The epidemiology of oesophageal and gastric cancer in England, 1998-2009

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Thesis submitted for the qualification of PhD

Declaration

I, Victoria Helen Coupland, declare that the work presented in this thesis is my own. I confirm that information derived from other sources has been indicated in the thesis. Where the work has resulted in published papers, I analysed and interpreted the data and drafted the manuscripts. My co-authors on the publications, helped to interpret the data and reviewed the manuscript.

Victoria Helen Coupland | Date

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Abstract

This thesis aimed to study the occurrence and treatment of oesophageal and gastric cancer patients in England between 1998 and 2009. Variation in incidence over time, by socioeconomic deprivation, and between ethnic groups for six subgroups of these cancers (upper and middle oesophagus, lower oesophagus, oesophagus not otherwise specified (NOS), cardia, non-cardia, gastric NOS) was investigated. Factors that affected who received surgery for these cancers were examined and survival in relation to hospital volume (measured as the annual number of operations per hospital) was assessed.

Key findings include an increase in the incidence of lower oesophageal cancer in men, a higher incidence of this and cardia cancers in men, a higher incidence of these subgroups in White men compared with the other ethnic groups studied, a higher incidence of upper and middle oesophageal cancer in Bangladeshi women compared with White women, and in each subgroup a higher incidence in more deprived areas and a poor prognosis. The different patterns of incidence are likely to be explained by differences in exposures to risk factors. These findings confirm patterns reported in other developed countries, and highlight the importance of preventative initiatives.

Older patients and patients resident in more deprived areas were less likely to undergo surgery. This could be explained by several valid reasons, including differences in performance status, disease stage, or willingness to undergo surgery. Data on these factors were not available for analysis but should be further investigated to ensure that surgery is available to all who will benefit clinically from it. This work found lower mortality with increasing hospital volume, both in the short- and long-term. For the first time in England, this work assessed the effect of hospital volume on survival and found that the centralisation of surgical services for these patients has been beneficial. The work supports the continued centralisation of these services.

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Acknowledgements

Firstly, I would like to thank my PhD supervisors Elizabeth Davies, Henrik Møller and Jesper Lagergren for their expert advice and encouragement during this work.

I would like to acknowledge the support from my friends and colleagues at Thames Cancer Registry. In particular, I would like to thank Ruth Jack for her advice and expertise and Ashu Sehgal, Karen Linklater, Margreet Lüchtenborg, Sharma Riaz and Julie Konfortion for their help and encouragement.

I would like to recognise additional colleagues from those that collected and entered the cancer registration data to those that provided technical support.

I am grateful to William Allum for his support through the upper gastrointestinal cancer Site Specific Clinical Reference Group and the co-authors on my papers for their comments and advice.

I am appreciative to my parents and brother for their continuous support and encouragement through my thesis.

Chapter 1 Introduction

This chapter describes patterns in the incidence and survival of oesophageal and gastric cancers worldwide and the variation in incidence between specific subgroups of these cancers. An overview of the treatment available for these patients is also described. Finally, a general outline of the thesis is provided.

1.1 Cancer

Cancer is a major health problem in the United Kingdom. The most common cancers include lung, colorectal, breast in females and prostate in males (Office for National Statistics, 2011a). The risk of developing cancer generally increases with age and almost two thirds of cancers occur in people aged over 65 (Cancer Research UK, 2011a). The number of new cases of cancer in England are estimated to increase by around a third by 2020, mainly due to the ageing population in this country (Møller *et al*, 2007). Although oesophageal and gastric cancers are not among the most common cancers in the United Kingdom, around 16,000 people are diagnosed with these cancers each year, making up about 5% of all cancer cases (Cancer Research UK, 2012a). Therefore oesophageal and gastric cancers are a significant health problem in this country.

1.2 Oesophageal and gastric cancer

The oesophagus is a muscular tube that extends from the mouth to the stomach through which food and liquid passes by peristalsis. The main histological types of malignant tumours in the oesophagus are squamous cell carcinoma and adenocarcinoma. Gastric cancer refers to tumours that occur in the stomach, and these are usually adenocarcinomas. Studies which have investigated oesophageal and gastric cancers and also more specific subgroups of these

cancers are described below. Interestingly, these subgroups are associated with different aetiologies and have different patterns in incidence.

Oesophageal cancer subgroups

Squamous cell carcinoma originates in the flat skin-like cells that line the oesophagus, whereas adenocarcinomas form in the columnar glandular cells that make and release mucus and other fluids in the oesophageal lining (Blot *et al*, 2006). The majority of oesophageal adenocarcinomas occur in the lower third of the oesophagus (Palser *et al*, 2008; Dikken *et al*, 2012b), whereas squamous cell carcinomas are more evenly distributed throughout the entire length of the oesophagus (Dikken *et al*, 2012b). Although, some studies have investigated oesophageal cancer subgroups by the anatomical location of the upper, middle, and lower third of the oesophagus (Dolan *et al*, 1999; Kocher *et al*, 2001), most have considered the histological groups of squamous cell carcinoma and adenocarcinoma (Vizcaino *et al*, 2002; Newnham *et al*, 2003; Pohl & Welch, 2005; Cooper *et al*, 2009; Dikken *et al*, 2012b; Thrift & Whiteman, 2012; Edgren *et al*, 2013; Hur *et al*, 2013).

Gastric cancer subgroups

The large majority of malignant gastric tumours are adenocarcinomas with the remainder most likely to be non-Hodgkin's lymphomas or leiomyosarcomas (Kelley & Duggan, 2003; Crew & Neugut, 2006). Therefore, it is the anatomical location of these tumours that are often studied as distinct subgroups. There are two main anatomical subtypes studied; tumours arising in the cardia (sometimes referred to as proximal tumours), the part of the stomach which joins to the oesophagus, and tumours arising in the rest of the stomach, collectively known as non-cardia tumours (sometimes referred to as distal tumours) (Shibata & Parsonnet, 2006).

1.3 Aetiology

Tobacco smoking and high alcohol consumption are the main risk factors for oesophageal squamous cell carcinoma (Lindblad *et al*, 2005; Blot *et al*, 2006; Shibata & Parsonnet, 2006; Holmes & Vaughan, 2007; Lagergren & Lagergren, 2010). Whilst smoking is a moderate risk factor for oesophageal adenocarcinoma no role of alcohol consumption has been established (Wu *et al*, 2001a; Lagergren, 2005; Lindblad *et al*, 2005; Blot *et al*, 2006; Holmes & Vaughan, 2007; Lubin *et al*, 2012; Hardikar *et al*, 2013). Chewing areca nut (also known as betel quid when combined with betel leaf) both with and without tobacco, and consumption of hot tea, have also been associated with an increased risk of developing oesophageal squamous cell carcinoma (Wu *et al*, 2001b; Islami *et al*, 2009; Akhtar *et al*, 2012).

Barrett's oesophagus, a condition in which the normal squamous mucosa in the lower part of the oesophagus is replaced with columnar epithelium (Watson & Shepherd, 2005) and chronic gastro-oesophageal reflux disease (GORD), the abnormal reflux of stomach acid into the oesophagus, in particular erosive GORD where reflux causes esophagitis (inflammation of the oesophagus), are known risk factors in the development of oesophageal adenocarcinoma (Lagergren *et al*, 1999a; El-Serag, 2008; Erichsen *et al*, 2012). Obesity, particularly abdominal obesity, may increase the risk of GORD and Barrett's oesophagus and therefore oesophageal adenocarcinoma, but studies have also shown an association with obesity independent of reflux (Wu *et al*, 2001a; Murray *et al*, 2003a; El-Serag *et al*, 2005; Hampel *et al*, 2005; Lindblad *et al*, 2005; Holmes & Vaughan, 2007; Merry *et al*, 2007; El-Serag, 2008; Wood & Yang, 2008; O'Doherty *et al*, 2012; Hardikar *et al*, 2013; Turati *et al*, 2013).

Helicobacter pylori infection has been established as a main risk factor for non-cardia gastric cancer (International Agency for Research on Cancer, 1994). However meta-analyses have found that such infection may be associated with a lower risk of oesophageal adenocarcinoma and possibly gastric cardia cancer which may be because infection causes achlorhydria (the

absence of hydrochloric acid in gastric fluid) and so reduces gastric acid reflux (Blot *et al*, 2006; Kamangar *et al*, 2006a; Rokkas *et al*, 2007; Islami & Kamangar, 2008). Tobacco smoking and a diet high in salt and preserved foods have been associated with increased risk of developing non-cardia gastric cancer (Tredaniel *et al*, 1997; Lindblad *et al*, 2005; World Cancer Research Fund / American Institute of Cancer Research, 2007).

A diet high in fresh fruit and vegetables is thought to decrease the risk of both oesophageal and gastric cancers (World Cancer Research Fund / American Institute of Cancer Research, 2007), and aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) use may also lead to a lower risk of oesophageal cancer (Lagergren & Lagergren, 2010; Liao *et al*, 2012).

1.4 Incidence of oesophageal and gastric cancers

1.4.1 Geographical patterns

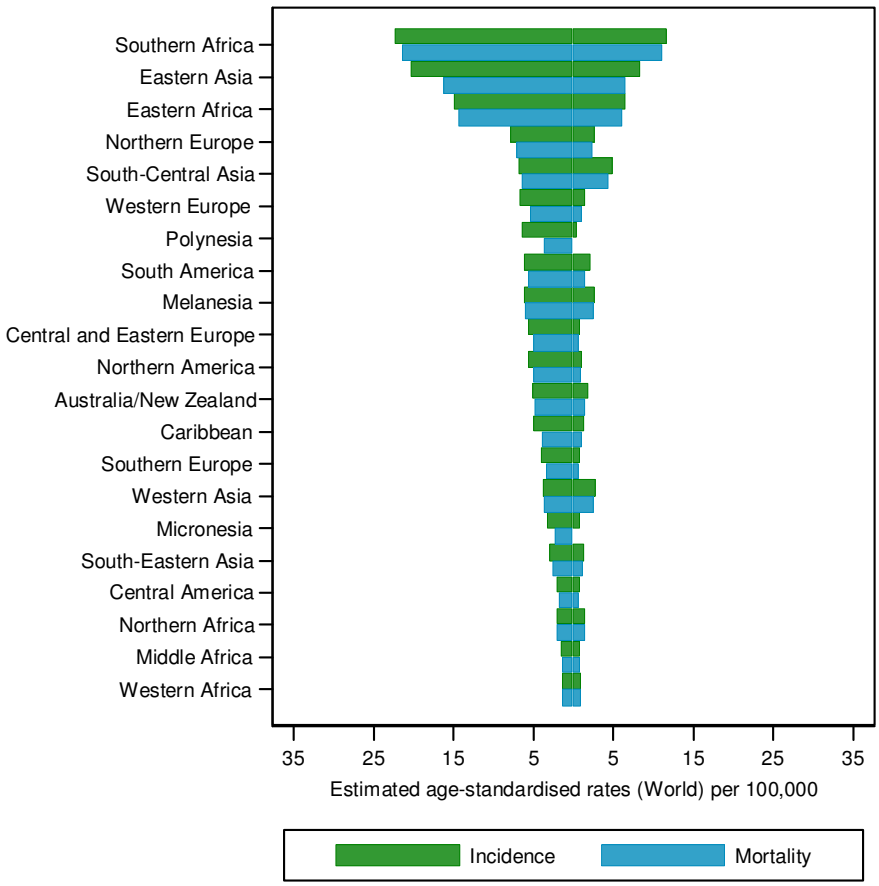
A comparison of the incidence of cancers worldwide is likely to be affected by differences in registration processes in each country and the proportion of the population covered by the registries (sometimes only major cities in developing countries) (International Agency for Research on Cancer, 2008). However, in 2008 the GLOBOCAN project produced estimated incidence and mortality rates for 184 countries around the world (International Agency for Research on Cancer, 2008).

Oesophageal cancer

According to GLOBOCAN, oesophageal cancer (of any histological type) was estimated to be the eighth most common cancer worldwide in 2008, with over 80% of cases occurring in developing countries (International Agency for Research on Cancer, 2010a). Internationally, wide variation in the incidence of this cancer is evident with the highest estimated age-standardised incidence rates found in Southern and Eastern Africa and Eastern Asia, over 14 per 100,000 World population for men and over 6 per 100,000 for women (Figure 1.1). The

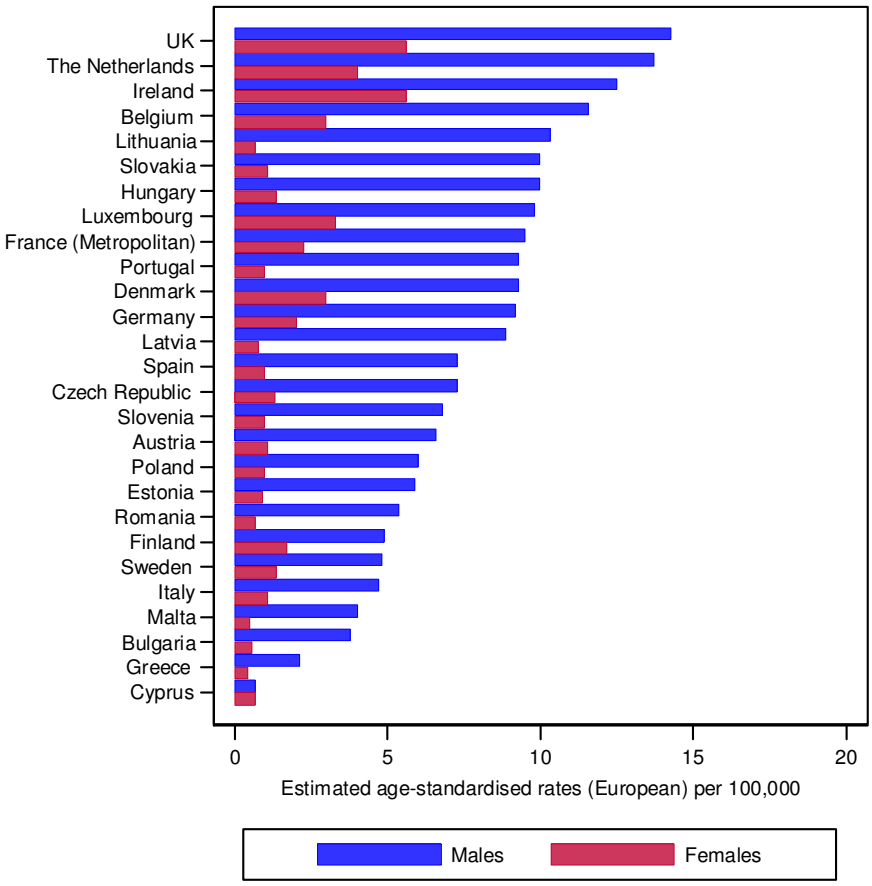
majority of oesophageal cancer tumours in these areas are squamous cell carcinoma (Curado *et al*, 2007; Holmes & Vaughan, 2007; Pennathur *et al*, 2013). In contrast, incidence rates in the UK were 9.5 per 100,000 for men and 3.6 per 100,000 for women in 2008, and the dominant histological type in this country is adenocarcinoma (Cooper *et al*, 2009; Lagergren & Lagergren, 2010).

Figure 1.1: Estimated age-standardised incidence and mortality rates per 100,000 World standard population for oesophageal cancer. Data taken from GLOBOCAN 2008 (International Agency for Research on Cancer, 2008)



However, compared with other European countries, the UK had the highest age-standardised incidence rates of oesophageal cancer in men (14.3 per 100,000 European standard population), and the UK and Ireland had the highest incidence rates in women (5.6 per 100,000 for both countries), (Figure 1.2). Reasons for the higher incidence of this cancer in the UK compared with other developed countries are not known.

Figure 1.2: Estimated age-standardised incidence rates per 100,000 European standard population for oesophageal cancer. Data taken from GLOBOCAN 2008 (International Agency for Research on Cancer, 2008)



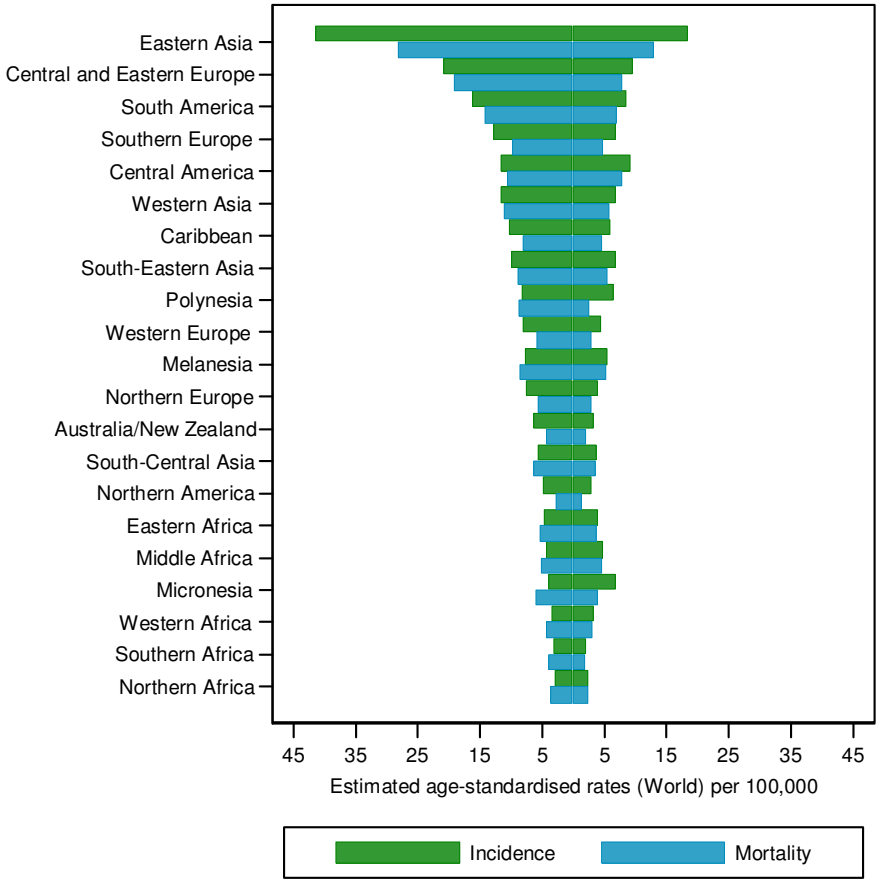
The mortality rates for oesophageal cancer are similar to the incidence rates due to the poor prognosis of this cancer (National Cancer Intelligence Network, 2011c). Therefore, the highest mortality rates are found in areas with the highest incidence rates (Figure 1.1). In the UK, oesophageal cancer was the sixth most common cause of cancer death in 2010, behind lung, colorectal, breast, prostate and pancreatic cancer (Cancer Research UK, 2012b).

Gastric cancer

In 2008, gastric cancer was estimated to be the fourth most common cancer worldwide with over 70% of cases occurring in developing countries (International Agency for Research on Cancer, 2010b). Of the world total, over one half of gastric cancers occur in Eastern

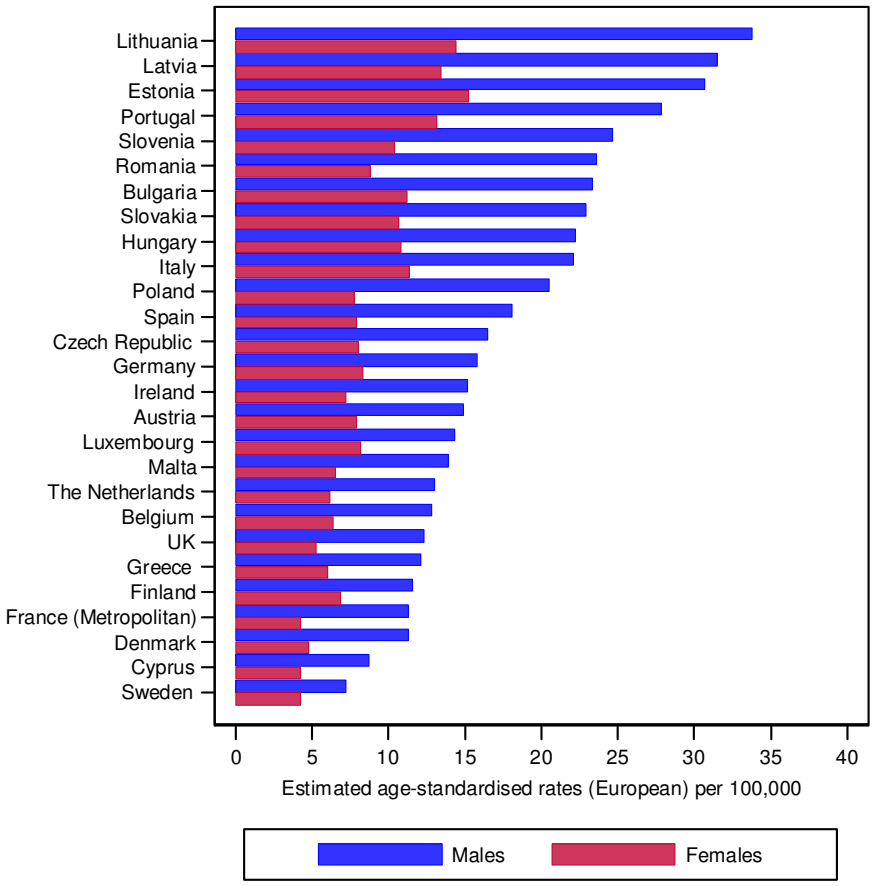
Asia (International Agency for Research on Cancer, 2010b), with age-standardised incidence rates estimated to be as high as 42.4 per 100,000 World population in men and 18.3 per 100,000 in women (Figure 1.3). Comparably, incidence rates in the UK were 8.0 per 100,000 for men and 3.4 per 100,000 for women.

Figure 1.3: Estimated age-standardised incidence and mortality rates per 100,000 World standard population for gastric cancer. Data taken from GLOBOCAN 2008 (International Agency for Research on Cancer, 2008)



In contrast to oesophageal cancer, the UK had a lower incidence of gastric cancer (12.4 per 100,000 European population for men and 5.3 for women) than most other European countries, with rates less than half those reported in Lithuania (33.8 and 14.4 respectively), (Figure 1.4).

Figure 1.4: Estimated age-standardised incidence rates per 100,000 European standard population for gastric cancer. Data taken from GLOBOCAN 2008 (International Agency for Research on Cancer, 2008)



For males and females combined, gastric cancer was the second most common cause of cancer death worldwide behind that of lung cancer in 2008 (International Agency for Research on Cancer, 2010b), whereas in the UK, gastric cancer was the seventh most common cause of cancer death in 2010 (Cancer Research UK, 2012b).

1.4.2 Time trend in incidence

Oesophageal and gastric cancer

Major changes in the incidence of oesophageal and gastric cancer have been reported over the last few decades. Since the mid-1970s, the incidence of oesophageal cancer in men has increased considerably in developed countries including the United States and United Kingdom, whereas the incidence in females has remained relatively stable (Cancer Research UK, 2011b; National Cancer Institute, 2011). The incidence of this cancer in England is expected to increase in the future particularly among men (Møller *et al*, 2007; Gatenby *et al*, 2011; Mistry *et al*, 2011). In contrast, the incidence of gastric cancer has declined dramatically in many developed countries for both men and women over the last few decades (Cancer Research UK, 2011c; National Cancer Institute, 2011). Despite this decline in incidence rates, a large number of people are still diagnosed with gastric cancer each year in the UK, and the number of cases is predicted to increase by 2030 due to the ageing population (Mistry *et al*, 2011; Cancer Research UK, 2012a). However, these overall trends obscure interesting patterns in the specific subgroups of these tumours.

Squamous cell carcinoma and adenocarcinoma of the oesophagus

The predominant histological type of oesophageal cancer worldwide is squamous cell carcinoma (Pennathur *et al*, 2013). Whilst the incidence of oesophageal squamous cell carcinoma has generally remained relatively stable or decreased in many developed countries, the incidence of oesophageal adenocarcinoma, particularly in men, has increased (Bollschweiler *et al*, 2001; Vizcaino *et al*, 2002; Newnham *et al*, 2003; van Blankenstein *et al*, 2007; Lepage *et al*, 2008; Cook *et al*, 2009; Cooper *et al*, 2009; Abrams *et al*, 2011; Dikken *et al*, 2012b; Thrift & Whiteman, 2012; Edgren *et al*, 2013; Hur *et al*, 2013). However, some recent studies have reported that the increasing incidence of oesophageal adenocarcinoma has begun to slow and in some countries decline (Pohl *et al*, 2010; Lagergren

& Mattsson, 2011). This increase in incidence of oesophageal adenocarcinoma has meant this histological group is more common in many developed countries including the United Kingdom (Pohl & Welch, 2005; Curado *et al*, 2007; Cooper *et al*, 2009; Dikken *et al*, 2012b). However, in Asia the incidence of adenocarcinoma remains low and squamous cell carcinoma remains the dominant histological type in this area (Hongo *et al*, 2009; Pennathur *et al*, 2013). Internationally, the highest incidence of oesophageal adenocarcinoma has been reported in the United Kingdom (Bollschweiler *et al*, 2001; Edgren *et al*, 2013), although reasons for this are currently not known. Differences in the prevalence and exposure to risk factors in these populations are likely to explain some of this variation.

Oesophageal adenocarcinoma and gastric cardia cancer

Like oesophageal adenocarcinoma, an increase in the incidence of cancers of the gastric cardia has been observed in many developed countries (Kocher *et al*, 2001; Newnham *et al*, 2003; Pohl & Welch, 2005; Abrams *et al*, 2011). However, some studies have found a more stable or slightly declining trend in the incidence of this cancer since the early 1990s (van Blankenstein *et al*, 2007; Lagergren & Mattsson, 2011; Dikken *et al*, 2012b). A decreased prevalence of *Helicobacter pylori* infection, and an increased prevalence of chronic GORD, Barrett's oesophagus, and obesity (Hongo *et al*, 2009; Abrams *et al*, 2011; Ness-Jensen *et al*, 2012) may have contributed to this rise in incidence.

Oesophageal adenocarcinoma and gastric cardia cancers have high male to female incidence rate ratios, with the incidence in males up to nine times higher than that of females (Blot *et al*, 1991; Kocher *et al*, 2001; El-Serag *et al*, 2002; Newnham *et al*, 2003; Dikken *et al*, 2012b; Edgren *et al*, 2013). It is currently not known why men have a greater risk of these cancers, although one theory suggested that the 'male pattern' of abdominal obesity, which may lead to higher levels of GORD, could partly explain this (Vaughan *et al*, 2002; El-Serag, 2008). Also, the prevalence of Barrett's oesophagus, a significant risk factor for oesophageal

adenocarcinoma, is estimated to be up to eight times higher in men than women, and the prevalence of erosive GORD is also higher in men (Cook *et al*, 2005; Wong & Fitzgerald, 2005; Wood & Yang, 2008; de Jonge *et al*, 2010). Other studies have considered a protective role of oestrogen, although current evidence is inconclusive (Lagergren & Nyren, 1998; Green *et al*, 2012; Lu & Lagergren, 2012).

Non-cardia gastric cancer

The incidence of non-cardia gastric cancer has declined over the past century in many developed countries (Powell & McConkey, 1990; Quinn *et al*, 2001; Crew & Neugut, 2006; Kamangar *et al*, 2006b). This has been attributed to the decreasing prevalence of *Helicobacter pylori* infection, brought about by improvements in living conditions (Crew & Neugut, 2006; Gajperia *et al*, 2009). A higher prevalence of this infection has been linked to socioeconomic factors, such as low income and overcrowding (Webb *et al*, 1994; Crew & Neugut, 2006), which could partly explain the strong association between non-cardia gastric cancer and socioeconomic deprivation. Changes in diet, such as an increase of fresh food, particularly fruit and vegetables, as opposed to salt-preserved foods may also be linked to this decrease in incidence (World Cancer Research Fund / American Institute of Cancer Research, 2007).

Socioeconomic deprivation and incidence

The higher overall incidence of oesophageal and gastric cancer in people resident in more socioeconomically deprived areas (National Cancer Intelligence Network, 2008b) is likely to be explained by the strong association between deprivation and oesophageal squamous cell carcinoma and non-cardia gastric cancers (Brewster *et al*, 2000; Crew & Neugut, 2006; Cooper *et al*, 2009). Other studies have found a higher incidence of oesophageal adenocarcinoma and gastric cardia cancer in more socioeconomically deprived areas, but this association was less pronounced than for the other subgroups (Jansson *et al*, 2005; Holmes & Vaughan, 2007; Gajperia *et al*, 2009). However, another study found a higher incidence of oesophageal

adenocarcinoma and gastric cardia cancer in more affluent areas (Lepage *et al*, 2008), and some studies have found no association with deprivation (Brewster *et al*, 2000; Cooper *et al*, 2009). These differences are likely to be related to the differences in aetiology for these subgroups.

Ethnicity and incidence

Variation in the incidence of oesophageal and gastric cancers has been reported between ethnic groups within countries (Curado *et al*, 2007; Goggins & Wong, 2009; National Cancer Intelligence Network, 2009; Ali *et al*, 2010; Ali *et al*, 2012). A recent report by the National Cancer Intelligence Network focusing on variation in cancer incidence between major ethnic groups found that South Asian (Indian, Pakistani, and Bangladeshi) and Black men and women had a lower incidence of oesophageal cancer compared with White men and women between 2002 and 2006 (National Cancer Intelligence Network, 2009). The same report found South Asian men and women had a lower incidence of gastric cancer and Black men and women a higher incidence than their White counterparts (National Cancer Intelligence Network, 2009).

Variation in the incidence between ethnic groups has also been reported for the specific subgroups of these cancers. Many studies carried out in the US (El-Serag *et al*, 2002; Vizcaino *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Curado *et al*, 2007; Cook *et al*, 2009) and two from the UK (Cooper *et al*, 2009; Ali *et al*, 2012) found the incidence of oesophageal squamous cell carcinoma was similar or higher in Black men compared with White men, whereas oesophageal adenocarcinoma was higher in White men. Similarly, to oesophageal adenocarcinoma, a higher incidence of gastric cardia cancer in White men has also been found (El-Serag *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Wu *et al*, 2009). Some studies have reported that Black men and women had a higher incidence of non-cardia gastric cancer compared with their White counterparts (Wu *et al*, 2006; Wu *et al*, 2009). Differences in exposures to risk factors between ethnic groups might contribute to this variation. No study

in England has so far focused on the variation in incidence between specific ethnic groups and these cancer subgroups.

1.5 Treatment of oesophageal and gastric cancers

Upper gastrointestinal cancer multidisciplinary teams bring together the relevant clinical expertise needed to make well-informed decisions about the treatment and care of patients with oesophageal and gastric cancer. These teams typically include surgeons, gastroenterologists, oncologists, radiologists, pathologists, supportive and palliative care physicians and nurses, and clinical nurse specialists (Lagergren & Lagergren, 2010; Okines *et al*, 2010). Each patient is discussed and the appropriate treatment is recommended taking into account factors such as the stage of their disease, tumour location, any other diseases they have (co-morbidities), their performance status, their nutritional status, and their preferences for treatment (Okines *et al*, 2010; Stahl *et al*, 2010; Allum *et al*, 2011).

Stage of disease is an important determinant of which treatment is most appropriate for each patient (Okines *et al*, 2010; Stahl *et al*, 2010; Allum *et al*, 2011; Pennathur *et al*, 2013). Only patients with localised disease will benefit from treatment with curative intent, and therefore the detection of these cancers at an early stage is important. However, as most oesophageal and gastric cancer tumours are diagnosed at an advanced stage (National Cancer Institute, 2012a; National Cancer Institute, 2012b), supportive and palliative care will be the most suitable treatment for the majority of patients. Recent advances in imaging techniques such as endoscopic ultrasonography, and computed tomography scans combined with ^{18}F-fluorodeoxyglucose positron emission tomography scans have led to more accurate staging of tumours (Lagergren & Lagergren, 2010; Pennathur *et al*, 2013). With these improvements it has become increasingly possible to offer the most appropriate treatment to each patient, rather than providing unnecessary aggressive treatment to patients with incurable disease (Lagergren & Lagergren, 2010).

Treatment with curative intent

The main curative treatment for patients with oesophageal or gastric cancer is surgery, but this is only possible in patients with localised disease (Cromwell *et al*, 2010). Twenty percent of patients with these cancers in England underwent curative surgery in 2005, which fell from 28% in 1998 (Palser *et al*, 2008). This decline has been attributed to better patient selection through improved diagnostic and staging investigations and better multidisciplinary team working (Palser *et al*, 2008). Growing clinical evidence has found that chemotherapy or chemo-radiotherapy given pre-operatively (before surgery) or peri-operatively (both before and after surgery) is beneficial and improves long-term survival (MRC, 2002; Cunningham *et al*, 2006) and these treatments are increasingly used (Palser *et al*, 2008).

Surgical procedures for oesophageal and gastric cancers include the partial or total removal of the oesophagus (oesophagectomy), the stomach (gastrectomy) or part of both the oesophagus and stomach (oesophagogastrectomy). These are demanding procedures which carry a high risk of post-operative complications, a significant risk of death shortly after surgery, and are associated with poor short- and long-term health-related quality of life (Blazeby *et al*, 2000; McCulloch *et al*, 2003; Jamieson *et al*, 2004; Djarv *et al*, 2008; Cromwell *et al*, 2010). Therefore, rigorous selection of patients is essential to ensure that those undergoing surgery have a good chance of recovery and should regain an acceptable quality of life.

Treatment with supportive and palliative intent

The majority of oesophageal and gastric cancer patients require palliative care interventions, which mainly aim to improve their quality of life by alleviating symptoms (Cromwell *et al*, 2010). External beam radiotherapy, brachytherapy (internal radiotherapy), chemotherapy, and laser treatment can all be used to relieve symptoms such as dysphagia (difficulty in swallowing), pain and discomfort, and bleeding. Stents can also be used to relieve dysphagia quickly by counteracting localised constrictions caused by the tumour (Allum *et al*, 2011). Pain

relief and feeding through gastrostomy (surgical opening into the stomach), jejunostomy (opening into the proximal section of the jejunum of the small intestine) or intravenously are also important palliative care treatments (Lagergren & Lagergren, 2010).

Changes to upper gastrointestinal cancer services

In 1995, the Calman-Hine Report recommended that cancer care should be provided by site-specialist multidisciplinary teams located in designated cancer units and centres (Calman-Hine Report, 1995). This was supported by the Improving Outcomes Guidance for upper gastrointestinal cancers, published in 2001, that proposed specialist oesophageal and gastric cancer treatment teams should draw patients from an area of around one to two million people (Department of Health, 2001). Substantial changes in upper gastrointestinal surgical services have occurred across England over the last decade because of this guidance (Palser *et al*, 2009), and currently there are 41 upper gastrointestinal specialist surgery centres (Allum *et al*, 2011).

