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Development of metrics of the care process for colorectal cancer in England and application to bowel cancer screening: Retrospective analysis of large datasets

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

By

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February 2016

In memory of Alan George Thurlwell

1954-2015

Proud husband, father and grandfather

A man of the country, but most at home with his family

Dedication

Above all, this thesis is dedicated to my wife Zoe and my baby daughter Libby.

I also owe a huge debt of gratitude to my sister Annie and to my Dad for their endless help, kindness and patience.

Acknowledgements

I would like to express profound thanks to my supervisors. Dr Keith Bodger has been a fine teacher and true gentleman; his grasp of both fine detail and the overall sweep of the project has been self-evidently crucial. Dr Sanchoy Sarkar is a passionate believer in the power of research to inform and better our care for patients. I am proud to have had you as supervisors and value your friendship and support over the last five years. I also wish to extend my thanks to Dr Mustafa Shawihdi who has been a gentle and consistent guide. To Elizabeth Devenport for the help she gave especially in the early days when everything was new and confusing. I also wish to thank the Professor Michael Pearson, who was instrumental along with Dr Bodger in developing this project.

I am also indebted to Professor Colin Rees and the team from University of Surrey, including Professor Stephen Halloran, Helen Seamen, Julia Snowball and Piers Butler. I also acknowledge the generous support provided by Cook Medical, without which none of the work would have been possible.

Abstract

Introduction: In England the 5-year survival for colorectal cancer (CRC) is 50%, significantly lower than in other countries of comparable wealth, largely due to patients presenting late with the disease. Late presentation is strongly correlated with emergency presentation to hospital.

The NHS Bowel Cancer Screening Programme (BCSP) has been the most significant nationwide intervention attempting to improve CRC outcomes. This programme began in 2006 and was active throughout the country by 2010. Screening programmes are notoriously difficult to evaluate and so far there is limited robust evidence of its effectiveness.

Administrative data from hospitals can be used to study diseases, including cancers. Through careful interrogation of the data, it may be possible to identify factors associated with improved CRC outcomes, including the impact of introducing the BCSP.

Aims: To develop a new methodology for identifying a national cohort of incident CRC cases, by applying clinical knowledge to the analysis of administrative data for English hospitals (Hospital Episode Statistics, HES).

To use this new methodology to identify which admission signifies a patient's first presentation to hospital care with CRC and identify which patients present as an emergency (**Chapter 2**).

To establish whether emergency presentation is a valid outcome measure for patients with CRC (**Chapter 3**).

To test whether the benefits of launching a BCSP extend beyond the minority of individuals targeted by the screening program, specifically, if there are early, indirect benefits for the population as a whole resulting from enhanced awareness regarding CRC (**Chapter 4**).

To ensure that the findings in Chapter 4 are robust and not accounted for by confounding (**Chapter 5**).

To determine whether the algorithm that dictates which Faecal Occult Blood test (gFOBt) results are referred for colonoscopy can be improved, to more effectively use the limited colonoscopy resources (**Chapter 6**).

Design and method: All hospital admissions relating to incident cases of CRC in England from 2006-2008 were extracted from HES data to form my main cohort. Traditionally HES-based studies mark a patient's presentation from the first admission containing a coding of CRC (CRC1). In my thesis, all codes indicative of CRC presentation to secondary care were identified and any admission occurring prior to CRC1, flagged as the presenting admission, and termed "first relevant admission" (REL1). The primary outcome measure was emergency presentation with CRC, while secondary outcomes were major surgical resection and mortality at one-year (**Chapter 2**). Data was analysed to assess the factors associated with, and outcomes related to, an emergency presentation (**Chapter 3**).

I then matched each patient to the date when their local Primary Care Trust (PCT) began referring to the BCSP to ascertain which patients were living in an area with an active BCSP at the time of their presentation ("exposed" group) and the length of exposure. To exclude confounding based on overall healthcare quality in an area, outcomes for a distinct cancer (Oesophageal and Gastric (OG)) presenting during the same period, were compared, based on their screening exposure (**Chapter 4**).

