this project. However, there are three good sources for evaluating the completeness and quality of the GCC cancer registries: the Cancer Incidence in Five Continents report (Curado et al. 2007); the Globocan database (Ferlay et al. 2004); and the GCC countries’ cancer incidence reports (Al-Zahrani et al. 2006, Al-Zahrani et al. 2008, Al-Zahrani et al. 2009). These will be discussed in the following paragraphs.

Cancer Incidence in Five Continents is a periodic report published by the International Agency for Research on Cancer (IARC). It includes cancer incidence data from cancer registries from all over the world, but only data of sufficiently high quality and completeness are included. In evaluating data from cancer registries, the editors of Cancer Incidence in Five Continents check for several indicators including:

- Abrupt changes in cancer registration and rate in the reference period, a measure of completeness.
- Use of mortality data as a source for registering cases which might have been missed.
- Coverage of the whole defined population.
- Proportion of cases with unknown basis of diagnosis.
- Quality measures such as age-specific curves for childhood cancers, microscopic verification.
Finally, datasets included in the volume are grouped according to accuracy as shown in Table 8. Datasets are excluded for many reasons including having a high percentage of death certificate only registrations, and ill-defined or unspecified cancers.

Table 8: Classification of datasets submitted by cancer registries according to accuracy

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death certificate only registrations (%)</td>
<td></td>
<td></td>
<td>No ad hoc study of completeness</td>
<td></td>
</tr>
<tr>
<td>&lt; 10, or zero</td>
<td>&gt;10 and &lt;20</td>
<td>No death certificates as a source of case finding</td>
<td>&gt; 20</td>
<td></td>
</tr>
<tr>
<td>Microscopic verification (%)</td>
<td>&gt; 80</td>
<td>&gt; 75 and &lt;80</td>
<td>-</td>
<td>Too high (99-100)</td>
</tr>
<tr>
<td>Ill-defined site (%)</td>
<td>&lt; 10</td>
<td>&gt;10 and &lt;20</td>
<td>-</td>
<td>&gt;20; overall MV% &lt;75</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>&lt; 10</td>
<td>&gt;10 and &lt;20</td>
<td>-</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Other</td>
<td>• Death reporting meets WHO recommendations</td>
<td>• 10% &lt; age unknown &lt;20%</td>
<td>• No official mortality data</td>
<td>• MV% low for selected sites</td>
</tr>
<tr>
<td></td>
<td>• No abrupt trends; Denominators OK</td>
<td>• No access to death certificates</td>
<td></td>
<td>• Mortality: Incidence threshold by site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Official mortality data not available by cause, or poor quality by cause</td>
<td></td>
<td>• Implausible incidence rates; specialized registries eg childhood, mesothelioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ≤ 2 years of data</td>
</tr>
</tbody>
</table>

Note: Table adapted from Curado et al. (2007)

Only three (Oman, Bahrain and Kuwait) of the six GCC countries are included in the latest report of the Cancer Incidence in Five Continents (covering incidence data in the period from 1998 to 2002; previous reports covered earlier periods). Data from Qatar, Saudi Arabia and UAE have never been included. Although this suggests better quality data in Oman, Bahrain and Kuwait, non-inclusion means either that the remaining countries have not submitted any data or that they have been excluded for not meeting the requisite criteria. According to the Supervisor of the Gulf Centre for Cancer Registration (GCCR) (personal communication, Ali Al-Zahrani, 2009), only Saudi Arabia, but not UAE or Qatar, submitted data to the IARC. The Saudi Arabian entry was declined (1998–2002 period) at least in part because of the high percentage of microscopic verification. Although microscopic verification is in itself a desirable thing, registries reporting higher percentages of microscopically verified diagnoses than expected may reflect an over-reliance on histopathology as a source of information for registering cancer cases. Cases diagnosed by other means (for example, surgical or clinical) may have been missed.

Globocan is a database developed by the Descriptive Epidemiology Group of IARC to estimate the incidence of cancer in the world in 2002. This group used incidence and mortality data published by those countries where the data were believed to be fairly
complete. In countries for which under-reporting was known, some corrections were applied. For countries that had no data or where they were extremely inaccurate, cancer incidence by site was estimated by partitioning “all cancers” estimates using age and sex-specific data from neighbouring countries. The Globocan estimates of the stomach cancer incidence rates for Oman, Qatar, Bahrain and Kuwait were based on the original data from these four GCC countries and thus were similar to those published in the GCC cancer incidence report 1998–2002 (Al-Zahrani et al. 2006). However, for UAE and Saudi Arabia, the Descriptive Epidemiology Group at IARC generated incidence rates by using “middle east”\(^1\) rates and the proportions of cancers published by the corresponding cancer registries. Although this method may not be accurate, the estimation was done because under-reporting was suspected. The published incidence rates in the GCC cancer incidence report for Saudi Arabia and UAE were therefore much lower than the estimated incidence rates presented in Globocan.

The GCCR, established in 1998, accumulates cancer incidence data from all the GCC countries. The GCCR also helps in directing the individual GCC cancer registries towards reporting complete and good quality data. To my knowledge, up to this point there has been no explicit technical evaluation carried out by the GCCR to compare the quality and completeness of the cancer incidence data between the GCC countries. Nevertheless, the centre publishes yearly cancer incidence data and five-yearly summaries comparing cancer incidence in the GCC countries in its GCC cancer incidence reports. These have been used to obtain additional information on the quality and completeness of the GCC cancer data.

The 1998–2002 GCC cancer incidence report (Al-Zahrani et al. 2006) reveals that, firstly, the percentage of microscopic verification (MV\%) as a basis of diagnosis for all cancers is very high in the GCC countries, at least in all cancer cases diagnosed from 1998–2002. Overall, 95\% of all cancer cases are diagnosed by means of microscopy, with some variation between the GCC countries. For example, Saudi Arabia reports the highest figure, at 97.4\%, while Kuwait reports only 85.2\%. The high percentage of microscopic verification as a source of diagnosis in Saudi Arabia reflects their over-reliance on it; clinically diagnosed cases may have been missed. Secondly, only Kuwait and Bahrain use death certificates as a source for registering cancer cases. Death certificates are an important cancer data source, but this requires a proper mortality database which is lacking

\(^1\) Unweighted average of Oman, Kuwait, Israel (Non-Jews) and Jordan.
in the other GCC countries. Death certificate only (DCO) registrations ensure registration of cases that have escaped documentation during life. However, because death certificates provide relatively imprecise information, where there is a high percentage of DCO registrations the data are deemed less valid (Curado et al. 2007). In contrast, a small percentage of DCO registrations may imply efficient case finding and therefore more complete data.

It is worth noting that, beyond the comments above, no specific comparison between the GCC countries is available of the quality and completeness indicators mentioned in the 1998–2002 cancer incidence report. From the above discussion, it appears that the data from Saudi Arabia and UAE may be less complete than data from the other GCC countries, but further evidence from studies designed to evaluate the completeness and quality of the data is required.

2.4. Cancer registration in Oman

Cancer registration started in Oman in 1985, albeit only hospital-based. In 1996, a national cancer registry was established to cover the whole population. However, it was not until 2001 that cancer notification became compulsory. A cancer notification form was developed to include all pertinent data in a standardised fashion (Appendix). Oman’s data were included in the latest two volumes of Cancer Incidence in Five Continents. Volume eight (Parkin et al. 2005b) included data from 1992 to 1996 and volume nine (Curado et al. 2007) included data from 1998 to 2002. In both volumes Oman’s incidence data were classified as group C in terms of accuracy (see Table 8). Because of this classification, the authors of the volumes note that readers should be cautious when using Oman’s incidence data for making inter-country comparisons. (Bahrain and Kuwait are classified as group B.)

2.5. Methods for the analysis of the incidence data in Oman and the GCC countries

The incidence of stomach cancer among citizens in Oman was examined using the annual cancer incidence reports published annually by the Omani National Cancer Registry (NCR). Overall, data spanning 12 years (1996–2007 inclusive) were used in the analysis. When comparing the incidence data by person and place, the 1996 report was not
included in the analysis because the age-categorisation used in the report was different from all the other reports, thus hindering uniform standardisation procedures.

Stomach cancer incidence data for citizens of the GCC countries were compared using the reports published by the Gulf Centre for Cancer Registration (GCCR). Data were available for seven years (1998–2004 inclusive), published in one five-year report (1998–2002) (Al-Zahrani et al. 2006) and two one-year reports (2003 and 2004) (Al-Zahrani et al. 2008, Al-Zahrani et al. 2009). The GCCR was chosen as the source for the data because it collects original incidence data from all the GCC countries, and the GCC reports provide fairly detailed incidence data by age and sex. On the other hand, Globocan has only estimated incidence rates for Saudi Arabia and UAE, and for 2002 only. In the present study, little weight is placed on comparisons between the incidence of stomach cancer in Oman and in Saudi Arabia and UAE, since the reported incidence rates for Saudi Arabia and UAE may be under-estimated because of under-reporting.

2.6. **Statistical analysis**

Data between 1997 and 2007 were used to analyse the incidence by sex and region and data between 1996 and 2007 to analyse the trend overtime using simple regression. The mid-year population in 2002 was used as the denominator when analysing the incidence data by sex and region during the period 1997–2007. The data were initially split into two periods, before and after 2001, which marked the commencement of mandatory cancer notification. In this case, the estimated population at the corresponding midpoint of the period was used as the denominator. Oman’s population by age, sex and region was obtained from the statistical year books published annually by the Ministry of National Economy.

Data on stomach cancer cases in the regions of Oman were available only as a total number (males and females combined) and these were not stratified by age. Therefore, to explore possible regional differences in Oman, indirect standardisation was carried out using age-specific incidence rates for Oman as a whole, in order to calculate the standardised morbidity ratios (SMR) for each region. To calculate confidence intervals for the standardised morbidity ratios, Byar’s approximation (Breslow and Day, 1987) was used if the observed number was more than 100 cases and a Poisson distribution if the observed number was less than 100.
Comparative analysis of the incidence of stomach cancer among citizens of the GCC countries was carried out using the combined seven years’ data (1998–2004). However, data from the two periods (1998–2002 and 2003–2004) were first analysed separately to explore any difference in the incidence rates among the GCC countries and to explore the impact of the late mandatory notification of cancer cases in Oman and UAE. The denominators for the GCC cancer incidence data when the total period was analysed were the averages of the mid-year populations in the respective countries in 2000 and 2003. However, the mid-year populations in 2000 and the averages of the populations in 2003 and 2004 were used when analysing, respectively, the 1998–2002 and the 2003–2004 data. These population data were obtained from the GCCR reports.

As well as comparing incidence of stomach cancer among citizens of the GCC countries by sex, the incidence was also compared in people below 45 years of age, or 45 years and above. This was done to explore in which age group most of the differences occur. Early onset gastric cancer, which is mostly governed by genes, occurs mostly in people below 45 years of age (Milne et al. 2007). In contrast, stomach cancer occurring in people above 45 years of age is mostly environmental.

Poisson regression was used to calculate the age and sex-adjusted relative risk of stomach cancer in the GCC countries compared to Oman.

Rates for both Oman and the GCC countries were standardised to the World Standard Population of Segi (Segi, 1960) and the confidence intervals for the age-standardised incidence rates were computed using the method proposed by Fay and Feuer based on gamma distribution (Fay and Feuer, 1997).

Including or excluding malignant gastric lymphoma in the analysis was determined by the availability of data. Unlike the data for the regional analysis in Oman, the data for the comparative analysis among the GCC countries excluded malignant gastric lymphoma as it was classified as a lymphoid cancer rather than a gastric cancer.
2.7. Results

2.7.1. Stomach cancer in Oman

From 1997 to 2007, an average of 45 and 25 cases per year, respectively, were recorded for males and females in Oman. The annual age-standardised incidence rates for males and females during the same period were 10.1 (95% CI 9.2–11.0) and 5.6 (95% CI 4.9–6.3) per 100,000 respectively. For males, 90% of cases occurred at ages 45 and above. In contrast, 83% of female cases were aged 45 and above.

Incidence rates for both sexes combined varied between the eight major regions of Oman (Figure 10). Musandam had the highest incidence rate, 6.5 per 100,000, and Addahahirah had the lowest rate, 1.1 per 100,000, followed by Al-Wusta. However, comparison of the crude rates may be distorted by age. Direct standardisation was not possible because regional age-specific incidence rates were unavailable. Therefore, rates were indirectly standardised using Oman’s age-specific incidence rates. Compared to the overall rate of Oman, three regions had a standardised morbidity ratio (SMR) lower than one and five regions had a SMR higher than one (Table 9). For Addahahirah and Addakhliyah, the upper bound of the 95% confidence interval for the SMR was less than one. For Al-Batinah and Muscat, the lower bound of the 95% confidence interval for the SMR was greater than one. In other words, the observed number of stomach cancer cases in Addahirah and Addakhliyah was lower than would be expected if the age-specific stomach cancer incidence rates were the same as those for Oman as a whole. In contrast,
Table 9: The observed number of stomach cancer cases (for both sexes combined) and the standardised morbidity ratio (SMR) using Oman’s age-specific incidence rates of stomach cancer, 1997–2007*  

<table>
<thead>
<tr>
<th>Region</th>
<th>Observed number of cases</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addhahirah</td>
<td>20</td>
<td>0.29 (0.18–0.45)</td>
</tr>
<tr>
<td>Al-Wusta</td>
<td>4</td>
<td>0.47 (0.13–1.20)</td>
</tr>
<tr>
<td>Addakhliyah</td>
<td>69</td>
<td>0.66 (0.51–0.83)</td>
</tr>
<tr>
<td>Asharqiyah</td>
<td>131</td>
<td>1.02 (0.98–1.07)</td>
</tr>
<tr>
<td>Al-Batinah</td>
<td>307</td>
<td>1.21 (1.17–1.24)</td>
</tr>
<tr>
<td>Muscat</td>
<td>165</td>
<td>1.15 (1.10–1.20)</td>
</tr>
<tr>
<td>Dhofar</td>
<td>81</td>
<td>1.26 (1.00–1.56)</td>
</tr>
<tr>
<td>Musandam</td>
<td>20</td>
<td>1.60 (0.98–2.47)</td>
</tr>
</tbody>
</table>

*Includes malignant gastric lymphoma

The observed number of stomach cancer cases in Al-Batinah and Muscat was higher than would be expected if the age-specific stomach cancer incidence rates were the same as those for Oman as a whole. The 95% confidence intervals of the SMRs for the remaining regions included one. The confidence intervals for the SMRs for Musandam and Al-Wusta were very wide due to the small population. In 2001, Musandam had a population of 27,000 and Al-Wusta only 17,000 (Mohammed et al. 2003).