The drive for centralisation of services began after a study by Luft *et al* (1979) which first demonstrated a lower mortality with increased surgical volume for twelve surgical procedures of different complexity in the United States. Since then many studies from Europe and the United States have demonstrated better outcomes such as lower post-operative mortality with increasing hospital volume or surgeon volume for various diseases including cancer (Begg *et al*, 1998; Bachmann *et al*, 2002; Birkmeyer *et al*, 2002; Hannan *et al*, 2002; Birkmeyer *et al*, 2003; Killeen *et al*, 2005; Pal *et al*, 2008; Wouters *et al*, 2008; Gruen *et al*, 2009; Lauder *et al*, 2010; Rouvelas & Lagergren, 2010; Skipworth *et al*, 2010; Anderson *et al*, 2011; Markar *et al*, 2012). Fewer studies have investigated the impact of hospital volume on long-term survival and these have found conflicting results (Birkmeyer *et al*, 2007; Rouvelas *et al*, 2007; Thompson *et al*, 2007; Gruen *et al*, 2009; Anderson *et al*, 2011; van de Poll-Franse *et al*, 2011; Dikken *et al*, 2012a).

1.6 Survival

The prognosis of both oesophageal and gastric cancer is poor with a five-year relative survival of only 12% and 16% respectively, and one-year relative survival of around 41% for both cancer types (National Cancer Intelligence Network, 2011c). According to EUROCARE-4 data, which includes population-based survival estimates across Europe, survival from oesophageal and gastric cancers was generally lower in the UK than in comparable European countries (Norway, Sweden, and Finland), (Sant *et al*, 2009). Also, higher five-year relative survival estimates of 17% for oesophageal cancer and 27% for gastric cancer were reported in the United States (National Cancer Institute, 2012a; National Cancer Institute, 2012b). It is not clear why survival for these cancers is lower in the UK, but studies that considered differences in breast cancer, colorectal cancer, and lung cancer survival between England, Norway and Sweden found excess mortality to be more pronounced in the first months and in the first year following diagnosis (Holmberg *et al*, 2010; Møller *et al*, 2010; Møller *et al*, 2012). The authors also suggested this could be due to a larger proportion of patients presenting with rapidly fatal disease in England. Whether or not this is also true for oesophageal and gastric cancers is not clear.

Between 2006 and 2008, the National Cancer Intelligence Network estimated that around one fifth of oesophageal cancer and one third of gastric cancer patients were diagnosed through an emergency presentation, and that cancers diagnosed through this route were associated with poorer one-year survival (Elliss-Brookes *et al*, 2012). The relatively high proportion of patients first diagnosed through an emergency admission is suggestive of tumours being identified at an advanced stage. Stage of disease is an important indicator of the prognosis of oesophageal and gastric cancers, with a much better chance of survival associated with early stage tumours (Gavin *et al*, 2012; National Cancer Institute, 2012a; National Cancer Institute, 2012b). However, the symptoms of oesophageal and gastric cancers including progressive dysphagia,

pain on swallowing, weight loss, pain and discomfort in the upper abdomen, and bleeding often occur at an advanced stage of the disease (van Soest *et al*, 2008; Lagergren & Lagergren, 2010), which is likely to explain why few patients are diagnosed early. Diagnosing these tumours at an earlier stage and raising awareness of symptoms in the general public will be important to improve survival from these cancers, but the non-specific nature of these symptoms is likely to make this challenging.

Although there are national screening programmes for other cancers such as breast, cervical and most recently bowel cancer (Weller *et al*, 2006; Cancer Screening Programmes, 2012a; Cancer Screening Programmes, 2012b), no screening test for oesophageal or gastric cancers exists which has adequate sensitivity and specificity. Oesophageal and gastric cancers are relatively uncommon and difficult to diagnose and it is unlikely that population-wide screening will be possible and cost-effective until specific high-risk groups can be identified. Even though the efficacy of endoscopic surveillance of patients with Barrett's oesophagus is unproven, such programmes do currently exist in the majority of gastrointestinal units in the UK (Loft *et al*, 2005). However, recent studies have found that the relative risk of oesophageal adenocarcinoma in these patients was much lower than previously reported adding further doubt over the cost-benefit of such surveillance (Murray *et al*, 2003b; Bhat *et al*, 2011; Hvid-Jensen *et al*, 2011). Future studies could help to identify a specific high-risk group that may be able to be screened in the future.

1.7 Summary

Oesophageal and gastric cancers are significant health problems in the United Kingdom, both in terms of the numbers of cases and deaths, and the severity of the diseases. The incidence of oesophageal cancer, especially oesophageal adenocarcinoma, has increased particularly in men, and is expected to continue to increase in the future, and although the overall incidence

of gastric cancer has declined, a large number of people are still diagnosed with these tumours each year (section 1.4.2).

Of particular interest are the differences in incidence in the subgroups of these cancers (section 1.4.2). For example, the increase of oesophageal adenocarcinoma has led to higher rates of this histological subgroup compared with oesophageal squamous cell carcinoma being reported in developed countries. In particular, the UK has the highest incidence of oesophageal adenocarcinoma compared with other European countries. Like oesophageal adenocarcinoma, the incidence of gastric cardia tumours has also increased, although in some countries the incidence has begun to plateau in recent years. These two adjacent anatomical subsites share similar aetiological characteristics and show similar trends in incidence.

Both oesophageal and gastric cancers are associated with poor prognosis due to the advanced stage of disease at presentation, and therefore curative surgery is only possible in a relatively small proportion of patients with these cancers (section 1.5). There are significant clinical challenges to improve outcomes and quality of life for these patients.

1.8 Outline of the thesis

This chapter has described what is known about differences in the incidence, survival, aetiology and treatment of oesophageal and gastric cancers. Chapter 2 examines the methods common to more than one of the chapters in this thesis and the variables that were used in the analysis. The data quality and completeness of the national dataset and its fitness for purpose are assessed in Chapter 3. Patterns in the incidence and survival of oesophageal and gastric cancer, and six subgroups of these cancers, are investigated in Chapter 4, and the variation in incidence between ethnic groups is considered in Chapter 5. The association between the case volume of the hospital in which a patient undergoes surgery and mortality, both in the short- and long-term is investigated in Chapter 6, and the factors that affect who

receives surgery for these cancers is considered in Chapter 7. A general discussion in the final chapter will highlight the new findings and the implications of these for clinical practice, public health, and health policy.

Chapter 2 General methods

This chapter describes the sources of data that are used in this thesis and the methods common to more than one chapter. Methods specific to individual chapters will be described within each one.

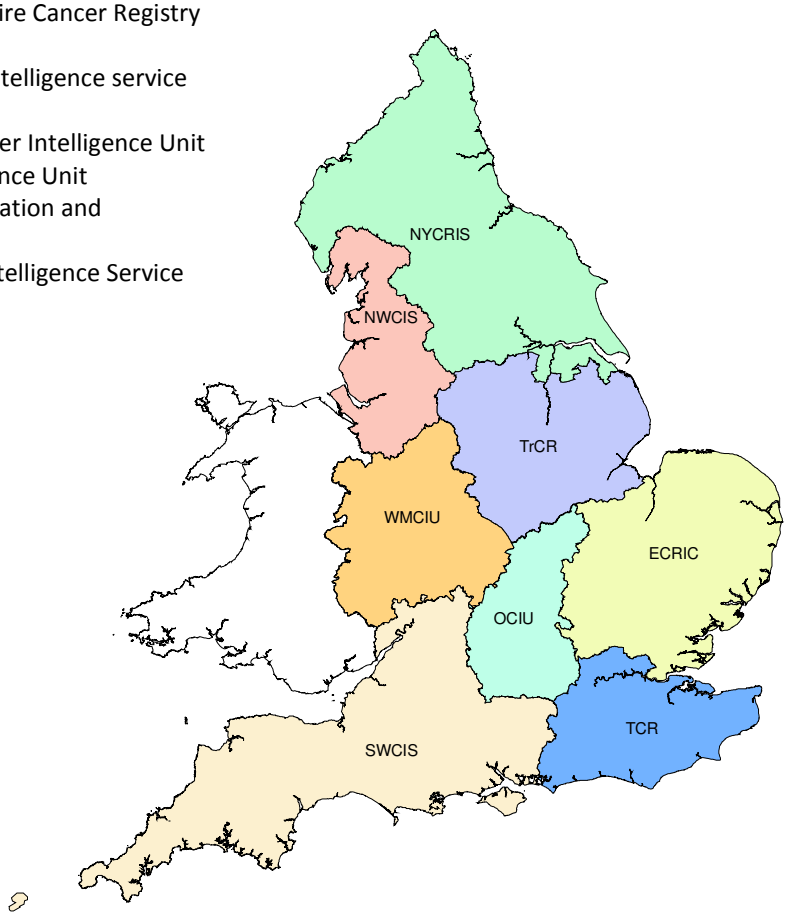
2.1 Datasets

2.1.1 Cancer registration dataset

Eight regional cancer registries in England collect data on all patients diagnosed with cancer in their resident populations (Figure 2.1). English cancer registries cover the whole population of England of 53 million people (Office for National Statistics, 2012).

Figure 2.1: Map of the areas covered by the regional cancer registries in England

NYCRIS – Northern and Yorkshire Cancer Registry and Information Service
NWCIS – North West Cancer Intelligence service
TrCR – Trent Cancer Registry
WMCIU – West Midlands Cancer Intelligence Unit
OCIU – Oxford Cancer Intelligence Unit
ECRIC – Eastern Cancer Registration and Information Centre
SWCIS – South West Cancer Intelligence Service
TCR – Thames Cancer Registry



The information collected by each of the regional cancer registries is extracted from multiple sources including hospitals, pathology laboratories, cancer centres, treatment centres, and cancer screening programmes. Most organisations have more than one source of data, for example, hospitals may record information on patients in their patient administrative system (PAS), in pathology reports, and in their medical records. Information is also extracted from data included on death certificates, in the Hospital Episode Statistics (HES) dataset (described in more detail in section 2.1.2), and the Cancer Waiting Times dataset, which was set up to monitor the waiting time standards along a cancer pathway. All the cancer registries participate in a cancer registration subgroup of the United Kingdom Association of Cancer Registries, which ensures that they all collect a common minimum dataset and follow a standardised set of rules for cancer registration.

Data from each registry have been combined to form a national cancer registration dataset of all patients diagnosed with cancer in England after 1985. These data are quality assured in each cancer registry before being combined into the English dataset (National Cancer Intelligence Network, 2011b).

Each cancer registration represents a tumour and patients diagnosed with more than one tumour can be identified through their patient identification number. The dataset includes information on patient demographics (name, sex, age, date of birth, NHS number, and postcode of residence) and tumour details (cancer type, anatomical subsite, date of diagnosis, and basis of diagnosis). It also includes basic treatment information (date of surgery, chemotherapy, radiotherapy or hormone therapy, and hospital of treatment), although this is not complete because not all registries collect it. Postcode of residence is used to assign each patient to geographical areas including those for lower super output areas (LSOAs), primary care trusts (PCTs), and cancer networks (CNs), so allowing investigation of geographical variation in cancer incidence, treatment and survival.

Information is also collected on tumour stage with 15 individual stage fields, including TNM stage, being collected in the national cancer registration dataset (Table 2.1). The TNM classification of malignant tumours is a globally used staging system for tumours that describes the extent the cancer has spread within the patient's body (Sobin *et al*, 2010). For solid tumours, the T component describes the size of the tumour, N whether regional lymph nodes are involved and M describes whether or not the patient was diagnosed with distant metastases. The presence of metastases indicates that the cancer has spread from its original location.

Table 2.1: Stage fields included in the cancer registration dataset

Group	**Description**
Stage information	T clinical
	N clinical
	M clinical
	TNM clinical
	T pathological
	N pathological
	M pathological
	TNM pathological
	T integrated
	N integrated
	M integrated
	TNM integrated
	Positive nodes (Y, N)
	Number of positive nodes
	Metastases (Y, N)

Pathological, clinical, and integrated TNM stage is recorded in this dataset. Clinical TNM stage is determined before surgery with information on the tumour obtained from physical examination or imaging. Pathological TNM stage is derived from additional information gained by microscopic examination of the tumour by a pathologist and is considered more reliable than clinical stage. Integrated stage is used by three cancer registries (ECRIC, WMCIU, and NWCIS) and includes a combination of both pathological and clinical stage information. The dataset also includes fields which record whether or not a patient had distant metastases, had

positive nodes, and the number of nodes that were positive. The availability of stage information in this dataset will be discussed in Chapter 3.

Death information is supplied by the National Health Service (NHS) Central Register via the Office for National Statistics. Some registrations are initiated by information on the patient's death certificate, which is used to trace patients within hospital systems, and if they can be found more details are added to form a complete registration. However, some cases will remain death certificate only registrations (DCOs) with only limited information and the date of diagnosis is recorded as the date of death. This means they have to be excluded from any survival analysis and the implications of this will be discussed in more detail in Chapter 3.

2.1.2 Hospital Episode Statistics dataset

Cancer registries in England have access to an extract of the HES dataset which is collated from data recorded in the PAS of NHS hospitals, and supplied to the registries by the NHS Information Centre. The HES extract contains details on all inpatient and day case admissions to NHS hospitals in England. Each record represents a finished consultant episode (FCE) which records a period of care where the patient is admitted under a consultant or allied healthcare professional in an NHS trust. An admission contains one or more FCE in which the care of the patient is transferred between consultants. The HES extract includes details on all patients with a diagnosis of cancer, or suspected cancer, between April 1997 and March 2010. All of the HES episodes for these patients in this period were obtained, including episodes where the cancer was not mentioned.

The HES dataset contains details of patient demographics, NHS number, and up to 20 diagnosis codes and 26 operation codes can be recorded for each episode. Diagnosis codes could relate to diseases that did not lead to the admission, for example, co-morbid conditions that may affect the treatment a patient can receive will be recorded in addition to their cancer diagnosis. Information about a patient's diagnosis and their operation (where applicable) are

recorded in their medical records by the clinician responsible for their treatment. This is then translated by clinical coders into the relevant International Classification of Diseases version 10 (ICD10) or Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures 4th revision (OPCS4) code (NHS Connecting for Health, 2011). These codes enable consistent comparison of diagnoses and operations across the country. Operation dates are recorded for each operation and the hospital and trust in which the patient was treated is recorded against each episode.

The HES dataset contains information about patients that are either not routinely recorded or incomplete in the cancer registration dataset such as their self-assigned ethnicity and details of other non-cancer diseases which can be used to derive a co-morbidity score. The registries only collect basic treatment information within six month of a patient's diagnosis date. This period could be extended beyond six months with treatment information recorded in the HES dataset.

2.1.3 National Cancer Data Repository (NCDR)

The cancer registration and HES datasets were linked in the Thames Cancer Registry (TCR) to form a National Cancer Data Repository (NCDR) dataset. The linkage methodology was defined by a national repository team including staff in TCR and the Northern & Yorkshire Cancer Registry and Information Service (NYCRIS). The aim was to ensure that there was a robust and systematic process in place to generate successive generations of the NCDR.

This section describes the stages involved in the matching of these two datasets. First, records were matched using a process called "blocking". Six sequential blocks were defined as outlined in Table 2.2.

Table 2.2: Blocks used in the matching of the cancer registration and Hospital Episode Statistics datasets

Block	Data items
1	NHS number
2	Postcode, day, month and year of birth, and day, month and year of death
3	Day, month and year of birth, day, month and year of death, gender
4	Postcode, year of birth, gender
5	Outer postcode, day, month and year of birth, gender
6	Outer postcode, day, month and year of death, gender

Each block identified records with similar characteristics and a weight for the similarity between the possible matched records was generated, ranging between 0 and 375. A threshold was defined to identify matched records which were most likely to be correct (Table 2.3). According to the threshold, matched records with a weight over 255 were considered accurately matched and were passed onto the next stage of the process.

Table 2.3: Weight threshold used in the matching process of the cancer registration and Hospital Episode Statistics datasets

Weight	Reason
295+	Highly likely to be correctly matched records
270-290	Likely to be correct, but will contain some false matched records
255-269	Mostly false, but will contain some correctly matched records
<255	Very few correctly matched records

Potential matched records were then considered against the data items that contributed to the weight in order to assess the quality of the match. Matched records were sub-classified into three groups; fully matched, partially matched, and non-matched. Both this weight and this sub-classification were then used to decide on the degree of confidence in each matched pair of records. The rules for this process can be found in Table 2.4.

Table 2.4: The process rules used in the matching of the cancer registration and Hospital Episode Statistics datasets

Weight	Rule
280+	Valid match
275-279	Valid match, unless match is on gender, date of birth, postcode and date of death
<275	Valid match if the NHS number was fully matched (except where it was null in both records) or the NHS number was partially matched

This method ensured that records with a reasonable match weight which were not good quality matches were excluded. A linkage table was generated which contained patient identifiers from the cancer registration dataset for each matched pair of records and their corresponding HES identifiers. This table was then used to link the two datasets to form the NCDR dataset. This linkage enriches the cancer registration dataset with data fields for self-assigned ethnicity, co-morbidity and treatment information which are described in more detail later in this chapter.

Currently, there are three generations of the NCDR dataset with an extra year of diagnosis included in each new release. Cancer registration data are continually updated so the newer iterations will contain more complete data for the earlier years of diagnosis as well. In this thesis, chapters were based on the dataset available at the time of the analysis. Table 2.5 outlines which generation was used for the analysis in each chapter.

Table 2.5: NCDR generations used in each chapter

Chapter		**NCDR generation**	**Diagnosis years included in the analysis**
2	General methods	NCDR_2009	2000-2009
3	Data quality and completeness of the oesophageal and gastric cancer dataset	NCDR_2009	2000-2009
4	Incidence and survival of oesophageal and gastric cancer in England	NCDR_2007	1998-2007
5	Ethnicity in relation to incidence of oesophageal and gastric cancer in England	NCDR_2007	2001-2007
6	Factors that affect who receives surgery for oesophageal and gastric cancer in England	NCDR_2009	1998-2009
7	Hospital volume, proportion resected and mortality from oesophageal and gastric cancer	NCDR_2008	2004-2008

2.1.4 Oesophageal and gastric cancer dataset

From the 2009 National Cancer Data Repository, data on 142,670 patients diagnosed with oesophageal (ICD10 C15) or gastric cancer (ICD10 C16) in England between 2000 and 2009 were extracted. A small number of patients were excluded because their recorded date of death was before their recorded date of diagnosis (n=15). Cancer registries collect information on their resident population, but patients can be registered by a different cancer registry if they were treated in the area it covers. These patients are flagged as extra-regional cases (n=9,922), and were excluded from the study dataset to avoid counting these patients more than once. The dataset was also checked for duplicates using an International Agency for Research on Cancer programme and duplicate records were excluded (n=574). This left 132,159 patients, 63,830 oesophageal cancer and 68,329 gastric cancer patients.

2.1.5 Population data

Population data were obtained from the Office for National Statistics and were available for males and females in five-year age groups in the English geographical areas outlined in section 2.1.1. The population in 2001 was taken from the census year and combined with mid-year population estimates between 1998 and 2000 and between 2002 and 2008 (Office for National Statistics, 2009). Population data were also available for different ethnic groups (Office for National Statistics, 2011b).

2.2 Oesophageal and gastric cancer subgroups

Oesophageal and gastric cancers were identified by the ICD10 3-digit codes C15 and C16, respectively. Many studies, however, have investigated specific subgroups of these cancers. For the purposes of this thesis six anatomical oesophageal and gastric cancer subgroups were defined based on knowledge of their aetiology and advice from clinicians. These included 1) upper and middle oesophagus, 2) lower oesophagus, 3) oesophagus with unspecified

anatomical site (from now on referred to as oesophagus "not otherwise specified" (NOS)), 4) gastric cardia, 5) gastric non-cardia, and 6) gastric with an unspecified anatomical site (from now on referred to as gastric NOS).

2.2.1 Oesophageal cancer subgroups

Oesophageal cancer subgroups can be defined by either anatomical subsite based on ICD10 4-digit codes or the histology of the tumour based on the International Classification of Diseases for Oncology (ICDO2) codes. Table 2.6 shows the ICD10 codes used to define the oesophageal cancer subgroups according to their anatomical subsite.

Table 2.6: Oesophageal cancer ICD10 4-digit codes and corresponding oesophageal cancer subgroups

International Classification of Diseases version 10 (ICD10)	**Oesophageal cancer subgroups**
C15 Malignant neoplasm of oesophagus	
C15.0 Cervical part of oesophagus	Upper and middle
C15.1 Thoracic part of oesophagus	Upper and middle
C15.2 Abdominal part of oesophagus	Lower
C15.3 Upper third of oesophagus	Upper and middle
C15.4 Middle third of oesophagus	Upper and middle
C15.5 Lower third of oesophagus	Lower
C15.8 Overlapping lesion of oesophagus	Not otherwise specified
C15.9 Oesophagus, unspecified	Not otherwise specified

Based on the histology of the tumour, oesophageal cancers can be divided into squamous cell carcinoma (ICD02 8050–8083), adenocarcinoma (ICD02 8140–8576), and "other histological types or unspecified". Using the ICD10 4-digit codes, 33,269 (52.1%) of 63,830 oesophageal cancer patients, diagnosed between 2000 and 2009, were classified as "not otherwise specified". Using the histology, 15.8% (n=10,069) of patients were in the "other and unspecified" group. Therefore, to ensure maximum use of all the available coding the oesophageal cancer subgroups were defined using a combination of both the anatomical

subsite and histological information, following discussions with clinicians who have expert knowledge in the field.

The oesophageal cancer subgroups were based primarily on the ICD10 codes to define their anatomical location (Table 2.7). As the large majority of oesophageal adenocarcinomas occur in the lower third of the oesophagus (Dikken *et al*, 2012b) patients in the oesophageal NOS subgroup who had a histological diagnosis of adenocarcinoma were reassigned into the lower oesophageal subgroup. Squamous cell carcinomas are more evenly distributed throughout the entire length of the oesophagus (Dikken *et al*, 2012b), so patients with oesophageal NOS cancer and squamous cell carcinoma were included in the upper and middle oesophageal cancer subgroup. This resulted in a smaller proportion of patients 7,097 (11.1%) with an unspecified oesophageal cancer.

Table 2.7: Oesophageal cancer subgroups based on anatomical subsite and supplemented with morphology information

Oesophageal and gastric cancer subgroups	**International Classification of Diseases version 10 (ICD10) and International Classification of Diseases for Oncology (ICDO2) codes**
Upper and middle oesophagus	C15.0–C15.1, C15.3–C15.4 including C15.8–C15.9 with a morphology code 8050–8083 (Squamous cell carcinoma)
Lower oesophagus	C15.2, C15.5 including C15.8–C15.9 with a morphology code 8140–8576 (Adenocarcinoma)
Oesophagus not otherwise specified	C15.8–C15.9 excluding C15.8–C15.9 with a morphology code 8050–8083 (Squamous cell carcinoma) or 8140–8576 (Adenocarcinoma)

The main focus for the analyses in this thesis was on anatomical subgroups so the oesophageal and gastric cancer subgroups could be defined consistently. However, because squamous cell carcinomas are more evenly distributed throughout the oesophagus the main misclassification from the method described above is likely to occur in this group. Therefore, as a sensitivity analysis the groups were also defined primarily on the histology of the tumour and supplemented with the anatomical subsite information. Using this method, only 6,471 (11.4%) of 56,733 patients who had known anatomical subsite or morphology information would have

been coded differently using the earlier method, which suggests there would be little difference in the results when using either method to define the subgroups.

As mentioned previously, these definitions aimed to make the best use of all available coding. However, as a further sensitivity analysis, the three oesophageal cancer subgroups based solely on the histological diagnosis of the tumour (squamous cell carcinoma, adenocarcinoma, and "other and unspecified"), were analysed in Chapters 4 and 5. This was to ensure that the results for the subgroups defined above were comparable to the more traditional approach of defining these subgroups based on the histological diagnosis.

2.2.2 Gastric cancer subgroups

The three gastric cancer subgroups were defined on the basis of ICD10 codes (Table 2.8). As the histology of around 90% of gastric cancer is adenocarcinoma (Cromwell *et al*, 2010) it was not possible to further re-assign any patients in the gastric NOS group to the gastric cardia or gastric non-cardia subgroups. Therefore, a limitation of these definitions was that over half 35,048 (51.3%) of 68,329 gastric cancers were "not otherwise specified".

Table 2.8: Gastric cancer ICD10 4-digit codes and corresponding gastric cancer subgroups

International Classification of Diseases version 10 (ICD10)	**Gastric cancer subgroups**
C16 Malignant neoplasm of stomach	
C16.0 Cardia	Cardia
C16.1 Fundus of stomach	Non-cardia
C16.2 Body of stomach	Non-cardia
C16.3 Pyloric antrum	Non-cardia
C16.4 Pylorus	Non-cardia
C16.5 Lesser curvature of stomach, unspecified	Non-cardia
C16.6 Greater curvature of stomach, unspecified	Non-cardia
C16.8 Overlapping lesion of stomach	Not otherwise specified
C16.9 Stomach, unspecified	Not otherwise specified

2.3 Socioeconomic deprivation

The Indices of Deprivation 2004 (Office of the Deputy Prime Minister, 2004), 2007 (Department for Communities and Local Government, 2008) and 2010 (Department for Communities and Local Government, 2011) provide a measure of deprivation for each of the 32,482 LSOAs in England, areas of around 1,500 people. A similar method was used to derive the deprivation scores for these three versions of the Indices of Deprivation to provide a consistent measure over time (Department for Communities and Local Government, 2011).

The Indices of Deprivation contain seven domains including 'income', 'employment', 'health and disability', 'education, skills and training', 'barriers to housing and services', 'living environment', and 'crime'. Data are collected on 38 indicators across these domains from many sources including the Census, the Office for National Statistics, the Department for Work and Pensions, Her Majesty's Revenue and Customs, the Home Office, the Department for Education, the Department for Communities and Local Government, and the Police (Department for Communities and Local Government, 2011). These data are combined to produce an overall deprivation score and a score for each other domain. The 'income' and 'employment' domains are considered the most important contributors to the overall deprivation score and therefore carry more weight than the other domains (Table 2.9).

Table 2.9: Domains and domain weights included in the Indices of Deprivation 2010 (Department for Communities and Local Government, 2011)

Domain	**Domain weight**
Income	22.5%
Employment	22.5%
Health and Disability	13.5%
Education, Skills and Disability	13.5%
Barriers to Housing and Services	9.3%
Crime	9.3%
Living Environment	9.3%

However, it is not appropriate to use the overall deprivation score for health-related studies due to the inclusion of the 'health and disability' domain within it, so socioeconomic deprivation in this thesis is based on the income domain only. For each LSOA, an income domain score was calculated based on the proportion of adults and children living in Income Support, Working Families Tax and Child Tax Credit, Pension Credit, Job Seekers Allowance and Disability Allowance households. These scores are then ranked and divided into quintiles of deprivation. The deprivation quintiles range from quintile one which represents the least deprived areas through to quintile five for the most deprived areas.

Patients were grouped into quintiles of socioeconomic deprivation based on their postcode and thus their lower super output area of residence. The 2007 Indices of Deprivation (ID) measure was used for the analysis in Chapters 4 and 7 as this measure was based on data available during the periods studied. For the analysis in Chapter 6, the patients' year of diagnosis was also used to assign the deprivation quintile. The 2004 ID (Office of the Deputy Prime Minister, 2004) was used for patients diagnosed between 1998 and 2002, the 2007 ID (Department for Communities and Local Government, 2008) for patients diagnosed between 2003 and 2006, and the 2010 ID (Department for Communities and Local Government, 2011) for patients diagnosed between 2007 and 2009. This allowed a deprivation quintile relevant to the period in which the patient was diagnosed to be assigned to each patient, which helped account for changes over time in the deprivation of the area in which they lived.

There are other measures of deprivation including the Carstairs Index and the Townsend Deprivation Index that are used in other English studies (Townsend *et al*, 1988; Carstairs & Morris, 1989). In both these measures, aggregate scores are derived from four variables recorded in the Census including unemployment, overcrowding, non-car ownership, low social class (Carstairs only), and non-house ownership (Townsend only). Therefore, one advantage of

the Indices of Deprivation measure is that it is based on a wider range of data that is drawn from administrative sources and not just from the Census. As a result, this measure can be updated more often than the Carstairs and Townsend Indices. This allows for the selection of a deprivation measure closer to the period being studied and not one that is based on data that could be up to ten years old. The income domain of the Indices of Deprivation measure is widely used in health related research in England (Lepage *et al*, 2008; National Cancer Intelligence Network, 2008b; Cooper *et al*, 2009). For these reasons, the Indices of Deprivation measures were chosen for the work in this thesis.

2.4 Ethnicity

Ethnicity is a socially defined concept which defines people belonging to a particular ethnic group as sharing a common culture or nationality. Self-assigned ethnicity was chosen in preference to other methods of defining ethnicity such as name analysis, or country of birth because the methods are prone to misclassifications. For example, country of birth will become increasing less able to define ethnicity as the number of children born in the UK to parents from other countries increases. Self-assigned ethnicity is also collected and recorded by the Census, and information collected through this forms the basis of the population estimates produced by the Office for National Statistics (Office for National Statistics, 2011b).

Historically, ethnicity information has been poorly recorded within the cancer registries, so data on self-assigned ethnicity was taken from the HES dataset, where it has been mandatory to collect ethnicity information since 1995 (The Health and Social Care Information Centre, 2011). Ethnicity in HES is defined as 'the ethnicity of a person, as defined by the person' (The Health and Social Care Information Centre, 2011), and therefore each patient is asked their ethnic group during their hospital visit. The proportion of FCEs with a valid known ethnic code improved over time, from 76.1% in the data year 2004-05 to 91.4% in 2009-10 (The Health and Social Care Information Centre, 2011). Of those with an unknown ethnicity, most were 'not

stated' (6.7%; 2009-10) which means that the patient either declined to state their ethnicity, or was genuinely unable to define it. The remainder were 'not known' (1.7%; 2009-10) where the patient was not asked or it was not possible to ask them as their condition prevented it. They may, for example, have had severe dementia or been unconscious. Therefore, the completeness of ethnicity coding in the HES dataset was good and improved with time.

Within HES, each patient may have had more than one ethnic code recorded across their episodes, so for the purpose of this thesis their most recent valid ethnic code was taken. This definition has been used in other cancer studies that have focused on ethnicity (Jack *et al*, 2010; Coupland *et al*, 2011; Downing *et al*, 2011; Jack *et al*, 2011; Jack *et al*, 2013). Other methods of assigning ethnicity were also possible, such as taking the most commonly recorded ethnic code or the first ethnic code recorded for each patient. However, a thesis that focused on ethnicity and cancer concluded that the ethnicity code assigned using all of these three methods was consistent, but favoured the use of the most recent ethnic code (Jack, 2010).

Ethnic groups were analysed for seven categories: White, Indian, Pakistani, Bangladeshi, Black Caribbean, Black African and Chinese (Table 2.10). Due to changes in ethnicity coding between the 1991 and 2001 census these categories were considered the most stable over time (Simpson & Akinwale, 2007).

Table 2.10: Ethnic groups analysed in this thesis with corresponding 1991 and 2001 Census ethnicity definitions

Ethnic groups used in this thesis	**1991 Census ethnicity definition**	**2001 Census ethnicity definition**
White	White	White - British
		White - Irish
		White - any other White background
Indian	Indian	Asian or Asian British - Indian
Pakistani	Pakistani	Asian or Asian British - Pakistani
Bangladeshi	Bangladeshi	Asian or Asian British - Bangladeshi
Black Caribbean	Black - Caribbean	Black or Black British - Caribbean
Black African	Black - African	Black or Black British - African
Chinese	Chinese	Chinese
Other	-	Mixed - White and Black Caribbean
		Mixed - White and Black African
		Mixed - White and Asian
		Mixed - any other Mixed background
	-	Asian or Asian British - any other Asian background
	Black - Other Black	Black or Black British - any other Black background
	Any other ethnic group	Any other ethnic group

2.5 Co-morbidity

Co-morbidity is the presence of one or more medical conditions or diseases in addition to a patient's principal diagnosis. Clinicians will consider co-morbid conditions when deciding which treatment is the most suitable or if the patient is well enough to undergo intensive regimes.

The Charlson co-morbidity index is a score that predicts mortality for a patient based on their coexisting conditions, with higher scores indicating a higher risk of death (Charlson *et al*, 1987). An advantage of this measure of co-morbidity is that it is relatively inexpensive and easy to use for population-based studies, as a score can be derived for almost all patients from diagnosis data recorded in routine administrative datasets, such as HES. A systematic review, published in 2003, concluded the Charlson Index was a valid and reliable method to assess co-morbidity

in health research (de Groot *et al*, 2003). For these reasons, an adapted Charlson co-morbidity score was chosen for the analysis carried out in this thesis.

Co-morbidity is not recorded directly during the cancer registration process and so was obtained from the linked HES admitted patient dataset. A co-morbidity score for each patient was derived from the 20 diagnosis codes recorded within all of their inpatient and day case episodes, between two years prior to and three months after their date of diagnosis. Fifteen disease groups were identified from the updated coding algorithm for the Charlson co-morbidity index developed by Quan *et al* (2005). Standard weights, taken from the original Charlson paper (Charlson *et al*, 1987), were assigned according to the severity of the condition (Table 2.11). Cancer diagnoses were excluded from the overall co-morbidity score.

The weights were aggregated to produce an overall co-morbidity score for each patient. However, codes within the same category were not aggregated, for example, if a patient had a diagnosis of both diabetes and diabetes with complications, only the latter disease group was included in the overall co-morbidity score. Similarly, if a patient had a diagnosis both of liver disease and severe liver disease, only the weight for severe liver disease was included. The resulting scores were aggregated into four categories of increasing severity of co-morbidity: 0 (no co-morbid conditions), 1 (co-morbidity score of 1), 2 (co-morbidity score of 2), or 3 (co-morbidity score 3 or higher).