To further exclude confounding, the effect of living in an area with active screening, yet restricted to those PCTs that began screening during the same time period (the middle year) was analysed (**Chapter 5**). The Bowel Cancer Screening System database was studied to identify individuals with two consecutive episodes of screening between April 2009 and March 2011. Each test kit was coded depending on the specific FOBt result for each round. The overall percentage of positive results was termed the Spot Positivity percentage (SP%). The results at Episode 1 were analysed for individuals with cancer diagnosed at Episode 2. This could identify a combination of FOBt results that would benefit from earlier colonoscopy (**Chapter 6**).

Results: Chapter 2 identifies 32,299 incident cases of CRC. Older patients and females were more likely to be diagnosed with proximal cancer and deprived patients had lower rates of surgical resection and survival. The overall rates of patient characteristics were similar to matched populations that used a different methodology. However the emergency presentation rate was higher in my cohort (36.1% vs. 32.0%, $p<0.001$) and the surgical resection and one-year survival rates were lower. Lower gastrointestinal endoscopy is the gold standard when establishing the CRC diagnosis. My new methodological approach of REL1, rather than the CRC1, increased the proportion of patients identified with an endoscopy at presentation (52.5% vs. 36.8%, $p<0.001$) suggesting a more accurate start of a patient's journey was identified.

Chapter 3 shows that patients presenting as an emergency were significantly less likely to have surgical resection, (35.4% vs. 59.1%, $p<0.001$). Furthermore, the Odds Ratio for mortality at one year following emergency presentation was 4.11 ($p<0.001$). This was the single strongest predictor of adverse outcomes. Within the first 30 days of presentation, the mortality rate was almost four times higher in emergency patients (6.5% vs.1.7%, $P<0.001$).

In **Chapter 4** patients "exposed" to local screening had significantly lower crude emergency presentation rates than the "non-exposed" group (34.9% [2,492/7,142] vs. 37.0% [7,599/20,520], $p=0.002$). Using exposure as a continuous variable, there was a 2% reduction in emergency presentations for every month "exposed" to local screening (OR =0.98 [CI: 0.97-0.99], $p<0.001$). By studying the non-screening age population, indirect effect of screening could be tested. Those with greater than 6 months screening exposure had an Odds Ratio (OR) of 0.85 (CI: 0.77-0.94, $p<0.001$) for emergency presentation compared to those non-exposed.

During the same period, 9,319 patients presented with OG cancer. These patients showed no significant difference in emergency presentation rates between patients "non-exposed" (28.0%), and those "exposed" for less than six months (29.7%) or longer (28.0%).

Chapter 5 analyses 48 PCTs that began screening in the middle year and demonstrated the same association with screening exposure as chapter 4. There were more daycase colonoscopies in the six months after screening was introduced (30,347 vs. 31,805). The 4.8% increase in activity, implies either extra capacity and/or extra referrals followed the introduction of screening. Analysis of PCTs that began screening in the first 6 months of the year, showed that prolonged exposure to screening (6-12 months) was associated with a significantly lower emergency presentation rate (34.1 vs. 38.9%, $p<0.001$).

Chapter 6 examines the data of 284,261 subjects that completed gFOBTs, of which 3,891 (1.4%) had a colonoscopy at Episode 2. As the SP% increased from 11 to 100%, so the CRC detection rate increased from 4 to 25%. At the lower SP%s, from 11% to 25%, the CRC risk was relatively static at 4%. Above an SP% of 25%, every 10-percentage points increase in the SP%, was associated with an increase in cancer detection of 2.5%.

Conclusion

Clinical knowledge may be applied to routine administrative data (HES) to more accurately identify incident cases of CRC. Using this clinical knowledge creates a better understanding than the traditional methods of when the presenting admission occurred. In particular, patients often present before CRC is recorded in the administrative data, evidenced by the higher rate of endoscopy coded at presentation, using the new methodology. Chapter 2 also demonstrated that more patients than previously thought had presented as an emergency.

There is strong evidence to suggest emergency presentation is a valid independent outcomes measure; one strongly associated with reduced access to surgical resection and an increased one-year mortality. Specifically, it is associated with an excess of early deaths after presentation, suggesting an association with the late presentation of cancer.