Although, there were noticeable fluctuations with time of the age-standardised incidence rates (ASR) for Oman, the trend shows an overall decrease for both sexes (Figure 11). Possible reasons for the observed fluctuations will be elucidated in the discussion.

**Figure 11**: The trend of age-adjusted annual incidence rate of stomach cancer in Oman*  
*Excludes malignant gastric lymphoma
Compulsory notification only started in 2001 in Oman, so the rates of stomach cancer by person, place and time were compared between the periods before and after 2001 to see whether there were any major differences. The difference in the age-standardised incidence rates between the two periods was negligible for both males and females. Further, almost all regional differences persisted even when the data were split (Table 10). Only for Asharqiyah was the direction different (lower than one prior to compulsory notification, but higher than one after compulsory notification), although in both periods the confidence interval included one. For Muscat, the confidence interval for the SMR included one for the two separate periods, but excluded one for the total period.

Table 10: The observed number of stomach cancer cases (for both sexes combined) and the standardised morbidity ratio (SMR) using Oman's age-specific incidence rates of stomach cancer for periods before and after compulsory notification (2001)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Observed number of cases</th>
<th>SMR (95% CI)</th>
<th>Observed number of cases</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addhahirah</td>
<td>6</td>
<td>0.20 (0.07–0.44)</td>
<td>14</td>
<td>0.36 (0.19–0.60)</td>
</tr>
<tr>
<td>Al-Wusta</td>
<td>1</td>
<td>0.32 (0.01–1.76)</td>
<td>3</td>
<td>0.56 (0.12–1.63)</td>
</tr>
<tr>
<td>Addakhliyah</td>
<td>29</td>
<td>0.66 (0.44–0.95)</td>
<td>40</td>
<td>0.66 (0.47–0.90)</td>
</tr>
<tr>
<td>Asharqiyah</td>
<td>46</td>
<td>0.88 (0.65–1.18)</td>
<td>85</td>
<td>1.11 (0.89–1.38)</td>
</tr>
<tr>
<td>Al-Batinah</td>
<td>122</td>
<td>1.17 (1.11–1.22)</td>
<td>185</td>
<td>1.23 (1.15–1.33)</td>
</tr>
<tr>
<td>Muscat</td>
<td>73</td>
<td>1.26 (0.99–1.58)</td>
<td>92</td>
<td>1.07 (0.86–1.31)</td>
</tr>
<tr>
<td>Dhofar</td>
<td>36</td>
<td>1.37 (0.96–1.89)</td>
<td>45</td>
<td>1.18 (0.86–1.58)</td>
</tr>
<tr>
<td>Musandam</td>
<td>10</td>
<td>1.85 (0.89–3.40)</td>
<td>10</td>
<td>1.41 (0.68–2.59)</td>
</tr>
</tbody>
</table>

*Includes malignant gastric lymphoma

This was probably due to the smaller number of cases when the data were split. A similar observation can be made for Dhofar, except that the confidence interval for the SMR for the total period just included one. Although the trend of the age-standardised incidence rates shows a decrease for the total period for both sexes, the trend was less clear when the data were split. The age-standardised incidence rate of males showed an increasing trend in the first period (1996–2000) and a decreasing trend in the second period (2001–2007). The opposite was seen for females: the trend showed a decrease in the first period, but an increase after compulsory notification (2001–2007). Above all, looking at the time trend in Figure 11, there seems to be no major change in 2001 in the observed rates after compulsory notification.
2.7.2. **Stomach cancer in GCC countries**

Age-standardised incidence rates of stomach cancer in the GCC countries showed wide variation. From 1998 to 2004, Oman had the highest age-standardised incidence rates for both sexes and in both age groupings, below 45 years and 45 years and above (Table 11). Saudi Arabia had the lowest rates for both sexes and both age-groups. Estimates of stomach cancer age-standardised incidence rates were not precise for countries like Qatar and Bahrain because of the small population.

**Table 11:** Age-standardised average annual incidence rate (per 100,000) of stomach cancer in the GCC countries stratified by sex and age, 1998–2004*

<table>
<thead>
<tr>
<th>Country</th>
<th>Males ASR (95%CI)</th>
<th>Females ASR (95%CI)</th>
<th>Below 45 years† ASR (95%CI)</th>
<th>45 years and above† ASR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oman</td>
<td>11.6 (10.4–12.9)</td>
<td>6.0 (5.2–7.0)</td>
<td>1.0 (0.8–1.3)</td>
<td>31.4 (28.5–34.4)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>3.1 (2.9–3.3)</td>
<td>1.7 (1.5–1.8)</td>
<td>0.26 (0.23–0.30)</td>
<td>8.4 (8.0–8.9)</td>
</tr>
<tr>
<td>UAE</td>
<td>6.6 (5.2–8.2)</td>
<td>3.4 (2.4–4.8)</td>
<td>0.54 (0.30–0.90)</td>
<td>18.3 (15–22.1)</td>
</tr>
<tr>
<td>Qatar</td>
<td>7.8 (5.0–11.6)</td>
<td>4.3 (2.3–7.8)</td>
<td>0.90 (0.30–1.8)</td>
<td>21.6 (14.7–30.7)</td>
</tr>
<tr>
<td>Bahrain</td>
<td>7.9 (6.0–10.1)</td>
<td>5.3 (3.8–7.1)</td>
<td>0.56 (0.30–0.98)</td>
<td>23.6 (19.1–28.9)</td>
</tr>
<tr>
<td>Kuwait</td>
<td>4.0 (3.0–5.3)</td>
<td>2.43 (1.7–3.4)</td>
<td>0.30 (0.20–0.50)</td>
<td>11.4 (8.9–14.3)</td>
</tr>
</tbody>
</table>

*Excludes malignant gastric lymphoma
†Males and females combined

To see whether chance could explain the higher rates of stomach cancer in Oman, the relative risk and the 95% CIs were calculated. Having Oman as the reference group, all the other GCC countries had a statistically significant lower risk in people aged 45 and above (Table 12), and among males (Table 13) with the exception of Qatar, where the confidence interval for the relative risk included one. Further, females and people aged below 45 years in UAE, Saudi Arabia and Kuwait had a statistically significant lower risk of stomach cancer than the corresponding group in Oman.
Table 12: Age and sex-standardised relative risks (RR) of stomach cancer in the GCC countries in reference to Oman by age-group, 1998–2004*

<table>
<thead>
<tr>
<th></th>
<th>Below 45 years</th>
<th>45 years and above</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95%CI)</td>
<td>RR (95%CI)</td>
</tr>
<tr>
<td>Oman</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>0.28 (0.21–0.37)†</td>
<td>0.26 (0.24–0.29)‡</td>
</tr>
<tr>
<td>UAE</td>
<td>0.54 (0.31–0.94)†</td>
<td>0.56 (0.45–0.69)‡</td>
</tr>
<tr>
<td>Qatar</td>
<td>0.78 (0.36–1.7)</td>
<td>0.69 (0.48–0.99)‡</td>
</tr>
<tr>
<td>Bahrain</td>
<td>0.57 (0.31–1.0)</td>
<td>0.74 (0.59–0.92)‡</td>
</tr>
<tr>
<td>Kuwait</td>
<td>0.32 (0.18–0.58)‡</td>
<td>0.37 (0.29–0.47)‡</td>
</tr>
</tbody>
</table>

*Excludes malignant gastric lymphoma
†P value <0.05
‡P value <0.01

Table 13: Age-adjusted relative risks (RR) of stomach cancer in the GCC countries in reference to Oman for males and females, 1998–2004*

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95%CI)</td>
<td>RR (95%CI)</td>
</tr>
<tr>
<td>Oman</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>0.26 (0.23–0.29)†</td>
<td>0.28 (0.23–0.33)†</td>
</tr>
<tr>
<td>UAE</td>
<td>0.55 (0.44–0.70)†</td>
<td>0.56 (0.40–0.79)†</td>
</tr>
<tr>
<td>Qatar</td>
<td>0.67 (0.44–1.0)</td>
<td>0.79 (0.46–1.4)</td>
</tr>
<tr>
<td>Bahrain</td>
<td>0.64 (0.49–0.84)†</td>
<td>0.85 (0.62–1.2)</td>
</tr>
<tr>
<td>Kuwait</td>
<td>0.33 (0.25–0.45)†</td>
<td>0.42 (0.30–0.59)†</td>
</tr>
</tbody>
</table>

*Excludes malignant gastric lymphoma
†P value <0.01

2.8. Discussion

Analysis of the incidence data in Oman revealed that the rate of stomach cancer differed by age, sex and region in Oman, with the time trend showing an overall decrease, albeit with significant fluctuations in the second period (2001–2007). Reported incidence data showed that Oman had higher age-standardised incidence rates of stomach cancer for both sexes and age-groups (below 45 years and 45 years and above) than most of the other GCC countries. Regression analysis showed that among males, all the GCC countries except Qatar had a statistically significant lower risk of stomach cancer than Oman. Among females, Saudi Arabia, UAE and Kuwait had a statistically significant reduced risk of stomach cancer than Oman. With regard to age groups, compared to Oman, all the GCC countries had a statistically significant lower risk of stomach cancer among people aged 45
years and above, but only Saudi Arabia, UAE and Kuwait had a statistically significant lower risk among people aged below 45 years. However, the incidence rates reported for Saudi Arabia and UAE may be under-estimated because of under-reporting.

To my knowledge, this is the first study to compare the incidence data of stomach cancer in Oman and the GCC countries. From the available incidence data published by the Omani National Cancer Registry, GCC cancer incidence reports, and the Cancer Incidence in Five Continents reports, Oman was thought to have higher stomach cancer rates than the surrounding GCC countries. Whether the higher reported incidence rates were genuine or false was still unknown. This was because, firstly, the various reports did not provide the 95% CI for the incidence rates in the GCC countries and, secondly, no data existed on the possible bias introduced by the variation in the completeness and quality of the cancer registration practices in the GCC countries. This study quantified the magnitude of the random fluctuation by calculating the RR and the 95% confidence intervals. In addition, a brief evaluation of the quality and completeness of the cancer registries was carried out in order to aid the discussion of the incidence rates in light of the quality and completeness of the data. Some in public health would argue against giving population-based estimates confidence intervals as there is no sampling involved, so they are not subject to that source of uncertainty. The contrary argument is that there are random environmental and biological processes that produce the cancers and affect the estimates (Brillinger, 1986).

This study has also analysed all the most recent available data in Oman and the GCC. Before combining data for the total period, separate analyses of the data before and after compulsory notification were carried out for Oman. Likewise, separate analyses were carried out for the GCC countries for the 1998–2002 and 2003–2004 periods (data not shown). This was done because Oman and UAE started compulsory notification only from around the beginning of 2001 (Mohammad et al. 2008, Tadmouri and Al-Sharhan, 2004) and it was thought that for the 2003–2004 period the uniform method for registering cancer cases among GCC countries might lead to more accurate comparisons.

However, a disadvantage of separating data (for both Oman and GCC countries) is lowering the stability of the results, given the low numbers of cases. Hence, because there were no major differences found between the two periods, Oman’s data were combined.

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1 Analysis was not possible using data before and after 2001, marking the onset of compulsory notification for Oman and UAE. This is because the data from 1998 to 2002 are combined in a single report. On the other hand, 2003 and 2004 data come in single reports.
Similarly, the data of the GCC countries were combined because the relative risk when comparing Oman to the other GCC countries was found to be similar (not statistically significantly different) for the two time periods (1998–2002 and 2003–2004). The only exception was Saudi Arabia in which the relative risk was found to be different in the two time periods when compared to Oman. Separate analyses for the 1998–2002 period and the 2003–2004 period showed that Saudi Arabia had a statistically significant reduced risk for both sexes and both age-groups in both periods compared with Oman. However, the risk was lower when using the 1998–2002 than when using the 2003–2004 data. This may be a sign of the improved completeness of the incidence data in Saudi Arabia, but the important point is that Saudi Arabia had a statistically significant reduced risk of stomach cancer compared to Oman. Nonetheless, even after comparing the relative risk for the different periods, bias from the varying degrees of completeness and quality of registering cancer cases in the GCC countries may still introduce spurious differences in the incidence of stomach cancer.

The limitations of this descriptive study were mostly related to the availability of information. Regarding Oman’s data, limitations could be identified when analysing regional variation and time trends. Firstly, for comparative analysis of the incidence rates in the regions indirect standardisation was carried out. Direct standardisation of the incidence rates was not possible because age and sex-specific incidence rates were not available. This may be a disadvantage of using published data rather than data from the cancer registry itself. Although both direct and indirect standardisation measures eliminate the confounding effect of age, direct standardisation is more useful in making cross-comparisons (for example, between regions). With only indirect standardisation, the standardised morbidity ratios calculated are not comparable to each other. The observed number of cases in individual regions could be interpreted only in relation to the standard population, which in this case was the population of Oman. However, indirect standardisation was appropriate in the context of Oman as the number of cancer cases stratified by region was very small.