Table 2.11: Disease groups with corresponding ICD10 codes and co-morbidity weight

Disease group	**International Classification of Diseases version 10 (ICD10)**	**Weight**
Acute Myocardial Infarction	I21-I22, I252	1
Congestive Heart Failure	I099, I110, I130, I132, I255, I420, I425-I429, I43, I50, P290	1
Peripheral Vascular Disease	I70-I71, I73, I77, I79, K551, K558-K559, Z958-Z959	1
Cerebral Vascular Accident	G45, G46, H340, I60-I69	1
Dementia	F00-F03, F051, G30, G311	1
Pulmonary Disease	I278-I279, J41-J47, J60-J67, J684, J701, J703	1
Connective Tissue Disorder	M05-M06, M32-M34, M353, M360	1
Peptic Ulcer	K25-K28	1
Diabetes	E100-E101, E106, E108, E110-E111, E116, E118-E119, E120, E121, E126, E128-E129, E130-E131, E136, E138-E139, E140-E141, E146, E148	1
Diabetes Complications	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	2
Paraplegia	G041, G114, G081-G082, G81-G82, G831-G834, G839	2
Renal Disease	I120, I131, N032-N037, N052-N057, N18-N19, N250, Z490-Z492, Z940, Z992	2
Liver Disease	B170, B18, K70, K73-K74, K760, K762-K764, K768-K769, Z944	1
Severe Liver Disease	I580, I859, I864, I982, K711, K721, K765-K767	3
HIV	B20-B22, B24	6

2.6 Treatment information

2.6.1 Surgical resection

Surgical information was extracted from the linked admitted patient dataset because surgical treatment information in HES was more complete than in the cancer registration dataset and recorded consistently in all of England. First, a list of all the procedures that oesophageal or gastric cancer patients underwent was extracted. This was then reduced to include OPCS4 codes listed within the upper digestive tract chapter of the OPCS4 coding documentation (NHS Connecting for Health, 2011). After discussions with surgeons in this field, the relevant major surgical procedures for oesophageal and gastric cancer were identified from this reduced list. In total, 32 OPCS4 codes were selected including codes for total or partial oesophagectomy, total or partial gastrectomy, oesophagogastrectomy, or other and unspecified total or partial excisions of the oesophagus or stomach (Table 2.12). Resections were identified as being undertaken for oesophageal cancer, for gastric cancer or for either cancer.

For each patient, surgery information from one month before to 12 months following their date of diagnosis was extracted from the HES dataset. This period was chosen to ensure the resection selected was most likely to be related to the identified tumour and not a recurrence of a patient's cancer. The period of 12 months after a patient's diagnosis was defined to ensure that resections for patients who underwent a course of pre-operative chemotherapy, radiotherapy, or chemo-radiotherapy were included.

Table 2.12: OPCS4 codes and descriptions of major surgical procedures for oesophageal and gastric cancer

OPCS4 code	Operation
Oesophageal and gastric cancer resections	
G011	Oesophagogastrectomy & anastomosis of oesophagus to stomach
G012	Oesophagogastrectomy & anastomosis of oesophagus to transposed jejunum
G013	Oesophagogastrectomy & anastomosis of oesophagus to jejunum NEC
G018	Other specified excision of oesophagus and stomach
G019	Unspecified excision of oesophagus and stomach
Oesophageal cancer resections	
G021	Total oesophagectomy and anastomosis of pharynx to stomach
G022	Total oesophagectomy and interposition of microvascularly attached jejunum
G023	Total oesophagectomy and interposition of jejunum NEC
G024	Total oesophagectomy and interposition of microvascularly attached colon
G025	Total oesophagectomy and interposition of colon NEC
G028	Other specified total excision of oesophagus
G029	Unspecified total excision of oesophagus
G031	Partial oesophagectomy and end to end anastomosis of oesophagus
G032	Partial oesophagectomy and interposition of microvascularly attached jejunum
G033	Partial oesophagectomy and anastomosis of oesophagus to transposed jejunum
G034	Partial oesophagectomy and anastomosis of oesophagus to jejunum NEC
G035	Partial oesophagectomy and interposition of microvascularly attached colon
G036	Partial oesophagectomy and interposition of colon NEC
G038	Other specified partial excision of oesophagus
G039	Unspecified partial excision of oesophagus
Gastric cancer resections	
G271	Total gastrectomy and excision of surrounding tissue
G272	Total gastrectomy and anastomosis of oesophagus to duodenum
G273	Total gastrectomy and interposition of jejunum
G274	Total gastrectomy and anastomosis of oesophagus to transposed jejunum
G275	Total gastrectomy and anastomosis of oesophagus to jejunum NEC
G278	Other specified total excision of stomach
G279	Unspecified total excision of stomach
G281	Partial gastrectomy and anastomosis of stomach to duodenum
G282	Partial gastrectomy and anastomosis of stomach to transposed jejunum
G283	Partial gastrectomy and anastomosis of stomach to jejunum NEC
G288	Other specified partial excision of stomach
G289	Unspecified partial excision of stomach

Resections were assigned to patients irrespective of their cancer, for example, if a patient had an oesophageal cancer diagnosis and a gastric cancer operation this patient was considered to have had surgery. This was because there is inevitably some misclassification between oesophageal and gastric cancers, particularly for tumours that occur near the gastro-oesophageal junction. Finally, if a patient had more than one of these operations the earliest operation was selected for the analysis in this thesis, as this operation was most likely to be associated with the diagnosed tumour.

2.6.2 Chemotherapy and radiotherapy

Information on chemotherapy and radiotherapy are recorded in both the cancer registration and HES datasets. However, this information is recorded in different ways by different regional cancer registries and some do not record this information at all. Therefore, this source of data for these treatments was considered incomplete. OPCS4 codes that indicate delivery of chemotherapy or radiotherapy were also extracted from the inpatient and day case admissions HES dataset. However, not all patients have chemotherapy in an inpatient setting and most radiotherapy is received in an outpatient setting so this source of data was also considered incomplete. The absence of information on chemotherapy and radiotherapy will make interpretation of studies considering treatment less robust.

2.7 Summary

This chapter has described the construction of the linked national cancer registration and HES datasets. It has outlined the data fields available for the analysis and how these were selected. The next chapter will discuss the data quality of these fields, the implications of missing data, and will estimate the completeness of case ascertainment in the cancer registration dataset.

Chapter 3 Data quality and completeness of the oesophageal and gastric cancer dataset

3.1 Introduction

This chapter aims to assess the data quality and completeness of the national dataset of patients diagnosed with oesophageal or gastric cancer between 2000 and 2009 in England. It is important to investigate the quality of the dataset to determine whether missing or poor quality data are likely to affect the results of the studies included in this thesis. Missing data may also mean that more detailed analysis on specific subgroups could be difficult or misleading.

3.2 Dataset

Data were extracted from the 2009 National Cancer Data Repository on 63,830 oesophageal cancer (ICD10 C15) and 68,329 gastric cancer (ICD10 C16) tumours diagnosed in England between 2000 and 2009.

3.3 Death certificate only registrations (DCO)

Many registrations for rapidly fatal cancers are initiated by the patient's death certificate. These are traced in hospital systems, in the HES dataset, or in general practitioner records. Many cases are found and their details are updated to form a complete registration, known then as a death certificate initiated (DCI) registration. However, some cases will not be found and these will remain as death certificate only registrations (DCOs). DCOs have incomplete information which reflects the limited details recorded on death certificates.

It is not possible to ascertain a definitive date of diagnosis for a DCO registration and therefore these registrations need to be excluded from any survival analysis. Their diagnosis date is set

to be their date of death and their survival is zero days, so the inclusion of these patients would bias any survival estimates. The proportion of DCO registrations is a good indication of how complete case ascertainment is in the registry, however there will always be some cases which are only ever registered from their death certificate. Incomplete case ascertainment could lead to any survival estimates being too high, particularly if the missing registrations represented patients with rapidly fatal disease (Robinson *et al*, 2007).

Table 3.1 shows the proportion of death certificate only registrations for oesophageal and gastric cancer in England. Overall, 2.3% of oesophageal and 3.3% of gastric cancer registrations were DCOs. The proportion decreased over time, falling from 3.7% in 2000 to 1.2% in 2009 for oesophageal cancer patients and from 4.3% to 2.2% respectively for gastric cancer patients (Table 3.1).

Table 3.1: Proportion of registrations that were registered as death certificate only registrations

Year of diagnosis	Oesophageal cancer (ICD10 C15)			Gastric cancer (ICD10 C16)		
	Total number of registrations	DCO registrations	%DCO	Total number of registrations	DCO registrations	%DCO
2000	5,988	224	3.7	7,912	344	4.3
2001	6,117	168	2.7	7,479	302	4.0
2002	6,152	167	2.7	7,364	260	3.5
2003	6,279	167	2.7	6,926	264	3.8
2004	6,230	155	2.5	6,756	230	3.4
2005	6,454	176	2.7	6,579	222	3.4
2006	6,482	116	1.8	6,383	189	3.0
2007	6,600	112	1.7	6,509	170	2.6
2008	6,817	103	1.5	6,268	150	2.4
2009	6,711	82	1.2	6,153	135	2.2
2000-2009	63,830	1,470	2.3	68,329	2,266	3.3

It is encouraging to find that the proportions of death certificate only registrations were generally low and decreased over the ten year period studied. This would suggest that there would be limited impact on survival analysis from the exclusion of these records. However, it

is important that work continues to reduce the proportion of these registrations and new sources of data should be exploited to ensure that a complete cancer registration record is created on all cancer patients.

The following data quality measures are not applicable to death certificate only registrations, and therefore they were excluded.

3.4 Basis of diagnosis

The basis of diagnosis is recorded for each cancer registration. Three categories were defined as follows: microscopically verified (including cytology, histology of primary tumour or histology of metastases), clinically verified (including clinical opinion, clinical investigation or specific tumour markers) and not known. Any registrations that still had a death certificate initiated flag were reassigned to the microscopically verified group if they had a valid morphology code, and the clinically verified group if their morphology was not known. Table 3.2 shows the number of registrations in each category for oesophageal and gastric cancers diagnosed between 2000 and 2009.

Table 3.2: Proportion of registrations by basis of diagnosis for oesophageal and gastric cancers diagnosed between 2000 and 2009

Basis of diagnosis	Oesophageal cancer (ICD10 C15)		Gastric cancer (ICD10 C16)	
	Number of registrations	Percentage (%)	Number of registrations	Percentage (%)
Microscopically verified	57,081	91.5	59,875	90.6
Clinically verified	4,912	7.9	5,793	8.8
Not known	367	0.6	395	0.6
Total	62,360	100.0	66,063	100.0

The majority of both oesophageal cancer (91.5%) and gastric cancer (90.6%) registrations were microscopically verified. Such examination of a tumour by a pathologist would lead to additional information being available for these patients. For example, of those that were

microscopically verified, 110,771 (94.7%) of 116,956 registrations had a known histological diagnosis compared with 1,761 (15.4%) of 11,467 that were not microscopically verified.

Around 8% of oesophageal cancer and 9% of gastric cancer registrations were clinically verified i.e. where information was obtained from physical examination or imaging. This is less conclusive than microscopic examination, but does include some investigative techniques to define the diagnosis. Encouragingly, a small proportion of patients were registered with an unknown basis of diagnosis.

3.5 Anatomical subsite and morphology

Information on the anatomical subsite and histology of the tumour is used to define specific subgroups of oesophageal and gastric cancer. Assigning cases where this information is missing to specific subgroups will be difficult and analyses are likely to be biased by some level of misclassification.

The anatomical subsite was defined as known if the ICD10 4-digit codes were either C15.0-C15.5 or C16.0-C16.6 and not known if the codes were C15.8 or C16.8 (overlapping lesion of oesophageal or gastric cancer) and C15.9 or C16.9 (unspecified anatomical subsite of oesophageal or gastric cancer). Patients with an unknown morphology included those registered with an ICDO2 code of 8000/3 malignant neoplasm, 8001/3 malignant tumour cells, 8010/3 carcinoma not otherwise specified, and those with no recorded morphology information. The remainder of patients were included in the known group.

Figure 3.1 shows the proportion of oesophageal and gastric cancer registrations with a known anatomical subsite or known morphology information. Around one half had a known anatomical subsite. This remained relatively stable over time for gastric cancer registrations, whereas the proportion of oesophageal cancer registrations with this information increased slightly between 2006 and 2008. Between 2000 and 2009 around 88% of oesophageal and

gastric cancer registrations had known morphology information (Figure 3.1). This proportion increased slightly between 2000 and 2009 for both oesophageal cancer (83.9% to 90.0%) and gastric cancer (85.5% to 88.6%).

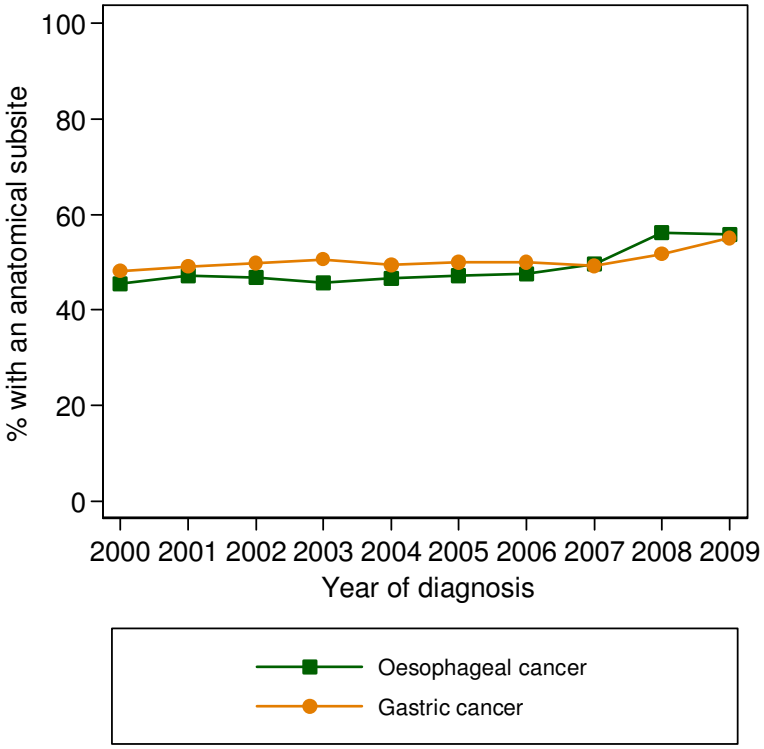
Large proportions of registrations with an unspecified anatomical subsite or morphology information limit the analysis of these cancers by specific subgroups. Around one half of oesophageal cancer registrations had no known anatomical subsite information so a combination of both the anatomical subsite and morphology was used to define the three oesophageal cancer subgroups in this thesis. This method is described in more detail in section 2.2.1. However, this is not ideal because it makes assumptions about the specific location of the tumour from morphology information.

The predominant histology of gastric cancers are adenocarcinomas (Cromwell *et al*, 2010) and so it was not possible to use the combination of both fields to define the gastric cancer subgroups. Therefore, the gastric cancer subgroups were based on only the anatomical subsite information, leading to 52% of cases in the gastric "not otherwise specified" group.

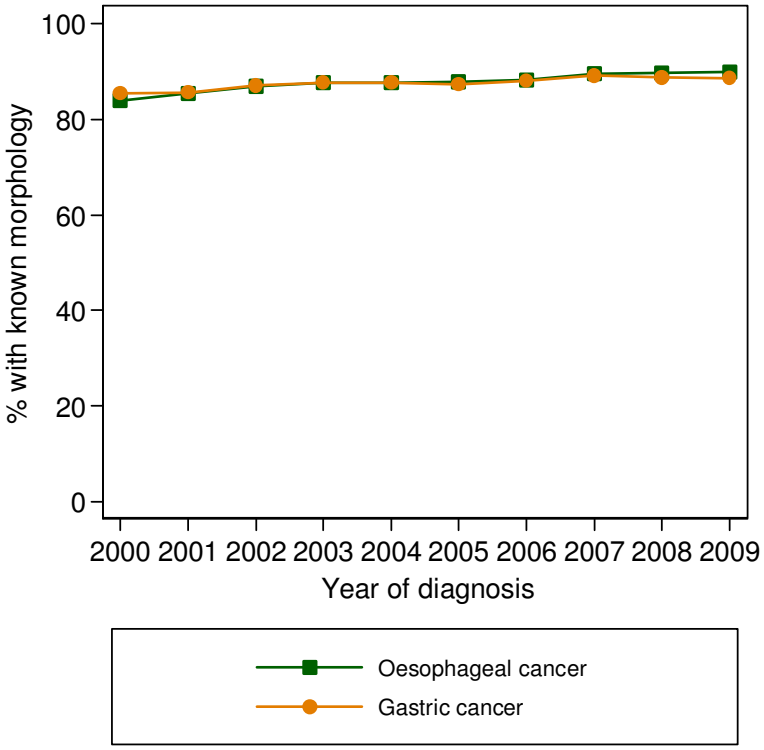
The incomplete information on anatomical subsite and morphological classification highlights the need for better recording of these data items for both oesophageal and gastric cancer tumours. This would enable specific subgroups to be defined more accurately.

Figure 3.1: Proportion of registrations with a) a known anatomical subsite and b) known morphology information for oesophageal and gastric cancers diagnosed between 2000 and 2009

a)



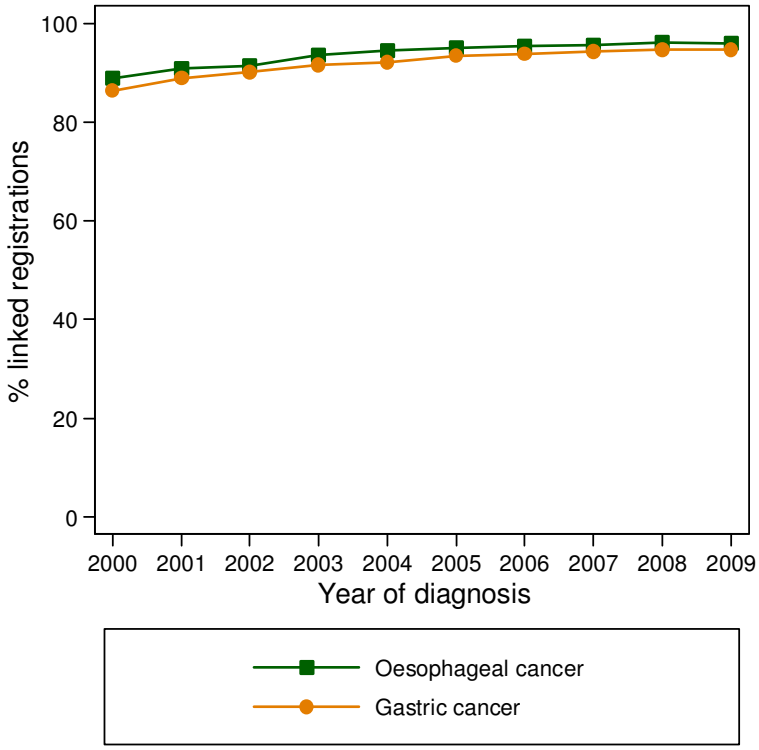
b)



3.6 Linked HES records

The subset of HES data received by the cancer registries includes all inpatient and day case episodes for patients with a record of cancer, or suspected cancer, in at least one HES episode. If a registration had no linked HES record this may mean that the patient was never admitted to a hospital or did not have a cancer diagnosis recorded in HES. However, it could also indicate that the matching process was not successful for that patient. If matching was unsuccessful, any information on surgery, co-morbidity, or self-assigned ethnicity for these patients would not be included in the NCDR because these fields are obtained from the HES dataset.

Figure 3.2: Proportion of registrations with a linked HES record for oesophageal and gastric cancers diagnosed between 2000 and 2009



In 2009, 96.0% of oesophageal cancer and 94.7% of gastric cancer registrations had a linked HES record (Figure 3.2). Between 2000 and 2009, there was an increase in the proportion of linked registrations for both cancer types, even though the proportions were high in 2000 (88.9% and 86.4%, respectively).

If large proportions of registrations had no link to HES it would be necessary to consider the impact of this on any analysis involving ethnicity, co-morbidity and surgery. Encouragingly, however, a high proportion of patients with a matched HES record were found.

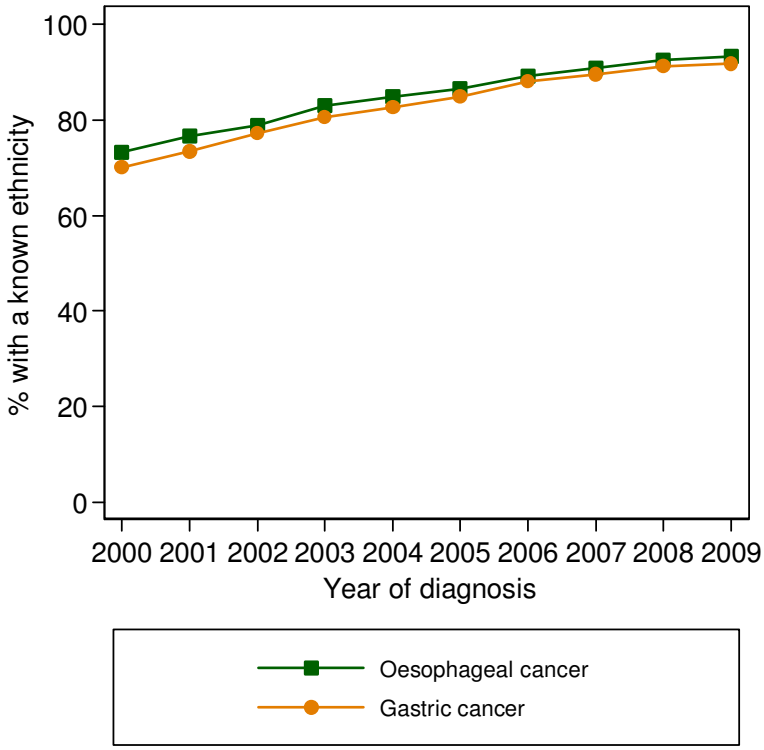
3.7 Co-morbidity

The proportion of patients with an unknown co-morbidity score is the same as the group of patients that had no linked HES record and as seen in the previous section this is a relatively small group. Therefore, the completeness of co-morbidity information was considered to be good. However, there are other concerns with the use of this method to derive co-morbidity. The method relies on information about all non-cancer diagnoses being accurately recorded during at least of one of the patient's hospital admissions, even if the condition was not relevant to their admission. Also, this method does not access information on co-morbidities from other sources such as from outpatient visits or visits to the patient's general practitioner (GP). It may be possible, therefore, that some co-morbidity information is missed. In the absence of this other information it was not possible to ascertain if the prevalence of co-morbidity is underestimated, and if it is, to what extent. However, data on major co-morbidities that could substantially influence prognosis or choice of treatment is likely to be more complete.

3.8 Ethnicity

Ethnicity has historically been poorly recorded in cancer registry datasets and therefore ethnicity was extracted from the linked HES dataset for the work in this thesis. Ethnicity was defined as not known if a registration had no ethnicity code or the ethnicity code was missing; otherwise patients were included in the known group.

Figure 3.3: Proportion of registrations with a known ethnicity for oesophageal and gastric cancers diagnosed between 2000 and 2009



The proportions of oesophageal and gastric cancer registrations with a known ethnicity have increased significantly over time, from 73.3% in 2000 to 93.2% in 2009 for oesophageal cancer and 70.1% to 91.8% for gastric cancer (Figure 3.3).

The increase in the proportion of registrations with known ethnicity is partly due to the improved linkage between the cancer registration and HES datasets, but also because of more comprehensive recording of ethnicity in HES in recent years (The Health and Social Care

Information Centre, 2011). Large proportions of patients with a missing ethnicity code will make studies that focus on ethnicity less robust. However, in this dataset there is a reasonable overall level of completeness of ethnicity information which allows the investigation of variation in incidence of these cancers between ethnic groups across England.

3.9 Tumour stage

This next section considers the availability of stage information in the NCDR. First, the availability of information in the individual stage fields was considered (section 3.9.1) and second, an aggregated stage was derived for each patient from data in these fields and proportion of patients with a known stage was ascertained (section 3.9.2).

3.9.1 Individual stage variables

Stage of disease is an important indicator of the prognosis of cancer and will affect which treatments are suitable for the patient. The NCDR contains pathological, integrated and clinical TNM stage information. The distinction between these is described in more detail in section 2.1.1. Other stage fields include whether or not distant metastases were present and whether or not there were positive nodes. The proportion of registrations with valid known stage information in each stage field was calculated.

Generally, there was an improvement in the proportion of registrations with known stage information in each stage field between 2000 and 2009, but overall proportions in each of the TNM stage fields remained low (often less than 10%) in both cancer types (Figure 3.4 & Figure 3.5). The distant metastases and nodes positive fields had a greater proportion of registrations with valid known information, but this was still only around 20% to 30%.

Figure 3.4: Proportion of oesophageal cancer registrations with a valid stage recorded

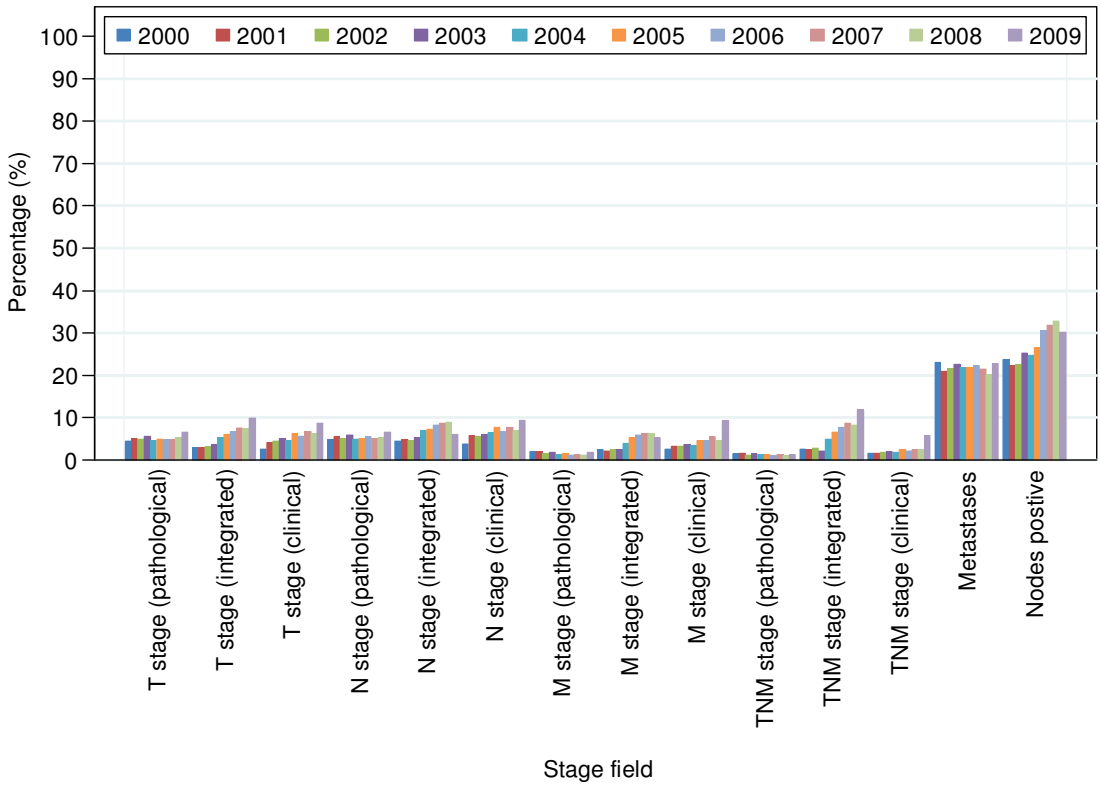
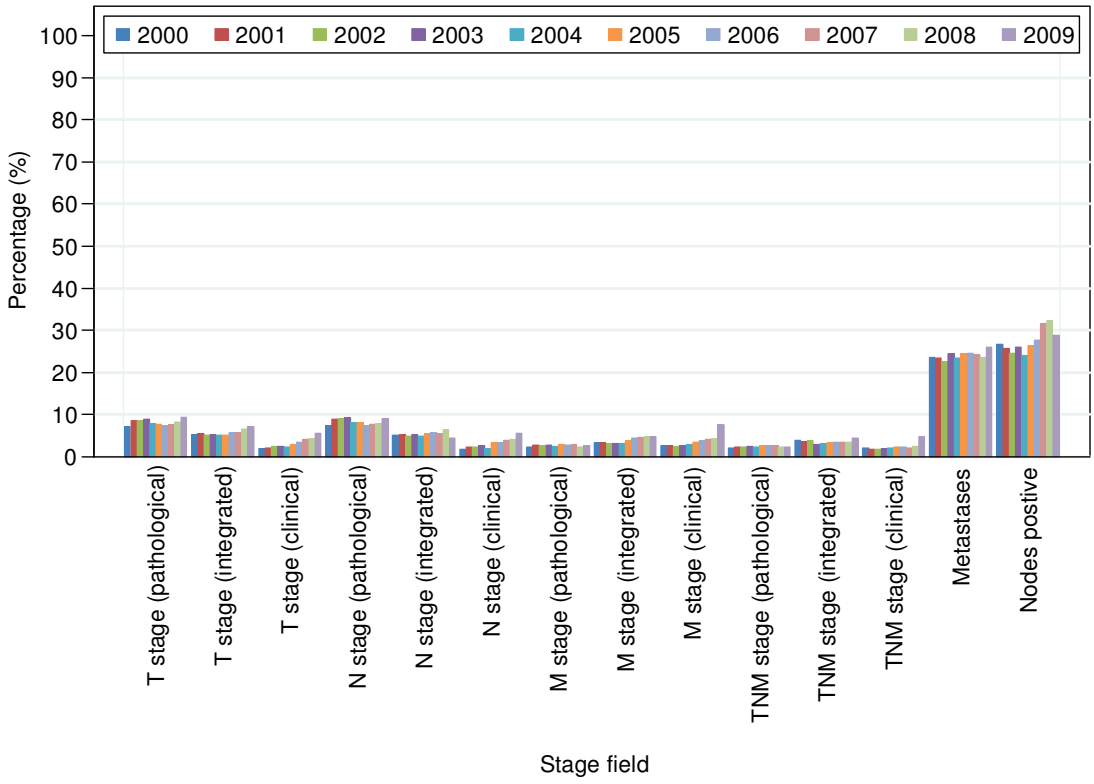


Figure 3.5: Proportion of gastric cancer registrations with a valid stage recorded



3.9.2 Aggregated stage

The individual stage fields were then combined to form an aggregate stage. This was based on the oesophageal and gastric cancer subgroups that had staging rules outlined in the TNM classification of malignant tumours 7th Edition (TNMv7) documentation (Sobin *et al*, 2010), (Table 3.3).

Table 3.3: Oesophageal and gastric cancer groups with corresponding ICD10 codes. Number of patients in England diagnosed between 2000 and 2009, and whether they were stageable according to TNM v7 documentation

Oesophageal and gastric cancer subgroups	**ICD10 code**	**Number of patients (excluding DCO registrations)**	**Stageable according to the TNMv7 documentation**
Oesophagus including oesophagogastric junction	C15.0-C15.9 & C16.0	80,444	Yes
Stomach (including fundus of stomach, body of stomach, pyloric antrum and pylorus)	C16.1-C16.4	8,654	Yes
Other stomach (including "not otherwise specified")	C16.5-C16.9	39,325	No

To generate the aggregated stage TNM information was considered in the order of (1) pathological stage, (2) integrated stage, and (3) clinical stage.

Derivation of M value

First, metastatic cases were identified. An M field was generated and where there was an indication of metastases from the distant metastases field or the pathological, integrated, or clinical M fields, then this M field was recoded as 1. Any remaining missing M values were replaced with 1 where the combined TNM fields indicated stage IV disease.

Derivation of N value

An N field was derived, taking pathological N values first, and then replacing any missing values with information from the integrated N field. Next, information on the number of positive nodes was used. Where values were between 1 or 2, N was coded to 1, values of 3 to 6 were

coded to 2, and values of 7 or more were coded to 3. If there was an indication of positive nodes, but the actual number of nodes was not known, N was coded to 1. Finally, any remaining missing values were replaced with information from the clinical N field.

Derivation of T value

A T field was derived by first taking the values recorded in the pathological, then integrated and finally the clinical T fields.

Derivation of an aggregated stage

The T, N and M fields were then used to define an aggregate stage. The full staging rules are outlined in Table 3.4 and Table 3.5. For example, if a patient with a diagnosis of oesophageal cancer had a T recorded as 3, an N as 2, and an M as 1 their aggregated stage would be stage IV. For any cases still not staged the pathological, integrated and clinical TNM combined fields were used to supplement the aggregated stage field. The subdivisions of A, B and C were not considered as the recorded information in the T fields were incomplete.

Table 3.4: Staging rule for cancer of the oesophagus including oesophagogastric junction (ICD10 C15 & C16.0) according to the TNMv7 documentation

Stage	**T**	**N**	**M**
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Table 3.5: Staging rule for gastric cancer (including fundus of stomach, body of stomach, pyloric antrum and pylorus), (ICD10 C16.1-C16.4) according to the TNMv7 documentation

Stage	**T**	**N**	**M**
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0, N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2, N3	M0
Stage IV	Any T	Any N	M1

Assumptions

An assumption used in this method was that if insufficient information was available the lower stage was taken. For example, an oesophageal tumour with a T value that was missing, a N value of 1, and a M value of 0 would be stage II. This method is therefore likely to down-stage some patients with limited stage information.

In addition to an overall staging rule for cancer of the oesophagus (including cancers occurring at the oesophago-gastric junction) there was a separate staging rule for squamous cell carcinoma and another for adenocarcinoma. However, the overall staging guidelines were

used in this analysis because there was relatively little staging information recorded overall, but it is possible that this could have led to some tumours being incorrectly staged.

Results

Following the method outlined above, the proportion of registrations with missing stage information was around 70% for both subgroups of oesophageal and gastric cancer (Table 3.6). A large proportion of gastric cancers (including the "not otherwise specified" group, ICD10 C16.5-C16.9) did not have a staging rule so an aggregated stage could not be generated.

Table 3.6: Proportion of registrations by aggregated stage group for oesophageal and gastric cancers diagnosed between 2000 and 2009

Stage	**Oesophageal cancer (including oesophagogastric junction)**		**Gastric cancer (including fundus of stomach, body of stomach, pyloric antrum and pylorus)**	
	C15 and C16.0		**C16.1-C16.4**	
	N	**%**	**N**	**%**
I	1,782	2.2	786	9.1
II	6,871	8.5	684	7.9
III	5,300	6.6	211	2.4
IV	9,571	11.9	999	11.5
Missing	56,920	70.8	5,974	69.0
Total	80,444	100.0	8,654	100.0

This method generated an aggregated stage for patients with limited stage information and therefore over-estimates the proportion with a known stage. If stage was to be used as a variable in this analysis then only patients with full stage information should be assigned an aggregate stage.

Tumour stage is strongly associated with survival. Stage of disease will also affect whether a patient is eligible for a particular treatment. Unfortunately, stage could not be used in the analyses included in this thesis, which is a major disadvantage. It is therefore not possible to ascertain how much of the differences seen in the studies on survival and treatment could be due to differences in stage distributions.

3.10 Completeness

The completeness of case ascertainment in the cancer registry has often been questioned so it is important to estimate how many cancer registrations are missed each year. Large proportions of missing registrations could affect survival analyses with results being too low if patients with better prognoses are missed.

From the HES dataset, patients who had a diagnosis of cancer and who had no matched record in the cancer registry dataset were identified as HES-only registrations. HES-only registrations were then narrowed down to include only those with a relevant surgical procedure code (Table 2.12). The combination of diagnosis and surgery codes taken together increased the certainty that these patients were in fact confirmed cancer cases, rather than just a record of a suspicion of cancer. These registrations were considered as potentially missed by the cancer registration process. The number of HES-only records was compared with the number of cancer registration records for each cancer type to estimate the level of incompleteness.