Areas with active screening were significantly associated with a reduced risk of emergency presentation. This reduction extended outside the screening age group, implying an indirect benefit to the population. The reduction became apparent within 6-12 months of the start-up of screening. Longer exposure was incrementally associated with improved CRC outcomes. The outcomes for OG cancer were unaffected by screening exposure, implying the effect was not due to broader differences between local services.

There was no obvious confounding factor to the findings in chapter 4 and increasing colonoscopy activity in the immediate six months after screening began, was likely to relate to increased CRC awareness.

The BCSP data demonstrated a strong correlation between SP% and cancer detection. Some subjects with an SP% of 11% proceed to colonoscopy, whereas others with an SP% of 22% do not. This suggests that the programme could be adjusted to increase the detection of CRCs without substantially increasing the colonoscopy workload.

Overall conclusion

My thesis describes how routine administrative data, augmented with clinical knowledge may be used to study CRC. Specifically, it describes how the introduction of the BCSP was associated with an early and population-wide reduction in the risk of emergency presentation. This demonstration of indirect benefits for symptomatic cases of CRC is likely to reflect enhanced public and/or professional awareness of CRC, leading to more timely clinical presentation and investigation in the symptomatic population.

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Definitions and Abbreviations

CRC1	The patient's first (earliest) hospital admission when a diagnostic code for CRC was recorded.
REL1	The patient's first (earliest) 'relevant' admission. This corresponds to the first admission with a diagnostic or procedural code consistent with a clinical presentation of CRC and occurring within six months of the first admission containing a cancer code (CRC1).
Index admission	The admission corresponding to the first clinical presentation with CRC. This is either **REL1** (where a clinically relevant admission occurred before the first coding of cancer) or CRC1 (if no such earlier admission was recorded).
Primary diagnosis (DIAG01)	The position one (or first) diagnostic code.
DIAG02-DIAG14	Position of the secondary diagnosis codes or associated co-morbidity in HES
Primary procedure (OPERTN01)	The position one (or first) procedure code.
OPERTN02-OPERTN14	Position of the secondary procedure code in HES
FCE	Episode of care or Finished Consultant Episode.
HESID	The identifier that is unique to each patient and their HES record.
ICD	International Statistical Classification of Diseases.
OPCS	Office of Population, Censuses and Surveys Classification of Interventions
IMD score	Index of Multiple Deprivation score. A score of deprivation, that ranks small geographical areas according to their relative deprivation.
PbR	Payment by Results. A national tariff of fixed prices for hospital procedures
FOBt	Faecal Occult Blood test
Patient delay	The time between noticing a symptom and consulting a GP.
Primary care delay	The time between a patient's first GP consultation and referral.

Secondary care delay	The time between referral and cancer diagnosis.
Short stay emergency admissions	Patients whose initial emergency admission length of stay was <1 day.
NBOCAP	National Bowel Cancer Audit
ONS	Office of National statistics
PCT	Primary Care Trust.
SHA	Strategic Health Authorities
LSUD	Local Start Up Date (LSUD) of screening. The date in which a patient's PCT began referring to the BCSP.
OG cancer	Oesophageal and Gastric cancer

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Chapter 1 - Introduction and general overview

1.1. Introduction

Colorectal cancer (CRC) is the second most common cause of cancer in the United Kingdom, accounting for 33,000 new cases and 16,000 deaths every year(1,2). Incidence increases with age(2) and the lifetime risk is 6.1% for men and 5.0% for women(3). If CRC is diagnosed at an early stage then the five year survival rate is over 90%, compared with less than 10% if it has spread(4,5). Furthermore, the disease is entirely preventable if the precursor adenomatous polyps are removed. Reducing the morbidity and mortality associated with the condition is a major health priority for the nation(6).