Secondly, for estimating the trend over time, only for the last seven years has it been compulsory to notify cancer cases in Oman. This study found that although the rate was increasing for males and decreasing for females prior to compulsory notification, these rates changed in opposite directions after compulsory notification, albeit with significant fluctuations in the last few years which might have affected the direction of the trends (possible explanations for the fluctuation will be discussed later). A point to note is that
age-standardised incidence rates (ASR) were used instead of crude rates to study the trend over time. Since, the denominator for the incidence rate includes the total population, it will be affected by the fertility rate and life expectancy. Therefore age-adjusted rates were used for trends as they are less affected by such biases. Above all, the small number of cases certainly affects the stability of the ASR estimates and trend over time.

Thirdly, there was insufficient information available for judging the completeness and quality of the various GCC cancer registries. This limited the interpretation of the results of the comparative analysis. In order to compare cancer incidence data between countries, a thorough review of the quality and completeness of the data is needed first. This allows judging whether completeness and quality of data may explain the observed differences. However, review of the performance of the various cancer registries requires detailed information, such as the methods of case ascertainment, the stability of cancer data, the use of death certificates, the percentage of unknown cases, the percentage of microscopic verification and ill-defined cases. Most of these measures were unavailable for this project, which makes it difficult to interpret the observed incidence data. In the introduction, some of the indicators were discussed. For Saudi Arabia and UAE, the consistently lower risk of stomach cancer compared to Oman may be a result of under-reporting. However, the under-reporting needs to be considerable for Saudi Arabia to have similar rates to Oman (see tables 11–13). If there truly was no difference in the incidence of stomach cancer in Saudi Arabia and Oman, at least 400 stomach cancer cases alone would need to remain unregistered annually in Saudi Arabia to explain a RR of about 0.3. Similarly, about 35 stomach cancer cases would need to remain unregistered annually in the UAE in order to explain a RR of about 0.55. This argues against under-reporting explaining all the differences between Saudi Arabia and UAE on the one hand and Oman on the other. However, until further thorough exploration of the completeness and quality of the GCC countries cancer incidence data, no firm conclusions can be drawn.

As already discussed, there are no descriptive studies to my knowledge that have specifically aimed to compare the incidence of stomach cancer in Oman and the other GCC countries. Although incidence data were available for the GCC countries, this study specifically focused on stomach cancer and examined whether Oman may truly have a higher risk than the other GCC countries.

The findings of this study agree with existing data regarding the characteristics of stomach cancer. Most of the cancer registries included in the Cancer Incidence in Five Continents found that males have twice the incidence of females (Curado et al. 2007).
Other studies found, like this study, that the male-to-female incidence rate ratio approaches one among those younger than 40 years old, as distinct from those older than 40 years (Kulig et al. 2008, Katai et al. 1996, Kaneko and Yoshimura, 2001). In addition, data from long-established cancer registries showed a clear decline in the incidence of stomach cancer (Ferlay et al. 2004). Similarly, 12 years of data in Oman showed an overall decline, albeit with considerable fluctuations.

For studies, like this one, which compare incidence data among countries, there is usually a thorough check on the quality and completeness of the data to ensure that they are comparable [see for example, (Curado et al. 2007, Engholm et al. 2009)]. Data on stomach cancer site and histology are also usually available. However, the data released by the GCCR and used in this study were simply incidence data for all cancers in the GCC, with inadequate focus on quality and completeness, and there were no data on cancer site or histology. The unavailability of measures of quality and completeness of data hindered the ability to exclude incomplete reporting as a source of bias, at least for UAE and Saudi Arabia. In addition, given the lack of site and histology data (which may be a drawback of using only published rather than original data1), it was not possible to know which cancer site (cardia or non-cardia) or histology type (diffuse or intestinal) accounted for the differences. Such information is crucial for exploring the underlying causes of the differences in the incidence rates.

So, what might be the mechanisms behind the study’s findings? Analysis of Oman’s data revealed that the incidence of stomach cancer in males was twice as high as in females. Additionally, the male-to-female incidence rate ratio approached one in the age group below 45 years as compared to 45 and above.

The reason for the higher incidence of stomach cancer among males is still unclear. Some think it may be due mainly to variation in the degree of exposure to causative factors rather than differing inter-sex susceptibilities (Stewart and Kleihues, 2003). Some of the risk factors, such as \textit{H. pylori} infection, have been shown to be more prevalent in males than females (Moayyedi et al. 2002). However, given that stomach cancer is a multifactorial disease, it is probably false to attribute the sex difference to a single risk factor.

Stomach cancer occurring below 45 years of age is called “early onset gastric cancer” (Milne et al. 2007). It has a higher genetic component than stomach cancer occurring in the 45 and above age group, which is more governed by the environment.

\footnote{1 I was able to obtain original data only for Oman, not the other GCC countries.}
Also, young patients (less than 40) have been shown to be more likely to be diagnosed with diffuse type stomach cancer than older patients (those over 40) (Katai et al. 1996, Kulig et al. 2008). This type of cancer has a higher genetic component to its aetiology than intestinal type stomach cancer. Given the higher governance of genetic factors in stomach cancer occurring at a young age, the study’s finding that the sex incidence ratio approaches one for the less-than-45 age group may reflect the diminished effect of environmental causes.

The differences that exist between different places, either between the regions of Oman or between GCC countries, may simply be due to variations in the completeness of the data. In Oman, stomach cancer cases in regions such as Al-Wusta and Musandam may have been missed. This is because Al-Wusta and Musandam are relatively isolated and health care facilities are not as dense as in other regions of Oman. However, any remaining differences in the incidence of stomach cancer are likely to be due to differing prevalence or susceptibility to risk factors. Comparative analysis of the incidence data between GCC countries, stratified by age groups below and above 45, showed that Oman had a higher risk of stomach cancer than Saudi Arabia, Kuwait and UAE in both age groups. If this higher rate cannot be fully explained by differences in reporting, then this suggests that both environmental and genetic factors may be responsible for the differences observed. But within Oman whether the reason for differences in incidence of stomach cancer is more environmental than genetic is still unclear. One interesting finding is that regions along the coast (Al-Batinah, Muscat, Dhofar, Musandam and Asharqiyah) have SMRs higher than one. More inland regions (Addahirah and Addakhliyah) have SMRs lower than one. A possible hypothesis is the higher intake of salt-preserved fish in coastal regions as opposed to interior regions, but there are still no up-to-date data to test the hypothesis. Other environmental and genetic factors might still play a role.

Data from which the wider GCC stomach cancer incidence rates were obtained were not sufficient to study the trends over time, especially since the data for the period 1998–2002 were combined. However, in this study, the trend of Oman’s stomach cancer incidence over 12 years was explored. From 1996 to 2002, incidence showed minimal fluctuations and linear regression showed an increasing trend in males as opposed to a decreasing trend in females. But in 2003 there was a large drop for both sexes and subsequently a large increase in 2004 and 2005. The 2003 drop and the 2004 unexpected, unbalanced increase were also seen to affect many other major cancers in Oman (Mohammad et al. 2008). It would be prudent to think about a systemic cause.
possible reason is a non-efficient surveillance system in registering new cancer cases, perhaps a lack of staff in that year (personal communication, the director of the department of the Non-Communicable Disease Control, Jawad Al-Lawati, 2009). Another potential explanation which was offered was that the 2004 increase could be due to the opening of the National Oncology Centre in Oman. As well as bringing all cancer patients to one specialised centre for treatment, the centre introduced radiotherapy treatment in Oman for the first time. This may have facilitated capturing some of the cancer cases which might otherwise have been missed. For example, patients who required radiotherapy used to be sent abroad for treatment prior to 2004.

Nevertheless, from the trends seen, even though compulsory notification started in 2001, no clear rising trend in the incidence rates was evident. It should be remembered that compulsory notification improves “passive” reporting of cancer cases to the cancer registry by the treating physician. However, if “active” collection of cancer cases by the cancer registry personnel from all corresponding hospitals was already efficient, an improvement in passive reporting through compulsory notification would not necessarily mean more cases being captured. Likewise, if passive notification had not improved after compulsory notification, the ASR would not change. Above all, the non-clear rise in incidence rate may be due to the small number of stomach cancer cases overall and so a decrease through normal variation in 2001 may have disguised the increase in incidence rate. In worldwide cancer registries in which data for stomach cancer has been available for a very long time, there is a clear decreasing in trend in the incidence rate (Parkin et al. 2005b). Such a decrease was not achieved through preventive measures in most countries and so has been called an unplanned triumph (Howson et al. 1986). Possible reasons include improvements in sanitation and using refrigeration.

This study’s implications are of more relevance to health policy makers in Oman than to clinicians. In the study, Oman was found to have a higher risk of stomach cancer for males than all the other GCC countries except Qatar, and a higher risk for females than Saudi Arabia, Kuwait and UAE. It is still uncertain whether the burden of stomach cancer in Oman is likely to persist or increase given that the trend of the incidence showed an overall decrease. Nevertheless, as the burden of non-communicable diseases rises in Oman from rising life expectancy (Al-Lawati et al. 2008), the burden of cancer overall will likely increase. Whether it relates only to stomach cancer or to all cancers, improving cancer registration practices is valuable. Completeness and quality of the data are two important entities and, if optimal, generate robust statistics about the disease. Completeness of the
data eliminates any uncertainty in the differences of incidence between places and enables reliable studies of trends over time. Also good quality data are required to analyse cancer incidence by site and histology. Site is especially important for exploring possible causes of stomach cancer. Unfortunately, the Omani cancer registry does not record cancer site reliably for stomach cancer (see chapter four), a problem which may arise from poor registration practices by clinicians, or by cancer registry personnel. In the meantime, the apparently higher incidence of stomach cancer in Oman warrants further research into potential risk factors. Until then the targets of primary preventive measures will be vague. Neither will screening be cost-effective, at least at present, as a measure of preventive control since the crude incidence rate in Oman is only about 3 per 100,000 for males and even less for females. If the trend of the incidence of stomach cancer is a continued decrease, there may be no need for instituting any preventive measures.

To conclude, it may seem odd that stomach cancer in Oman is the most common cancer among males, given that it is not even among the top five most common cancers in most GCC countries (Al-Zahrani et al. 2006). Although the GCC countries share much in terms of customs and lifestyle, it is still uncertain whether the higher rate of stomach cancer in Oman, compared to at least Saudi Arabia and UAE, is real or whether it is due to differences in the completeness of the data. Future studies may aim to evaluate the completeness and quality of the data in the GCC countries. In addition, exploring the difference in the incidence of stomach cancer between Oman and the GCC countries by histology and sub-site would be useful for estimating the contribution of certain risk factors to the overall incidence. Comparing the prevalence of known risk factors for stomach cancer among the GCC countries may be a good start in hypothesising a reason for the apparent higher risk of stomach cancer in Oman. Chapter three aims to do just that.
3. CHAPTER THREE – RISK FACTORS FOR STOMACH CANCER IN THE GULF COOPERATION COUNCIL COUNTRIES: AN ECOLOGICAL STUDY

3.1. Introduction

Knowledge of the distribution of causal factors of a disease at a population level is important, especially to health policy makers, for instituting preventive measures. However, when the burden of a disease might be caused by several factors it may be difficult to establish which preventive strategy would be the most effective.

Traditionally, because of the numerous biases involved, the use of ecological studies has been associated with hypothesis generation rather than establishing causal relationship. In particular, the ecological fallacy may occur where a relationship observed between an exposure and an outcome at a population level is different from that seen at an individual level. Later, when hypotheses get supported by more robust analytical studies, ecological studies of such causes may become pointless. They can, however, be of benefit in making inter-country comparisons when only population aggregate data are available for exposure and outcome. This presumes exposure and outcome are measured in a similar way across countries, otherwise the statistics may not be comparable.

In chapter two, it was found that the age-standardised incidence rate of stomach cancer in Oman appears to be higher than in the other neighbouring Gulf Cooperation Council (GCC) countries. Estimated relative risks showed that all the GCC countries except Qatar had a lower risk of stomach cancer than Oman among males. Among females, Saudi Arabia, UAE and Kuwait had significantly lower risks of stomach cancer than Oman. Given that the GCC countries are generally believed to have similar lifestyles, the seemingly higher incidence of stomach cancer in Oman compared to the GCC countries merits investigation. As discussed in chapter one, factors which have been explored in analytical studies and subsequently shown to be associated with stomach cancer include *H. pylori* infection, high salt intake, smoking, body overweight, low fruit and vegetable intake and low socioeconomic status.
This chapter explores possible reasons for why Oman might have a higher incidence of stomach cancer than the other GCC countries. The aims are listed below.

3.2. **Aims**

A) To review the literature regarding the prevalence of the known risk factors for stomach cancer in the general population in the GCC countries.

B) For any available data, to undertake an ecological analysis to see whether such risk factors may explain Oman’s high stomach cancer incidence rate.

3.3. **Methods**

3.3.1. **Data sources**

A review of health literature and key websites was carried out. A search of the medical or health literature was made using Medline to find information on the prevalence of the following factors which are known to either increase or decrease the risk of stomach cancer: *Helicobacter pylori*, salt/salty food intake, fruit and vegetable intake, body overweight, smoking. The search was made for each country separately. When searching Medline, a very broad search strategy was used in order to capture as many papers as possible. Keywords included: the individual GCC country names, “Helicobacter pylori”, “salt intake”, “dietary sodium”, “fruit”, “vegetable”, “body mass index”, “overweight”, “obesity” and “smoking”.