In 2008, only 17 (0.3%) of 6,671 oesophageal cancer and 23 (0.4%) of 6,124 gastric cancer patients were estimated to have been missed by the cancer registration process. However, the majority of oesophageal and gastric cancer patients will not be eligible for surgery, and as this method relies on the presence of surgical procedures it may over-estimate the completeness of the dataset.

3.11 Conclusions

The work in this chapter investigated the data quality and completeness of the registrations held within the NCDR on oesophageal and gastric cancer. During the period studied, a high and increasing proportion of registrations for these cancers had a linked record which led to reasonably complete information on co-morbidity and self-assigned ethnicity. This is

encouraging and it is likely these trends will continue alongside improvements in the linkage between the two datasets and improvements in the collection of ethnicity data in HES.

Overall, the availability of stage information was poor and could not be used in this thesis. Although it has begun to improve there is still a long way to go until it will be complete enough to use in any analysis. Currently, a large national project is focusing on improving the availability of staging information across all cancer types, so with time further analyses should be possible.

Better anatomical and morphological classification of oesophageal and gastric tumours is also needed to be able to define more specific subgroups for analyses.

Encouragingly, the proportion of death certificate only registrations was low for both cancer types. Also, the completeness analysis identified only a very small proportion of potentially missed cancer registrations. Therefore, it is likely that this dataset is a practically complete representation of all patients diagnosed in England with oesophageal and gastric cancer.

Chapter 4 Incidence and survival of oesophageal and gastric cancer in England, 1998-2007

The information included in this chapter resulted in the following publication:

Coupland VH, Allum W, Blazeby J, Mendell M, Hardwick RH, Linklater KM, Møller H, Davies EA (2012) Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. *BMC Cancer* 12:11.

http://www.biomedcentral.com/1471-2407/12/11

4.1 Introduction

In 2007, oesophageal cancer was the seventh most common cancer in England in males and the fourteenth in females, with age-standardised incidence rates (per 100,000 European standard population) of around 14.0 and 5.3, respectively (Office for National Statistics, 2010). Despite the decline in the incidence of gastric cancer in developed countries over the last century it was still the eighth most common cancer in England in males and the sixteenth in females in 2007 (Office for National Statistics, 2010). The population mortality rates from oesophageal and gastric cancer closely reflect the population incidence because of the poor prognosis of these cancers.

Over the last 30 years the incidence of oesophageal adenocarcinoma (primarily located in the lower third of the oesophagus) and cancers of the gastric cardia has increased in many developed countries, particularly in males (Powell & McConkey, 1990; Blot *et al*, 1991; Devesa *et al*, 1998; Dolan *et al*, 1999; Bollschweiler *et al*, 2001; Kocher *et al*, 2001; El-Serag *et al*, 2002; Vizcaino *et al*, 2002; Newnham *et al*, 2003; Pohl & Welch, 2005; Cooper *et al*, 2009; Dikken *et al*, 2012b; Thrift & Whiteman, 2012; Edgren *et al*, 2013; Hur *et al*, 2013). A US study in 1991 found that the annual increase of oesophageal adenocarcinoma in males was greater than any other malignancy in that population (Blot *et al*, 1991). The fact that the increase in incidence has been predominately in males suggests that the rising trends in these cancers cannot completely be

explained by changes in the classification of the diseases or improvements in diagnosis (Powell & McConkey, 1990; Pohl & Welch, 2005). Both adenocarcinoma of the oesophagus and the gastric cardia are typically characterised by high male to female ratios, with the incidence in males being reported as three to nine times higher that of females (Blot *et al*, 1991; Kocher *et al*, 2001; El-Serag *et al*, 2002; Newnham *et al*, 2003; Dikken *et al*, 2012b; Edgren *et al*, 2013). Internationally, the highest incidence of oesophageal adenocarcinoma has been reported in the United Kingdom (Bollschweiler *et al*, 2001; Edgren *et al*, 2013).

Recent national studies have described the incidence and survival of oesophageal and gastric cancer (National Cancer Intelligence Network, 2008a; National Cancer Intelligence Network, 2008b; National Cancer Intelligence Network, 2008c), but have not explored specific subgroups of these cancers. This study aims to describe the incidence and survival of patients with oesophageal and gastric cancers in England using a national cohort of patients diagnosed between 1998 and 2007.

4.2 Methods

Data on 133,804 patients (85,361 males; 48,443 females) diagnosed with oesophageal or gastric cancer in England between 1998 and 2007 were extracted from the NCDR. These data were divided into six subgroups: 1) upper and middle oesophagus, 2) lower oesophagus, 3) oesophagus NOS, 4) gastric cardia, 5) gastric non-cardia, and 6) gastric NOS**.** The definitions of these subgroups are described in more detail in section 2.2.

For each cancer group, age specific incidence rates were calculated in five-year age groups ranging from 0 to 4 through to 85 and over for males and females. Age-standardised incidence rates per 100,000 European standard population, ASR(E), and male to female incidence rate ratios were calculated for each of the six cancer subgroups by year of diagnosis and sex.

Incidence rates were also calculated by socioeconomic deprivation quintile for patients diagnosed between 2003 and 2007.

Survival was estimated using the Kaplan-Meier method for each of the six subgroups. Survival was based on patients diagnosed between 1998 and 2007 and followed up until the end of 2007. 4,990 (3.7%) of the 133,804 patients were death certificate only registrations and were excluded from the survival analysis as they had no relevant date of diagnosis, leaving 128,814 patients. The total person time of follow-up was 142,187 years.

4.3 Results

4.3.1 Upper and middle oesophageal cancer

Just over half of upper and middle oesophageal cancers were in females (Table 4.1). The median age at diagnosis was 73 years. Incidence remained constant over time (Figure 4.1) and was similar in males and females (Figure 4.2). Incidence was higher in more deprived areas, especially in males where the ratio between the most deprived (quintile 5 (Q5)) and the most affluent (quintile 1 (Q1)) groups was 2.2:1 males and 1.7:1 females (Figure 4.3). The age specific incidence rates were similar in males and females (Figure 4.4). 30.3% [95% confidence interval 29.6-31.0%] of patients survived one year and 8.3% [7.8-8.7%] survived five years after diagnosis (Figure 4.5). The results for the oesophageal squamous cell carcinoma subgroup were similar to the upper and middle oesophageal cancer subgroup.

4.3.2 Lower oesophageal cancer

The majority of oesophageal cancers were located in the lower oesophagus, and almost three quarters were in males (Table 4.1). The median age at diagnosis was 72 and the number of cases increased over the period. Lower oesophageal cancer in males had the highest incidence of all the oesophageal cancer subgroups. The incidence rose from 8.1 per 100,000 in 1998 to 10.1 in 2007 (Figure 4.1). The difference in incidence between males and females was most evident in

this subgroup (M:F 4:1, Figure 4.2) and incidence was higher in more deprived areas (Q5:Q1 1.2:1 males; 1.3:1 females, Figure 4.3). 36.4% [35.9-36.8%] of patients survived one year and 9.4% [9.1-9.8%] survived five years after diagnosis (Figure 4.5). The results for the oesophageal adenocarcinoma subgroup were similar to the lower oesophageal cancer subgroup.

4.3.3 Oesophageal NOS

A small proportion of oesophageal cancer patients had NOS disease and the median age at diagnosis was 78 (Table 4.1). The incidence decreased over the period (Figure 4.1), and was higher in males than females (Figure 4.2), and in more deprived areas (Figure 4.3). 14.8% [13.9-15.7%] of patients survived one year and 3.7% [3.2-4.3%] survived five years after diagnosis (Figure 4.5). The results for the oesophageal other and unspecified morphology subgroup were similar to the oesophageal NOS cancer subgroup.

4.3.4 Gastric cardia

Over three quarters of gastric cardia cancers were in males (Table 4.1). The median age at diagnosis was 71. Incidence declined slightly over the period falling from 5.7 to 4.2 per 100,000 in males and from 1.4 to 1.1 in females (Figure 4.1). Like lower oesophageal cancer the incidence of gastric cardia cancer was much higher in males than females (M:F 4:1, Figure 4.2) and was higher in the most deprived quintiles (Q5:Q1 1.5:1 males; 1.7:1 females, Figure 4.3). 40.0% [39.3-40.7%] of patients survived one year and 10.9% [10.4-11.4%] survived five years after diagnosis (Figure 4.5).

4.3.5 Gastric non-cardia

Sixty-two per cent of gastric non-cardia cancers were in males (Table 4.1). The median age at diagnosis was 75 and the annual number of cases declined over time. Incidence also declined (Figure 4.1), was twice as high in males (Figure 4.2), and higher in more deprived areas (Q5:Q1

2.0:1 males; 1.9:1 females, Figure 4.3). 40.8% [40.0-41.6%] of patients survived one year and 15.6% [15.0-16.3%] survived five years after diagnosis (Figure 4.5).

4.3.6 Gastric NOS

Over half of gastric cancers were NOS (Table 4.1). The median age at diagnosis was 76. The incidence decreased from 9.4 per 100,000 in 1998 to 6.3 in 2007 in males and from 4.2 to 3.0 in females (Figure 4.1). Incidence was higher in males (M:F 2:1, Figure 4.2), in the more deprived groups (Q5:Q1 2.1:1 in both sexes, Figure 4.3), and was particularly high in the oldest age groups (Figure 4.4). 28.5% [28.0-29.0%] of patients survived one year and 10.1% [9.8-10.5%] survived five years after diagnosis (Figure 4.5).

Table 4.1: Characteristics of patients diagnosed with oesophageal and gastric cancers in England between 1998 and 2007

	Upper and middle oesophagus		Lower oesophagus		Oesophagus NOS		Gastric cardia		Gastric non-cardia		Gastric NOS		Oesophageal or gastric cancer	
	18,128		35,849		7,898		18,728		15,340		37,861		133,804	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex														
Male	8,228	45.4	26,495	73.9	4,323	54.7	14,107	75.3	9,531	62.1	22,677	59.9	85,361	63.8
Female	9,900	54.6	9,354	26.1	3,575	45.3	4,621	24.7	5,809	37.9	15,184	40.1	48,443	36.2
Age group														
<50	706	3.9	1,682	4.7	180	2.3	1,043	5.6	595	3.9	1,568	4.1	5,774	4.3
50-54	937	5.2	1,986	5.5	227	2.9	1,025	5.5	384	2.5	961	2.5	5,520	4.1
55-59	1,513	8.3	3,149	8.8	396	5.0	1,626	8.7	699	4.6	1,671	4.4	9,054	6.8
60-64	1,864	10.3	3,980	11.1	552	7.0	2,124	11.3	1,196	7.8	2,646	7.0	12,362	9.2
65-69	2,320	12.8	4,775	13.3	707	9.0	2,680	14.3	2,010	13.1	4,326	11.4	16,818	12.6
70-74	2,851	15.7	5,687	15.9	1,030	13.0	3,162	16.9	2,735	17.8	6,013	15.9	21,478	16.1
75-79	3,018	16.6	6,170	17.2	1,444	18.3	3,185	17.0	3,056	19.9	7,293	19.3	24,166	18.1
80-84	2,496	13.8	4,735	13.2	1,364	17.3	2,218	11.8	2,497	16.3	6,585	17.4	19,895	14.9
85+	2,423	13.4	3,685	10.3	1,998	25.3	1,665	8.9	2,168	14.1	6,798	18.0	18,737	14.0
Quintile of deprivation 2007 (based on patients diagnosed between 2003 and 2007)														
1 = Affluent	1,503	16.1	3,589	18.8	592	16.6	1,554	17.5	1,058	15.0	2,607	15.3	10,903	16.8
2	1,793	19.2	4,133	21.6	701	19.7	1,855	20.9	1,320	18.7	3,094	18.1	12,896	19.8
3	1,980	21.2	4,143	21.7	741	20.8	1,941	21.8	1,503	21.3	3,409	20.0	13,717	21.1
4	1,994	21.4	4,000	20.9	791	22.2	1,811	20.4	1,625	23.0	3,782	22.2	14,003	21.5
5 = Deprived	2,058	22.1	3,256	17.0	738	20.7	1,730	19.5	1,561	22.1	4,180	24.5	13,523	20.8
Year of diagnosis														
1998	1,702	9.4	3,067	8.6	929	11.8	2,022	10.8	1,752	11.4	4,446	11.7	13,918	10.4
1999	1,754	9.7	3,191	8.9	905	11.5	2,020	10.8	1,546	10.1	4,301	11.4	13,717	10.3
2000	1,805	10.0	3,292	9.2	923	11.7	2,014	10.8	1,669	10.9	4,261	11.3	13,964	10.4
2001	1,751	9.7	3,574	10.0	810	10.3	1,854	9.9	1,679	10.9	3,959	10.5	13,627	10.2
2002	1,788	9.9	3,604	10.1	768	9.7	1,927	10.3	1,627	10.6	3,822	10.1	13,536	10.1
2003	1,861	10.3	3,678	10.3	745	9.4	1,827	9.8	1,565	10.2	3,538	9.3	13,214	9.9
2004	1,793	9.9	3,732	10.4	717	9.1	1,777	9.5	1,472	9.6	3,514	9.3	13,005	9.7
2005	1,920	10.6	3,813	10.6	730	9.2	1,820	9.7	1,375	9.0	3,390	9.0	13,048	9.8
2006	1,871	10.3	3,887	10.8	722	9.1	1,740	9.3	1,369	8.9	3,264	8.6	12,853	9.6
2007	1,883	10.4	4,011	11.2	649	8.2	1,727	9.2	1,286	8.4	3,366	8.9	12,922	9.7
Death certificate only														
1998-2007	63	0.3	98	0.3	1,769	22.4	117	0.6	51	0.3	2,892	7.6	4,990	3.7

Figure 4.1: Age-standardised incidence rates per 100,000 European standard population for patients diagnosed with oesophageal and gastric cancers in England between 1998 and 2007

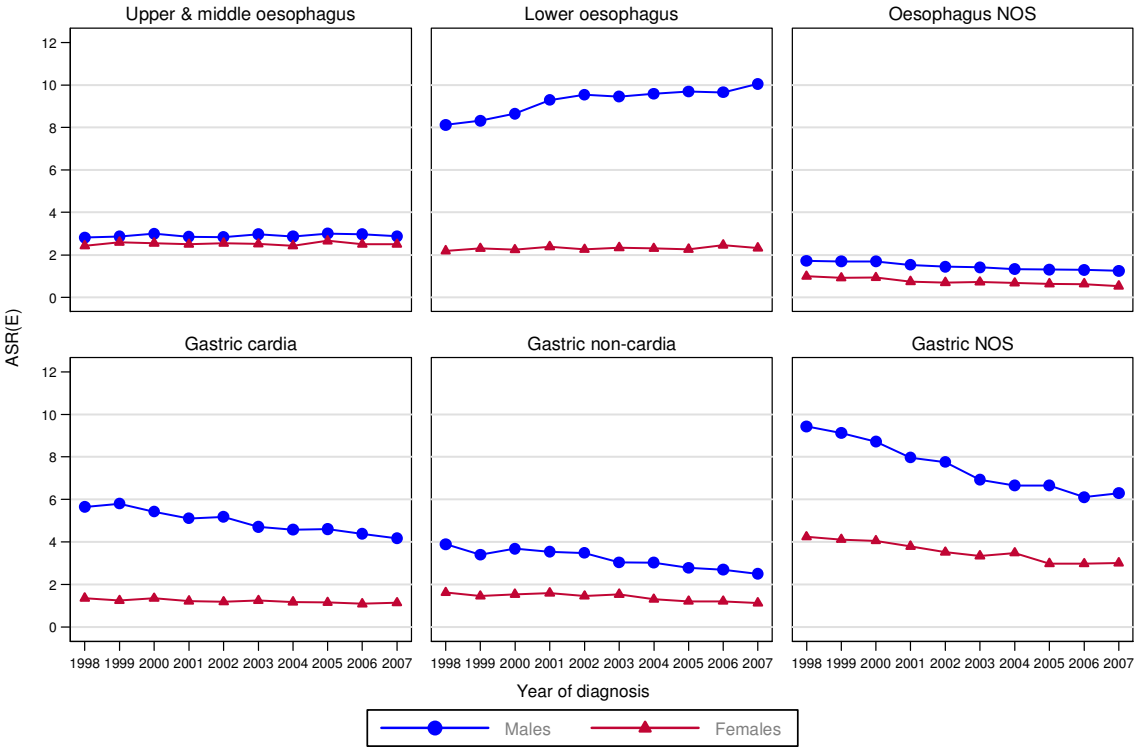


Figure 4.2: Male to female incidence rate ratios for patients diagnosed with oesophageal and gastric cancers in England between 1998 and 2007

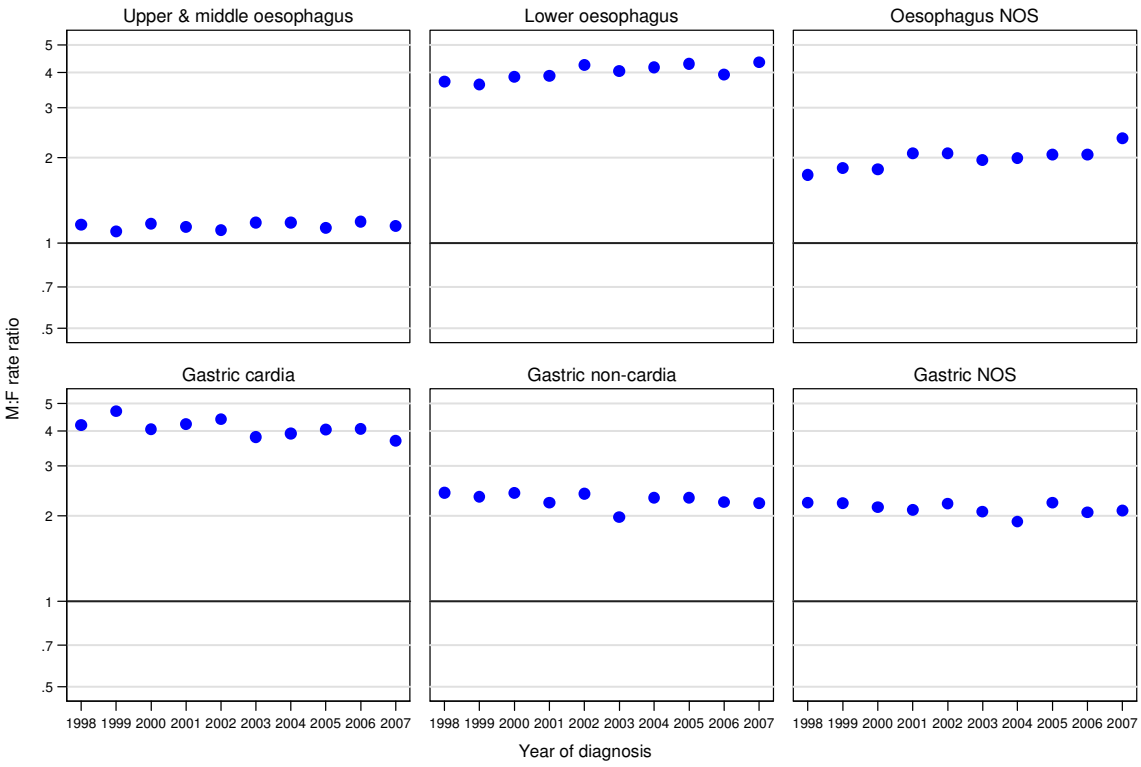


Figure 4.3: Age-standardised incidence rates per 100,000 European standard population for patients diagnosed with oesophageal and gastric cancers in England between 2003 and 2007, by deprivation quintile

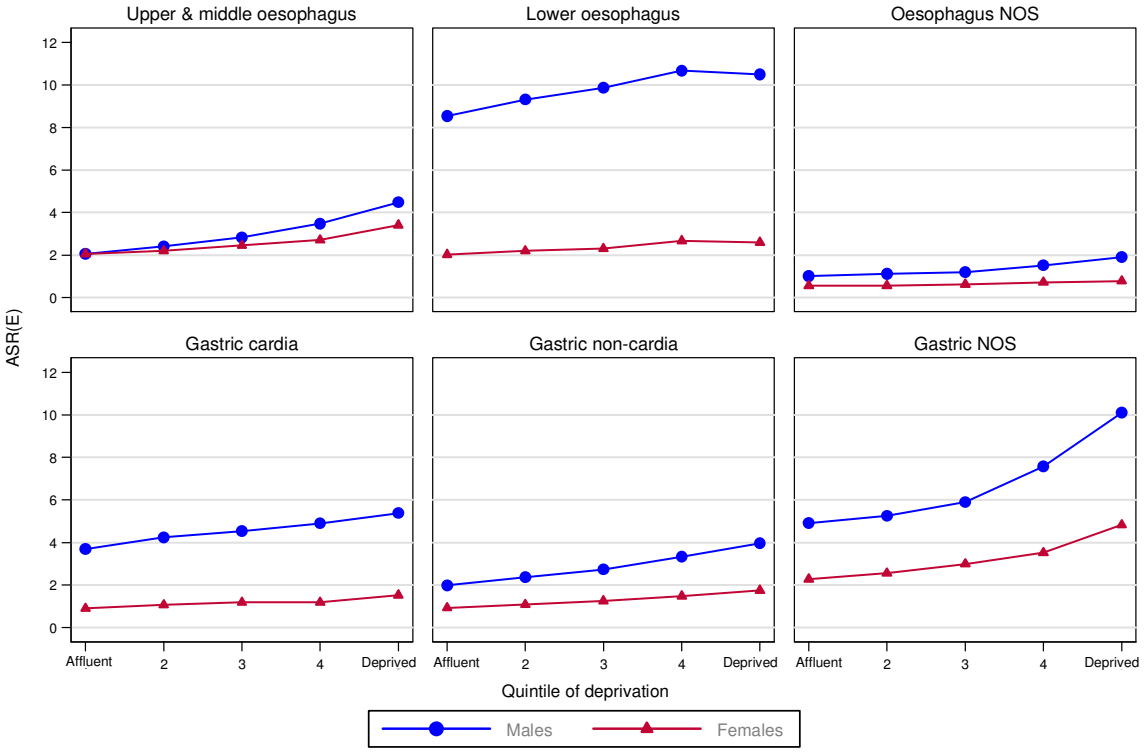


Figure 4.4: Age specific incidence rates for patients diagnosed with oesophageal and gastric cancers in England between 1998 and 2007

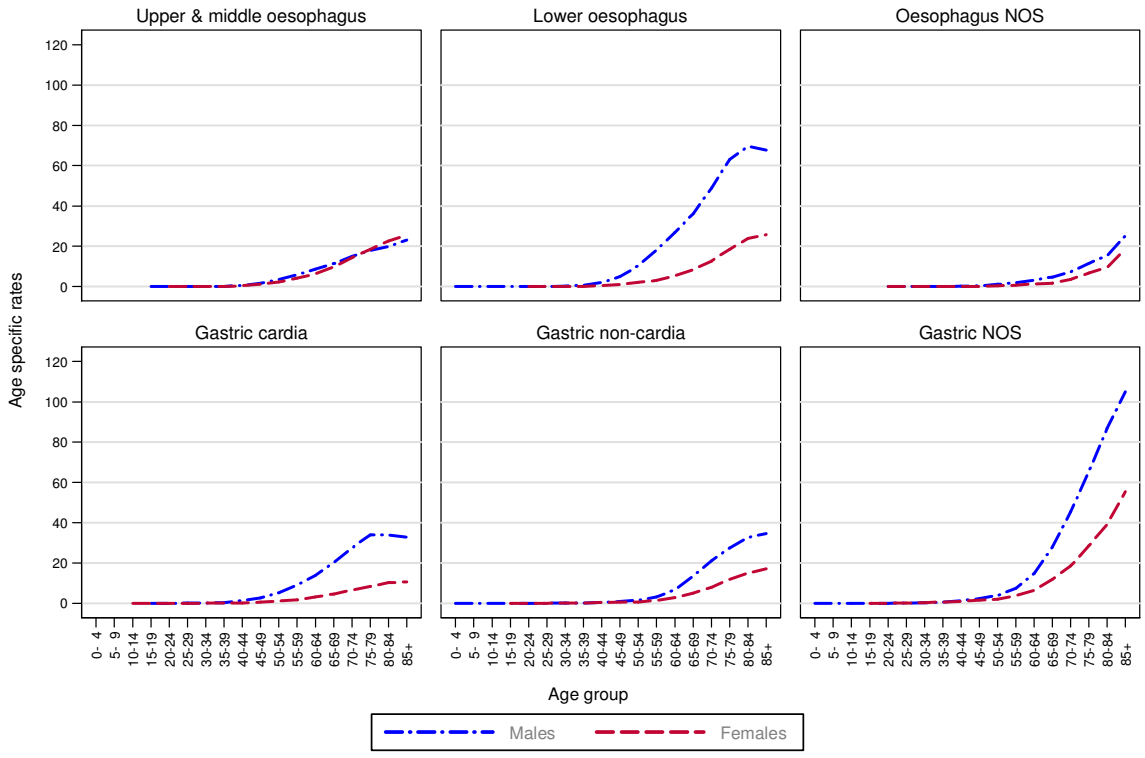
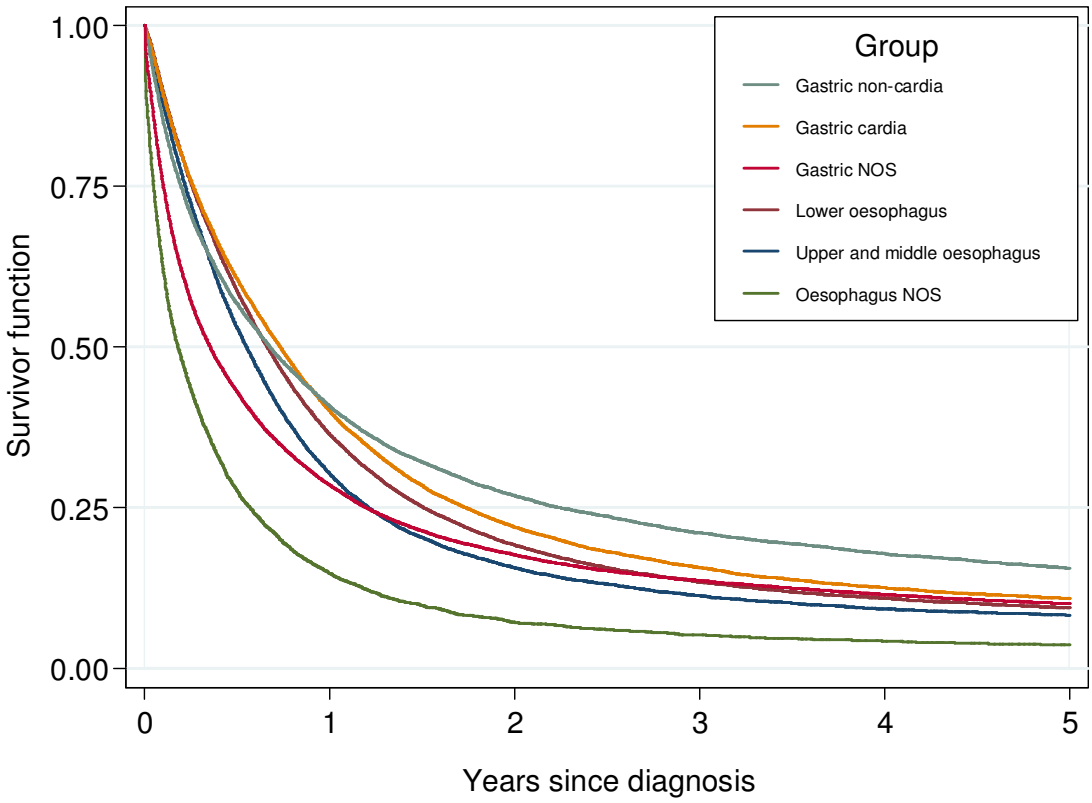


Figure 4.5: Kaplan-Meier survival functions for oesophageal and gastric cancers diagnosed in England between 1998 and 2007, with follow-up to the end of December 2007



4.4 Discussion

4.4.1 Main findings

This work investigated the incidence and survival of oesophageal and gastric cancers in England from data on 133,804 patients diagnosed between 1998 and 2007. The incidence of lower oesophageal cancer increased until 2002 and then remained relatively stable, whereas the incidence of cancers of the gastric cardia, gastric non-cardia and gastric NOS declined over the study period. The incidence was clearly higher in males compared with females for all oesophageal and gastric cancer subgroups, but was most evident in lower oesophageal and gastric cardia cancers where the incidence was around four times higher in males. In general the incidence rates of all oesophageal and gastric cancers were higher in the more deprived areas. Overall survival was poor in all subgroups with one-year survival ranging from 14.8% to 40.8% and five-year survival ranging from 3.7% to 15.6%.

4.4.2 Strengths and weaknesses

This national study included a large number of patients diagnosed with oesophageal or gastric cancer over a ten year period. It was therefore possible to investigate differences in incidence by six cancer subgroups rather than only the traditional groups of oesophageal (C15) and gastric (C16) cancer, which obscure the unique features of the lower oesophageal and gastric cardia tumours.

One limitation of the dataset was the relatively large proportion of patients with an unspecified anatomical subsite, particularly for gastric cancers where over half (52.6%) fell into this subgroup. This meant that these patients could not be assigned to either the gastric cardia or gastric non-cardia subgroup. Oesophageal cancer subgroups were defined from both the anatomical site and tumour morphology which led to a smaller proportion of patients in the “not otherwise specified” subgroup (12.8%) compared with the subgroups based on tumour

morphology alone (17.5%). The sensitivity analysis demonstrated similar patterns in incidence between the oesophageal squamous cell carcinoma subgroup and the upper and middle oesophageal subgroup, the oesophageal adenocarcinoma subgroup and the lower oesophageal subgroup, and the "other and unspecified" and the oesophageal "not otherwise specified" subgroup. Finally, another limitation was that 4,990 patients (4%) had to be excluded from the survival analysis because their registrations were based only on data from the death certificate.

4.4.3 Comparison to other studies

In most developed countries the incidence of oesophageal squamous cell carcinoma has remained constant or declined over the last 30 years (Vizcaino *et al*, 2002; Dikken *et al*, 2012b; Thrift & Whiteman, 2012) whilst the incidence of oesophageal adenocarcinoma, primarily found in the lower third of the oesophagus (Dikken *et al*, 2012b) has increased, particularly in males (Powell & McConkey, 1990; Blot *et al*, 1991; Devesa *et al*, 1998; Dolan *et al*, 1999; Bollschweiler *et al*, 2001; Kocher *et al*, 2001; El-Serag *et al*, 2002; Vizcaino *et al*, 2002; Newnham *et al*, 2003; Pohl & Welch, 2005; Cooper *et al*, 2009; Dikken *et al*, 2012b; Thrift & Whiteman, 2012; Edgren *et al*, 2013; Hur *et al*, 2013). In Sweden the increase in oesophageal adenocarcinoma incidence peaked in the mid-2000s and then remained stable (Lagergren & Mattsson, 2011). The current study found stable incidence rates of upper and middle oesophageal cancer over the ten year period and an initial increase in the incidence of lower oesophageal cancer in males which slowed after 2002.

The increase in the incidence of lower oesophageal cancer is mirrored in this work by a decrease in the incidence of cancers of the gastric cardia. Previous studies have noted an increase in both these cancer subgroups (Powell & McConkey, 1990; Blot *et al*, 1991; Devesa *et al*, 1998; Dolan *et al*, 1999; Kocher *et al*, 2001; Newnham *et al*, 2003; Pohl & Welch, 2005; Abrams *et al*, 2011), although others have found a similar stable or slightly declining trend in gastric cardia cancer incidence since the early 1990s (Devesa *et al*, 1998; El-Serag *et al*, 2002; Lagergren & Mattsson,

2011; Dikken *et al*, 2012b). It is possible that the trends in these two adjacent sites were influenced by changes in diagnostic classification. However, after 2002 when the incidence of lower oesophageal cancer remained stable in males the incidence of gastric cardia cancer continued to decline. If changes in diagnostic classification were responsible these trends would be expected to stabilise at a similar time. It is also possible that some of the oesophageal NOS cancers could have been gastric cardia cancers. Reassigning those with a histological diagnosis of adenocarcinoma to the lower oesophageal subgroup may have also influenced the trends. A decline in the incidence of non-cardia gastric cancer in more developed countries has been seen in the past century (Powell & McConkey, 1990; Quinn *et al*, 2001; Crew & Neugut, 2006; Kamangar *et al*, 2006b). The current study supports the finding of a continued decline of gastric non-cardia cancers.

The decline in the incidence of gastric cancers in this study and other studies (Powell & McConkey, 1990; Quinn *et al*, 2001; Crew & Neugut, 2006; Kamangar *et al*, 2006b) may be associated with a decline in the prevalence in developed countries of *Helicobacter pylori* infection, the strongest known risk factor for gastric cancer (International Agency for Research on Cancer, 1994; Crew & Neugut, 2006). Meta-analyses have found that infection with the most common *Helicobacter pylori* strains (CagA+) may be associated with a lower risk of oesophageal adenocarcinoma, possibly because infection causes achlorhydria and so reduces gastric acid reflux, a risk factor associated with the development of oesophageal adenocarcinoma (Kamangar *et al*, 2006a; Rokkas *et al*, 2007; Islami & Kamangar, 2008). A systematic review did find a lower prevalence of *Helicobacter pylori* infection in patients with GORD (Raghunath *et al*, 2003). Therefore, the decline in the prevalence of *Helicobacter pylori* infection could contribute to the increased incidence of lower oesophageal cancer found here.

The increase in incidence of oesophageal adenocarcinoma found in this work may also be associated with the increased prevalence of obesity in England (The Information Centre, 2009).

Other studies have found that an increase in body mass index is associated with a higher risk of oesophageal adenocarcinoma and gastric cardia cancer (Lagergren *et al*, 1999b; Lindblad *et al*, 2005; El-Serag, 2008).

Consistent with previous studies (Powell & McConkey, 1990; Blot *et al*, 1991; Dolan *et al*, 1999; Kocher *et al*, 2001; El-Serag *et al*, 2002; Newnham *et al*, 2003; Pohl & Welch, 2005; Dikken *et al*, 2012b; Edgren *et al*, 2013) lower oesophageal and gastric cardia cancer incidence rates were much higher in males compared with females (M:F 4:1). The reasons for this are not known, but an abdominal distribution of body fat, which is more common in men, may lead to higher levels of GORD and therefore to an increased risk of developing these cancers (Vaughan *et al*, 2002; El-Serag, 2008). Barrett's oesophagus, secondary to chronic GORD, is another risk factor which occurs more commonly in men (Jankowski *et al*, 2000; Wong & Fitzgerald, 2005; Wood & Yang, 2008; de Jonge *et al*, 2010) and has been linked to abdominal obesity (Vaughan *et al*, 2002; El-Serag *et al*, 2005; El-Serag, 2008). Different patterns of past smoking behaviour in males and females could also partly explain the differences in the incidence of these cancers. The risk of squamous cell carcinoma of the oesophagus declines steadily following smoking cessation, although the risk of both oesophageal adenocarcinoma and gastric cardia cancer does not decline until 30 years after cessation (Gammon *et al*, 1997).

The finding that lower oesophageal and gastric cardia cancer have a higher incidence in the more socioeconomically deprived groups contradicts some studies which have found no association (Brewster *et al*, 2000; Cooper *et al*, 2009), but is in line with other studies (Jansson *et al*, 2005; Holmes & Vaughan, 2007; Gajperia *et al*, 2009). Squamous cell carcinoma and non-cardia gastric cancer have been associated with deprivation in previous studies (Brewster *et al*, 2000; Crew & Neugut, 2006; Cooper *et al*, 2009), which is consistent with these findings. The known lifestyle risk factors already discussed are likely to be more common in those resident in deprived areas and so explain the higher incidence found in this study.

4.4.4 Interpretation and implications

The poor prognosis of both oesophageal and gastric cancer highlights the need to concentrate efforts on primary prevention. Smoking and high alcohol consumption are risk factors for gastric cancer and squamous cell carcinoma of the oesophagus (Tredaniel *et al*, 1997; Lindblad *et al*, 2005; Blot *et al*, 2006; Shibata & Parsonnet, 2006; Lagergren & Lagergren, 2010), whilst smoking is a moderate risk factor for oesophageal adenocarcinoma alcohol consumption does not seem to increase the risk (Blot *et al*, 2006; Lubin *et al*, 2012; Hardikar *et al*, 2013). Public health initiatives aimed at reducing smoking and encouraging sensible alcohol consumption would help reduce the incidence of these cancers. A systematic review found that reducing weight may improve symptoms of GORD although not all studies have found this association (El-Serag, 2008). Other public health initiatives aimed at reducing obesity may help to decrease the prevalence of chronic GORD which is one of the main risk factors for developing oesophageal adenocarcinoma.

The particularly high incidence of lower oesophageal and gastric cardia tumours in males may have implications for earlier diagnosis. Current guidelines for referral and investigation of upper gastrointestinal symptoms do not specify this increased risk in males, but advise a similar threshold for males and females (National Institute for Health and Clinical Excellence, 2005). Raising awareness in primary care of the differences in incidence should be considered, and a lower threshold for referral in males or a higher threshold in females investigated. The poor prognosis of all patients suggests that evaluation of a national programme of earlier investigation of non-specific upper gastrointestinal symptoms may be warranted, and new tools such as the cytosponge for identifying Barretts' epithelium may have a role to play in the future (Lao-Sirieix *et al*, 2009; Kadri *et al*, 2010).

Since oesophageal and gastric tumours are relatively uncommon and difficult to diagnose population-wide screening is unlikely to be cost effective. Efforts to identify high-risk groups, for

example, for oesophageal adenocarcinoma males with regular chronic reflux and obesity could perhaps be considered when developing focused screening efforts in the future, but evidence on the effectiveness of screening these groups will be needed. At present endoscopic screening is not considered feasible (Lagergren & Lagergren, 2010). However, an American study in 2010 did suggest that the incidence in White males over 60 with weekly GORD or over 55 with daily GORD was high enough to investigate the effectiveness of screening in these groups (Rubenstein *et al*, 2011).

The poor prognosis of these cancers also suggests the need for greater focus on earlier diagnosis. Raising public awareness and knowledge of symptoms, particularly in more deprived areas and in males, will be important. A recent study found that 21% of oesophageal and 32% of gastric cancers were diagnosed through an emergency admission and that emergency admissions were associated with poorer one-year survival (Elliss-Brookes *et al*, 2012). Therefore, greater awareness of these cancers and improved knowledge of symptoms could help to identify earlier stage tumours and consequently improve the prognosis of these cancers.

Finally, these data also show that better classification of oesophageal and gastric tumours by site is needed to understand outcomes. It is important that both the cancer site and the morphology of these cancers are identified and recorded in clinical practice where possible. This information needs to be passed to the cancer registries to ensure that further studies can investigate these groups with more accuracy.

4.5 Conclusion

In England, the incidence of lower oesophageal cancer in males increased, whereas the incidence of gastric cardia and gastric non-cardia cancers declined between 1998 and 2007. Cancers of the lower oesophagus and gastric cardia were much more likely to occur in males than females and the incidence for all oesophageal and gastric cancer subgroups was higher in more deprived areas. The prognosis for these cancers remains very poor. An increased focus on prevention and early diagnosis, especially in deprived areas and in males, is required to improve outcomes for oesophageal and gastric cancers. Improved recording of tumour site and tumour morphology and the evaluation of focused early diagnosis programmes are also needed. The poor survival reinforces the need for prevention, early detection and multidisciplinary care.

Chapter 5 Ethnicity in relation to incidence of oesophageal and gastric cancer in England

The information included in this chapter resulted in the following publication:

Coupland VH, Lagergren J, Konfortion J, Allum W, Mendall MA, Hardwick RH, Linklater KM, Møller H, Jack RH (2012) Ethnicity in relation to incidence of oesophageal and gastric cancer in England. *British Journal of Cancer* **107:** 1908-1914.

http://www.nature.com/bjc/journal/v107/n11/full/bjc2012465a.html

5.1 Introduction

Internationally there is wide variation in the incidence of oesophageal and gastric cancers (Curado *et al*, 2007). Variation in the incidence of these cancers has also been reported between ethnic groups within countries (Curado *et al*, 2007; Goggins & Wong, 2009; National Cancer Intelligence Network, 2009; Ali *et al*, 2010; Ali *et al*, 2012). A large English study found a lower incidence of oesophageal cancer in South Asian (including Indian, Pakistani, and Bangladeshi groups) and Black men and women compared with White men and women (National Cancer Intelligence Network, 2009). The same report found South Asian men and women had a lower incidence of gastric cancer and Black men and women a higher incidence compared with their White counterparts (National Cancer Intelligence Network, 2009).

Oesophageal and gastric cancer subgroups are associated with different risk factors and show different patterns in incidence as outlined in sections 1.3 and 1.4. Several studies in the United States (Yang & Davis, 1988b; Corley & Buffler, 2001; El-Serag *et al*, 2002; Vizcaino *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Curado *et al*, 2007; Cook *et al*, 2009; Hongo *et al*, 2009) and two in the United Kingdom (Cooper *et al*, 2009; Ali *et al*, 2012) found that the incidence of oesophageal squamous cell carcinoma was higher or similar in Black men compared with White men, whereas oesophageal adenocarcinoma was found to be higher in White men. Although

the incidence of gastric cardia cancer is higher in White men in these studies (Yang & Davis, 1988a; Corley & Buffler, 2001; El-Serag *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Wu *et al*, 2009), the incidence of gastric non-cardia cancer has been found to be higher in Black men and women compared with their White counterparts (Yang & Davis, 1988a; Wu *et al*, 2006; Wu *et al*, 2009).

A recent national English study investigated differences in the incidence of oesophageal and gastric cancer using broad ethnic groups (South Asian and Black) (National Cancer Intelligence Network, 2009). To date, the majority of studies that have investigated the variation in incidence between ethnic groups for the more specific subgroups of these cancers have been conducted in the US. This work aimed to assess the variation in incidence in more specific ethnic groups (White, Indian, Pakistani, Bangladeshi, Black Caribbean, Black African, and Chinese) and for the six subgroups of oesophageal and gastric cancer in England.

5.2 Methods

5.2.1 Population

Data on 44,307 patients diagnosed with oesophageal cancer (ICD10 C15) and 47,898 patients diagnosed with gastric cancer (ICD10 C16) in England between 2001 and 2007 were extracted from the NCDR.

Ethnicity was classified using the most recent valid self-assigned ethnicity code from the HES dataset. Ethnic groups were analysed for seven categories: White, Indian, Pakistani, Bangladeshi, Black Caribbean, Black African and Chinese. The corresponding population data for each age and ethnic group were obtained from the Office for National Statistics with 2001 populations taken from the census year and combined with the mid-year population estimates between 2002 and 2007 (Office for National Statistics, 2011b).

Analysis was carried out on all oesophageal and gastric cancer cases and the six subgroups of these cancers, which are described in more detail in section 2.2. A sensitivity analysis was also carried out in oesophageal cancer subgroups defined by their histological diagnosis. Three groups were analysed: squamous cell carcinoma, adenocarcinoma and "other and unspecified".

5.2.2 Statistical analysis

Age-standardised incidence rates per 100,000 European standard population were calculated for all males and females diagnosed with oesophageal and gastric cancer and for the six cancer subgroups. This was then repeated for each ethnic group. Not all patients had an ethnic group recorded so any age-standardised incidence rates calculated would be too low, as there was no corresponding population data for these patients. Therefore, male and female age-standardised incidence rate ratios (IRRs) were calculated for each ethnic group, using White males and White females as the references. 95% confidence intervals (CIs) were calculated using the method described in Boyle and Parkin (1991).

5.3 Results

5.3.1 Patients

Among the total of 92,205 oesophageal or gastric cancer patients diagnosed in England between 2001 and 2007, ethnicity information was available for 76,130 (82.6%). The White, Indian, Pakistani, Bangladeshi, Black Caribbean, Black African and Chinese groups made up 98.8% of those with a recorded ethnicity (75,180). Table 5.1 shows the number and proportion of patients in each ethnic group for each cancer type and subgroup. The incidence of oesophageal and gastric cancer was higher in males (14.0 and 14.7, respectively) compared with females (5.6 and 5.9, respectively). This was particularly the case in lower oesophageal and gastric cardia cancer with males having incidence rates around four times higher than females.

Table 5.1: Number and percentage of males and females in each ethnic group for patients diagnosed with oesophageal cancer or gastric cancer in England between 2001 and 2007, by sex and subgroup

Ethnic group	Oesophagus		Upper and middle oesophagus		Lower oesophagus		Oesophagus NOS		Gastric		Gastric cardia		Gastric non-cardia		Gastric NOS		Oesophageal or gastric cancer	
	44,307		12,872		26,299		5,136		47,898		12,672		10,373		24,853		92,205	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Males																		
White	23,603	83.1	4,875	82.8	16,797	85.5	1,931	67.1	24,509	79.4	8,145	85.6	5,294	82.2	11,070	74.2	48,112	81.1
Indian	138	0.5	64	1.1	57	0.3	17	0.6	141	0.5	21	0.2	32	0.5	88	0.6	279	0.5
Pakistani	25	0.1	8	0.1	16	0.1	1	<0.1	81	0.3	13	0.1	26	0.4	42	0.3	106	0.2
Bangladeshi	22	0.1	12	0.2	7	<0.1	3	0.1	37	0.1	3	<0.1	9	0.1	25	0.2	59	0.1
Black Caribbean	132	0.5	71	1.2	42	0.2	19	0.7	332	1.1	40	0.4	94	1.5	198	1.3	464	0.8
Black African	33	0.1	11	0.2	18	0.1	4	0.1	76	0.2	10	0.1	18	0.3	48	0.3	109	0.2
Chinese	22	0.1	14	0.2	4	<0.1	4	0.1	60	0.2	3	<0.1	17	0.3	40	0.3	82	0.1
Mixed	37	0.1	10	0.2	25	0.1	2	0.1	73	0.2	14	0.1	14	0.2	45	0.3	110	0.2
Other	193	0.7	60	1.0	110	0.6	23	0.8	313	1.0	55	0.6	71	1.1	187	1.3	506	0.9
Not known	4,214	14.8	765	13.0	2,576	13.1	873	30.3	5,257	17.0	1,214	12.8	862	13.4	3,181	21.3	9,471	16.0
All	28,419		5,890		19,652		2,877		30,879		9,518		6,437		14,924		59,298	
Females																		
White	12,683	79.8	5,729	82.1	5,535	83.3	1,419	62.8	12,687	74.5	2,617	83.0	3,147	80.0	6,923	69.7	25,370	77.1
Indian	91	0.6	71	1.0	13	0.2	7	0.3	81	0.5	6	0.2	19	0.5	56	0.6	172	0.5
Pakistani	15	0.1	12	0.2	3	<0.1	0	0.0	43	0.3	5	0.2	10	0.3	28	0.3	58	0.2
Bangladeshi	34	0.2	26	0.4	6	0.1	2	0.1	21	0.1	2	0.1	5	0.1	14	0.1	55	0.2
Black Caribbean	56	0.4	36	0.5	15	0.2	5	0.2	153	0.9	15	0.5	27	0.7	111	1.1	209	0.6
Black African	22	0.1	15	0.2	4	0.1	3	0.1	44	0.3	5	0.2	8	0.2	31	0.3	66	0.2
Chinese	10	0.1	4	0.1	4	0.1	2	0.1	29	0.2	5	0.2	9	0.2	15	0.2	39	0.1
Mixed	17	0.1	10	0.1	5	0.1	2	0.1	35	0.2	7	0.2	10	0.3	18	0.2	52	0.2
Other	115	0.7	57	0.8	42	0.6	16	0.7	167	1.0	19	0.6	40	1.0	108	1.1	282	0.9
Not known	2,845	17.9	1,022	14.6	1,020	15.3	803	35.5	3,759	22.1	473	15.0	661	16.8	2,625	26.4	6,604	20.1
All	15,888		6,982		6,647		2,259		17,019		3,154		3,936		9,929		32,907	

5.3.2 Ethnicity and risk of oesophageal cancer

Compared with White men, Indian (IRR 0.42, 95%CI 0.37-0.46), Pakistani (IRR 0.17, 95%CI 0.15-0.20), Bangladeshi (IRR 0.39, 95%CI 0.29-0.53), Black Caribbean (IRR 0.58, 95%CI 0.50-0.67), Black African (IRR 0.39, 95%CI 0.31-0.50) and Chinese (IRR 0.36, 95%CI 0.27-0.47) men had a lower incidence of oesophageal cancer (Figure 5.1). Compared with White women, Bangladeshi women (IRR 2.02, 95%CI 1.24-3.29) had a higher incidence of oesophageal cancer and Black African women (IRR 0.86, 95%CI 0.57-1.30) had a more similar incidence, whereas Indian (IRR 0.68, 95%CI 0.57-0.81), Pakistani (IRR 0.26, 95%CI 0.20-0.33), Black Caribbean (IRR 0.56, 95%CI 0.46-0.69) and Chinese (IRR 0.42, 95%CI 0.28-0.62) women had a lower incidence (Figure 5.1).

5.3.3 Ethnicity and risk of gastric cancer

Indian (IRR 0.41, 95%CI 0.37-0.45), Pakistani (IRR 0.47, 95%CI 0.40-0.55) and Bangladeshi (IRR 0.62, 95%CI 0.47-0.82) men had a lower incidence of gastric cancer compared with White men. Black Caribbean men had a higher incidence (IRR 1.39, 95%CI 1.22-1.60) and Black African (IRR 1.04, 95%CI 0.80-1.35) and Chinese (IRR 0.99, 95%CI 0.75-1.31) men had a similar incidence to White men (Figure 5.2). Compared with White women, Indian (IRR 0.57, 95%CI 0.48-0.67) and Pakistani (IRR 0.71, 95%CI 0.54-0.93) women had a lower incidence of gastric cancer and Black Caribbean (IRR 1.57, 95%CI 1.28-1.92) women had a higher incidence. No statistically significant difference between Bangladeshi, Black African and Chinese women was found (Figure 5.2).

Figure 5.1: Age-standardised incidence rate ratios (IRR) for men and women diagnosed with oesophageal cancer in England between 2001 and 2007 by ethnic group. White men and women used as references

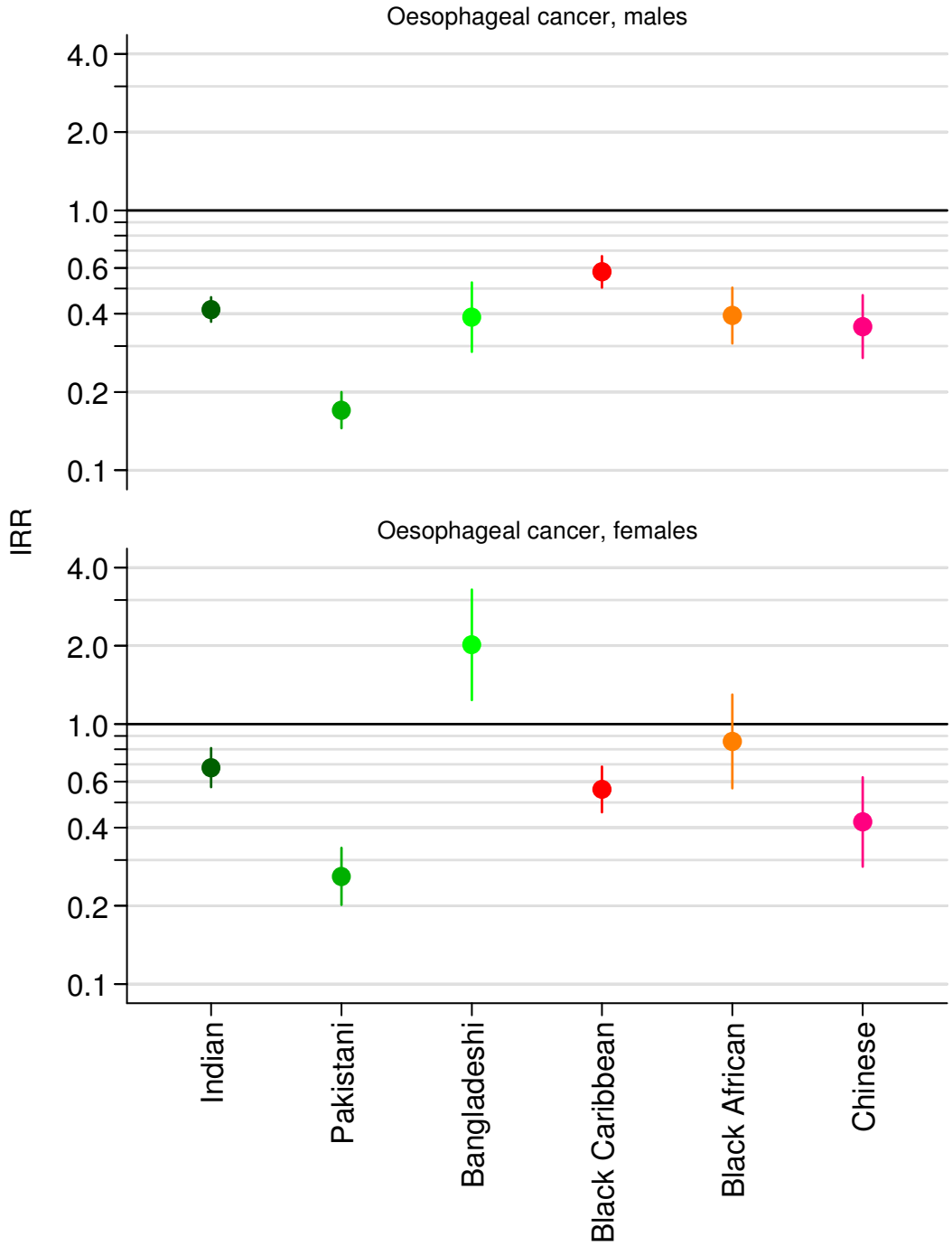
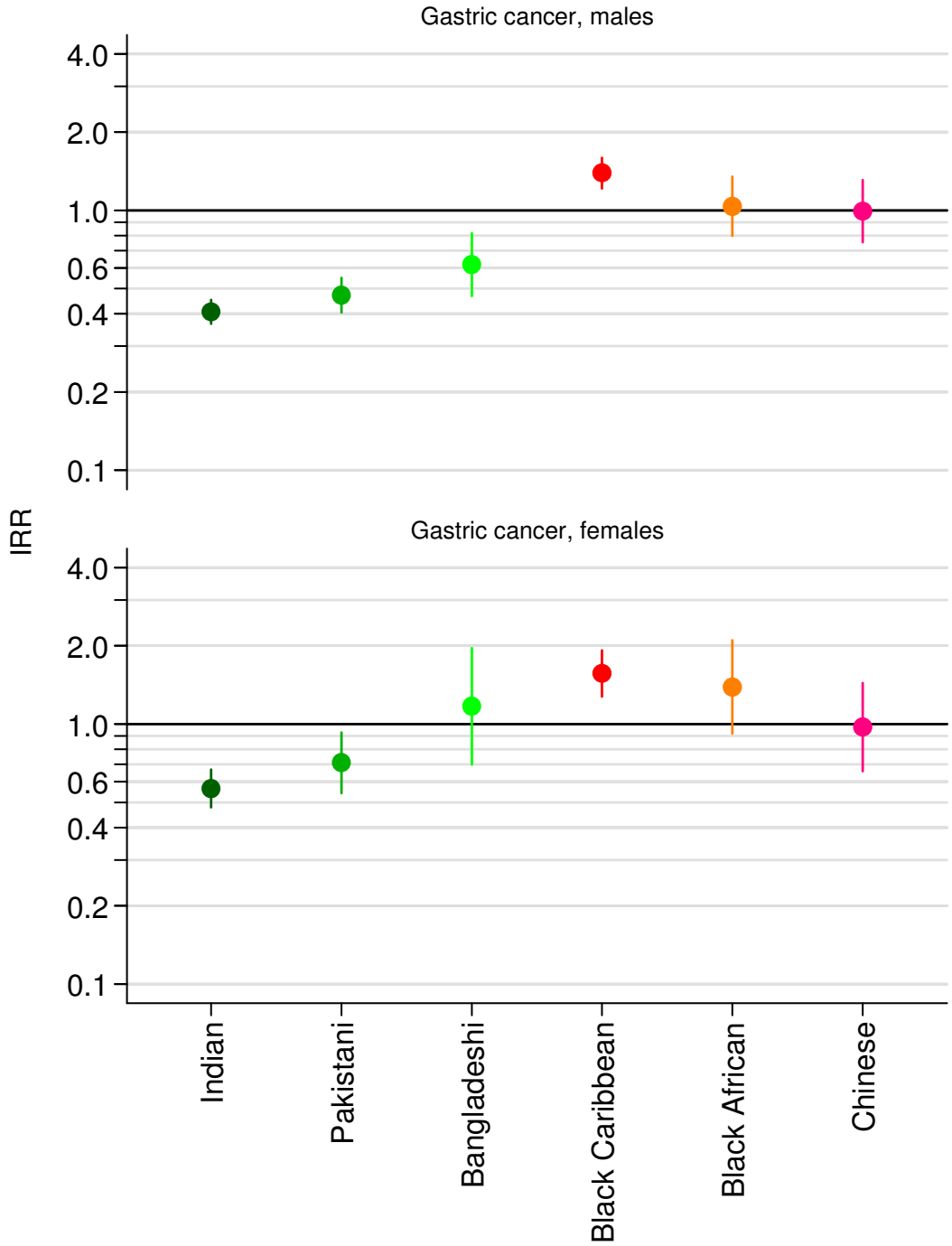


Figure 5.2: Age-standardised incidence rate ratios (IRR) for men and women diagnosed with gastric cancer in England between 2001 and 2007 by ethnic group. White men and women used as references

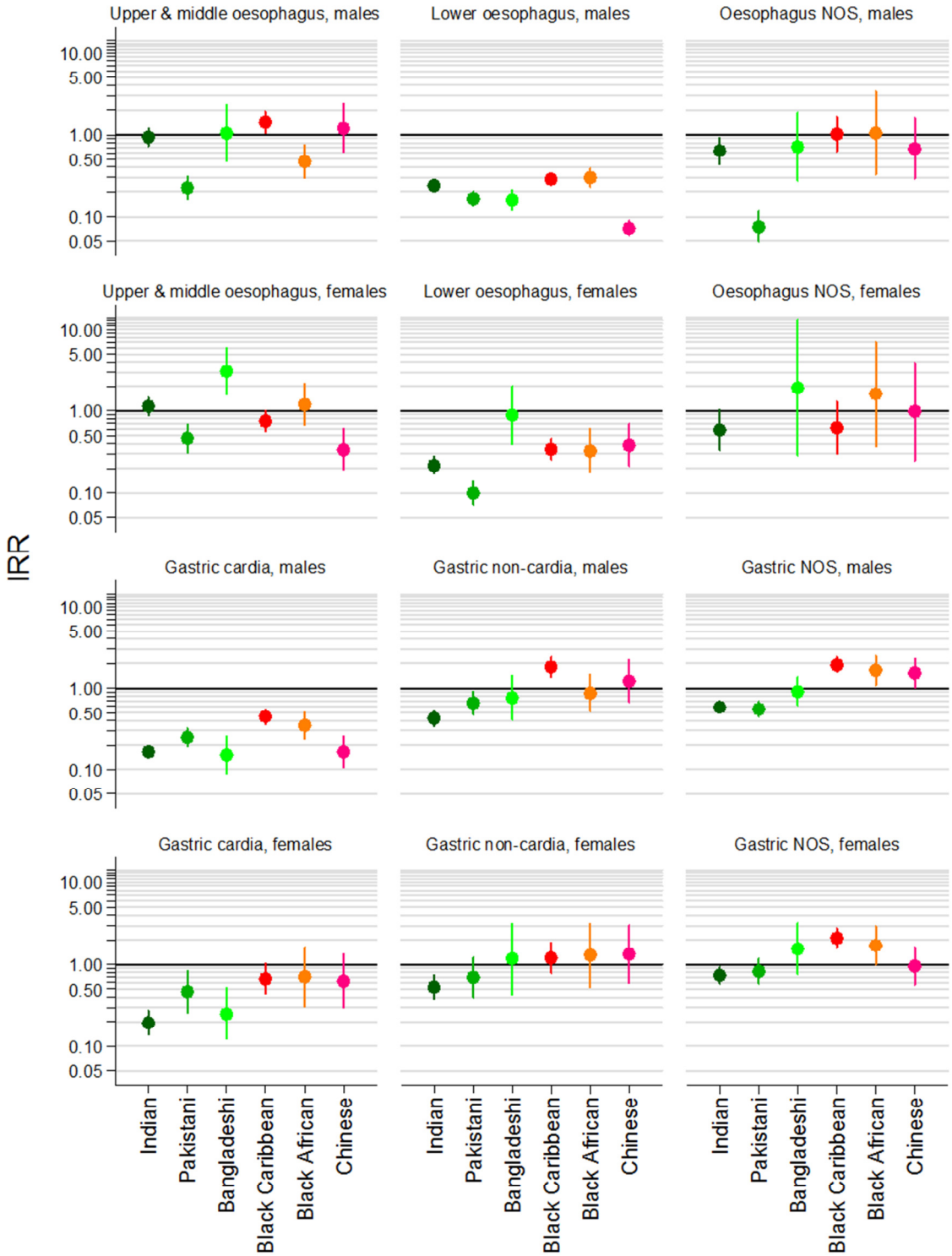


5.3.4 Ethnicity and risk of oesophageal cancer by subgroup

Bangladeshi women had a higher incidence of upper and middle oesophageal cancer (IRR 3.10, 95%CI 1.60-6.00), while Pakistani men (IRR 0.22, 95%CI 0.16-0.31) and Chinese women (IRR 0.34, 95%CI 0.19-0.59) had a lower incidence compared with their White counterparts. White men had a higher incidence of lower oesophageal cancer compared with all other ethnic groups studied (Figure 5.3). Compared with White women, the incidence of lower oesophageal cancer was lower in all ethnic groups except Bangladeshi women who had a similar incidence (IRR 0.89, 95%CI 0.40-2.00). There were a small number of cases of oesophageal NOS cancer in most ethnic groups studied (Figure 5.3).

A sensitivity analysis found that the lower oesophageal and adenocarcinoma subgroups, the upper and middle oesophageal and squamous cell carcinoma subgroups, and the oesophageal NOS and “other and unspecified” subgroups had similar patterns in incidence between ethnic groups.

Figure 5.3: Age-standardised incidence rate ratios (IRR) for men and women diagnosed with oesophageal or gastric cancer in England between 2001 and 2007 by ethnic group and subgroup. White men and women used as references



5.3.5 Ethnicity and risk of gastric cancer by subgroup

White men had a higher incidence of gastric cardia cancer than other ethnic groups studied (Figure 5.3). Indian (IRR 0.20, 95%CI 0.14-0.27), Pakistani (IRR 0.46, 95%CI 0.26-0.83) and Bangladeshi (IRR 0.25, 95%CI 0.12-0.51) women had a lower incidence of this cancer compared with White women, while Black Caribbean, Black African and Chinese women had a similar incidence. Compared with White men and women, Indian men (IRR 0.43, 95%CI 0.34-0.54) and women (IRR 0.53, 95%CI 0.38-0.74) and Pakistani men (IRR 0.66, 95%CI 0.48-0.92) had a lower incidence of gastric non-cardia cancer and of gastric NOS cancer (IRR 0.59, 95%CI 0.50-0.69, IRR 0.74, 95%CI 0.58-0.93, and IRR 0.56, 95%CI 0.44-0.70 respectively). Compared with their White counterparts, Black Caribbean men (IRR 1.81, 95%CI 1.36-2.42) had a higher incidence of gastric non-cardia cancer. Black Caribbean men (IRR 1.94, 95%CI 1.58-2.38) and women (IRR 2.11, 95%CI 1.60-2.78), Black African men (IRR 1.66, 95%CI 1.10-2.49) and Chinese men (IRR 1.53, 95%CI 1.01-2.31) had a higher incidence of gastric NOS cancer. All other ethnic groups had a similar incidence compared with their White counterparts.

5.4 Discussion

5.4.1 Main findings

A previous large English study found a lower incidence of oesophageal cancer in South Asian and Black men and women compared with White men and women (National Cancer Intelligence Network, 2009). In general this work is consistent with these findings, but also demonstrates some variations between the more specific ethnic groups. For example, whilst Indian and Pakistani women had a lower incidence of oesophageal cancer, Bangladeshi women had a higher incidence compared with White women. The same report found that South Asian men and women had a lower incidence of gastric cancer and Black men and women a higher incidence compared with their White counterparts (National Cancer Intelligence Network, 2009). Again, this work is consistent with these finding of lower incidence in the South Asian

ethnic groups, except for Bangladeshi women who were found to have a similar incidence to White women. However, the higher incidence of gastric cancer found in Black individuals might be due to the larger Black Caribbean group.

Variation in incidence between ethnic groups in subgroups of oesophageal and gastric cancers has previously been reported. Studies in the US have found the incidence of oesophageal squamous cell carcinoma to be up to six times higher in Black men compared with White men (Yang & Davis, 1988b; Corley & Buffler, 2001; Vizcaino *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Cook *et al*, 2009). This work found a higher incidence of upper and middle oesophageal cancer in Black Caribbean men, but a lower incidence in Black African men compared with White men. This work also found that White men had a higher incidence of lower oesophageal and gastric cardia cancers, which is consistent with findings of previous studies in the US (Yang & Davis, 1988b; Yang & Davis, 1988a; Corley & Buffler, 2001; El-Serag *et al*, 2002; Vizcaino *et al*, 2002; Kubo & Corley, 2004; Wu *et al*, 2006; Cook *et al*, 2009; Cooper *et al*, 2009; Hongo *et al*, 2009; Wu *et al*, 2009) and in the UK (Cooper *et al*, 2009; Ali *et al*, 2012).

5.4.2 Strengths and weaknesses

This nationwide English work included a large number of patients over a seven year period. Due to the diverse population in England it was possible to investigate the variation in incidence between more specific ethnic groups and different subgroups of these cancers than have been analysed in previous UK studies. This work also benefits from extracting ethnicity for the majority of patient records (83%). The completeness of oesophageal and gastric cancer registrations was also estimated to be over 99% (section 3.10).

A major limitation was that it was not possible to adjust the results for known risk factors, including socioeconomic deprivation. However, as White individuals are less likely to live in the most deprived areas compared with the other ethnic groups studied (Tinsley & Jacobs,

2006) and because the incidence of both oesophageal and gastric cancer is higher in more deprived areas (National Cancer Intelligence Network, 2008b), the effect of adjusting for deprivation would most likely reduce the estimated IRRs. This would rather strengthen some of the identified differences, in particular the predominance of lower oesophageal and gastric cardia cancer in White males, and could lead to findings such as the higher incidence of upper and middle oesophageal cancer among Bangladeshi women being attenuated, resulting in a similar or lower incidence when compared with White women.

Around 17% of patients had no known recorded ethnicity so age-standardised rates could not be presented. A sensitivity analysis based on an extreme assumption that all patients with an unknown ethnicity were actually White, found the results were slightly attenuated, but that there was no material difference in the overall findings. However, this extreme assumption will have misclassified some patients from other ethnic groups.

Over half (51.9%) of gastric cancer patients had tumours that were classified as NOS, which meant they could not be assigned to either the cardia or non-cardia subgroup. Also, even after reassigning patients in the oesophageal NOS group to either the upper and middle or lower oesophageal groups based on their morphology, 11.6% of cases were still classified as NOS. However, these oesophageal subgroups made better use of all available coding, with a sensitivity analysis based on subgroups defined by morphology alone having a higher proportion (16.0%) of cases classified as “other and unspecified”. The sensitivity analysis found that the lower oesophageal and adenocarcinoma subgroups, the upper and middle oesophageal and squamous cell carcinoma subgroups, and the oesophageal NOS and “other and unspecified” subgroups had very similar patterns in incidence between ethnic groups, which was reassuring.

There was no information on country of birth, age at migration or length of time resident in England, which may be important in terms of exposure to early environmental risk factors. In the absence of information on patients’ migration histories, age could be used as a proxy, but

due to the small number of cases in some specific age and ethnic groups it was not possible to investigate variation in incidence by age. However, there was variation in the age distribution of individuals between ethnic groups. The highest median age was in the White group at 73 years. For the other ethnic groups studied the median age ranged from 63 years for the Chinese group to 71 years for the Black Caribbean group.

5.4.3 Interpretation and implications

Oesophageal and gastric cancer subgroups are associated with different risk factors (section 1.2). Tobacco smoking and high alcohol consumption are the main risk factors for squamous cell carcinoma of the oesophagus (Lindblad *et al*, 2005; Blot *et al*, 2006; Shibata & Parsonnet, 2006; Lagergren & Lagergren, 2010). One possible explanation for the lower incidence of upper or middle oesophageal cancer in some ethnic groups could be a lower prevalence of smoking or alcohol consumption compared with the general population. However, this does not explain why some groups smoke and drink less than the general population (Sproston & Mindell, 2006), but have a similar incidence of this cancer compared with the White group.

Chewing areca nut (also known as betel quid when it is chewed with a betel leaf) both with and without tobacco has been associated with an increased risk of developing oesophageal squamous cell carcinoma (Wu *et al*, 2001b; Akhtar *et al*, 2012). In 2004, around 16% of Bangladeshi women in England reported that they chewed tobacco including betel quid, a higher proportion than Indian (1%) and Pakistani women (1%) in the survey (Sproston & Mindell, 2006). This may contribute to the higher incidence of upper and middle oesophageal cancer in Bangladeshi women.