The websites of the Ministries of Health in the GCC countries were searched for any population-based surveys measuring any of the risk factors. In addition, the WHO global info database ([http://apps.who.int/infobase/report.aspx](http://apps.who.int/infobase/report.aspx)) and publications were searched for the prevalence of smoking, body overweight and fruit and vegetable intake in the GCC countries. The Food and Agriculture Organization (FAO) statistical database ([http://faostat.fao.org/site/291/default.aspx](http://faostat.fao.org/site/291/default.aspx)) was also searched for fruit and vegetable consumption. Finally, information on socioeconomic status (SES) was searched for in the United Nations ([http://www.un.org](http://www.un.org)) and the Central Intelligence Agency (CIA) ([https://www.cia.gov/](https://www.cia.gov/)) websites.

3.3.2. **Inclusion criteria**

Data on the estimates of prevalences of risk factors in each of the GCC countries were restricted to citizens because the incidence rates of stomach cancer were for GCC
citizens only. Comparing the estimated prevalences of risk factors in the GCC countries where expatriates are included may bias the results as the proportion and the ethnicity of expatriates may differ between the countries. In addition, prevalence estimates were included if the data were obtained from a randomly selected sample which was likely to be representative of the whole population. In cases where more than one estimate was available for a particular country, studies which were thought to cover a larger proportion of the population and were no less recent than the studies found from other regions were chosen. Estimates of the prevalence of *H. pylori* infection were limited to those studies assessing individuals free from upper gastrointestinal tract symptoms. Prevalence estimates from all studies meeting the inclusion criteria are presented in the results section.

3.4. **Statistical analysis**

Age-standardised incidence rates of stomach cancer in the GCC countries for the period 1998–2004 were used in the ecological analysis. These were derived from the GCC cancer incidence reports as described in chapter two.

Where data were available, prevalences of risk factors were age-standardised to the World Standard Population of Segi (Segi, 1960). Confidence intervals for the age-standardised prevalence of current smokers come from the source. However, confidence intervals for the age-standardised prevalence of body overweight were calculated using methods for confidence intervals for weighted sums of proportions. The ecological graphs were produced using the software STATA 10.1.

3.5. **Results**

3.5.1. *Helicobacter pylori*

An estimate of the prevalence of *H. pylori* infection in individuals free from upper gastrointestinal tract symptoms was available only for Saudi Arabia.

A study by Al-Moagel et al. (1990) aimed to investigate *H. pylori* infection among Saudis living in the capital city of Riyadh. A random sample of 80 families was selected from each of six chosen primary health care centres which were thought to be representative of the total population (total families=480). Members of each family were invited to attend the primary health care clinic for participation in the study. Results showed that 66% of asymptomatic subjects tested positive for *H. pylori* serology. Investigators reported that at least 1 member from each of 377 families agreed to
participate giving a response rate of 78% at a family level. A response rate for all participants invited was missing, which is likely to be even lower than 78% because families are composed of at least 2 people. Therefore, the low response rate may have affected the true estimation of *H. pylori* infection prevalence. For example, the estimated prevalence may be underestimated in the case where the majority of non-attendees were of lower SES, because of the higher *H. pylori* infection rate in this group.

Another study, carried out in another city (Mekkah) in Saudi Arabia, investigated the prevalence of *H. pylori* infection among healthy individuals accompanying patients to four main hospitals. It found that the prevalence of positive *H. pylori* serology was only 51% (Khan et al. 2007). Again, there was no response rate given, but more importantly, the age span of subjects was from 15–50 years. In contrast to the previously mentioned study, where there was no restriction on age, the age restriction of this study might have led to the lower reported rates because *H. pylori* infection prevalence had earlier been found to increase with age (Al-Moagel et al. 1990).

Both studies, by Al-Moagel et al. and Khan et al. did not report confidence intervals for their estimated prevalence of *H. pylori* infection.

### 3.5.2. Salt intake

No data were found for salt intake for any of the GCC countries.

### 3.5.3. Body overweight

The characteristics of the studies which met the inclusion criteria, and from which prevalence data regarding body overweight were used in the present study, varied greatly (Table 14). For Oman, another study by Al-Riyami and Afifi (2003) met the inclusion criteria but it was found to have analysed the same data as the study by Al-Lawati and Jousilahti (2004). The Coronary Artery Disease in Saudis (CADIS) study in Saudi Arabia (Saudi Heart Association, 2000) met the inclusion criteria, but raw data for this study were missing.

Comparison of the prevalence of body overweight in GCC countries, obtained from the different studies, was restricted to those 30–60 years old, and it was age-standardised. The estimated prevalence of body overweight in this age range was found to be statistically significantly lower in Oman than in the other GCC countries for both sexes.
3.5.4. Smoking

Although, in the literature, there were many studies which assessed the prevalence of smoking in the GCC countries, they differed greatly in terms of the age group studied, their definitions of current or former smoker, and the type of smoking. However, the WHO “Report on the Global Tobacco Epidemic” (World Health Organization, 2008b), reports age-standardised prevalence in the WHO member countries with a clear standard definition and type of smoking. Therefore, to compare the prevalence of smoking in the GCC countries, data were obtained from this report. It is worth noting that the studies from which the report obtained its data match the inclusion criteria for the present study. The

Table 15: The estimated prevalence of current cigarette smokers in the GCC countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oman</td>
<td>24.4 (20.6–28.1)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>25.2 (21.4–28.9)</td>
<td>3.0 (1.2–4.8)</td>
</tr>
<tr>
<td>Bahrain</td>
<td>25.7 (22.1–29.4)</td>
<td>2.1 (0.9–3.4)</td>
</tr>
<tr>
<td>Kuwait</td>
<td>Not Available</td>
<td>Not Available</td>
</tr>
<tr>
<td>Qatar</td>
<td>Not Available</td>
<td>Not Available</td>
</tr>
<tr>
<td>UAE</td>
<td>26.8 (21.6–32.1)</td>
<td>1.7 (0.2–3.2)</td>
</tr>
</tbody>
</table>

* Standardised to the World Standard Population
literature was searched for any newer studies which might not have been included in the report, but none were found.

The estimated prevalence of current smokers for males was about a quarter for all the GCC countries, with no evidence of a difference (Table 15). For females, the prevalence estimates of current cigarette smokers were much lower than for males, and lowest for Oman. However, the absolute differences between countries were very small. Among females, bias may play a big role because smoking for females in many Islamic countries including the GCC countries is perceived as immoral. Females are therefore likely to hide their smoking habit.

### 3.5.5. Fruit and vegetable intake

Figures on fruit and vegetable intake from the Food and Agriculture Organization were not used in this study because they are representative of the total population, not only citizens. Using such figures might not reflect estimates specifically for a country’s citizens. Additionally, figures for Oman, Qatar and Bahrain were not available.

**Table 16:** The characteristics of the studies used for comparing the prevalence of fruit and vegetable intake in the GCC countries

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Number</th>
<th>Sample</th>
<th>Response Rate (%)</th>
<th>% Never/rare intake</th>
<th>% Daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fruit</td>
<td>Vegetable</td>
</tr>
<tr>
<td>Oman</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>F 420</td>
<td>NA</td>
<td></td>
<td>F 2.6</td>
<td>F 3.3</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>2000</td>
<td>M 8,189</td>
<td>Cross-sectional survey; &gt;30 years.</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F 8,952</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 17,141</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>F 8,952</td>
<td>Cross-sectional survey; &gt;30 years.</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 17,141</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>M 270</td>
<td>Health clinics survey; &gt;19 years.</td>
<td>&quot;low&quot;</td>
<td>M 9.3</td>
<td>M 7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F 316</td>
<td></td>
<td></td>
<td>F 15.2</td>
<td>F 14.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 586</td>
<td></td>
<td></td>
<td>B 12.5</td>
<td>B 10.9</td>
</tr>
<tr>
<td>Kuwait</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qatar</td>
<td></td>
<td>M 150</td>
<td>Out-patient clinic; &gt;20 years.</td>
<td>NA</td>
<td>M 1.3</td>
<td>M 1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F 125</td>
<td></td>
<td></td>
<td>F 10.7</td>
<td>F 10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 275</td>
<td></td>
<td></td>
<td>B 6.2</td>
<td>B 5.5</td>
</tr>
<tr>
<td>UAE</td>
<td>1993</td>
<td>M 1,122</td>
<td>Cross-sectional survey; &gt;20 years.</td>
<td>NA</td>
<td>M 5.2</td>
<td>M 2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F 1,090</td>
<td></td>
<td></td>
<td>F 4.5</td>
<td>F 2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 2,212</td>
<td></td>
<td></td>
<td>B 4.8</td>
<td>B 2.7</td>
</tr>
</tbody>
</table>

NA=Not available  M=Male  F=Female  B=Both sexes  *Survey for both fruit and vegetable

References:
1(Musaiger et al. 2005b); 2(Saudi Heart Association, 2000); 3(Musaiger et al. 2005a); 4(Musaiger and Al-Mulla, 1998); 5(Musaiger and Abuirmelik, 1998)
Studies from which data on the prevalence of fruit and vegetable intake were used varied in terms of the targeted sample of the population and the method of sampling (Table 16). There seems to be a lower percentage of females who are rare or never consumers of fruit and vegetables in Oman than in the other GCC countries and a higher percentage of females who are daily consumers of fruit and vegetables in Oman than in the other GCC countries.

3.5.6. Socioeconomic status

Socioeconomic status indicators were obtained from the Central Intelligence Agency (2009). The CIA obtains information for each country from census and population-based surveys. Among the GCC countries, Oman’s literacy rate\(^1\) and annual income per capita were found to be among the lower ones (Table 17). Additionally, the unemployment rate in Oman and Bahrain was found to be higher than in the other GCC countries.

<table>
<thead>
<tr>
<th>Table 17: Socioeconomic indices in the GCC countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socioeconomic status</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Oman</td>
</tr>
<tr>
<td>Saudi</td>
</tr>
<tr>
<td>Bahrain</td>
</tr>
<tr>
<td>Kuwait</td>
</tr>
<tr>
<td>Qatar</td>
</tr>
<tr>
<td>UAE</td>
</tr>
</tbody>
</table>

* Only available for males

3.5.7. Risk factors in relation to stomach cancer in the GCC countries

To help interpret the data in relation to stomach cancer, stomach cancer incidence rates and the estimated prevalence of smoking, socioeconomic status and BMI in the GCC countries are shown in Figure 12. The size of the dots reflects the number of stomach cancer cases in the country. Note that it is important not to infer any causal relationship from this figure. Inaccuracies in the estimates of incidence of stomach cancer and

\(^1\) Proportion of the population who are above 15 years old who can read and write (reading and writing level were not specified).
prevalence of risk factors, the multi-causal nature of stomach cancer, and biases in ecological studies, can all affect the relationship of a risk factor to stomach cancer.

Figure 12: The age-standardised incidence rates of stomach cancer in the GCC countries and the prevalence of risk factors associated with stomach cancer
Key: O=Oman  S=Saudi Arabia  U=UAE  B=Bahrain  K=Kuwait  Q=Qatar
3.6. **Discussion**

This study found that Oman seems to have lower SES, and lower levels of smoking and body overweight, than the other GCC countries. In addition, there seems to be a higher percentage of daily consumers, and lower percentage of rare/never consumers, of fruit and vegetables among females in Oman compared to the other GCC countries. Data on the prevalence of *H. pylori* infection and salt intake were largely unavailable. In relation to stomach cancer, only SES, but not the prevalence of smoking, body overweight, or fruit and vegetable intake, was found to possibly explain the higher stomach cancer incidence rate in Oman compared to the other GCC countries.

This is the first study to try to find a potential explanation for the apparently higher stomach cancer incidence rate in Oman than the other GCC countries. The prevalences of all known environmental risk factors for stomach cancer were sought for all the GCC countries. Such risk factors had been previously tested in more robust studies and were presumed to be causal. This study sought to make cross-group comparisons of the prevalences of risk factors for stomach cancer and subsequently hypothesised whether any differences might explain the apparent higher incidence of stomach cancer in Oman than the other GCC countries. Looking across countries where there is variation in cancer incidence rates provides an opportunity to identify risk factors which may be important at a population level.

Prevalence estimates of risk factors that are known to differ by sex and age, such as smoking and BMI, were age-standardised and stratified by sex. This removed any distorting effects of differing age and sex structures. However, the design of this study limited the ability to examine the independent effects of various risk factors when a single risk factor was studied. This is especially important for stomach cancer given the many risk factors associated with its development. Therefore, although this study tested each risk factor independently, attempting to relate the differences in the incidence rates of stomach cancer in the GCC countries to a single factor may be oversimplifying. Also, some factors may be interlinked such as socioeconomic status with smoking or *H. pylori* infection. Another limitation of this study was the lack of precision in the estimated prevalences of risk factors. Confidence intervals for the estimated prevalences (for example, smoking and overweight) were wide. For others, like socioeconomic status, confidence intervals were missing. Lastly, the availability of data for the prevalences of risk factors in the GCC countries limited the risk factors which could be analysed.
Information on the prevalence of *H. pylori* infection and salt intake in the GCC countries was scant. Therefore, no conclusion was possible regarding these two risk factors although both are important for stomach cancer (Crew and Neugut, 2006). Unfortunately, no information was available for salt intake, and despite an abundance of studies on the prevalence of *H. pylori* infection among dyspeptic patients in the GCC countries, they were inappropriate for the purpose of this study [see for example, (Abahussain et al. 1998, Al Qabandi et al. 2005, Zaitoun, 1994, Akbar et al. 2005, Ayoola et al. 2004, Bindayna et al. 2006)]. This is because *H. pylori* is known to cause peptic ulcers and gastritis (Stewart and Kleihues, 2003) so that the prevalence of *H. pylori* infection among such individuals may not truly reflect the prevalence in the general population. Parkin (2004) estimated the prevalence of *H. pylori* infection among asymptomatic individuals in the GCC countries to be 65–74%. The estimate was based on reported figures for the prevalence of *H. pylori* infection from neighbouring countries. In reality, such estimates may not be correct as the prevalence of *H. pylori* infection is governed by many factors, including socioeconomic status, crowdedness (Moayyedi et al. 2002) and age (Rothenbacher and Brenner, 2003). Parkin was exploring global differences and therefore averaging over all the GCC countries, whereas the present study attempts to find differences between the GCC countries.