Barrett's oesophagus, chronic GORD and increasing body mass index (BMI) are associated with an increased risk of developing oesophageal adenocarcinoma (Lagergren *et al*, 1999a; Lagergren *et al*, 1999b; Lagergren *et al*, 2000; Wu *et al*, 2001a; Hampel *et al*, 2005; Lindblad *et al*, 2005; Crew & Neugut, 2006; Merry *et al*, 2007; El-Serag, 2008; Wood & Yang, 2008;

Lagergren & Lagergren, 2010; Hardikar *et al*, 2013). A UK study found that White individuals had a higher risk of developing Barrett's oesophagus compared with South Asians and Afro-Caribbeans (Ford *et al*, 2005). Also, in 2004 the male general population were typically more likely to be overweight or obese compared with Indian, Pakistani, Bangladeshi and Chinese men, whilst Black African and Black Caribbean men had a similar level of obesity (Sproston & Mindell, 2006).

Whilst infection with the most common virulence strain (CagA+) of *Helicobacter pylori* has been established as a risk factor for non-cardia gastric cancer (International Agency for Research on Cancer, 1994) meta-analyses have found that such infection may be associated with a lower risk of oesophageal adenocarcinoma and possibly also of gastric cardia cancer (Wu *et al*, 2001a; Blot *et al*, 2006; Kamangar *et al*, 2006a; Rokkas *et al*, 2007; Islami & Kamangar, 2008). Studies in the US have found *Helicobacter pylori* infection to be lower in White compared with Black individuals (Taylor & Blaser, 1991; Everhart *et al*, 2000), which was partly explained by socioeconomic factors such as lower income (Everhart *et al*, 2000). No population-wide studies that have investigated differences in the prevalence of *Helicobacter pylori* infection between ethnic groups have been reported in England. However, it is plausible that differences in *Helicobacter pylori* infection and socioeconomic factors between ethnic groups could partly explain some of the observed variation in the incidence of these cancers.

5.5 Conclusions

This work highlights the importance of investigating variation in incidence between more specific ethnic groups in subgroups of oesophageal and gastric cancer. There were substantial differences in the incidence of these cancers between specific ethnic groups in England. Different patterns were also seen in the cancer subgroups. Differences in exposures to risk factors between ethnic groups might contribute to this variation. However, there are relatively few studies that investigate these factors in ethnic groups in England, which could help to elucidate why the observed variation in incidence exists.

Chapter 6 Hospital volume, proportion resected and mortality from oesophageal and gastric cancer

The information included in this chapter resulted in the following publication:

Coupland VH, Lagergren J, Lüchtenborg M, Jack RH, Allum W, Holmberg L, Hanna GB, Pearce N, Møller H (2012) Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: Population-based study in England, 2004-2008. *Gut* **62**(7): 961-966

http://gut.bmj.com/content/62/7/961.full

6.1 Introduction

In England, around 13,000 people are diagnosed with oesophageal or gastric cancer each year (Coupland *et al*, 2012a). The prognosis of these cancers is poor, with a five-year relative survival of 12% and 16%, respectively (National Cancer Intelligence Network, 2011c). Surgical resection can offer long-term survival in patients with localised disease (Department of Health, 2001). Only 20% of oesophageal and gastric cancer patients in England underwent resection with curative intent in 2005, compared with 28% in 1998 (Palser *et al*, 2008).

In 2001, the Improving Outcomes Guidance proposed that specialist multidisciplinary teams located in cancer centres should aim to draw oesophageal and gastric cancer patients from a catchment area of at least one to two million people (Department of Health, 2001). The report stipulated that for a population of around one million, teams could expect to manage at least 100 patients with oesophageal cancer and 150 with gastric cancer per year (Department of Health, 2001). These recommendations led to substantial changes in the delivery of upper gastrointestinal cancer services in England over the last decade, with centralisation of surgical referrals to nominated centres (Palser *et al*, 2009).

Centralisation of upper gastrointestinal cancer services is intended to improve outcomes for patients with oesophageal and gastric cancer (Department of Health, 2001). The results of

studies that consider hospital volume and survival for these cancers are heterogeneous. Differences in terms of study design, quality, sample sizes, cut-off values for annual volume, and ability to adjust for potentially important confounders may partly explain the variation of these findings (Birkmeyer *et al*, 2007; Gruen *et al*, 2009). However, there is substantial evidence that an increase in hospital and surgeon volume is associated with lower short-term mortality i.e. 30-day or in-hospital mortality (Begg *et al*, 1998; Bachmann *et al*, 2002; Birkmeyer *et al*, 2002; Hannan *et al*, 2002; Birkmeyer *et al*, 2003; Killeen *et al*, 2005; Rouvelas *et al*, 2007; Pal *et al*, 2008; Wouters *et al*, 2008; Gruen *et al*, 2009; Lauder *et al*, 2010; Rouvelas & Lagergren, 2010; Skipworth *et al*, 2010; Anderson *et al*, 2011; Markar *et al*, 2012). Fewer studies have considered the impact of hospital volume on long-term survival and these have shown conflicting results (Birkmeyer *et al*, 2007; Rouvelas *et al*, 2007; Thompson *et al*, 2007; Gruen *et al*, 2009; Anderson *et al*, 2011; van de Poll-Franse *et al*, 2011; Dikken *et al*, 2012a). Surgical resection remains the mainstay for cure and therefore the resection rate may also need to be considered.

The purpose of this work was to assess the associations between oesophageal and gastric cancer hospital resection volumes (the annual number of resections), resection rates (the proportion of patients that have resections), and mortality rates for patients with these cancers in England. The hypothesis was that increasing volume would be associated with lower mortality for resected patients, both in the short- and long-term perspectives. Another hypothesis was that as resection rates increase, mortality will be lower for all patients, and possibly higher among the resected patients because higher-risk patients may be resected in areas with high resection rates.

6.2 Methods

6.2.1 Patients

Data on 64,711 oesophageal (ICD10 C15) or gastric (ICD10 C16) cancers diagnosed in England between 2004 and 2008 were extracted from the NCDR. Registrations which only had information from death certificates (n=1,611) and without an NHS number (n=174) were excluded. Only the first tumour for each patient was selected, which excluded a further 111 records on patients with more than one tumour. Finally, four patients were excluded as their recorded date of death was before their operation date. The final dataset included 62,811 patients.

6.2.2 Patient characteristics

Patients were aggregated into five-year age groups based on their age at diagnosis (<55 years, 55-59 through to 80-84 and 85+). Patients were grouped into quintiles of socioeconomic deprivation based on their postcode and lower super output area of residence, using the income domain of the Indices of Deprivation 2007 (Department for Communities and Local Government, 2008).

Co-morbidity information was obtained from the linked HES admitted patient dataset, as described in section 2.5. It was not possible to derive a co-morbidity score for 2,426 (3.9%) patients because they had no linked HES record.

6.2.3 Surgical resection

Surgery information was also obtained from the HES dataset. Tumour resections from one month before to 12 months after the patient's diagnosis date were extracted. If a patient had more than one of these operations the earliest operation was selected for the analysis.

6.2.4 Hospital volume

The number of resections was available at the organisation level of NHS hospital trust. In England, an NHS hospital trust manages one or more local hospitals. In this work, NHS hospital trusts are simply referred to as "hospitals" and the annual number of resections in an NHS hospital trust is referred to as the "hospital volume".

For each patient that underwent surgery, hospital volume was computed as the number of oesophageal or gastric cancer resections carried out in the hospital in which they were treated and in the same year as their diagnosis. Hospital volumes were aggregated into five groups: <20 resections per year, 20-39, 40-59, 60-79, and 80+ resections per year.

Hospitals could contribute to more than one volume group when the number of resections in each hospital varied between diagnosis years. There were 144 individual hospitals included in the analysis, of which 108 individual hospitals contributed to the <20 volume group in at least one diagnosis year and seven individual hospitals to the 80+ group.

6.2.5 Resection quintile

The resection rate was defined as the resected proportion of patients resident in each geographical primary care trust area in each year of diagnosis. These proportions were then divided into quintiles which represented areas with increasing proportions of patients who had surgery.

6.2.6 Statistical analysis

The numbers and proportions of patients who had surgery by hospital volume, resection quintile and case-mix variables, i.e. sex, age, socioeconomic deprivation, co-morbidity and type of cancer, were tabulated. P-values for trend or heterogeneity were calculated, as appropriate.

Univariate and multivariate Cox proportional hazards regression analyses were used to estimate the all-cause mortality hazard ratios (HRs) and 95% confidence intervals (CIs) according to hospital volume, resection quintile, and the case-mix variables. Analyses of resection quintile were performed separately for all patients and for patients who had surgery.

For all patients, survival time was calculated from the diagnosis date until death from any cause, and patients who were alive at the end of follow-up were censored on 31st December 2009. In the analysis restricted to patients that underwent surgery, survival time was calculated from the date of the operation. In the multivariate Cox proportional hazards analyses hospital volume and resection quintile were adjusted for the available case-mix variables and mutually adjusted. For each variable included in the models, p-values for heterogeneity and trend were calculated as appropriate.

To assess the HRs according to hospital volume in different time periods after surgery, the follow-up period was divided into three pre-defined periods: short-term (<30 days post-surgery), medium-term (30-365 days post-surgery), and long-term (>365 days post-surgery). These analyses were adjusted for case-mix variables and resection quintile.

6.3 Results

6.3.1 Patients

Of the 62,811 included patients diagnosed with oesophageal or gastric cancer in England between 2004 and 2008, 13,189 (21%) underwent surgical resection (Table 6.1). The number of patients who underwent surgery, in each hospital in each diagnosis year, ranged from 1 to 132. The proportions of patients that underwent surgical resection in each of the 152 primary care trust areas of residence in each diagnosis year ranged from 4% to 46%. There was a positive association between hospital volume and resection quintile with patients operated in high volume hospitals being more likely to live in areas where a higher proportion of patients underwent surgery (Spearman's rho=0.27, p<0.0001).

Table 6.1: Hospital volume and proportion resected for patients with oesophageal or gastric cancer in England between 2004 and 2008

	Total number of patients	**Total number resected**	**% resected**
Total	62,811	13,189	21.0
Hospital volume			
<20		1,944	
20-39		4,014	
40-59		3,367	
60-79		2,095	
80+		1,769	
No surgery	49,622		
Resection quintile			
Quintile 1 (3.8-15.8)	12,651	1,656	13.1
Quintile 2 (15.9-19.0)	12,484	2,200	17.6
Quintile 3 (19.1-22.4)	12,646	2,621	20.7
Quintile 4 (22.4-26.2)	12,577	3,051	24.3
Quintile 5 (26.3-46.2)	12,453	3,661	29.4

Surgical resection rates were lower in females than males (17% versus 23%, p<0.0001) and for oesophageal cancer compared with gastric cancer (17% versus 25%, p<0.0001, Table 6.2). The proportion of patients that underwent surgical resection decreased with increasing age, socioeconomic deprivation, and severity of co-morbidity (all with p-value for trend<0.0001).

Table 6.2: Proportion of patients that underwent surgical resection for oesophageal or gastric cancer in England between 2004 and 2008, by case-mix variables.

	Total number of patients	**Total number resected**	**% resected**
Sex			
Male	41,027	9,486	23.1
Female	21,784	3,703	17.0
χ2 (1)		**χ2 (1)**	**319.25**
p-value		**p-value**	**<0.0001**
Age group			
<55	5,257	1,742	33.1
55-59	4,649	1,601	34.4
60-64	6,310	2,067	32.8
65-69	7,852	2,296	29.2
70-74	9,616	2,510	26.1
75-79	10,925	1,890	17.3
80-84	9,693	854	8.8
85+	8,509	229	2.7
χ2 (1)			**3982.36**
p-value for trend			**<0.0001**
Deprivation quintile			
1 = Least deprived	10,574	2,461	23.3
2	12,651	2,740	21.7
3	13,309	2,799	21.0
4	13,465	2,692	20.0
5 = Most deprived	12,812	2,497	19.5
χ2 (1)			**59.67**
p-value for trend			**<0.0001**
Co-morbidity score			
0	35,970	8,262	23.0
1	15,385	3,439	22.4
2	5,412	1,010	18.7
3+	3,618	478	13.2
Not known	2,426	-	-
χ2 (1) excluding not known			**179.61**
p-value for trend			**<0.0001**
Type of cancer			
Oesophageal cancer	31,632	5,403	17.1
Gastric cancer	31,179	7,786	25.0
χ2 (1)			**583.71**
p-value			**<0.0001**

6.3.2 Hospital volume and mortality of patients who had surgery

Increasing hospital volume was associated with lower mortality (p-value for trend=0.0001), with a HR of 0.87 (95%CI 0.79 to 0.95) in hospitals carrying out 80+ resections compared with those carrying out less than 20 resections a year (Table 6.3). Following adjustment for case-mix variables, hospital volume estimates did not change materially. Adjustment for resection quintile strengthened the association (HR 0.81, 95%CI (0.74 to 0.89), in hospitals carrying out 80+ resections compared with those carrying out less than 20 resections a year). Without any adjustment the absolute risk of dying within five years ranged from 69% in the lowest of the five hospital volume groups to 61% in the highest.

Table 6.3: Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) according to hospital volume for patients who had surgery diagnosed with oesophageal or gastric cancer between 2004 and 2008

	Unadjusted		**Adjusted for sex, age, deprivation, co-morbidity score, type of cancer**		**Adjusted for sex, age, deprivation, co-morbidity score, type of cancer and resection quintile**	
Hospital volume	**HR**	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**
<20	1.00		1.00		1.00	
20-39	0.96	(0.89-1.03)	0.97	(0.90-1.05)	0.96	(0.89-1.03)
40-59	0.91	(0.84-0.98)	0.92	(0.85-1.00)	0.91	(0.84-0.98)
60-79	0.87	(0.80-0.95)	0.89	(0.81-0.97)	0.84	(0.77-0.92)
80+	0.87	(0.79-0.95)	0.86	(0.79-0.95)	0.81	(0.74-0.89)
$\chi 2$ (1)	**15.59**		**15.55**		**28.57**	
p for trend	**0.0001**		**0.0001**		**<0.0001**	

6.3.3 Mortality of patients who had surgery, stratified by period of follow-up

The inverse association between hospital volume and mortality was, in relative terms, strongest during the first month after surgery in the fully adjusted model (p-value for trend<0.0001), with a HR of 0.52, (95%CI 0.39 to 0.70) in hospitals carrying out 80+ resections compared with less than 20 resections a year (Table 6.4). A similar pattern was seen in the medium- and long-term periods after surgery (p-value for trend=0.0370, HR 0.88, 95%CI (0.76 to 1.01), and p-value for trend=0.0011, HR 0.82, 95%CI (0.72 to 0.95), in hospitals carrying out 80+ resections compared with those carrying out less than 20 resections a year, respectively). Without any adjustment, the absolute risk of dying within 30 days ranged from 7.3% in the lowest of the five hospital volume volume groups to 4.1% in the highest.

Table 6.4: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) according to hospital volume for patients who had surgery diagnosed with oesophageal or gastric cancer between 2004 and 2008, by period of follow-up. Adjusted for sex, age, deprivation, co-morbidity score, type of cancer and resection quintile

Hospital volume	<30 days		30-365 days		>365 days	
	HR	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**
<20	1.00		1.00		1.00	
20-39	0.91	(0.74-1.12)	0.93	(0.83-1.05)	0.99	(0.89-1.10)
40-59	0.69	(0.55-0.87)	0.87	(0.77-0.99)	1.00	(0.89-1.12)
60-79	0.65	(0.50-0.84)	0.88	(0.77-1.01)	0.84	(0.74-0.96)
80+	0.52	(0.39-0.70)	0.88	(0.76-1.01)	0.82	(0.72-0.95)
$\chi 2$ (1)	**28.29**		**4.35**		**10.61**	
p for trend	**<0.0001**		**0.0370**		**0.0011**	

6.3.4 Resection rate and mortality of all patients

The overall mortality was higher in females than males (HR 1.09, 95% CI (1.07 to 1.11), p<0.0001, Table 6.5). Mortality was higher with increasing age (p-value for trend<0.0001, HR 2.70, 95%CI (2.60 to 2.81), for patients aged 85 and over compared with patients under 55 years old), in patients living in more socioeconomically deprived areas (p-value for trend<0.0001, HR 1.15, 95%CI (1.11 to 1.18), for those resident in the most compared with the least deprived areas) and in patients with increased severity of co-morbidity (p-value for trend<0.0001, HR 1.49, 95%CI (1.43 to 1.54), for patients with the highest co-morbidity score compared with no co-morbidity). Mortality was similar in oesophageal compared with gastric cancer patients (HR 0.98, 95%CI (0.96 to 1.00)).

Table 6.5: Unadjusted hazard ratios (HR) and 95% confidence intervals (95%CI) for all patients diagnosed with oesophageal or gastric cancer between 2004 and 2008

	Unadjusted	
	HR	**(95%CI)**
Sex		
Male	1.00	
Female	1.09	(1.07-1.11)
χ2 (1)	**94.62**	
p-value	**<0.0001**	
Age group		
<55	1.00	
55-59	1.02	(0.97-1.07)
60-64	1.08	(1.03-1.13)
65-69	1.16	(1.11-1.21)
70-74	1.29	(1.24-1.34)
75-79	1.60	(1.54-1.67)
80-84	2.01	(1.94-2.09)
85+	2.70	(2.60-2.81)
χ2 (1)	**4783.22**	
p-value for trend	**<0.0001**	
Deprivation quintile		
1 = Least deprived	1.00	
2	1.07	(1.04-1.10)
3	1.08	(1.05-1.11)
4	1.13	(1.10-1.16)
5 = Most deprived	1.15	(1.11-1.18)
χ2 (1)	**105.99**	
p-value for trend	**<0.0001**	
Co-morbidity score		
0	1.00	
1	1.08	(1.06-1.10)
2	1.25	(1.21-1.29)
3+	1.49	(1.43-1.54)
Not known	1.80	(1.72-1.88)
χ2 (1) excluding not known	**572.46**	
p-value for trend	**<0.0001**	
Type of cancer		
Oesophageal cancer	1.00	
Gastric cancer	0.98	(0.96-1.00)
χ2 (1)	**6.37**	
p value	**0.0116**	

Increasing resection rates were associated with lower mortality (p-value for trend<0.0001), with a HR of 0.86 (95%CI 0.84 to 0.89) in the highest resection quintile compared with the lowest resection quintile, (Table 6.6). Adjustment for case-mix attenuated the association somewhat, but a relevant and statistically significant association remained (p-value for trend<0.0001, HR 0.90, 95%CI (0.87 to 0.92), in the highest resection quintile compared with the lowest resection quintile).

Table 6.6: Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) according to resection rate for all patients diagnosed with oesophageal or gastric cancer between 2004 and 2008

	Unadjusted		**Adjusted for sex, age, deprivation, co-morbidity score, type of cancer**	
Resection quintile	**HR**	**(95%CI)**	**HR**	**(95%CI)**
Quintile 1 (3.8-15.8)	1.00		1.00	
Quintile 2 (15.9-19.0)	0.94	(0.92-0.97)	0.96	(0.93-0.98)
Quintile 3 (19.1-22.4)	0.93	(0.91-0.96)	0.96	(0.94-0.99)
Quintile 4 (22.4-26.2)	0.90	(0.88-0.93)	0.93	(0.91-0.96)
Quintile 5 (26.3-46.2)	0.86	(0.84-0.89)	0.90	(0.87-0.92)
$\chi 2$ (1)	**117.52**		**61.09**	
p for trend	**<0.0001**		**<0.0001**	

6.3.5 Resection rate and mortality of patients who underwent surgery

In patients who underwent surgery, the overall mortality was lower in females than males (HR 0.88, 95%CI (0.83 to 0.93), p<0.0001) and higher with age (p-value for trend<0.0001, HR 2.09, 95%CI (1.76 to 2.47), for patients aged 85 and over compared with patients under 55 years old), and with increased severity of co-morbidity (p-value for trend<0.0001, HR 1.51, 95%CI (1.34 to 1.70), for patients with the highest co-morbidity score compared with no co-morbidity, Table 6.7). Mortality after surgery was similar between deprivation quintiles (p=0.1373) and between oesophageal and gastric cancer patients (p=0.6628).

Table 6.7: Unadjusted hazard ratios (HR) and 95% confidence intervals (95%CI) for patients who had surgery diagnosed with oesophageal or gastric cancer between 2004 and 2008

	Unadjusted	
	HR	**(95%CI)**
Sex		
Male	1.00	
Female	0.88	(0.83-0.93)
χ^2 (1)	**20.59**	
p-value	**<0.0001**	
Age group		
<55	1.00	
55-59	1.07	(0.97-1.18)
60-64	1.07	(0.97-1.17)
65-69	1.05	(0.96-1.15)
70-74	1.20	(1.09-1.31)
75-79	1.31	(1.20-1.44)
80-84	1.60	(1.43-1.78)
85+	2.09	(1.76-2.47)
χ^2 (1)	**119.15**	
p-value for trend	**<0.0001**	
Deprivation quintile		
1 = Least deprived	1.00	
2	0.98	(0.91-1.06)
3	1.01	(0.93-1.09)
4	1.04	(0.96-1.12)
5 = Most deprived	1.04	(0.96-1.12)
χ^2 (1)	**2.21**	
p-value for trend	**0.1373**	
Co-morbidity score		
0	1.00	
1	0.98	(0.92-1.03)
2	1.18	(1.08-1.29)
3+	1.51	(1.34-1.70)
χ^2 (1)	**32.72**	
p-value for trend	**<0.0001**	
Type of cancer		
Oesophageal cancer	1.00	
Gastric cancer	1.01	(0.96-1.06)
χ^2 (1)	**0.19**	
p value	**0.6628**	

Increasing resection rates were associated with higher overall mortality (p-value for trend<0.0001), with a univariate HR of 1.20, 95%CI (1.10 to 1.31) in the highest resection quintile compared with the lowest quintile (Table 6.8). Following adjustment for case-mix variables the HRs remained similar in each resection quintile (HR 1.20, 95%CI (1.10 to 1.30), in the highest compared with the lowest resection quintile). Further adjustment for hospital volume slightly strengthened this association (HR 1.26, 95%CI (1.15 to 1.37), in the highest resection compared with the lowest resection quintile).

Table 6.8: Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) according to resection rate for patients who underwent surgery diagnosed with oesophageal or gastric cancer between 2004 and 2008

	Unadjusted		**Adjusted for sex, age, deprivation, co-morbidity score, type of cancer**		**Adjusted for sex, age, deprivation, co-morbidity score, type of cancer and volume group**	
Resection quintile	**HR**	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**
Quintile 1 (3.8-15.8)	1.00		1.00		1.00	
Quintile 2 (15.9-19.0)	1.07	(0.97-1.17)	1.08	(0.98-1.18)	1.08	(0.98-1.18)
Quintile 3 (19.1-22.4)	1.12	(1.02-1.22)	1.12	(1.02-1.22)	1.12	(1.03-1.23)
Quintile 4 (22.4-26.2)	1.14	(1.05-1.25)	1.14	(1.05-1.25)	1.17	(1.08-1.28)
Quintile 5 (26.3-46.2)	1.20	(1.10-1.31)	1.20	(1.10-1.30)	1.26	(1.15-1.37)
$\chi 2$ (1)	**22.25**		**19.18**		**32.82**	
p for trend	**<0.0001**		**<0.0001**		**<0.0001**	

6.4 Discussion

6.4.1 Main findings

Increasing hospital volume was associated with decreased mortality among the patients who underwent surgery, which is consistent with previously published literature (Begg *et al*, 1998; Bachmann *et al*, 2002; Birkmeyer *et al*, 2002; Hannan *et al*, 2002; Killeen *et al*, 2005; Birkmeyer *et al*, 2007; Rouvelas *et al*, 2007; Pal *et al*, 2008; Gruen *et al*, 2009; Lauder *et al*, 2010; Rouvelas & Lagergren, 2010; Skipworth *et al*, 2010; Anderson *et al*, 2011; van de Poll-Franse *et al*, 2011; Dikken *et al*, 2012a; Markar *et al*, 2012). In relative terms, the association between hospital volume and mortality was strongest in the first 30 days following surgery, but a clinically relevant and statistically significant association was also evident in the longer-term. These

findings were unaffected by adjustment for the available case-mix variables despite these variables being in general independently associated with the risk of dying. This is because these factors are not materially associated with hospital volume or resection rate. In absolute terms, the risk of dying within 30 days ranged from 7% in the lowest hospital volume group to 4% in the highest. The risk of dying within five years ranged from 69% to 61%. These crude estimates are not adjusted for covariates and therefore are likely to be conservative.

Increasing resection rates for oesophageal or gastric cancer were associated with lower mortality among all patients, but higher mortality among those who underwent surgical resection which is consistent with a previous study of lung cancer patients in England (Riaz *et al*, 2012b). These findings suggest that in areas where a greater proportion of patients have surgery some higher-risk patients may be included in the resected population, leading to the higher mortality in this group. Conversely, in areas where a lower proportion of patients have surgery, some patients with potentially resectable tumours may not be operated on therefore leading to the lower mortality. Future detailed investigation will be important in understanding the exact mechanisms that drive this pattern. Therefore, at present, caution needs to be exercised over whether surgical resection should be offered to more patients. Recommendations should take into account tumour stage, use of combined chemotherapy modalities and the quality of surgery as indicated by lymph node counts, resection margins, rate of completeness of the resection (R0) and local recurrence failure rates.

6.4.2 Strengths and weaknesses

The population-based design and the large national sample of patients diagnosed with oesophageal or gastric cancer over a five-year period across the whole of England are among the strengths of this work. This work also benefited from covering a period when centralisation of upper gastrointestinal cancer services in England was on-going, leaving a wide range of variation in hospital volumes (Palser *et al*, 2009). In this work the percentage of patients that had surgery in hospitals carrying out 80 or more operations increased from 7% in

2004 to 20% in 2008 with a corresponding decrease in the less than 20 volume group of 22% to 7%. The high volumes of resections conducted in many of the hospitals enabled an analysis of truly high volume hospitals, including those that operated on 80 or more patients per year. This work was also able to consider both short- and long-term survival outcomes.

One of the limitations of this work is that the surgery information was taken from the HES dataset, which might not be entirely complete and accurate. However, a systematic review found acceptable accuracy for procedure codes from NHS administrative data (Burns *et al*, 2012).

There is inevitably some misclassification between oesophageal cancer and gastric cancer, particularly for the cancers occurring near the gastro-oesophageal junction. The analysis was repeated for patients with oesophageal cancer and patients with gastric cancer separately and the results were not materially different from those reported overall (Table 6.9 & Table 6.10).

Table 6.9: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) for oesophageal cancer patients who had surgery and were diagnosed between 2004 and 2008

	Adjusted for sex, age, deprivation, co-morbidity score, type of cancer		**Adjusted for sex, age, deprivation, co-morbidity score and mutually adjusted**	
	HR	**(95%CI)**	**HR**	**(95%CI)**
Hospital volume				
<10	1.00		1.00	
10-19	0.94	(0.84-1.05)	0.92	(0.82-1.03)
20-29	0.83	(0.74-0.94)	0.81	(0.71-0.91)
30-39	0.81	(0.70-0.93)	0.77	(0.66-0.88)
40+	0.98	(0.85-1.13)	0.89	(0.77-1.04)
χ2 (1)	**3.43**		**9.35**	
p-value for trend	**0.0638**		**0.0022**	
Resection quintile				
Quintile 1 (0.0-11.1)	1.00		1.00	
Quintile 2 (11.3-14.9)	0.99	(0.84-1.17)	1.02	(0.86-1.20)
Quintile 3 (15.0-18.9)	1.06	(0.91-1.24)	1.10	(0.94-1.29)
Quintile 4 (19.0-22.7)	1.12	(0.96-1.30)	1.18	(1.01-1.37)
Quintile 5 (22.8-52.4)	1.18	(1.02-1.37)	1.24	(1.07-1.45)
χ2 (1)	**10.72**		**14.54**	
p-value for trend	**0.0011**		**0.0001**	

Table 6.10: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) for gastric cancer patients who had surgery and were diagnosed between 2004 and 2008

	Adjusted for sex, age, deprivation, co-morbidity score, type of cancer		Adjusted for sex, age, deprivation, co-morbidity score and mutually adjusted	
	HR	**(95%CI)**	**HR**	**(95%CI)**
Hospital volume				
<10	1.00		1.00	
10-19	1.03	(0.93-1.14)	1.01	(0.91-1.11)
20-29	0.95	(0.86-1.05)	0.93	(0.84-1.03)
30-39	0.92	(0.82-1.02)	0.89	(0.79-0.99)
40+	0.88	(0.79-0.98)	0.84	(0.75-0.93)
χ2 (1)	**10.73**		**16.98**	
p-value for trend	**0.0011**		**<0.0001**	
Resection quintile				
Quintile 1 (0.0-18.3)	1.00		1.00	
Quintile 2 (18.4-23.3)	1.01	(0.89-1.14)	1.02	(0.90-1.15)
Quintile 3 (23.3-26.9)	1.06	(0.94-1.19)	1.07	(0.95-1.21)
Quintile 4 (27.0-31.4)	1.18	(1.05-1.32)	1.21	(1.08-1.35)
Quintile 5 (31.5-66.7)	1.15	(1.03-1.28)	1.19	(1.06-1.34)
χ2 (1)	**12.90**		**18.76**	
p-value for trend	**0.0003**		**<0.0001**	

The co-morbidity score and treatment information included in this work were obtained from an inpatient and day-case admissions dataset. Therefore, as the co-morbidity score for each patient is only based on diagnosis codes recorded in this setting it may under ascertain the co-morbidity in these patients. Not all patients receive chemotherapy as an inpatient and most radiotherapy is received in an outpatient setting which meant it was not possible to ascertain accurately how many patients received non-surgical treatment. Therefore, information on non-surgical treatments for these cancers was considered incomplete and was not included in this analysis. Also, as there was no information available on the referral patterns of patients it was not possible to ascertain if the proportion of patients referred was different between hospitals. Finally, tumour stage is strongly associated with long-term survival. Tumour stage is poorly recorded in the English cancer registries, and it was not possible to take account of stage in these analyses. Other known prognostic factors, including sex, age, socioeconomic

deprivation, and co-morbidity were adjusted for, and did not materially change any of the main results.

6.4.3 Interpretation and implications

Taken at face value, these data suggest that an increase of the annual hospital volume to about 60 or higher would be available to 70% of the patients who had surgery and represent a relative mortality reduction of up to 20%. If this was a medical treatment without major side effects, it would almost certainly become standard care. However, the work was not designed to identify an optimum number of resections in hospitals and the figure of 60 presented here is an arbitrary but pre-defined cut-off point for the analysis.

Hospital volume and outcome has been widely investigated since Luft *et al* first published their study in 1979 that demonstrated lower mortality with increased surgical volume for 12 surgical procedures of varying complexity in the US (Luft *et al*, 1979). Many studies from Europe and the US have found that in general centralisation of services into high-volume hospitals or to high-volume surgeons is beneficial for complex surgery for various diseases including cancer (Begg *et al*, 1998; Bachmann *et al*, 2002; Birkmeyer *et al*, 2002; Hannan *et al*, 2002; Birkmeyer *et al*, 2003; Birkmeyer *et al*, 2005; Killeen *et al*, 2005; Birkmeyer *et al*, 2007; Rouvelas *et al*, 2007; Thompson *et al*, 2007; Pal *et al*, 2008; Wouters *et al*, 2008; Gruen *et al*, 2009; Wouters *et al*, 2009; Jensen *et al*, 2010; Lauder *et al*, 2010; Rouvelas & Lagergren, 2010; Skipworth *et al*, 2010; Anderson *et al*, 2011; Finks *et al*, 2011; van de Poll-Franse *et al*, 2011; Dikken *et al*, 2012a; Markar *et al*, 2012). However, the methods of some of these studies have been criticised (Kozower & Stukenborg, 2012). Other studies have found no evidence of a benefit of high volume (Thompson *et al*, 2007; Pal *et al*, 2008; Kozower & Stukenborg, 2012).

The specific aspects of care in high volume hospitals that act to improve short- and long-term outcomes are not known. Hospital volume is probably an indicator for institutional factors that may influence survival more directly. Two possible explanations of the association

between high volume and lower mortality have been put forward (Luft *et al*, 1987). The first suggests that the "selective referral" of patients to hospitals that already have superior outcomes would result in a higher volume of patients in these settings (Luft *et al*, 1987; Bachmann *et al*, 2002). The second explanation, "practice makes perfect", proposes that more experience gained in hospitals treating a greater number of patients could lead to improvements in the management of patients across the whole treatment pathway (Luft *et al*, 1987). For example, higher volumes could (1) improve the processes of care along defined protocols in a multidisciplinary approach; (2) further the experience in managing postoperative complications, and (3) increase the technical experience of surgeons in performing complex oesophageal and gastric cancer surgery. Such factors may contribute to the lower postoperative mortality in high volume hospitals. The improved long-term survival in high volume settings may be due to more accurate cancer staging, appropriate use of combined oncological modalities and superior surgical techniques (Bachmann *et al*, 2002). It is also possible that surgeons that already achieve better outcomes are attracted to work in higher volume hospitals, which could result in the decreased mortality observed in these settings. If the latter point is true, merely increasing hospital volume will not necessarily lead to improved outcomes. Identifying the mechanisms that drive the improved outcomes in high volume providers will be important in future more detailed studies.

6.5 Conclusions

The recommendations of the 2001 Improving Outcomes Guidance for upper gastrointestinal cancers have led to increased centralisation of surgical referrals to nominated centres (Department of Health, 2001; Palser *et al*, 2009). With evidence of lower short- and longer-term mortality for patients undergoing surgical resection in high volume settings, this work lends support to the further centralisation of oesophageal and gastric cancer surgical services in England.

Chapter 7 Factors that affect who receives surgery for oesophageal and gastric cancer in England

7.1 Introduction

The risk of developing cancer generally increases with age and almost two thirds of cancers occur in people aged over 65 (Cancer Research UK, 2011a). Over the next 25 years this age group is expected to increase significantly in the English population (Office for National Statistics, 2009). The number of cancer patients has also been predicted to increase in England mainly due to the ageing population, with future cancer patients likely to be on average older than today's cancer patients (Møller *et al*, 2007; Maddams *et al*, 2012). A recent Cancer Patient Experience Survey carried out in 2011-2012 identified inequalities in older patients' experiences of care in cancer services, for example fewer older patients had access to clinical nurse specialists or received information about the benefits that they were entitled to (Department of Health, 2012c). Also, older patients have been found to be less likely to receive the most clinically effective treatment, and concerns have been raised over current methods of assessing elderly patients as they often do not provide enough information to identify the appropriate treatment (Department of Health, 2012b). It is therefore becoming increasingly important to consider how cancer services need to adapt to deliver high quality services to a greater number of older patients (Department of Health, 2012a; Department of Health, 2012b; Maddams *et al*, 2012).

Surgical resection is the main curative treatment for oesophageal and gastric cancer and can offer long-term survival in appropriately selected patients (Cromwell *et al*, 2010). The main reasons for the exclusion of patients from curatively intended oesophageal or gastric cancer treatment are poor general health, disease stage and location of the tumour. The resection rates (proportion of patients that undergo surgery) for patients with these cancers in England are lower than the rates reported in other European countries such as Denmark (Dikken *et al*,

2013) and the Netherlands (Faiz *et al*, 2012; Dikken *et al*, 2013). However, no conclusions can be drawn as to whether the English resection rates are too low or the rates in Europe are too high (Dikken *et al*, 2013).

A recent report found that the proportion of patients that underwent surgery for a variety of different procedures declined with age, despite the diseases often being more common in the older population (Whitaker *et al*, 2012). The Cancer Reform Strategy states that age alone should not be a barrier to treatment and that poor patient health or the refusal of the patient to undergo surgery should be the only acceptable reasons for not giving clinically appropriate treatment (Department of Health, 2007). The 2010 Equality Act supports this strategy and set out to eliminate age discrimination in the provision of public services (Home Office, 2010). Therefore, it is increasingly important to ensure that cancer patients are not being excluded from potentially curative surgery simply because of their chronological age, and assumptions about their ability to tolerate treatment or personal preferences should be avoided (Bernardi *et al*, 2006; Macmillian Cancer Support, 2012; Mulley *et al*, 2012).

The purpose of this work was to assess the characteristics of oesophageal and gastric cancer patients who underwent surgery in England between 1998 and 2009, focusing on age at diagnosis. The hypothesis was that the proportion of patients who undergo surgery would decrease with age. The proportion of patients undergoing surgery over time was also considered and survival over time was explored for both patients who underwent surgery and those who did not.

7.2 Methods

7.2.1 Patients

Data on 159,668 oesophageal (ICD10 C15) or gastric (ICD10 C16) cancers diagnosed in England between 1998 and 2009 were extracted from the NCDR. Registrations which only had information from death certificates (n=5,159) and had no NHS number (n=470) were excluded. Only the first tumour for each patient was selected, which excluded a further 349 records on patients with multiple tumours. Finally, four patients were excluded as their recorded date of death was before their operation date. The final dataset included 153,686 patients.

7.2.2 Patient characteristics

Patients were aggregated into age groups based on their age at diagnosis (<40 years, 40-44, 45-49 through to 75-79, and 80+) and were grouped into quintiles of socioeconomic deprivation using the income domain of the Indices of Deprivation. Four categories of co-morbidity were defined: 0 (no co-morbid conditions), 1 (co-morbidity score of 1), 2 (co-morbidity score of 2), or 3 (co-morbidity score 3 or higher). For oesophageal cancer, three histological subgroups were defined as squamous cell carcinoma, adenocarcinoma, and "other or unspecified". These variables are described in more detail in Chapter 2.

7.2.3 Surgical resection

Information on whether a patient underwent surgery for their oesophageal or gastric tumour was obtained from the HES admitted patient dataset, as described in Chapter 2. Surgical resections from one month before to 12 months after the patient's diagnosis date were included.

7.2.4 Statistical analysis

The numbers and proportions of oesophageal and gastric cancer patients who underwent surgery by case-mix variables including age, sex, socioeconomic deprivation, co-morbidity, histology (for oesophageal cancer patients), and year of diagnosis were examined separately. P-values for trend or heterogeneity were calculated, as appropriate.

Univariate and multivariate logistic regression analyses were used to calculate the odds of having surgery according to these variables. Odds ratios were adjusted for the case-mix variables and then back transformed into adjusted proportions of patients that had surgery. P-values for heterogeneity and trend were calculated as appropriate for each variable included in the models.

Cox proportional hazards regression analyses were used to estimate the difference in all-cause mortality hazard ratios (HRs) and 95% confidence intervals (CIs) for a ten year period overall, and according to age group, for both patients who had surgery and those that did not. For patients who had surgery, survival time was calculated from the date of operation until death from any cause, and patients who were alive one year after their operation date were censored at that point. As the final censor date was the end of December 2010 and patients may have had their operation up to twelve months after their date of diagnosis it was not possible to follow all patients who had surgery and were diagnosed in 2009 for a full year after their operation. Therefore, all patients diagnosed in this year were excluded from the survival analysis. For the patients who did not have surgery, survival time was calculated from their diagnosis date.

7.3 Results

Between 1998 and 2009, 12,465 (17.1%) oesophageal cancer patients and 21,593 (26.7%) gastric cancer patients had surgery. The unadjusted proportion of patients who had surgery decreased with age for both oesophageal (p-value for trend<0.0001) and gastric (p-value for

trend<0.0001) cancer, from 32.5% in patients less than 40 years old to 1.6% in patients 80 and over, and 34.5% in the <40 group to 11.2% in the 80 and over group, respectively (Table 7.1 and Table 7.2). This association remained after adjustment for sex, socioeconomic deprivation, co-morbidity, histology (for oesophageal cancer), and year of diagnosis (p-value for trend<0.0001 for both cancer types).

In the unadjusted analysis, women were less likely to have surgery than men (12.5% vs 19.7% for oesophageal cancer; 23.7% vs 28.4% for gastric cancer) however, after adjustment for case-mix variables the proportions of women that underwent surgery were more similar to men (Table 7.1 and Table 7.2), although it was primarily adjustment for age that drove this pattern. Patients resident in more deprived areas were less likely to have surgery than those resident in the least deprived areas (p-value for trend<0.0001 for both cancer types, Table 7.1 and Table 7.2). Also, patients with more severe co-morbidity were less likely to have surgery (p-value for trend<0.0001 for both cancer types). After adjustment for case-mix variables, the association with deprivation remained (p-value for trend<0.0001 for both cancers). The association with co-morbidity remained for oesophageal cancer (p-trend<0.0001), but was attenuated for gastric cancer (p-value for trend=0.9310, Table 7.1 and Table 7.2). For oesophageal cancer, a lower proportion of patients with squamous cell carcinoma (13%) had surgery compared with patients with adenocarcinoma (23%), (Table 7.1).

Table 7.1: Number of oesophageal cancer patients and unadjusted and adjusted proportions (including 95% confidence intervals) of patients that underwent surgery, England, 1998-2009

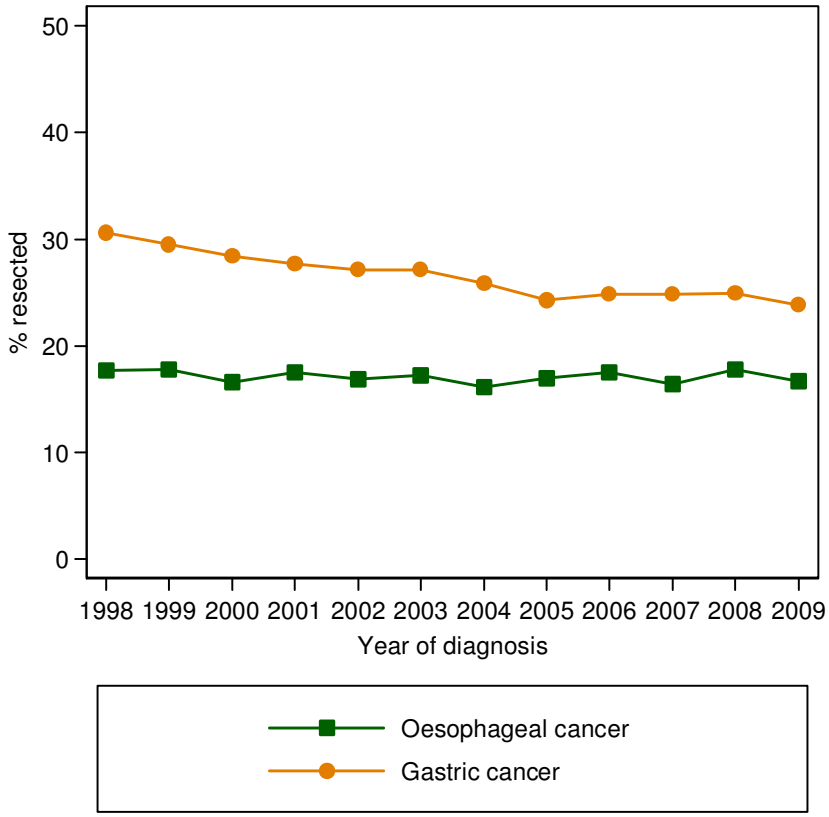
	Number of patients	Number of patients that had surgery	Unadjusted	Adjusted for sex, deprivation score, co-morbidity, histology, and year of diagnosis		
			%	%	95% LCI	95% UCI
Age group						
<40	453	147	32.5	31.7	27.3	36.5
40-44	826	282	34.1	32.0	28.7	35.6
45-49	1,783	594	33.3	31.8	29.4	34.3
50-54	3,679	1,123	30.5	29.0	27.3	30.9
55-59	6,118	1,893	30.9	30.0	28.4	31.6
60-64	7,899	2,301	29.1	28.5	27.1	30.0
65-69	9,401	2,377	25.3	25.0	23.7	26.3
70-74	11,247	2,154	19.2	19.2		
75-79	12,248	1,278	10.4	10.3	9.6	11.0
80+	19,274	314	1.6	1.7	1.5	1.9
χ2 (1)			**5332.64**	**4279.98**		
p-value for trend			**<0.0001**	**<0.0001**		
Sex						
Male	46,707	9,182	19.7	19.7		
Female	26,221	3,281	12.5	20.2	19.4	21.0
χ2 (1)			**596.08**	**1.92**		
p-value			**<0.0001**	**0.1661**		
Deprivation quintile						
1 = Most affluent	12,504	2,410	19.3	19.3		
2	15,017	2,777	18.5	18.7	17.7	19.7
3	15,599	2,637	16.9	17.2	16.3	18.2
4	15,656	2,539	16.2	16.2	15.4	17.2
5 = Most deprived	14,152	2,100	14.8	13.9	13.1	14.8
χ2 (1)			**120.09**	**145.78**		
p-value for trend			**<0.0001**	**<0.0001**		
Co-morbidity score						
0	45,895	9,410	20.5	20.5		
1	14,520	2,353	16.2	17.7	16.9	18.5
2	4,324	496	11.5	13.5	12.4	14.8
3+	2,825	204	7.2	9.1	7.9	10.4
NK	5,364	0	-	-		
χ2 (1) excluding not known			**538.87**	**254.9**		
p-value for trend			**<0.0001**	**<0.0001**		
Morphology						
Squamous cell carcinoma	23,168	3,178	13.7	13.3	12.8	13.9
Adenocarcinoma	39,268	8,887	22.6	22.6		
Other and unspecified	10,492	398	3.8	5.0	4.5	5.5
χ2 (2)			**1961.74**	**1432.93**		
p-value for trend			**<0.0001**	**<0.0001**		

Table 7.2: Number of gastric cancer patients and unadjusted and adjusted proportions (including 95% confidence intervals) of patients that underwent surgery, England, 1998-2009

	Number of patients	Number of patients that had surgery	Unadjusted	Adjusted for sex, deprivation score, co-morbidity, histology, and year of diagnosis		
			%	%	95% LCI	95% UCI
Age group						
<40	983	339	34.5	35.5	32.4	38.8
40-44	1,074	409	38.1	39.8	36.7	43.1
45-49	1,688	667	39.5	40.1	37.5	42.7
50-54	2,759	1,073	38.9	39.1	37.0	41.2
55-59	4,568	1,846	40.4	40.8	39.0	42.5
60-64	6,841	2,687	39.3	39.2	37.8	40.7
65-69	10,114	3,643	36.0	36.0	34.7	37.3
70-74	13,360	4,359	32.6	32.6		
75-79	15,164	3,853	25.4	25.8	24.8	26.8
80+	24,207	2,710	11.2	11.8	11.2	12.4
χ2 (1)			**3422.45**	**2968.68**		
p for trend			**<0.0001**	**<0.0001**		
Sex						
Male	52,505	14,900	28.4	28.4		
Female	28,253	6,686	23.7	27.6	26.9	28.3
χ2 (1)			**207.99**	**4.29**		
p-value			**<0.0001**	**0.0384**		
Deprivation quintile						
1 = Most affluent	12,287	3,430	27.9	27.9		
2	14,945	4,117	27.5	27.8	26.7	29.0
3	16,742	4,556	27.2	27.4	26.3	28.5
4	17,774	4,583	25.8	25.9	24.8	26.9
5 = Most deprived	19,010	4,900	25.8	24.8	23.8	25.8
χ2 (1)			**29.35**	**52.37**		
p for trend			**<0.0001**	**<0.0001**		
Co-morbidity						
0	42,711	12,837	30.1	30.1		
1	19,302	6,111	31.7	34.2	33.4	35.1
2	6,558	1,780	27.1	31.4	30.1	32.8
3+	4,189	858	20.5	25.1	23.6	26.7
NK	7,998	0	-	-		
χ2 (1) excluding not known			**104.56**	**0.01**		
p for trend			**<0.0001**	**0.931**		

Over the twelve-year period studied, the proportion of patients that underwent surgery for oesophageal cancer remained relatively stable at around 17%, whereas for gastric cancer the proportions fell from 31% in 1998 to 24% in 2009 (Figure 7.1).

Figure 7.1: Proportion of oesophageal and gastric cancer patients that had surgery by cancer type, 1998-2009



One-year survival for patients that underwent surgery was higher than those that did not. Overall, one-year survival for oesophageal cancer patients who underwent surgery increased from 56.7% in 1998 to 75.2% in 2008 and for gastric cancer one-year survival increased from 61.4% in 1998 to 74.1% in 2008 (Figure 7.2). One-year survival for patients who did not have surgery increased from 18.8% in 1998 to 29.1% in 2008 for oesophageal cancer and from 15.7% to 26.6% for gastric cancer patients (Figure 7.2).

Figure 7.2: One-year survival estimates for oesophageal and gastric cancer patients who had surgery and those that did not, who were diagnosed between 1998 and 2008

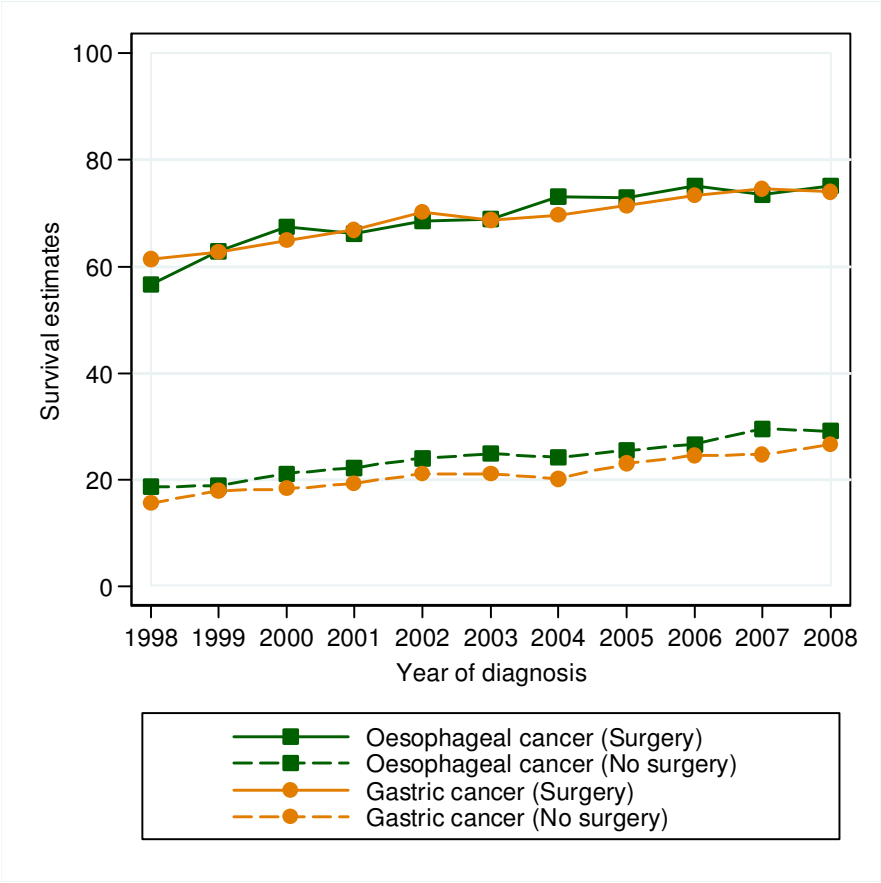
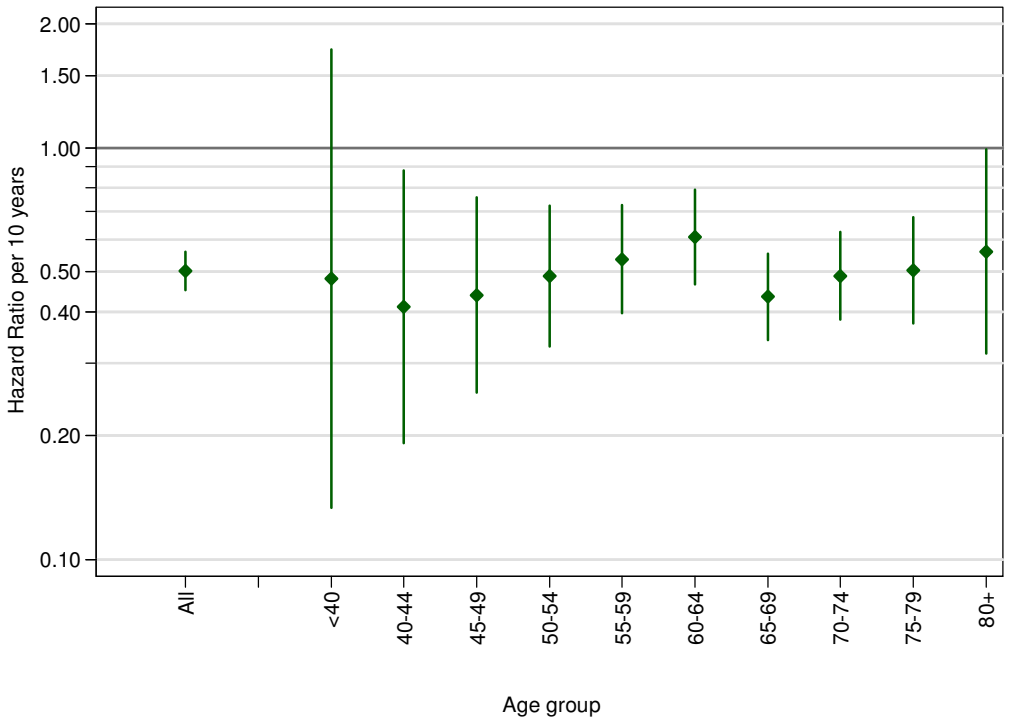


Figure 7.3 and Figure 7.4 show the difference in survival for a ten-year period overall and in each age group. Adjustment was made for sex, socioeconomic deprivation, co-morbidity, histology (for oesophageal cancer), and year of diagnosis. Among patients that underwent surgery, survival improved overall for both oesophageal cancer patients (HR=0.50 95%CI [0.45-0.56]) and gastric cancer patients (HR=0.57 95%CI [0.52-0.61]) with a similar improvement found in each age group (Figure 7.3). A similar but smaller improvement in survival among patients that did not have surgery was found overall for both cancer types (HR=0.73 95%CI [0.71-0.76] for oesophageal cancer and HR=0.75 95%CI [0.73-0.77] for gastric cancer) and in each age group (Figure 7.4).

Figure 7.3: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) per ten years for patients who underwent surgery diagnosed with a) oesophageal cancer and b) gastric cancer

a)



b)

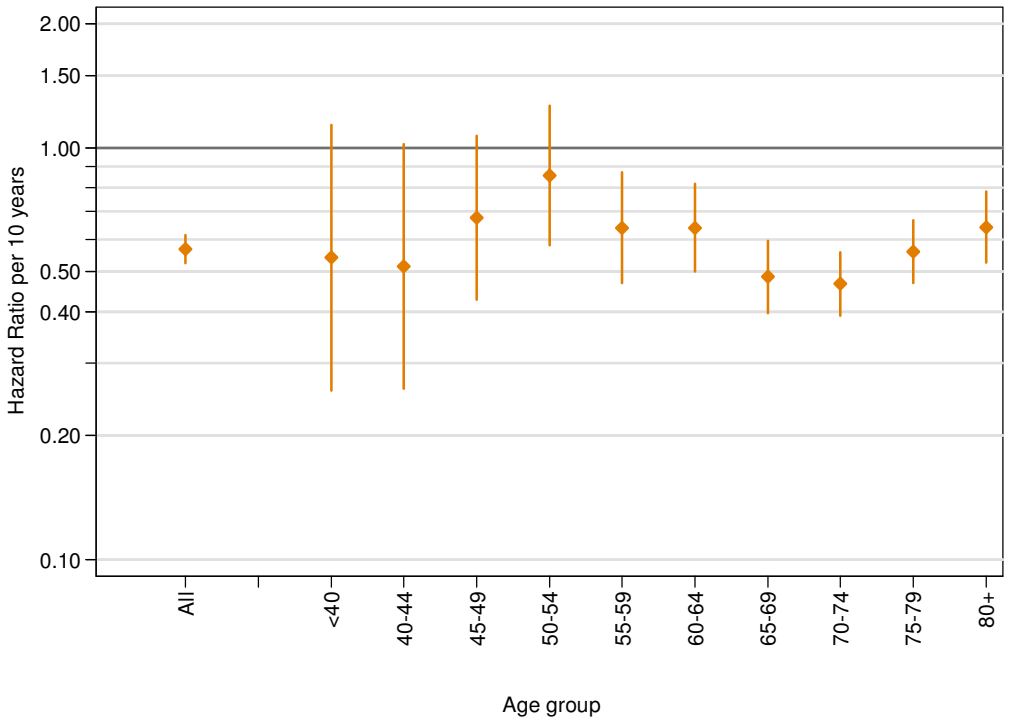
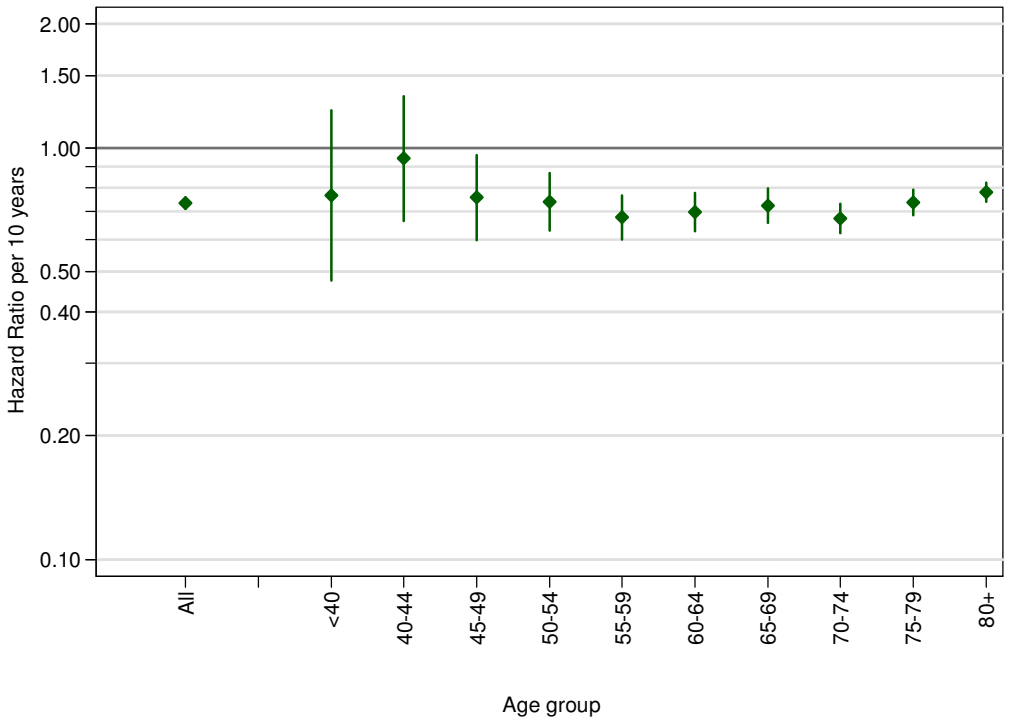
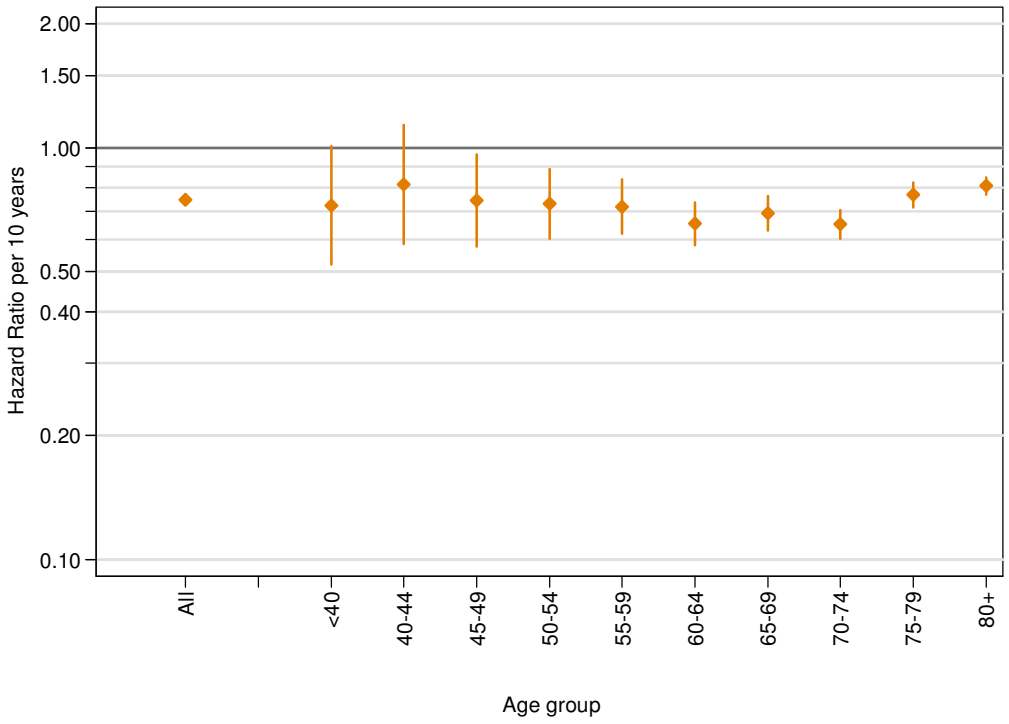


Figure 7.4: Adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) per ten years for patients that did not have surgery diagnosed with a) oesophageal cancer and b) gastric cancer

a)



b)



7.4 Discussion

7.4.1 Main findings

This work found that older patients and those resident in more deprived areas were less likely to undergo surgery than younger and more affluent patients. These associations remained after adjustment for case-mix variables including age, sex, socioeconomic deprivation, co-morbidity, histology (for oesophageal cancer patients), and year of diagnosis. Between 1998 and 2009, the proportion of oesophageal cancer patients that had surgery remained relatively stable, whereas the proportions of gastric cancer patients that had surgery declined. Over time, survival improved for patients that had and did not have surgery, with an improvement occurring across all age groups.

7.4.2 Comparison to other studies

Factors that affect who received surgery

Many studies have found that the proportion of patients that undergo surgery for a variety of different conditions decline with age (National Cancer Intelligence Network, 2011a; Koppert *et al*, 2012; Whitaker *et al*, 2012). The results in this chapter are consistent with these findings, with older patients less likely to undergo surgery for both oesophageal and gastric cancer than younger patients. There could be several valid reasons for this finding. For example older patients may be less fit for surgery, have many co-existing health conditions, an increased risk of complications and post-operative death, lack the social support needed during recovery, or simply choose not to have the operation (Winslet *et al*, 1996; Department of Health, 2012b; Whitaker *et al*, 2012). However, older people remained less likely to have surgery after adjustment for co-morbidity which suggests that this association was not entirely explained by differences in co-existing health conditions between older and younger patients. It was not possible to evaluate the role of other factors, for example, co-morbid conditions that are not

recorded in the Charlson score and which may influence the overall fitness of the patients for surgery.

The proportion of patients that had surgery also declined with increasing socioeconomic deprivation. A similar association has been reported for these and other cancer types (Lyratzopoulos *et al*, 2009; National Cancer Intelligence Network, 2011a; McGhan *et al*, 2012; Riaz *et al*, 2012a). The reasons for this are not known. One possible explanation could be related to a lower awareness of cancer symptoms in patients resident in more deprived areas, which may delay access to primary care and therefore diagnosis (Macleod *et al*, 2009). Another possible reason could be that patients resident in these areas have an increased prevalence of other health conditions (Mercer & Watt, 2007; Gordon-Dseagu, 2008), although the association between surgery and deprivation remained following adjustment for co-morbidity. It was also not possible to adjust for other factors that may affect the decision to operate and that may be more prevalent in more deprived areas such as tobacco smoking and alcohol consumption.

In the unadjusted analysis, women were less likely to undergo surgery than men, but this association was attenuated after adjustment for the case-mix variables. This was largely a result of women being older than men (median age 76 versus 70 for oesophageal cancer and 77 versus 73 for gastric cancer). In oesophageal cancer patients, women were also more likely to be diagnosed with squamous cell carcinoma, which are less likely to be surgically resected than adenocarcinoma.

Trend in the proportion of patients that had surgery

Over the twelve year period studied, the proportion of patients that had surgery remained relatively stable for oesophageal cancer and declined for gastric cancer. A similar decline in the proportion of patients that underwent surgery for gastric cancer has also been reported in the first national oesophago-gastric cancer audit (Palser *et al*, 2008). However, that report

also found a decline in the proportion of oesophageal cancer resections (Palser *et al*, 2008). The decline in the proportion of patients that had surgery in England has been attributed to the more appropriate selection of suitable patients for surgery due to improved staging and multidisciplinary team management (Palser *et al*, 2008). This is likely to be a result of the increased centralisation of surgical services following the publication of the Improving Outcomes Guidance in 2001 (Department of Health, 2001; Palser *et al*, 2009). It is likely that this more selective process started earlier in oesophageal cancer patients and is increasingly being adopted in gastric cancer patients and this may partly explain the differences in surgical resection rates between these two tumours.

Survival

This work found overall improvements over time in survival for oesophageal and gastric cancer patients who had surgery, and across all age groups. Patients who underwent surgical resection in 2008 were around twice as likely to survive for one year after surgery compared with those who had their operation in 1998. This could support the suggestion that better patient selection, as indicated by the decline in the proportion of patients that had surgery for gastric cancer, has led to surgery being offered to patients for whom it is more appropriate. Therefore the poorer survival in the earlier years may be the result of some patients undergoing surgery who, may not have been operated on in the later years. However, there was a similar improvement in survival for oesophageal cancer patients who had surgery despite the relatively stable trend in the proportion having surgery over time. Survival also improved among oesophageal and gastric cancer patients who did not have surgery. This suggests that other factors, and not only better patient selection, are likely to have also contributed to the improvements in survival.

One such factor could be the increased use of pre-operative treatment. After the expansion of evidence on the clinical effectiveness of pre-operative chemotherapy (and chemo-radiotherapy), particularly for oesophageal and gastro-oesophageal junctional tumours, the

use of these treatment modalities has increased over time (MRC, 2002; Cunningham *et al*, 2006; Palser *et al*, 2008; Faiz *et al*, 2012). In this work, the median length of time between diagnosis and surgery increased for both oesophageal cancer (34 days in 1998 to 127 days in 2008) and gastric cancer patients (25 days in 1998 to 92 days in 2008), which could suggest that patients were more likely to receive pre-operative treatment in the later years.

As shown in Chapter 6, patients that underwent surgery in high volume hospitals had better short- and longer-term survival than those that had surgery in lower volume hospitals (Coupland *et al*, 2012b). In England, a greater proportion of patients now have surgery in higher volume hospitals because of the centralisation of surgical referrals to specialist centres. These specialist centres will be better equipped to assess and treat patients than lower volume hospitals. Centralisation is likely to have allowed surgeons to develop greater technical experience in performing these complex procedures and further the experience of other staff involved in the management of care for these patients, both pre-operatively and post-operatively. These factors are likely to have contributed to the improvement in survival over time for patients who underwent surgical resection.

Improvements in survival may also have been caused by the increased awareness of Barrett's oesophagus and alarm symptoms which may have led to earlier diagnosis in more patients in more recent years. Also, the incidence of adenocarcinoma of the oesophagus has increased, while the incidence of squamous cell carcinoma has remained stable or decreased (section 1.4.2). Since the prognosis is better for patients with adenocarcinoma after surgery (Siewert *et al*, 2001), this change in histological distribution might contribute to the improved prognosis for oesophageal cancer.

7.4.3 Strengths and weaknesses

This large population-based study included all patients diagnosed with oesophageal or gastric cancer over a twelve-year period across the whole of England. The work benefitted from the

extraction of consistent surgery information from the HES dataset, which is more complete than the information collected by the cancer registries. A systematic review found that there was an acceptable level of accuracy for procedure codes from NHS administrative data (Burns *et al*, 2012).

One limitation of this work was that it was not possible to take account of tumour stage, as this information is poorly recorded in the English cancer registries. Tumour stage is strongly associated with propensity to operate and with survival. Therefore, it is possible that the observed differences reported in this work could reflect differences in stage at diagnosis and other unmeasured factors, such as performance status (ASA grade) or patient preference. However, other factors including sex, socioeconomic deprivation, co-morbidity, and histology were adjusted for, and did not materially affect the main findings.

The co-morbidity score for each patient is derived from diagnosis codes recorded in inpatient and day-case admissions and therefore could be under-ascertained. Information on non-surgical treatments, for example, chemotherapy and radiotherapy for these cancers was considered incomplete. Patients may have received these non-surgical treatments which could have affected their survival, but this information could not be included in the analysis.

7.4.4 Interpretation and implications

This work demonstrated variation in the characteristics of patients who underwent surgical resection for oesophageal or gastric cancers in England. This study is based on observational data, and because it could not take into account several factors that would influence the decision to operate it was not possible to conclude directly whether surgical resection could be extended overall or in specific subgroups, such as the older patients. It is possible that the observed differences are accounted for by clinical factors for which data were not available. Further investigation, using clinical datasets, will be necessary to understand whether there is scope to increase the proportion of patients that have surgery.