The link between body overweight and stomach cancer seems to be site-specific. Overweight has been shown to increase the incidence of stomach cancer of the cardia (Kubo and Corley, 2006, Hampel et al. 2005), but is less closely associated with stomach cancer of the non-cardia (Whiteman et al. 2008, Sjodahl et al. 2008, Merry et al. 2007) which comprises the majority of stomach cancer cases. From the available information, cancer of the cardia appears to make a very small proportion of stomach cancer cases in Kuwait, Bahrain and Oman (Curado et al. 2007) (data are unavailable for UAE, Saudi Arabia and Qatar). Unfortunately, the incidence of stomach cancer specific to the cardia was not available for all the GCC countries. Thus, the incidence of total stomach cancer was used in this study.

Many observational studies have shown an increased risk of stomach cancer (both cardia and non-cardia) with both longer duration and higher intensity of cigarette smoking (International Agency for Research on Cancer, 2004). Only prevalence for current and daily tobacco use is reported in the WHO publication on the global tobacco epidemic. Therefore comparing current (as in the present study) or daily smokers in the different
countries may not truly reflect the risk for stomach cancer, as both duration and intensity are not taken into account.

Caution should be taken before drawing any conclusions from the comparison of the frequency of fruit and vegetable intake in this study. This is because the studies from which prevalences were obtained varied in their sampling methods and inclusion criteria. Age-standardisation was not possible because data by age and sex were largely unavailable in the studies. Also, a response rate was missing for many studies. Oman’s study was only for females aged 20–70 years, and the other GCC countries reported figures for different age groups and included both sexes. Above all, given that data on the prevalences came from different studies, they were prone to interviewing bias. This might be the cause for the huge difference in daily fruit and vegetable intake between Qatar and the other GCC countries (Table 16). Lastly, the available studies on fruit and vegetable intake in the GCC countries all used interviewer-administered food frequency questionnaires. Although quantity may be more specific than frequency, estimating quantity using food diaries is much more difficult in practice, and takes more time and money, than using food frequency questionnaires (McNeill et al. 2009). Some observational studies have found that recall of past consumed food can be altered by current dietary habits (Jensen et al. 1984, Thompson et al. 1987). This is especially important for stomach cancer patients as they might change their diet due to gastritis.

Although this study showed that individuals living in Oman on average have a lower socioeconomic status than most GCC countries, the missing 95% confidence intervals for the estimates precluded firmer conclusions. Also it is still uncertain whether the socioeconomic indicators used in this study (literacy, income and unemployment) reflect the true socioeconomic status. The link between lower socioeconomic status and stomach cancer is likely to be indirect because socioeconomic status is linked to smoking, diet and *H. pylori* infection. A nested case-control study which used education as a measure for socioeconomic status found that, in fact, *H. pylori* might be the causal factor behind the higher incidence of stomach cancer among lower socioeconomic status individuals (Nagel et al. 2007). Until the prevalence of *H. pylori* infection is explored in the GCC countries, the link between *H. pylori* infection and socioeconomic status, and their roles in the higher incidence of stomach cancer in Oman, must stand on speculative ground.

No previous studies have explored the reason for the apparent higher rate of stomach cancer in Oman compared to the other GCC countries, but there are a few studies
which have examined a similar problem elsewhere. Kneller et al. (1992) measured the prevalence of known risk factors for stomach cancer in 65 counties in China, in order to explore the disparities in the observed mortality rates. Results showed that a higher prevalence of *H. pylori* infection and higher salt intake were associated with higher mortality rates, whereas a higher intake of green vegetables was found to possibly decrease mortality. In contrast to the present study, Kneller et al. (1992) measured risk factors directly (by testing a randomly selected 100 residents from a randomly selected pair of towns in each county and testing them for *H. pylori* infection) rather than obtaining data from different sources. Measuring risk factors directly has the advantage of consistency in the measurements and a better understanding of the associated limitations. Another study carried out in the United States aimed to determine the reason for the difference in stomach cancer incidence rates in two different states (Correa et al. 1990). The study found that *H. pylori* infection and socioeconomic status were both possible reasons for the higher incidence rate of stomach cancer in one of the states.

From the available data, the present study hypothesises that the lower socioeconomic status in Oman may be a reason for the higher stomach cancer incidence rates there compared to the other GCC countries. The link may be mediated through a higher rate of *H. pylori* infection. Other factors such as smoking, body overweight and fruit and vegetable intake seem less likely to explain the observed difference in the incidence rates. For other risk factors such as salt intake, the unavailability of data means no conclusion can be drawn.

Because of the uncertainty in some of the estimates of the prevalences of risk factors, it may be imprudent to make recommendations for policy makers or clinicians. Before doing so, more robust epidemiological studies should be undertaken to test this study’s hypothesis for the reason behind the apparent higher incidence of stomach cancer in Oman compared to the other GCC countries. Because of the multi-factorial aetiology of stomach cancer, there is also likely to be more than one reason. Until such studies are done, strong evidence for instituting any preventive measures will remain lacking. Nevertheless, there are other good health reasons, such as prevention of cardiovascular diseases, to increase fruit and vegetable intake, decrease cigarette smoking, decrease obesity and address SES disparities.

The reason for the higher incidence of stomach cancer in Oman compared to the other GCC countries still warrants further research. In the future, second phase work may explore this research question using analytical studies. One such proposal might involve
recruiting people from all the Gulf countries and exploring the prevalence of the known risk factors for stomach cancer.
4. CHAPTER FOUR – MORTALITY AND SURVIVAL OF OMANI STOMACH CANCER PATIENTS

4.1. Introduction

Stomach cancer is the most common cancer among males in Oman (Mohammad et al. 2008). What is more, the age-adjusted incidence rate of stomach cancer in Oman appears to be higher than in the neighbouring Gulf Countries (Al-Zahrani et al. 2006). Despite the availability of incidence data, information regarding mortality from stomach cancer in Oman is still lacking. This undoubtedly leaves a big gap in understanding the magnitude of its burden. But there are aggregate hospital-based death figures (Figure 13).

![Figure 13: Trend of hospital-based mortality (per 100,000) from stomach cancer in Oman](image)

Note: Figure generated by accumulating figures reported in the Omani cancer incidence reports

Although there seem to be decreasing and increasing trends, respectively, in mortality from stomach cancer in males and females, one should be cautious in assuming that the figures are representative of the whole population, as many do not die in hospital. Further, the reported mortality rates are lower than what is expected from worldwide mortality and survival studies of stomach cancer (Parkin et al. 2005a). Thus, it would be prudent to view the reported figures from hospital-based deaths as an underestimate of the true mortality from stomach cancer in the total population of Oman.
Studies of cancer survival in Oman, to my knowledge, are all hospital-based [see for example, (Faris, 2003, Al-Moundhri et al. 2004, Al-Moundhri et al. 2006, Al-Moundhri et al. 2007)]. Patients who do not die in hospital and are lost to follow-up are censored. At the time this research was initiated, Oman had only recently established a national vital registration system, the Directorate General of Civil Status (DGCS). Hence, for the first time it was theoretically possible to establish the vital status of cancer patients on a national scale.

Given that Oman appears to have high stomach cancer rates, an accurate understanding of the health effects of stomach cancer is important. This chapter presents research undertaken to determine the mortality and survival of Omani stomach cancer patients. The specific aims are set out below.

4.2. **Aims**

A) To describe the methods of collecting mortality data in Oman.

B) If accurate and complete causes of death data are available, to calculate population-based age-standardised stomach cancer mortality rates in Oman.

C) To obtain a population-based estimate of median and relative survival of people with stomach cancer in Oman by linking the records at National Cancer Registry to the Directorate General of Civil Status.

D) To assess the feasibility of routinely linking the records at the National Cancer Registry to the Directorate General of Civil Status to calculate population-based cancer-specific survival rates.

4.3. **Mortality: A vital registration**

Combating health problems and their causes requires genuine knowledge of the extent and spread of a particular problem and its change over time. Indeed, such timely information, while it necessitates continuous monitoring, is vital for policy makers in order to effectively prioritise health care. Certainly one important statistic is mortality. Most, if not all countries, legislate in order to institute and maintain a well planned registration system for documenting deaths and their causes. Alas, utilisation of such statistics is still far from optimal, especially in Africa, the Eastern Mediterranean, South East Asia and Western Pacific (Mathers et al. 2005).
Ideally, vital registration systems should cover the whole defined population, achieve 100% completeness and reliably record age, sex and cause of death (Mathers et al. 2005). For improved comparability of data between countries, the United Nations set up guidelines for vital registration in 1953 (revised in 1973 and 2001) (Mahapatra et al. 2007). In addition, the World Health Organization (WHO) adopted the “International Classification of Diseases” for documenting cause-of-death data. Medical certification of cause-of-death data has been standardised to include direct, underlying cause, and any co-morbidity (World Health Organization, 1979). As a result, consistency in ascertaining causes of death from data can be achieved between countries.

A proper mortality system needs to be adequately funded and well instituted. Whereas richer countries achieve data with high-quality and completeness, poorer countries often fail to do so, thus making vital registrations non-comparable among many nations. Also, in both more- and less-developed countries, there are often societal or legal reasons which can compromise completeness and quality of vital registration data.

4.4. Oman’s mortality system

Mortality registration in Oman is relatively young. Although civil registration started gradually after 1970, a proper mandatory birth and mortality registration system for the whole country was only established in May 2004. Prior to 2004, mortality registration in Oman was mostly based on deaths in Ministry of Health (MOH) institutions (i.e. governmental health care centres). Deaths in the community occasionally were documented at a paper-based system in regional directorates of health services, especially if a death certificate was needed. At that period, completeness and quality of mortality data were known to be poor. Mathers et al. (2005) used life tables estimated by the World Health Organization (WHO) (Lopez et al. 2002) to assess completeness of death registration of all WHO members submitting mortality data. The authors also used the percentage of ill-defined causes of death as an indicator of data quality. Subsequently, they

<table>
<thead>
<tr>
<th>Class</th>
<th>Completeness of death registrations</th>
<th>Ill-defined causes of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-quality</td>
<td>&gt;90%</td>
<td>and</td>
</tr>
<tr>
<td>Medium-quality*</td>
<td>70–90%</td>
<td>or</td>
</tr>
<tr>
<td>Low-quality</td>
<td>&lt;70%</td>
<td>or</td>
</tr>
</tbody>
</table>

*Includes datasets with high quality but using non ICD codes
categorised countries into three sets: those with high, medium and low quality data. Table 18 shows the categorisation criteria. In general, findings showed that high-income countries had high quality mortality data, save for a few like France and Germany (categorised as medium). Conversely, low-income populations had low quality data. Oman’s mortality data were classified as low quality. It’s worth mentioning that this evaluation was based on 1997, 2000 and 2001 data from Oman which at the time were still mostly based on deaths from MOH institutions only. The result of the evaluation of Oman’s data was not surprising since the MOH institutions cannot be regarded as a representative or random sample of the population. In addition, mortality from health care centres only might be biased by several factors including the nature of the disease and access to health care.

Hence, in May 2004, the Directorate General of Civil Status (DGCS), a population-based registry, was established as the body where all vital registrations (births, deaths, marriages and divorces) should be reported to. The DGCS also took over the issuing of vital registration certificates from the MOH. Laws were enacted to ensure maximum completeness. Notification of deaths occurring in hospitals, outside hospitals and outside the country was established as a legal requirement for, respectively, all health care centres, families and Omani missions outside the country (Figure 14). Unfortunately, the DGCS lacked the capability of documenting all deaths and causes of death, and was deficient in other areas like recording the mothers of new born children (Ministry of Health, 2008a). Therefore, since May 2004, all deaths notified to the DGCS were sent to the MOH,
primarily to record cause-of-death data. A parallel mortality database (PMD) was set up at the MOH; it records deaths from MOH institutions and those redirected from the DGCS.

The efficiency of flow of data is still unknown, but coordination between the PMD and DGCS may not be optimum for various bureaucratic reasons (personal communication with Director of Health Information and Statistics (MOH) and Operation Manager (DGCS), 2009). One of the problems is that the DGCS database is held within the police IT network,\(^1\) and they have concerns regarding letting non-police personnel (for example, MOH) have access to it. However, this problem could be avoided if the DGCS were simply to send electronic mortality data files to the PMD. The Ministry of Health has succeeded in putting in place their electronic database in some private health care centres such as Sultan Qaboos University Hospital (SQUH), by May 2004, and the Armed Forces Medical Services (AFMS) (see Figure 15). This is to ensure a better flow of data.

With the establishment of the DGCS, coverage and completeness is thought to have improved since May 2004, albeit by unknown magnitude, but the improvement in the quality of cause-of-death data may be much less satisfactory. Unfortunately, as already discussed the DGCS does not record cause-of-death data and the cause-of-death data in the PMD is far from being accurate, at least from 2006 until 2008. An external reviewer of the Omani national health statistics and information system has found that physicians get the underlying cause of death wrong 91% of the time because the coding personnel

\(^1\) It is convenient for the DGCS database to be held within the police IT network because the police IT network is also responsible for issuing ID cards and passports which are part of the civil status.
(physicians) are not trained coders and the computer program put in place forces coders to choose from an incorrect list of the International Classification of Diseases (Ministry of Health, 2008a).