Many studies have concluded that advanced chronological age alone should not be considered as an exclusive selection criteria for oesophageal or gastric cancer resection in otherwise suitable patients (Brown *et al*, 1999; Ruol *et al*, 2007; Saif *et al*, 2010). It is important to ensure decisions regarding who undergoes surgery are made based on the patient's fitness and not their chronological age (Macmillian Cancer Support, 2012). Multidisciplinary teams could consider these findings to ensure that patients are not being excluded from surgery unnecessarily and that clinical decision making is appropriate. Outdated perceptions about how demanding operations are for older patients should be reviewed and provision of resources and training to ensure the needs of older patients are met should be provided (Department of Health, 2012a; Macmillian Cancer Support, 2012; Maddams *et al*, 2012; Whitaker *et al*, 2012).

Older people tend to be under-represented in clinical trials (Aapro *et al*, 2005; Stewart *et al*, 2007) and as a result there is less evidence of the best approach to operating on this group which could make clinicians reluctant to operate. Therefore the results of this study could be used to help plan clinical trials to assess which treatments this group of patients would benefit from.

Some studies have noted that elderly patients had an advanced stage of gastric cancer at diagnosis (Winslet *et al*, 1996; Kunisaki *et al*, 2006). However, another study found a similar stage distribution between older and younger patients (Biondi *et al*, 2012). The lower proportion of older patients having surgery in this work could possibly suggest that they are more likely to be diagnosed when their cancer is more advanced. Therefore, initiatives aimed at earlier diagnosis of these tumours could be targeted at older patients and could lead to a greater proportion of patients being suitable for surgery.

7.5 Conclusion

Older oesophageal and gastric cancer patients are less likely than younger patients to have surgery. This could be for several valid reasons such as their fitness for surgery or simply patient choice. Whether there is scope for increasing the number of resections specifically in older patients is uncertain. Future studies which take into account factors that were missing in this dataset, such as stage of disease, performance status and willingness to undergo surgery, would be useful. Encouragingly, survival has improved over time and continued assessment of the treatment of these patients will be important to ensure this continues.

Chapter 8 General discussion

In this chapter the main results of the analyses in this thesis are outlined and the strengths and weaknesses of the work are reviewed. Finally, the interpretation and wider implications of the work are discussed.

8.1 Summary of main results

The work in this thesis examined the incidence, survival, and treatment of oesophageal and gastric cancers in England. A summary of the incidence and survival results in Chapters 4 and 5, are outlined in Table 8.1. Key results include an increase in the incidence of lower oesophageal cancer in England particularly in men which slowed after 2002, and a higher incidence of this and gastric cardia cancers in men, with rates around four times higher in men than in women. This work also found that White men had a higher incidence of these two cancer types compared with the other ethnic groups studied (Indian, Pakistani, Bangladeshi, Black Caribbean, Black African, and Chinese). The incidence of upper and middle oesophageal cancer remained relatively stable over time with a similar incidence in both men and women. A higher incidence of upper and middle oesophageal cancer was found among Bangladeshi women compared with their White counterparts. A decline in the incidence of non-cardia gastric cancer and gastric "not otherwise specified" cancer was also observed, with rates in men around twice that of women. The incidence of all six of the oesophageal and gastric cancer subgroups was higher in men and women resident in more deprived areas.

The prognosis for all six subgroups of these cancers was poor. One and five-year survival rates were lowest in oesophageal "not otherwise specified" cancer (15% and 4%, respectively) and highest in gastric non-cardia cancer (41% and 16%, respectively).

Table 8.1: Summary of key results reported in Chapters 4 and 5

Cancer type		Oesophageal cancer			Gastric cancer		
		Upper and middle	**Lower**	**NOS**	**Cardia**	**Non-cardia**	**NOS**
Trends in age-standardised incidence rates between 1997 and 2008		Relatively stable in both men and women	Increased in men until 2002, then relatively stable. Relatively stable in women	Decreased in both men and women	Decreased in both men and women	Decreased in both men and women	Decreased in both men and women
Male : Female rate ratio		1 : 1	4 : 1	2 : 1	4 : 1	2 : 1	2 : 1
Most deprived : Least deprived rate ratio		M: 2.2 : 1 F: 1.7 : 1	M: 1.2 : 1 F: 1.3 : 1	M: 1.9 : 1 F: 1.4 : 1	M: 1.5 : 1 F: 1.7 : 1	M: 2.0 : 1 F: 1.9 : 1	M: 2.1 : 1 F: 2.1 : 1
One-year survival		30.3%	36.4%	14.8%	40.0%	40.8%	28.5%
Five-year survival		8.3%	9.4%	3.7%	10.9%	15.6%	10.1%
Variation in incidence between ethnic groups							
Males	White	1.00	1.00	1.00	1.00	1.00	1.00
	Indian	0.93	**0.24***	**0.63***	**0.17***	**0.43***	**0.59***
	Pakistani	**0.22***	**0.17***	**0.08***	**0.25***	**0.66***	**0.56***
	Bangladeshi	1.05	**0.16***	0.71	**0.15***	0.77	0.92
	Black Caribbean	**1.42***	**0.28***	1.02	**0.45***	**1.81***	**1.94***
	Black African	**0.47***	**0.30***	1.06	**0.35***	0.78	**1.66***
	Chinese	1.21	**0.08***	0.68	**0.17***	1.23	**1.53***
Females	White	1.00	1.00	1.00	1.00	1.00	1.00
	Indian	1.13	**0.22***	0.59	**0.20***	**0.53***	**0.74***
	Pakistani	**0.46***	**0.10***	-	**0.46***	0.70	0.82
	Bangladeshi	**3.10***	0.89	1.93	**0.25***	1.17	1.56
	Black Caribbean	0.75	**0.34***	0.63	0.66	1.21	**2.11***
	Black African	1.20	**0.33***	1.62	0.71	1.30	1.72
	Chinese	**0.34***	**0.38***	0.99	0.63	1.34	0.95

* Highlighted figures where p<0.05, higher incidence (figures in red) or lower incidence (figures in green) compared with their White counterparts

A lower mortality with an increase in hospital volume measured as the number of operations carried out in each hospital in each year was found. In relative terms, this association was strongest in the first 30 days after surgery, but a clinically relevant and statistically significant association was also evident in the longer-term. This remained after adjustment for case-mix variables which included sex, age, socioeconomic deprivation, co-morbidity and type of cancer.

Another result found was the lower mortality among all oesophageal and gastric cancer patients with increasing resection rates (the resected proportion of patients resident in a geographical area), but a higher mortality among the patients who underwent surgery. This may indicate differences in who undergoes surgery or differences in how surgical services are supplied in different areas. For example, in areas with higher resection rates more high-risk patients may be resected whereas in areas with lower resection rates some patients that may benefit from surgery may not be offered it. However, the exact mechanisms driving this pattern cannot be determined from this study.

Analysis in this thesis demonstrated variation in who received surgery for oesophageal and gastric cancer. In particular, older patients and patients resident in more socioeconomically deprived areas were less likely to undergo surgery. Although this variation persisted after adjustment for several case-mix variables including age, sex, socioeconomic deprivation, co-morbidity, histology (for oesophageal cancer patients), and year of diagnosis, it was not possible to include all factors such as stage of disease that could affect the decision to operate.

8.2 Strengths and weaknesses

A major strength of the analyses in this thesis is that they were based on a large national cancer registration dataset. A low proportion of registrations in this dataset remained as death certificate only registrations and analysis based on the HES dataset identified a very small proportion of potentially missed cancer registrations. Therefore, as English cancer registries cover the whole population of England, it is likely that this dataset is a practically

complete representation of patients diagnosed with oesophageal and gastric cancer in this country. HES information was available for around 90% of patients which allowed the cancer registration dataset to be enriched with additional information on self-assigned ethnicity, co-morbidity, and treatment.

Historically, self-assigned ethnicity has been poorly recorded in cancer registries. The more complete ethnicity information recorded in HES meant that an ethnic code could be assigned to the majority of patients. However, 17% of patients still had no recorded ethnicity information. Consequently, any age-standardised incidence rates calculated would be too low because there was no population denominator for the 'missing' ethnicity group, and therefore this group had to be excluded. It was assumed that patients in this 'missing' ethnicity group were proportionately distributed between all ethnic groups, and therefore the overall results would be the same. However, if they were from a specific ethnic group this could have altered the results. Proportionally, the majority of these patients would be White so a sensitivity analysis which included all patients, with patients in the 'missing' ethnicity group recoded to White, was also carried out. Incidence rate ratios calculated from this method were slightly attenuated, but there was no material difference in the main results. This extreme assumption would make it possible to calculate incidence rates, but the rates for the other ethnic groups would be underestimated due to the misclassification of some of these patients.

Information on non-cancer diagnoses recorded in HES was used to generate a co-morbidity score for the majority of the cancer patients. This method did not exploit other sources of information such as outpatient data or general practitioner records so it is acknowledged that use of the HES dataset alone probably under-estimates the co-morbidity for at least some patients. The method chosen used weights outlined in the original paper by Charlson *et al* which was published in 1987 (Charlson *et al*, 1987). A paper by Quan *et al* (2011) re-evaluated and generated a new set of weights for these diseases in order to take account of improvements in treatment and disease management over time. These new weights may have

provided a more accurate measure of co-morbidity that was more relevant to the current period of study. Although work in this thesis found poorer survival and a lower likelihood of surgery with an increase in the severity of co-morbidity, statistical adjustment for this factor did not materially alter the main results. Therefore, the results appear to be independent of differences in co-morbidity, and it is unlikely that the score based on the updated weights would have made a major difference to the main results.

Only information on treatment received up to six months after diagnosis was available in the cancer registration dataset, and not all cancer registries collected this information. Using HES it was possible to extend this period to one year after diagnosis. Patients who underwent pre-operative treatment and may have had surgery over six months after diagnosis would therefore still be included in the resected group. Another advantage was that these data were available across the whole country and were recorded consistently. Previously the accuracy of HES has been questioned, but a recent systematic review concluded there was an acceptable level of accuracy for procedure codes in NHS administrative data (Burns *et al*, 2012).

The lack of complete information on anatomical sub site and histological diagnosis prevented the accurate definition of specific subgroups of oesophageal and gastric cancers. Assumptions about the anatomical location of oesophageal tumours based on their histological diagnosis may have led to an incorrect classification of some tumours. However, the sensitivity analysis that defined these groups on morphology alone found similar results suggesting that misclassification was likely to be limited. Another concern was the large proportion of gastric cancers that were "not otherwise specified", which made it difficult to separate cardia and non-cardia tumours. It is likely that the incidence of cardia and non-cardia cancers are therefore underestimated, and this could possibly explain why the incidence of cardia cancers decreased in men, whilst an increase in the incidence had been found in other studies (Powell & McConkey, 1990; Blot *et al*, 1991; Devesa *et al*, 1998; Dolan *et al*, 1999; Kocher *et al*, 2001; Newnham *et al*, 2003; Abrams *et al*, 2011). However, some studies reported a similar or

declining rate of this cancer type (Devesa *et al*, 1998; El-Serag *et al*, 2002; Lagergren & Mattsson, 2011; Dikken *et al*, 2012b) so this decline may also reflect the true situation in England. Without more accurate coding it is not possible to ascertain the true incidence of these subtypes in this country.

Stage of disease at diagnosis is poorly recorded in the English cancer registries, and it was not possible to adjust statistically for tumour stage in these analyses. Tumour stage is strongly associated with the propensity to operate and the strongest predictor of long-term survival. The possible effect of stage on the analysis that investigated the association between hospital volume and mortality and the analysis that considered the factors that affect who received surgery for these cancers is described below.

In terms of the hospital volume analysis in chapter 6, it is plausible that the high volume hospitals are able to undertake a more thorough assessment of the patients and are more likely to ascertain an accurate stage of disease compared with lower volume hospitals that have less comprehensive preoperative assessment procedures. This may mean that high volume hospitals have a better patient selection process than lower volume hospitals which contributes to the improved survival in these settings. Differences in the stage distribution between high and low volume settings are difficult to hypothesise. It may be that high volume hospitals have more patients with advanced tumours referred to them due to their role as specialist centres, but equally more patients with advanced disease could be admitted through an emergency route to low volume settings. Some studies that have included stage of disease found that the better survival in higher volume settings remained after adjustment for stage and other case-mix variables such as age and sex (Begg *et al*, 1998; Birkmeyer *et al*, 2007; Anderson *et al*, 2011). However, Wouters *et al* (2008) found no overall survival benefit in high volume hospitals after exclusion of post-operative deaths due to the unfavourable case mix in high volume settings, including a higher proportion of patients with stage IV disease. One of the studies, which found improved 30-day mortality with higher hospital volume independent

of stage, was carried out in South East England, which covers around one fifth of the population in this country (Anderson *et al*, 2011). Therefore, while it would have been relevant and appropriate to adjust for stage, it is unlikely that stage would have materially changed the results reported in this thesis at least in the short-term perspective. Whether this carries through to the long-term is unclear since no improvement in survival beyond a year after diagnosis was found in this South East England study (Anderson *et al*, 2011). However, the magnitude of the effects found here should be interpreted with caution.

For the analysis that investigates factors that predict characteristics of patients who receive surgery for oesophageal and gastric cancer in Chapter 7, it is possible that some of the variation may be explained by differences in stage of disease between patient characteristics. For example, it may be that older people are diagnosed at a later stage of disease and are therefore unsuitable for surgery. However, whilst some studies have found more advanced disease in older patients (Winslet *et al*, 1996; Kunisaki *et al*, 2006), Biondi *et al* (2012) found a similar stage distribution between patients 70 years or younger compared with those older than 70. Equally, it is plausible that younger patients could be diagnosed at a later stage since cancer is less likely to be suspected which may delay investigation in these age groups. Patients resident in more socioeconomically deprived areas generally have poorer health and can find it harder to access primary care (Mercer & Watt, 2007), which could potentially delay diagnosis and lead to more advanced disease in this group. Differences in stage of disease between these groups may partly explain the variation observed between age and socioeconomic deprivation and these results should be interpreted cautiously.

Lack of information on whether a patient underwent chemotherapy, radiotherapy or chemo-radiotherapy is also an important limitation. It is plausible that these treatments are used more often in higher volume hospitals compared with low volume hospitals. Given pre-operatively or peri-operatively these treatments have been found to improve long-term

survival (MRC, 2002; Cunningham *et al*, 2006; Allum *et al*, 2011), so differences in their use could partly explain the improvement in survival in higher volume settings.

8.3 Interpretation and implications

Oesophageal and gastric cancers are significant public health problems in England, both in terms of numbers of cases and deaths, and the severity of the diseases. The main curative treatment for patients with these cancers is surgery, but this is only possible in local disease (Cromwell *et al*, 2010). However, most patients are diagnosed at an advanced stage of disease (Dikken *et al*, 2012b; National Cancer Institute, 2012a; National Cancer Institute, 2012b), when they are no longer suitable to undergo curative treatment. Therefore, this reinforces the need to understand the aetiology of these tumours for prevention initiatives, particularly focussed on the specific subgroups of these cancers, and to develop earlier diagnosis strategies in order to improve outcomes and quality of life for these patients.

Primary prevention

The poor prognosis of these cancers highlights the need to focus efforts on primary prevention. Specific public health messages should be targeted at groups at the highest risk of these cancers. For example, services aimed at reducing tobacco smoking and encouraging sensible alcohol consumption would help to reduce the incidence of these cancers overall. If the higher incidence of upper and middle oesophageal cancer in Bangladeshi women can be attributed to their use of chewing tobacco products, then additional public health initiatives that warn of the danger of these products could help reduce the incidence in this group specifically. A recent report suggested that many smokeless tobacco products, which are easily available in areas with large Asian populations in England, do not carry the appropriate health warnings even though it is required by law (Longman *et al*, 2010). Therefore, an important public health strategy could be to ensure health warnings are clearly displayed and

appropriate culturally sensitive cessation services are available in areas with large Asian populations (Millward & Karlsen, 2011).

Prevention initiatives targeted at different ethnic groups should take account of generational differences in incidence and prevalence of risk factors. For example, studies of Japanese migrants to the US found first generation migrants had a similar incidence of gastric cancer to their native country, whereas subsequent generations had a risk similar to that of their host country (Haenszel & Kurihara, 1968). Possible explanations suggest a change in diet, from Asian diets that include highly salted food to more Westernised diets, and differences in *Helicobacter pylori* infection which is usually acquired in childhood (Kolonel & Wilkens, 2006). The 2004 Health Survey for England reported that among Bangladeshi women, older generations had a higher prevalence of the use of chewing tobacco (Sproston & Mindell, 2006). Generational differences in the prevalence of risk factors including *Helicobacter pylori* infection, diet, tobacco smoking, alcohol consumption and use of chewing tobacco in different ethnic groups should therefore be considered in such initiatives.

Obesity, specifically abdominal obesity, is associated with an increased risk of oesophageal adenocarcinoma as it is thought to promote GORD, but studies have also shown an increased risk independent of reflux (Lagergren *et al*, 1999a; Lagergren *et al*, 1999b; Lagergren *et al*, 2000; El-Serag *et al*, 2005; Hampel *et al*, 2005; Lindblad *et al*, 2005; Crew & Neugut, 2006; Merry *et al*, 2007; El-Serag, 2008; Wood & Yang, 2008; Lagergren & Lagergren, 2010; O'Doherty *et al*, 2012; Hardikar *et al*, 2013). Therefore, public health initiatives to reduce the prevalence of obesity may help reduce the prevalence of GORD and could lead to a decline in the incidence of oesophageal adenocarcinoma (Lagergren & Lagergren, 2010; O'Doherty *et al*, 2012). A particular focus on White men who have a higher incidence of this cancer could be considered.

It is plausible that the eradication of *Helicobacter pylori* infection would help to lower the incidence of gastric cancer (Fuccio *et al*, 2007; Hung & Wong, 2009; Malfertheiner *et al*, 2012).

As presence of this infection possibly reduces gastric acid reflux, this may increase the prevalence of GORD and therefore oesophageal adenocarcinoma (Rokkas *et al*, 2007; Islami & Kamangar, 2008; Sachs & Scott, 2012). Recent evidence suggests that eradication would not significantly cause or exacerbate GORD, and therefore the benefits of this are believed to outweigh the risks (Hung & Wong, 2009; Malfertheiner *et al*, 2012; Sachs & Scott, 2012). However, because the incidence of gastric cancer and the prevalence of *Helicobacter pylori* infection in Western countries are both relatively low (International Agency for Research on Cancer, 2010b; Malfertheiner *et al*, 2012) and eradication is not straightforward, it would not be cost-effective in this country to identify and eradicate *Helicobacter pylori* infection in the entire population. Currently, it is recommended that high-risk patients, such as those with precancerous gastric lesions and patients, who have first-degree relatives diagnosed with gastric cancer, should undergo eradication treatment (Fuccio *et al*, 2007; Malfertheiner *et al*, 2012).

Particular attention should also be paid to people resident in socioeconomically deprived areas who generally have both poorer health and a higher risk of these cancers than those in more affluent areas. The association between incidence and deprivation may also confound the variation observed between ethnic groups, with a higher proportion of all ethnic groups resident in more deprived areas than their White counterparts (Tinsley & Jacobs, 2006). For example, a higher prevalence of *Helicobacter pylori* infection is associated with increased deprivation (Crew & Neugut, 2006). Black men in the US had a higher prevalence of this infection compared with White men, although this was, in part, linked to differences in socioeconomic factors for example lower income (Taylor & Blaser, 1991; Everhart *et al*, 2000). These factors may contribute to the higher incidence of non-cardia gastric cancer in patients resident in more deprived areas and among Black Caribbean men observed in this thesis. Therefore, resources should be targeted at groups with the highest risks of oesophageal and gastric cancers.

Earlier diagnosis

The majority of oesophageal and gastric cancer patients are diagnosed at an advanced stage (Dikken *et al*, 2012b; National Cancer Institute, 2012a; National Cancer Institute, 2012b), when curative treatment is no longer possible. Efforts need to be focussed on earlier diagnosis of these patients. Between 2006 and 2008, a high proportion of patients diagnosed with these cancers came through an emergency or two week wait route (where alarm symptoms are required before referral), (Elliss-Brookes *et al*, 2012). Decreasing the proportion of patients diagnosed through these routes and increasing the proportion diagnosed through a routine GP referral route would seem important but the symptoms of these tumours are unspecific and often only become evident when the tumour is advanced (Lagergren & Lagergren, 2010). Therefore, significant challenges exist for earlier diagnosis of these tumours. While specific warning symptoms for the general population will be difficult to identify, raising awareness and knowledge of alarm symptoms could help patients not to postpone seeking medical help.

The current National Institute for Health and Clinical Excellence (NICE) guidelines for referral and investigation of upper gastrointestinal cancer symptoms (National Institute for Health and Clinical Excellence, 2005), do not specify the increased risk of lower oesophageal and gastric cardia cancer in men that has been found in this thesis and in previous studies (Blot *et al*, 1991; Kocher *et al*, 2001; El-Serag *et al*, 2002; Newnham *et al*, 2003; Dikken *et al*, 2012b; Edgren *et al*, 2013). Raising awareness in primary care of the differences in incidence between men and women should therefore be considered, and the implementation of a lower threshold for referral of men or a higher threshold for women investigated.

A national programme of earlier investigation of non-specific upper gastrointestinal symptoms should also be considered, although this is likely to be difficult. For example, many people will experience GORD symptoms, but not go on to develop cancer and some people with oesophageal adenocarcinoma do not report a history of GORD or have very few GORD symptoms (Lagergren *et al*, 1999a; van Soest *et al*, 2008). Therefore it would not be

cost-effective to refer everyone with GORD for further investigation and such surveillance would not include everyone at risk of this cancer. However, the presence of GORD has been associated with an increased risk of Barrett's oesophagus (Wood & Yang, 2008). The cytosponge, a new oesophageal sampling device, has shown promise as a relatively inexpensive and easily administered test that could be used in the future for screening for Barrett's oesophagus in a primary care setting, but further evaluation is required (Lao-Sirieix *et al*, 2009; Kadri *et al*, 2010). Once diagnosed, endoscopic surveillance for some patients with Barrett's oesophagus does exist in the majority of gastrointestinal units in the UK, even though the efficacy of such surveillance is unproven (Loft *et al*, 2005). It identifies cancers at an earlier curative stage, but the cost-effectiveness of this strategy remains questionable since new studies estimate a much lower relative risk of cancer in these patients than previously reported (Murray *et al*, 2003b; de Jonge *et al*, 2010; Bhat *et al*, 2011; Hvid-Jensen *et al*, 2011). Due to the non-specific symptoms of these cancers a definite high-risk group will be hard to identify, but necessary if a national programme is to be established. Critically, it would be important to ensure diagnostic departments are not over-burdened with too many patients.

Screening aims to identify precancerous changes in cells or asymptomatic early stage tumours. However, oesophageal and gastric cancers are hard to diagnose and population-based screening is not likely to be cost-effective for these cancers. For this to be possible a high-risk group would need to be identified. For example, the analysis in this thesis, like other studies (Blot *et al*, 1991; Kocher *et al*, 2001; El-Serag *et al*, 2002; Newnham *et al*, 2003; Dikken *et al*, 2012b; Edgren *et al*, 2013), found men had a higher risk of oesophageal adenocarcinoma and gastric cardia cancer than women. Aetiological studies have linked chronic GORD and obesity, specifically 'male pattern' abdominal obesity, with an increased risk of these cancer types (Lagergren *et al*, 1999b; El-Serag *et al*, 2005; Lindblad *et al*, 2005; El-Serag, 2008; O'Doherty *et al*, 2012). Therefore, one high-risk group might be older obese men with chronic and severe GORD, but the effectiveness of screening this group would need to be assessed. The relatively low incidence of oesophageal adenocarcinoma and gastric cardia cancer and the

high prevalence of GORD means it is likely that a much more specific group would need to be defined for screening to be feasible (Lagergren *et al*, 2000; Lagergren & Lagergren, 2010). Therefore, before screening can be considered this specific high-risk group must be identified and further studies on incidence and aetiology may play a role in this. Randomised controlled trials with long-term follow-up might then determine the efficacy of screening for these cancers.

Treatment

Work in this thesis clearly demonstrated lower mortality for patients that undergo surgery in high volume hospitals, both in the short- and long-term. This is the first time, since the implementation of the Improving Outcomes Guidance in 2001, that the effect of hospital volume on survival across the whole country has been assessed. This work demonstrated that the implementation of the recommendation to centralise upper gastrointestinal cancer surgical services has benefitted patients who had surgery for oesophageal and gastric cancer. This process may also have benefitted non-surgical patients through improvement in the care pathways. The full implementation of the policy is not yet complete with some areas yet to centralise their services (Palser *et al*, 2009). However, this work proves that this process was worthwhile, and supports the completion of centralisation of these services in England.

It is difficult to ascertain a universal hospital volume threshold over which mortality is definitely lower. The range of the number of operations carried out in a hospital in each year varied between studies, with the annual volume being defined in some studies as high and in others as low (Wouters *et al*, 2008; Gruen *et al*, 2009; Lauder *et al*, 2010; Dikken *et al*, 2012a). Although this study was not specifically designed to establish the optimum number of resections carried out in each hospital, taken at face value, these data suggest if the 70% of patients undergoing surgery in the lower volume hospitals were operated on in hospitals that operate on 60 or more patients a year, it would represent a relative mortality reduction of up

to 20%. If this was a medical treatment without major side effects, it would almost certainly become standard care.

The only outcome this thesis investigated in relation to hospital volume was differences in survival, and other outcomes, such as quality of life or disease recurrence could not be considered. These outcomes are also important and improvements in them could add weight to the arguments supporting higher volume hospitals. However, a review found two studies that investigated health-related quality of life after oesophagectomy and reported no significant improvement after operations in high compared with low volume hospitals (Rouvelas & Lagergren, 2010). A possible problem with centralisation is the increased distance that some patients would need to travel to attend specialist centres, which may be difficult for older and poorer patients, and patients in remote rural areas (Department of Health, 2003; Mungall, 2005). Despite these potential issues, policies that recommend centralisation have been developed and a process of centralisation is currently underway (Department of Health, 2001; Palser *et al*, 2009). It will still be important to ensure that this centralisation does not lead to inequity in who receives curative treatment for oesophageal and gastric cancers in the most beneficial environment.

Specialist multidisciplinary teams were recommended in the National Health Service Cancer Plan published in 2000 (Department of Health, 2000). Such teams discuss each patient and recommend an appropriate course of treatment. This thesis demonstrated variation in who received surgery for oesophageal and gastric cancer, with older and more deprived patients being less likely to have surgery. However, key data items including stage of disease, performance status, and willingness to undergo surgery were not available, and consequently it was not possible to determine if surgery was available to all who would benefit from it. If the variation persists between these groups after these additional factors are taken into account, multidisciplinary teams and clinicians should aim to reduce any inequity and ensure surgery is available to all patients who will benefit.

The number of cancers diagnosed is predicted to increase in England, mainly due to the ageing population with future cancer patients likely to be, on average, older than cancer patients today (Møller *et al*, 2007; Maddams *et al*, 2012). It will be essential that upper gastrointestinal cancer services adapt to meet the needs of the older population to ensure high quality care is available to all. Outdated perceptions about how demanding operations are for older patients should be reviewed, and extra training to ensure the needs of older patients are met should be provided (Whitaker *et al*, 2012).

The lower mortality among all patients, but higher mortality among resected patients with increasing resection rates was also found in a study on lung cancer patients in England (Riaz *et al*, 2012b). Resection rates in a particular area may be driven by patient characteristics such as stage of disease, co-morbidity, performance status or willingness to undergo surgery, or by supply factors such as the availability of specialist oesophageal and gastric surgeons, or differences in the decision process in multidisciplinary teams of who to operate on. Adjustment for case-mix including co-morbidity in this work did not materially change the main results. This suggests that the demand for services was probably not lower in areas where a smaller proportion of people underwent surgery. If findings in how surgical services are supplied explain these differences then policies to ensure services are delivered equitably will be important. Since, the exact mechanisms driving this pattern cannot be determined in this thesis it is important that these mechanisms are understood so that evidence-based decisions about offering surgical resection to more patients can be made. To understand these differences more detailed prospective clinical data should be collected to study this further.

The proportion of patients that had surgery in England was found to be lower than rates in Denmark (Dikken *et al*, 2013) and the Netherlands (Faiz *et al*, 2012; Dikken *et al*, 2013). However, it is not possible to conclude which country has the most reasonable resection

rate (Dikken *et al*, 2013). Variation could be explained by differences in case-mix or clinical policy, but further investigations would be needed to determine reasons for these differences.

Data quality

It is important that information on both the anatomical subsite and histological diagnosis of these cancers are identified, recorded in clinical practice, and passed to the cancer registries. This needs to improve to enable differences in incidence and treatment between the more specific subgroups of oesophageal and gastric cancers to be monitored in future analysis. This is particularly important because of the very different aetiological and incidence patterns found in these subgroups, which would be obscured if these tumours were only investigated as a whole.

Improvements in the completeness of stage of disease at diagnosis will be essential. Other data items including performance status, willingness to undergo surgery, and information on risk factors would also be useful in the interpretation of the results of this thesis.

8.4 Future studies

There are several questions that remain unanswered. For example, why does the United Kingdom have the highest incidence rates of oesophageal adenocarcinoma compared with other European countries? Why is survival in this country lower than in comparable European countries? Why is the proportion of patients who have surgery lower here than in other European countries? Joint studies with European colleagues are needed to investigate these questions further. Even then differences in data collection will make such studies difficult. Dikken *et al* (2013) recently recommended the development of a European-wide upper gastrointestinal cancer audit, with common data definitions, to help understand differences in outcomes and resection rates. Within England, future analyses should confirm whether there is inequity in who receives surgery for oesophageal and gastric cancers, whether the way in

which the patient is diagnosed is likely to affect their chance of surgery, and how non-mortality related outcomes compare with hospital volume.

8.5 Summary

This thesis investigated the occurrence of oesophageal and gastric cancer and the treatment of patients across the whole of England. In particular it reports for the first time the variation in incidence between the more specific ethnic groups for the distinct subgroups of these cancers in this country. It is also the first study to assess the effect of hospital volume on survival across the whole of England since the introduction of the Improving Outcomes Guidance in 2001.

The patterns in incidence found in this thesis largely confirm the reported patterns in other developed countries including the US, Australia, and in Europe (Chapter 4 and Chapter 5). A new result was the higher incidence of upper and middle oesophageal cancer in Bangladeshi women, which has not previously been reported.

Of particular importance is the finding that lower mortality was associated with an increase in hospital volume, both in the short- and long-term. Whilst it is generally accepted that higher hospital volumes are associated with lower short-term mortality, fewer studies have investigated the impact of volume on long-term survival and these have shown conflicting results (Chapter 6).

This work also demonstrated that older patients and patients resident in more socioeconomically deprived areas were less likely to have surgery for oesophageal and gastric cancer (Chapter 7). However, this dataset lacked several important data items, for example, stage of disease which would have helped in the interpretation of these results.

Despite recent improvements in survival, the overall prognosis for these cancers is still poor with the majority of patients being diagnosed at an advanced stage when curative treatment is

no longer possible (section 1.6). Although this highlights the need for earlier diagnosis initiatives the non-specific nature of the symptoms of these tumours, which often become evident only when the tumour is advanced makes early diagnosis difficult. Focussed efforts on primary prevention initiatives which include modifying the known risk factors of tobacco smoking, alcohol consumption, chewing tobacco, and obesity may be more effective at present in reducing the disease burden in the population.

Future research should investigate the variation discovered in who receives surgery with more detailed datasets to determine whether there is equity in its availability. Most importantly, the work in this thesis has demonstrated that the centralisation of upper gastrointestinal surgical services has benefitted surgical oesophageal and gastric cancer patients, and supports the continued centralisation of these services in England.

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Appendix 1 Publications resulting from PhD work

Coupland VH, Allum W, Blazeby J, Mendell M, Hardwick RH, Linklater KM, Møller H, Davies EA (2012) Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. *BMC Cancer* 12:11
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Appendix 2 Other outputs resulting from PhD work

Coupland VH, Linklater KM, Davies EA
Incidence and survival (1998-2006)
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, March 2010

Coupland VH, Linklater KM, Davies EA
Incidence and survival
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, May 2010

Coupland VH, Linklater KM, Davies EA
On-going upper gastrointestinal cancer analysis
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, October 2010

Coupland VH, Linklater KM, Davies EA
Cancer registry analysis (1998-2006)
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Tumour Site Specific Group Clinical Leads Workshop, London, November 2010

Coupland VH, Konfortion J, Linklater KM, Jack RH, Lagergren J, Davies EA, Møller H
On-going upper gastrointestinal cancer analysis
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, May 2011

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On-going upper gastrointestinal cancer analysis
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, October 2011

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
On-going and planned analysis of upper gastrointestinal cancer data
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Tumour Site Specific Group Clinical Leads Workshop, London, October 2011

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
Overview of progress in 2011/2012
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, February 2012

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
Presentation of on-going analysis and key messages
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, October 2012

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
Current and on-going data analyses
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Tumour Site Specific Group Clinical Leads Workshop, London, December 2012

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
Scene setting: Network approaches to the recording of diagnosis, its verification, and approaches to staging in Hepato-biliary and Pancreatic Cancer
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Tumour Site Specific Group Clinical Leads Workshop, London, December 2012

Coupland VH, Konfortion J, Jack RH, Linklater KM, Lagergren J, Davies EA, Møller H
Review of 2012/2013 and on-going analysis
National Cancer Intelligence Network (NCIN) Upper Gastrointestinal Cancer Site Specific Clinical Reference Group (UGI SSCRG) meeting, London, March 2013

Poster presentations to conferences

Coupland VH, Allum W, Novelli M, Linklater KM, Møller H, Davies EA
The epidemiology and survival of oesophago-gastric cancers in England, 1998-2006
Poster presented at National Cancer Intelligence Network / United Kingdom Association of Cancer Registries conference, Birmingham (Jun 2010) and National Cancer Research Institute conference, Liverpool (Nov 2010)

Coupland VH, Linklater KM, Allum W, Møller H, Davies EA
Data quality and completeness of the upper gastrointestinal National Cancer Repository Dataset, 1998-2007.
Poster for National Cancer Intelligence Network / United Kingdom Association of Cancer Registries conference 2011

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Does the incidence of oesophageal cancer vary between ethnic groups in England?
Poster for National Cancer Intelligence Network / United Kingdom Association of Cancer Registries conference 2011 & National Cancer Research Institute conference 2011 & International Association of Cancer Registries conference 2011

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Poster for National Cancer Intelligence Network / United Kingdom Association of Cancer Registries conference 2012 & National Cancer Research Institute conference 2012 & International Association of Cancer Registries conference 2012

Appendix 3 Other publications

Coupland VH, Okello C, Davies EA, Bray F, Møller H (2010) The future burden of cancer in London compared with England. *Journal of Public Health* **32**(1): 83-89

Coupland VH, Lee W, Madden P, Sykes N, Heal R, Møller H, Davies EA (2010) Is it possible to determine use of hospice palliative care services by matching hospice and cancer registry data? *Palliative Medicine* **24**(8): 807-811

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