4.5. Methods for determining the survival of stomach cancer patients in Oman

The original plan was to link records between the National Cancer Registry (NCR) and the DGCS only. Once it was discovered that the DGCS database might not be complete, the plan was changed to seek deaths from the PMD also. However, it was discovered that the cause-of-death data, although available at the PMD, might possibly be inaccurate or incomplete, so that it was not possible to calculate population-based mortality rates, given that they require accurate and complete documentation of cause-of-death data.

Despite the changes shown in Figure 15, for survival studies to overcome the non-optimal flow of death data (if authentic), deaths occurring in Ministry of Health institutions are better sought from the PMD and deaths occurring outside Ministry of Health institutions (at home, in private health institutions or outside the country) are better sought from DGCS.

The fairly young population-based mortality system in Oman limited the study population to patients diagnosed with stomach cancer after May 2004 only. Again, due to the time lag at the NCR (two years), records of patients were available only up to 31 December 2006 (see chapter two for background about the NCR). Therefore, records of Omani stomach cancer patients diagnosed from the beginning of May 2004 to the end of December 2006 were linked, firstly, to the DGCS (primarily to identify deaths outside MOH institutions) and, secondly, to the PMD (primarily to identify deaths in MOH institutions). The retrospective follow-up time was until 31 December 2008. It was expected that the deaths of some cases would be registered in both DGCS and PMD because of the normal flow of information depicted in Figure 14. Data obtained from the NCR included all the available information recorded on the “Oman National Cancer Registry Form”.

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1 Available in the appendix.
Although the initial intention was to use the civil number\(^1\) as the main identifier, it was discovered that the civil number is not routinely collected by the NCR, despite the fact that there is an allocated field for it in the cancer registry form. This is because the civil number is missing in the medical records from which the cancer registry mainly obtains demographic information. Therefore, full name\(^2\), sex, permanent village address and year of birth were used as identifiers to link records from the NCR to DGCS and PMD. To ensure accuracy of linkage, full name and sex needed to be available in the cancer registry. Year of birth was used instead of date of birth because many of the study subjects had an estimated age (not a specific date) as they were born prior to 1970 when birth certification commenced. Moreover, because of somewhat arbitrary assignment of year of birth in the medical records, a one year difference was allowed. In addition, because the NCR recorded information in English while DGCS and PMD recorded information in Arabic, identifiers from the NCR had to be translated into Arabic and then provided to the DGCS and PMD to be linked.

Information about potential matches was obtained from the DGCS and PMD. These data included the full name, sex, year of birth, permanent village address, date and cause of death. A potential match between NCR records and documented deaths in the DGCS and PMD was classified as a \textit{definite match} (i.e. confirmed death of a person previously diagnosed with stomach cancer) if the full name, sex, and village address in the NCR were the same as those recorded in the DGCS and/or PMD, or if the full name, sex, and year of birth (within one year) matched. A potential match was classified as a \textit{possible match} (i.e. possible death of a person previously diagnosed with stomach cancer) if the full name and sex matched, but permanent village address and year of birth were both missing, or the village address was different and the year of birth was not within one year of the year of birth given by the NCR.

Lastly, the matched records with the DGCS and PMD were combined to categorise whether a person had died or not. Two sets for analysis were generated so that sensitivity analysis could be carried out. Set A included only definite matches, “confirmed deaths” (either found at the DGCS or PMD or both; a definite match at one database overriding a possible match at the other database). Set B included definite matches (set A) as well as records that were found to be possible matches, “possible deaths” in either DGCS or PMD.

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1. A unique identification number given to all citizens from birth.
2. Includes first name, father’s name, grandfather’s name and last name (tribe’s name)
or both (effectively including matches for full name and sex irrespective of village address or year of birth).

4.6. **Inclusion criteria**

Patients included were all Omani stomach cancer patients registered by the NCR between the beginning of May 2004 and the end of December 2006, whose cancer registration contained at least the full name and sex to ensure accuracy of linkage.

4.7. **Statistical analysis**

Analysis was carried out on the two datasets (A and B) separately. Survival was calculated from the date of diagnosis until the date of death, or the end of follow-up (31 December 2008) for patients who were not known to have died. Firstly, the Kaplan-Meier method was used to determine overall and median survival. The log rank test was used in a univariate analysis to identify important prognostic factors. Secondly, the relative survival\(^1\) was calculated because the cause-of-death data were either missing or unreliable. Hakulinen’s method (Hakulinen, 1982) was used to calculate the relative survival. Expected survival probabilities were calculated using Oman’s 2006 abridged life-table (World Health Organization, 2006). The abridged life-table was expanded to a complete life-table using the methods proposed by Elandt-Johnson and Johnson (Elandt-Johnson and Johnson, 1980, p.111), using six-point Lagrangian interpolation formulae for ages 1–74 years and fitting to a Gompertz distribution for ages 75 years and above. The international Cancer Survival Standard (ICSS) age distributions proposed by Corazziari et al. (2004) were used to standardise the relative survival rates. Age-standardisation was computed using the Brenner method (Brenner et al. 2004). Analysis was carried out using Stata 10.1 software.

4.8. **Results**

4.8.1. **National Cancer Registry data**

There were 209 stomach cancer cases registered at the NCR between 1 May 2004 and 31 December 2006. Twenty two cases were excluded. Seven were duplicate entries and another fifteen did not meet the inclusion criteria (five expatriates; ten with incomplete full name). Of the 187 cases that met the inclusion criteria, there were 111 males and 76

\(^1\) The ratio of observed survival (with the disease) to the expected survival without the disease.
females (Table 19). The mean ages for males and females were 62.6 and 57.1 respectively. The percentage of cases aged below 45 was 7.2 for males and 15.8 for females. Most cases (n=159 [85%]) had stomach carcinoma according to the WHO classification [see (Hamilton and Aaltonen, 2000)]. Malignant lymphoma accounted for 13 cases (7%) and 15 cases (8%) were either rare tumours or recorded as “unknown”. Stage and treatment were not recorded or were recorded as “unknown” for the majority of the patients. Lastly, anatomical region was classified as “not otherwise specified” for more than 90% of records.

<table>
<thead>
<tr>
<th>Table 19: Demographic characteristics of stomach cancer patients that met the inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Total number (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Number of people aged below 45 (%)</td>
</tr>
</tbody>
</table>

4.8.2. Linkage

Of the 187 records from the NCR, 99 records (87 definite and 12 possible) matched with death records at the DGCS and 97 records (77 definite and 20 possible) matched with death records at the PMD (Figure 16). Although the total number of matched records was similar for both DGCS and PMD, NCR records which matched with the DGSC may not have necessarily matched with the PMD and vice versa. For example, of the definite deaths captured by the DGCS, only 77% (74% definite and 3% possible) of those were captured by the PMD and, similarly, of the definite deaths captured by the PMD, only 84% (83% definite and 1% possible) were captured by the DGCS. Even assuming that possible matches were definite matches, each party captured only around 75% of the deaths captured by the other.

Combining the matched records from the DGCS and PMD, there were 100 deaths that met the criteria for set A (definite only) and another 21 records (total=121) met the criteria for set B.

When linking records, there were instances where a record was found to be a definite match in one database (DGCS or PMD) but a possible match in another. Likewise, there were instances where a record was found to be a possible match in both databases. Interestingly enough, the recorded dates of deaths for such records were exactly the same. Therefore, no further action was needed (i.e. accepted as a match).  

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Lastly, there were eight records (six records in set A) where date of death came before the date of diagnosis, a situation which arises if death is recorded before the results of a biopsy or an autopsy are reported. Such records were assigned a survival of one day as exclusion of these cases could lead to an overestimation of the survival rates.

**Figure 16:** Flow diagram showing the results of the linkage procedure
- **Definite** matches* between NCR and DGCS and/or PMD (n=100)
- **Possible** matches† between NCR and DGCS and/or PMD (n=121)

* If the full name, sex, and village address all matched, or if the full name and sex matched and the year of birth was within one year of the year of birth recorded by the NCR
† If the full name and sex matched, but permanent village address and year of birth were both missing, or the village address was different and the year of birth was not within one year of the year of birth given by the NCR

Note: NCR=National Cancer Registry; DGCS=Directorate General of Civil Status; PMD=Parallel Mortality Database at the Ministry of Health
4.8.3. *Survival*

The median survival for the total cohort was found to be 30 months and 14.7 months, respectively, for set A and set B (Table 20).

**Table 20:** Median survival (in months) of stomach cancer patients for set A and set B*

<table>
<thead>
<tr>
<th>Set</th>
<th>Total (95% CI)</th>
<th>Male (95% CI)</th>
<th>Female (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set A</td>
<td>30 (16.3–25.8)</td>
<td>17.3 (9.9–23.9)</td>
<td>.</td>
</tr>
<tr>
<td>Set B</td>
<td>14.7 (9.9–23.9)</td>
<td>13.4 (7.4–21.4)</td>
<td>16.3 (8.6–23.9)</td>
</tr>
</tbody>
</table>

*It was not possible to estimate the median survival for females for set A because less than half of the number of females had died. In addition, it was not possible to calculate the upper bound of the 95% CI for the total cohort for set A, and for females for set B, because of the closeness of the proportion of deaths to half of the total cohort or number of females respectively.

Survival over time is better represented with the Kaplan-Meier survival curves (Figure 17). As can be seen, the results were sensitive to the inclusion of possible deaths in the analysis (set B compared to set A). Less than half of the females included in set A died in the follow-up period; hence, the missing median survival in Table 20. The log rank test showed that in set A, females had statistically significant ($p$ value <0.01) better survival than males, an observation clearly shown by the non-overlapping confidence interval bounds for the Kaplan-Meier curves of males and females throughout the follow-up period (Figure 18). However, this effect was not observed for set B because two thirds (14) of the

![Figure 17: Kaplan-Meier survival curves for set A and set B*](image)

*Males and females combined

Note: The shaded area represents the 95% confidence interval (CI)
21 extra deaths included in set B compared to set A were in fact females (data not shown). The survival in people aged less than 45 years was not significantly different from those aged 45 and above in either set. The closeness of the proportion of deaths to half of the total cohort resulted in some missing confidence interval bounds for the median survival (Table 20).

![Kaplan-Meier curves for males and females of set A](image)

**Figure 18:** Kaplan-Meier curves for males and females of set A
Note: The shaded area represents the 95% confidence interval (CI)

Relative survival rates (ratio of observed survival in people with stomach cancer to the expected survival in people without stomach cancer, i.e. excess mortality) were found to be 0.70 at one year and 0.58 at three years for the total cohort of set A (Table 21). However, the rates for set B were greatly lower than for set A. The one- and three-year relative survival rates were 0.60 and 0.44 respectively. Lastly, for the sake of making comparisons, the age-adjusted relative survival rates for the total cohort were 0.73 and 0.66 at one and three years respectively for set A. For set B, the one- and three-year age-adjusted relative survival rates were 0.60 and 0.48 respectively. It is important to note that in set A, the relative survival rates differ greatly between males and females. However, the difference diminished when set B was analysed because of the larger number of extra female rather than male deaths included in the set.
In the present study, it was found that the median survival of Omani stomach cancer patients (both genders) was 30 months when only confirmed deaths (set A) were analysed. Including possible deaths in the analysis revealed that the median survival dropped to about half of the median survival for confirmed deaths only. Because cause-of-death data were missing or unreliable, relative survival rates were computed to find the difference in observed survival in people with stomach cancer as opposed to the expected survival in people without stomach cancer. The one- and three-year relative survival rates of Omani stomach cancer patients were 0.70 and 0.58 for set A, and 0.60 and 0.44 for set B, respectively. As can be seen, survival rates vary greatly between set A and set B. This is because an extra 21 deaths were included in set B compared to set A. Given that the deaths included in set A might be conservative and those included in set B might be inaccurately high, the true value for the survival of Omani stomach cancer patients is likely to lie between the upper bound of the confidence intervals of set A and the lower bound of the confidence intervals of set B. However, the bounds of the confidence intervals were not available for the median survival when the total number of deaths was close to half (Table 20).

### Table 21: One- and three-year observed and relative survival rates for set A and set B

<table>
<thead>
<tr>
<th></th>
<th>Observed Survival (95% CI)</th>
<th>Relative survival (95% CI)</th>
<th>Age-adjusted relative survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Male Female</td>
<td>Total Male Female</td>
<td>Total Male Female</td>
</tr>
<tr>
<td>1 year</td>
<td>0.63 (0.56–0.70) 0.57 (0.47–0.65) 0.72 (0.61–0.81)</td>
<td>0.70 (0.62–0.78) 0.66 (0.54–0.76) 0.77 (0.64–0.86)</td>
<td>0.73 (0.64–0.81) 0.67 (0.55–0.78) 0.85 (0.71–0.96)</td>
</tr>
<tr>
<td>3 years</td>
<td>0.47 (0.40–0.54) 0.39 (0.29–0.48) 0.60 (0.48–0.70)</td>
<td>0.58 (0.49–0.67) 0.51 (0.39–0.63) 0.67 (0.54–0.78)</td>
<td>0.66 (0.55–0.76) 0.54 (0.41–0.68) 0.87 (0.70–1.0)</td>
</tr>
</tbody>
</table>

### 4.9. Discussion

In the present study, it was found that the median survival of Omani stomach cancer patients (both genders) was 30 months when only confirmed deaths (set A) were analysed. Including possible deaths in the analysis revealed that the median survival dropped to about half of the median survival for confirmed deaths only. Because cause-of-death data were missing or unreliable, relative survival rates were computed to find the difference in observed survival in people with stomach cancer as opposed to the expected survival in people without stomach cancer. The one- and three-year relative survival rates of Omani stomach cancer patients were 0.70 and 0.58 for set A, and 0.60 and 0.44 for set B, respectively. As can be seen, survival rates vary greatly between set A and set B. This is because an extra 21 deaths were included in set B compared to set A. Given that the deaths included in set A might be conservative and those included in set B might be inaccurately high, the true value for the survival of Omani stomach cancer patients is likely to lie between the upper bound of the confidence intervals of set A and the lower bound of the confidence intervals of set B. However, the bounds of the confidence intervals were not available for the median survival when the total number of deaths was close to half (Table 20).
Because a vital registration system has only recently been established in Oman, this is a pioneering study to find out survival from a disease in Oman using population-based mortality datasets. Previous studies of survival in Oman were hospital-based (Faris, 2003, Al-Moundhri et al. 2004, Al-Moundhri et al. 2006, Al-Moundhri et al. 2007). In such studies, patients who did not die in hospital and were lost to follow-up, were censored. Survival would have been biased if censorship was skewed to those of better prognosis or those of worse prognosis. With mortality as the outcome, events could be sought from population-based mortality databases as was done in this study. Also, this study applied manual linkage of records to avoid any missed matches due to differences in spellings which might have occurred if electronic linkage had been performed. This was especially important given that identifiers from the NCR had to be manually translated from English to Arabic to be matched with the DGCS and PMD.

There are some limitations to this linkage study. In the course of this study, it was discovered that the DGCS mortality database may not be complete and that it lacks cause-of-death data. However, this study tried to minimise the problem of incompleteness by seeking deaths from the PMD. Although, the cause-of-death data at the PMD were available, they were found to be unreliable, hence the calculation of relative survival rates in this study. The other limitations of this study can be divided into limitations/challenges of the linkage procedure and limitations of the available data for survival analysis. The linkage procedure limitations/challenges originated after the discovery of the missing civil number at the NCR. Although the mortality databases (DGCS and PMD) in Oman record the civil number, the NCR does not record the civil number despite the fact that there is an allocated field for it in the Omani NCR form (which can be found in the appendix). Since the civil number is a unique identifier code given to every citizen in Oman, if recorded routinely and correctly, it will allow accurate record matching. As well as being a very good linkage identifier, the civil number can be utilised by the NCR in easily identifying duplicate entries from multiple primaries. This study found seven duplicates among the 209 records obtained.

The unavailability of the civil number necessitated the use of full name, village address and year of birth as identifiers. Each of the latter identifiers has some limitation associated with its use.

1 A person may have multiple primary tumours diagnosed at different times.
Firstly, the NCR records names from medical records which are in English. Such names are not filled in by the individual patients but rather by the medical records department which translates the patient’s name from Arabic to English; this procedure is prone to spelling mistakes. The DGCS and PMD record names in Arabic so that the names in English from the NCR had to be translated back to Arabic for the matching process. Certainly, there will have been records where the original name was lost in the translation process, first by the medical records to English and then by me back to Arabic. Some deaths may have been missed for this reason, thus overestimating survival.

The challenge of using the full name as a main identifier poses another limitation. It might seem that a name composed of first, father, grandfather and tribe names should be unique to an individual, but in reality this is not the case for some common names in Oman. This challenge was obvious when performing linkage with the DGCS. The DGCS is not only a mortality registry but also a body for issuing ID cards for citizens and expatriates, and for registering births and divorces. Thus their database contains the civil status of virtually all individuals in Oman. When it came to matching records, there were multiple records (irrespective of died or not) that matched the NCR records for full name, sex and even village address. In this situation, the matching record was chosen to be the one with date of birth closest to the date of birth given by the NCR. However, this problem was not apparent with the PMD as it is solely a mortality register.

Secondly, this study used year of birth instead date of birth for the linkage procedure because date of birth may not be accurately recorded in hospitals’ medical records departments (from which the NCR obtains patients’ demographic information). This is partly because many individuals over 40 (the majority of the study’s subjects) have only an estimated age, as they were born prior to the era of recording and registration of births in Oman. Medical records departments sometimes give a date of birth according to what the person thinks his/her age is. Therefore, even using year of birth and allowing for a one-year difference in the linkage, there may have been instances where a match was missed.

Thirdly, using village address as an identifier may be problematic for individuals who change address between diagnosis and death, and thus again miss potential matches. To overcome the shortcomings of date of birth and village address, the study used either of two combinations of identifiers for definite matches: one, if full name, sex and village address matched, or two, if full name and sex matched and the year of birth was within one year of that recorded by the NCR. The findings of the study that the NCR record of an
individual could be a “definite” match with the records in one mortality database but only a “possible” match with the records in the other, although having the same date of death, supports the argument that village addresses and dates of birth may not be accurate.

To summarise, given that there will be some missed deaths due to the limitations of using full name, sex, village address and year of birth as identifiers, the reported survival rates are likely to be overestimated. Further, although identifiers recorded by the NCR were used in the linkage procedure, the identifiers themselves may not be accurate.

There are also limitations associated with the data analysed in this study. The first is related to the small number of stomach cancer cases. The number of subjects was restricted by the relatively recent vital registration system for deaths (established in May 2004) and the delay in the availability of cancer records in the NCR (a two-year lag). Therefore, the start date for including cases was limited by the newness of the vital registration system and the end date by the delay at the NCR. Overall, from May 2004 until December 2006, only 209 cases of stomach cancer were recorded. Twenty two cases had to be excluded (seven duplicates, five expatriates and ten incomplete names) and so only 187 cases were left for analysis. It is uncertain whether the excluded ten incomplete names would have made any difference to the reported survival rates. Such records cannot be linked with sufficient certainty. What is known though is that six of the ten records come from Twam Hospital, in the United Arab Emirates, a neighbouring country. Twam Hospital is a specialist in oncology and, because of its closeness, some Omanis may opt to be treated and followed-up there. The NCR obtains records of all Omani cancer patients diagnosed or treated in this hospital. However, opting to be treated at Twam Hospital is likely to be independent of the prognosis for the tumours and it is therefore unlikely that exclusion of these patients would have affected the estimated survival. Further, the ten records of people excluded because of incomplete names were of five males and five females, which argues against the possibility that the exclusion of these ten people contributed to the differing estimated median and relative survival rates between males and females in the analysis using set A.

What could, however, greatly impact on survival is the inclusion of the 21 possible deaths in the survival analysis (set B) as was seen in Table 20 and Table 21. There were two major differences found between the survival results of sets A and B. The first was the loss of statistical significance in the improved survival of females compared to males in set B when compared to set A. The second and more important was the differences in the overall survival rates. The reason for the former is simply that 14 out of the 21 extra deaths
included in set B were females. For the latter, it would be naive to ask why an extra 21 deaths make a difference in the observed survival of only 187 study subjects. The question here is whether a proportion of the extra 21 deaths in set B could have been definite matches, and thus diminish the difference in survival between sets A and B. Consideration of this requires us to review the original protocol of classification of potential matches and to study the characteristics of the extra 21 deaths. Possible deaths were those records that match with name and sex but had a missing or different village address and a missing year of birth or one not within a one-year difference from the year of birth given by the NCR. Ten of the extra 21 possible deaths included in set B were where the village address and/or the year of birth were missing. If village address and year of birth were recorded by the PMD for those 10 records, they could have been definite deaths, which would therefore minimise the difference of overall survival between set A and set B. In addition, 9 of these 10 records were for females and this would have decreased sex-specific survival differences between set A and set B.

There is another interesting finding that can have an impact on the results of survival: the non-optimum flow of information between the DGCS and the PMD as was evident from the discrepancies in the percentages of recorded deaths at one database compared to the other (see 4.8.2 above). In the case of optimum flow of information between the DGCS and the PMD, both parties should have identical records. The results showed otherwise. Nevertheless, the records from the NCR that matched only with the PMD death records (but not the DGCS death records), were mostly females (15 out of 22), whereas the NCR records that matched only with the DGCS death records (but not the PMD death records) were mostly males (20 out of 24), irrespective of whether the match was classified as a definite or a possible death. The 22 deaths found at the PMD only should be hospital-based deaths and the 24 deaths found at the DGCS only should be mostly home deaths (given non-optimum flow of information). Assuming the numbers found are genuine, one might ponder on the difference in sex ratio.

A possible explanation is as follows. One of the major pathways for notification of deaths to the DGCS, either at home or in hospital, arises from the need for a death certificate by the family of the deceased. The death certificate is needed for claiming the deceased’s money from the banks and the deceased’s retirement wages. In Omani society, at least for those of the older generation, the father tends to be relied on for work and saving money. Therefore there is a greater need for obtaining a death certificate for a father’s death than for a mother’s. And so, assuming limited flow of information between
the DGCS and the PMD, there is no way for a home male or female death to be recorded by the PMD. However, of the deaths in hospital (recorded by the PMD), males are more likely to also be recorded at the DGCS from the death certificate obtained by the family of the deceased. This creates the sexual differences in registering deaths.

This certainly has an implication for the reported survival rates because female home deaths may have been missed from not being recorded by the DGCS nor the PMD, resulting in overestimating survival, but it is important to keep in mind that this happens only in case of non-optimum flow/exchange of data between the DGCS and the PMD.

Many studies conduct survival analysis using population-based cancer registry data. The Eurocare study (Verdecchia et al. 2007) is probably the largest multi-population-based collaborative study on cancer survival. Survival is calculated for all types of cancers using the various populations’ respective NCR data. In fact, most studies of survival that use cancer registry data have the vital status of the patients recorded by the cancer registry [see for example, (de Vries et al. 2006, Condon et al. 2005, Pisani and Forman, 2004, Dickman et al. 1999, Verdecchia et al. 2003)]. Whereas in this study, because the Omani NCR does not routinely collect data on the status of patients, I had to link the NCR records to the newly founded mortality datasets in Oman to find, firstly, who died and, secondly, when. This study should certainly help in understanding the challenges the Omani NCR may face when initiating the follow-up of registered cases.

The five-year survival rate is almost always chosen to report survival from malignant tumours. This is because the chance of reoccurrence declines significantly for most cancers after five years (Casciato and Territo, 2008, p14). While the studies mentioned above report five-year survival rates, the retrospective follow-up period of this study was only four years and a half at maximum. Therefore, only one- and three-year survival rates were reported. In Europe the one- and three-year survival rates for stomach cancer vary between countries. The combined one- and three-year age-adjusted relative survival rates of European countries that participated in the Eurocare-4 study were 0.44 and 0.28 respectively (http://www.eurocare.it/DatabaseEU4/tabid/78/Default.aspx). These rates are far lower than even the result from the analysis of set B. However, comparison of the relative survival rates between nations requires much caution. Even after removing the effect of age, by age-standardisation to the same age distribution (as I have done), survival is still affected by earlier diagnosis or better management (Berrino, 2003), in addition to the differences in the quality of ascertaining cancer cases. Furthermore, it might be misleading to compare relative survival rates of patients diagnosed in different years...
because the management/treatment of disease changes as evidence-based research continues. Indeed, the above mentioned Eurocare age-adjusted relative survival rates were for the period 1995–1999. In both the Eurocare study and this study, treatment and stage were not available [though the Eurocare group does conduct high resolution studies where the rates are standardised to stage and so any difference in survival could be attributed more to management (Berrino, 2003)]. Whereas there were no death-certificate-only registrations in this study, there were death-certificate-only registrations in the Eurocare study, but these were excluded because of the unknown date of diagnosis (Berrino, 2003). This means that the reported relative survival rates by the Eurocare study may be over-rather than underestimated. The question of the survival difference between this study and the Eurocare study remains open for interpretation.

The apparently better relative survival of Omani stomach cancer patients compared to the European countries may be due to several reasons, including earlier diagnosis, over diagnosis, lower rates of cardia stomach cancer,\(^1\) better management, missed deaths or higher age-specific rates of deaths in Oman from other diseases than in Europe. Alternatively, the difference may not be genuine. It could be due just to differences in data quality, or the instability of this study’s results arising from its small population, or the different ability to determine the status of patients (dead/alive) between this study and the cancer registries involved in the Eurocare study. Similar arguments apply when comparing this study’s survival rates to those from other countries like India, Thailand, the Philippines and China (Sankarnarayanan et al. 1998) in which survival rates were calculated for cases diagnosed in the 1980s and 1990s and were found to be lower than this study’s survival rates.

Perhaps one might compare cause-specific mortality data rather than survival as it is less affected by biases of diagnosis such as screening biases or stage of the disease. However, mortality data in Oman are not available and this project could not derive them due to missing or unreliable cause-of-death data. As a result, comparison of mortality data between Oman and other nations is not possible.

In 2006, a hospital-based study in Oman, carried out by Al-Moundhri et al. (2006) to determine clinicopathological features, management and survival of Omani stomach cancer patients, found a median survival of 12.3 months (95% CI 9.7–14.4) and a five-year survival rate of less than 20%. Advanced stage stomach cancer constituted more than two

\(^1\) Stomach cancer of the cardia has been shown to have lower survival than non-cardia stomach cancer (Doglietto et al. 2000).
thirds of the entire cohort, an observation which stayed constant throughout the study period (1993–2004). The result for the median survival found in the study by Al-Moundhri et al. was shorter than that found in the current study. In this study, the status of patients (dead or alive) was determined using population-based mortality databases, whereas the study by Al-Moundhri et al. was hospital-based and survival was determined from the date of diagnosis to the date of death in hospital, or censored at the last known follow-up. If censoring was biased towards patients who had better prognosis, and so no longer attended follow-up, then this might explain the lower survival rates found. Alternatively, the difference in survival rates could be due to the difference in disease stage, management or even simply due to chance because of the insufficient power of both studies, as relatively low numbers of subjects were involved in both. It is important to note that the study by Al Moundhri et al. included people with adenocarcinoma only, whereas in the present study all types of stomach cancer were involved, although the majority of cases were adenocarcinoma. Even with the exclusion of gastric lymphoma patients, who make up the majority of non-adenocarcinoma patients in this study, there were no major differences in the survival estimates.

As was mentioned above, this study was the first, to my knowledge, to find the survival of a group of patients using the population-based mortality databases. Perhaps the challenges/limitations faced during the course of conducting the study have more implications for Oman than the findings themselves. For routine linkage of NCR records with mortality databases to find the status (dead/alive) of patients, I propose the following recommendations:

1) For the National Cancer Registry (NCR):
   a) Recording the civil number. The civil number, a unique identifier code for all Omanis, should be recorded. Documenting the civil number will not only help the NCR in identifying duplicate entries from multiple primaries but will also be a robust identifier in linking records with the mortality databases to find the status of patients. Recording the civil number will also be helpful in the future to link records to databases held by other bodies like pharmacies, for example, in order to find the effect of prescription drugs on the development or course of the disease.
   b) Obtaining complete and good quality data on cancer site, stage and treatment. The NCR should try to obtain complete and good quality data on the cancer site, stage and treatment. By doing that, future studies examining survival differences could explain these in light of prognostic factors. However, before improving the
capabilities of the NCR, it should be remembered that all the data obtained by the NCR, apart from death-certificate-only cancer registrations, is dependent primarily on the medical records of patients. Enhancing the quality and completeness of the NCR data cannot be achieved without accurate and complete documentation of the civil number, site, stage and treatment of patients in the medical records. Therefore, part of solving the problem is actually dependent on the structure/system of medical records and particularly on the clarity and appropriateness of clinical notes by clinicians.

2) For the mortality system in Oman.
   a) Efficiency of flow of death notification. At the level of mortality databases in Oman, perhaps the first thing that needs to be improved is the efficiency of the flow of death data from all external bodies to the DGCS, as it is the official mortality register in Oman. This study has found that not all the records found at the PMD could be found at the DGCS and vice versa. This argues against the completeness of the official mortality registry in Oman. This needs to be looked at seriously. The death documentation is a public good which not only benefits the country at an individual level, for example in securing inheritance and finances, but more importantly at a societal level in planning and prioritising health care, or even internationally in finding epidemics (Setel et al. 2007).
   b) Is the PMD necessary? The PMD was founded to compensate for the weaknesses by the DGCS in documenting cause-of-death data and other data, like mother of the new born (2008a). It may be more efficient and cost-effective to invest in improving the system of the DGCS, and the flow of information, rather than having another parallel mortality database at the Ministry of Health. This may include steps such as the DGCS taking an active role in obtaining information on deaths which occurred at Ministry of Health institutions, and possibly training their personnel to code cause-of-death data.

There are still some questions for the future that remain to be answered. The first is whether the result of stomach cancer survival is truly at the magnitude estimated here, or whether it is overestimated due to the weaknesses of this study. In terms of future linkage studies, the non-uniform language of documenting cases between the NCR and the mortality registries together with the limited time and resources of this study hindered the
use of electronic probabilistic linkage of records. Instead, a manual deterministic method of linkage was used even though it has been shown to be inferior to the probabilistic method (Oberaigner, 2007). In Oman’s context, at least in the circumstance where the civil number is missing, probabilistic linkage may be a better choice than deterministic linkage.
5. CHAPTER FIVE – CONCLUSION

Stomach cancer is the fourth most common cancer worldwide (Parkin et al. 2005a). Its poor prognosis makes it the second most frequent cause of cancer deaths. Incidence data show wide variation between nations (Ferlay et al. 2004). High incidence rates are recorded in Eastern Asia, Eastern Europe and South America. Conversely, Australia, North America, Western Europe and the Arab world have lower incidence rates. Oman, in contrast to the neighbouring Gulf Cooperation Council (GCC) countries, is estimated to have higher incidence rates. In Oman, stomach cancer is the most frequent neoplasm among males (Mohammad et al. 2008). This problem, although known about, has not been explored. Therefore, this project aimed to examine the epidemiology of stomach cancer in Oman. This was done through conducting three small studies. The purpose of the first was to describe the incidence data in Oman and to compare the incidence rates between Oman and the surrounding Gulf countries. The second study aimed at finding possible risk factors which might account for the higher incidence rate of stomach cancer in Oman compared to the other GCC countries. Lastly, the aims of the third study were to find out mortality, the median and relative survival from stomach cancer in Oman, and the feasibility of routinely linking cancer records in Oman to find out survival from cancer. Although mortality data in Oman existed, population-based mortality was not known for any cancer, including stomach cancer.

5.1. Main findings and interpretation

This project found that stomach cancer in Oman showed characteristics which are similar to other nations. Males had twice the incidence of stomach cancer than females, and, above the age of 45 years, a higher proportion of males had stomach cancer than females. Also, there were regional variations in the incidence of stomach cancer.

In addition, Oman seemed to have a higher incidence of stomach cancer than most GCC countries, with some variation in terms of age and sex-specific comparisons. The random variation of the incidence rates was not found to be a possible explanation for the higher incidence of stomach cancer in Oman. However, the possible role of bias introduced by variation in the completeness and quality of cancer registration practices in the GCC countries could not be ruled out. A review of the available information about the
quality and completeness of the GCC cancer registries suggests that Saudi Arabia and UAE may have some underreporting of cancer cases. Hence the results of the comparative analyses should be interpreted with caution.

In terms of possible risk factors, there was a paucity of information about the prevalence of *H. pylori* infection and salt intake. However, data on the estimated prevalences of smoking, body overweight and fruit and vegetable intake in the GCC countries were available but were found unlikely to explain the high incidence of stomach cancer in Oman. Data from the CIA World Factbook showed that Oman might be at a lower socioeconomic status (SES) than the other GCC countries. The lower SES in Oman may explain the higher incidence of stomach cancer because some studies (Nagel et al. 2007) have shown that lower SES is associated with higher *H. pylori* infection.

In the linkage study to find mortality and survival from stomach cancer, several challenges were faced that necessitated some changes to the initial plan. Firstly, it was found that the newly established official mortality database, the Directorate General of Civil Status (DGCS), might not have complete death records because of the inefficient flow of notification of death. Therefore data on deaths were sought from the Ministry of Health’s parallel mortality database (PMD). Secondly, it was discovered that the NCR does not record the civil number and that their records are in English. Thus, other identifiers such as full name, sex, year of birth and village address were used in the linkage procedure, but had to be translated back to Arabic because the DGCS and PMD records are in Arabic. Thirdly, it was found that the cause-of-death data were missing or unreliable so that it was not possible to calculate the mortality rate from stomach cancer.

Findings showed that the analysis was sensitive to the inclusion of possible deaths of people known to have stomach cancer. The median survival for males and females combined was found to be about 30 months if only definite deaths were analysed but the median survival dropped to half of that if possible deaths were included in the analysis. Relative survival was also calculated and it differed again when possible deaths were included. The relative survival rates of stomach cancer found in this project were higher than in other studies in Oman and elsewhere. The limitations of this linkage study in finding all relevant deaths may explain the difference but other prognostic factors which were not available for this project could also be a reason. For complete and better characterisation of matches in linking records between the NCR and the mortality datasets, more robust identifiers need to be used, such as the civil number in Oman.
5.2. **Strengths and limitations**

This project was the first to examine the epidemiology of stomach cancer in Oman. In doing so, three small studies explored incidence, risk factors and mortality. When examining the incidence data, particular attention was directed towards the quality and completeness of the cancer registration practices. Also, any difference due to the normal variation of the data, or chance, was eliminated. In finding the prevalences of risk factors in the GCC countries, only those studies which were considered representative of the whole population were used. Age-standardisation of the prevalences was carried out to control for confounding introduced by differences in age structure. Lastly, the study which examined mortality using record linkage not only was useful in estimating the survival of stomach cancer patients but also served as a good pilot study for assessing the feasibility of routinely linking records. The study linked the National Cancer Registry (NCR) records to both the Directorate General of Civil Status (DGCS) and the Ministry of Health parallel mortality database (PMD) to overcome non-optimal flow of death notification.

There were some limitations to this project. The most important one relating to the analysis of the incidence data was the degree of completeness and quality of cancer registration. In Oman, the fluctuations seen overtime may have been caused by incomplete or variable cancer surveillance. Bias introduced by the varying degrees of the quality and completeness of cancer registration within Oman or between the GCC countries could not be completely ruled out. The unavailability of information regarding the prevalence of *H. pylori* infection and salt intake prevented valuable comparisons between the GCC countries. Also, no firm conclusions could be drawn regarding risk factors in which prevalence was available due to the non-uniform characteristics of the studies used. Systematic error from the differences in study populations or method could explain any differences in the prevalence of risk factors. The study involving finding mortality for stomach cancer patients using record linkage had limitations mostly attributable to the linkage identifiers. Shortcomings of using name, sex, date of birth and address were likely to have resulted in missed deaths, thus overestimating survival. Had it not been for the missing civil number at the National Cancer Registry (NCR), using it in the record linkage would have overcome many of the limitations faced.
5.3. **Implications of the findings**

Many of the implications of this project are relevant to health policy makers in Oman. Over the past four decades, health in Oman has moved from an era dominated by infectious diseases to one in which chronic diseases prevail. In 2002, chronic diseases accounted for more than 75% of all hospital deaths in Oman (Al-Lawati et al. 2008). As life expectancy improves further, the burden of chronic diseases such as cancer is likely to increase. Therefore, there will likely be a higher demand for statistics on chronic diseases in the future.

The Omani National Cancer Registry, although attaining a relatively fine level in terms of cancer registration practices, still has areas that need to be improved. The quality and completeness of the data must be enhanced. This will facilitate accurate interpretation and comparisons of the incidence data. Follow-up of patients registered at the cancer registry is pertinent especially for survival studies. The availability of treatment and the status (dead or alive) of the patients is important for appreciating the burden of cancer.

The recent establishment of a vital registration system in Oman aids in collecting mortality data for cancer patients. The civil number, if collected routinely and accurately by the NCR, will greatly facilitate regular collection of mortality data for cancer patients. However, before doing so, incompleteness in the mortality data resulting from the non-optimal flow of death notification, as found in this study, will need to be rectified. The improvement in the quality and completeness of mortality registration in Oman is essential for appreciating the burden of diseases and reforming health policies. The DGCS may need to make cause-of-death data available in their system to help in shaping a complete mortality registry where a single body contains all the relevant information. Having another mortality database at the Ministry of Health may be effective in the short term, but in the longer term it may not be so efficient and cost-effective to have two mortality databases when one can suffice.

This project has helped in attaining a deeper understanding of the extent of the problem of stomach cancer in Oman. Whereas the incidence of stomach cancer in Oman seems to be higher than the other GCC countries, the size of the burden does not seem to require instituting preventive measures, at least in the meantime. This is because the crude incidence rate is below 4 per 100,000 and the trend seems to be decreasing. Nevertheless, stomach cancer needs to be continuously monitored. If the problem persists or increases, investigating risk factors such as *H. pylori* infection or high salt intake would be prudent.
REFERENCES


alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *Journal of the National Cancer Institute*, 89, 1277-85.


# Annex 2

## OMAN NATIONAL CANCER REGISTRY FORM

<table>
<thead>
<tr>
<th>1. Patient's Registration No.</th>
<th>2. Date of Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Patient's Hospital File No.</td>
<td>4. National/Civil No.</td>
</tr>
<tr>
<td>5. Hospital Name</td>
<td>6. Department of</td>
</tr>
<tr>
<td>7. First Name</td>
<td>8. Father's Name</td>
</tr>
<tr>
<td>9. Grandfather's Name</td>
<td>10. Tribe Name</td>
</tr>
<tr>
<td>11. Sex</td>
<td>12. Marital Status</td>
</tr>
<tr>
<td>17. Ethnic Group</td>
<td>18. Occupation</td>
</tr>
<tr>
<td>19. Telephone/GSM</td>
<td>20. Other Contact Tel No.</td>
</tr>
<tr>
<td>21. Waliyat:</td>
<td>22. Village:</td>
</tr>
<tr>
<td>23. Date of First Diagnosis</td>
<td>24. If under 18 years, give Lab. Biopsy Specimen No.</td>
</tr>
<tr>
<td>25. Primary Site of Cancer</td>
<td>26. Histological Type of Cancer</td>
</tr>
<tr>
<td>27. Laterality</td>
<td>28. Extent of Disease</td>
</tr>
<tr>
<td>29. Histologic Grading</td>
<td></td>
</tr>
</tbody>
</table>

### TNM Classification

- **Clinical**
  - **Stage:** (Clinical)
    - T: T = T1 T2 T3 T4
    - N: N0 N1 N2 N3
    - M: M0 M1 M2 M3

### Histologic Grading

- Grade I: Well differentiated/Differentiated, NOS
- Grade II: Moderately differentiated/Moderately well differentiated/Intermediate differentiation.
- Grade III: Poorly differentiated
- Grade IV: Undifferentiated/anaplastic

### Sequence of Treatment

- 1. Surgery
- 2. Radiotherapy
- 3. Chemotherapy
- 4. Hormonal Therapy
- 5. Immunotherapy
- 6. None
- 7. Other Treatment

### Cause of Death

- 1. Cancer or Cancer related
- 2. Unrelated to Cancer
- 3. Other
- 4. Unknown

### Source of Information

- 1. Medical File
- 2. Death Certificate
- 3. Other
- 4. Unknown

**Doctor's Name:**

**Doctor's Designation:**

**Date:**

---

1. Send White copy to NCD Section Fax: 24695480 2. Keep Pink Copy in Patient's Case Notes (File) 3. Send Blue Copy to Medical Records Deptt. MPA-123