Knowledge about the genetics and pathophysiology of CRC has improved over the last few decades, as have diagnostic tests and treatments(7). Despite this, many patients continue to present with advanced disease. In such cases not only is survival drastically reduced, but these patients require significantly greater amounts of treatment and incur much greater costs to manage the condition(8). For these reasons patients with early cancer or those at risk of cancer must be identified rapidly and managed expectantly. This will require improvements at all levels of healthcare: from the patients and family recognising and acting on symptoms; to primary and secondary care referring and managing patients quickly. To do this there must be greater emphasis on educating the general public about the symptoms of CRC. There need to be rapid referral pathways from primary to secondary care. There must be adequate endoscopy services to offer rapid and accurate examination of the colorectum. Once diagnosed, patients need to be assessed by cancer networks teams and have surgery and/or chemotherapy and radiotherapy offered promptly. Finally, at a national level there should be a programme for quality improvement initiatives to identify variability in practice and implement strategies to eliminate bad variation.

Currently the UK has worse outcomes for CRC than countries of comparable wealth(9). The main reason for this is not the standard of treatment provided once diagnosed, but the late presentation of patients. Therefore any serious attempt to improve the quality of CRC care in the UK needs to address this problem. An example of a national intervention to reduce late presentation and improve outcomes was the introduction of the two week wait (2WW) rule; which aims to reduce delays in the diagnosis of symptomatic patients by speeding the referral from primary to secondary care. However no evidence has yet shown that interventions to reduce these delays improve outcomes(10). The second major national intervention was the NHS Bowel Cancer Screening Programme (BCSP), which sought to identify cancer in asymptomatic patients. Diagnosing these asymptomatic patients is likely to be beneficial, with studies showing that patients enrolling in a screening programme, had a 25% reduction in their CRC mortality(11). However there was no reduction in overall mortality and this group of asymptomatic patients only represent 3% of all CRC patients. Hence any intervention looking to see a larger change in outcomes would also need to focus on the 97% of cases still presenting to the symptomatic service.

My central thesis was that the major intervention of the BCSP was not with the 3% of asymptomatic cancers diagnosed but with the 97% of symptomatic patients. I propose that the mechanism of action was through an indirect effect on these patients by increasing awareness of CRC among patients and health professionals. I hope to describe the impact of its introduction, to identify which patient groups, if any, improve most and identify the mechanisms by which these improvements occur. I also want to study whether within the BCSP itself, the algorithms for referral to colonoscopy can be adjusted to maximise the programmes efficiency in terms of CRC diagnosis.

The most common routinely collected healthcare data are the Hospital Episode Statistics (HES). This provides the primary dataset I have used in chapters 2-5 investigating variation in national CRC care. In chapter 6 I have used separate data from the Bowel Cancer Screening System database.

This chapter reviews the pathology, epidemiology, clinical presentation, diagnosis, staging and treatment of CRC. It then describes how patients with CRC are managed within the NHS in England and why, compared to other countries of comparable wealth, prognosis is worse. I then describe some of the strategies attempted so far to improve the situation, with particular focus on the NHS BCSP. Finally, this chapter explores using routinely collected NHS data to describe CRC care pathways, identify important outcomes measures and interrogate why variations in outcomes exist.

Reasons why some patients have poor outcomes is vital. Some reasons may be based on individual characteristics, such as a patient's age or level of deprivation. Others factors could relate to the local healthcare system managing the patient, examples of variation include; the local referral practices for patients with gastrointestinal symptoms and the quality of the treating hospital. Outcomes may also be affected by national interventions, such as the BCSP. Ultimately understanding these factors will allow recommendations to be made to the way CRC healthcare is delivered. This will in turn lead to a reduction in unwanted variation and poor outcomes.

Overview of the colorectum

1.1.1. Anatomy of the colon and rectum

The large intestine (colon) is approximately 6 cm wide and 1.5 m long, beginning at the ileocaecal valve (ICV) in the right iliac fossa and finishing at the junction with the anal canal. The large intestine is comprised of the caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum.

The ICV is typically on the last fold before the caecum is reached and traditionally termed a physiological, but not anatomical, sphincter. However, recent cadaveric studies have shown local thickening at the ileal papilla base, indicative of an intrinsic anatomical sphincter(12). Approximately 2 L of fluid (chyme) enter the large bowel discontinuously every day and the ICV has a crucial role in reducing the flow of colonic contents back into the small bowel. When the terminal ileum distends the ICV will relax from a resting tone of 20 mmHg and allow contents to enter the large bowel. The ICV is

also opened by the gastro-ileal reflex, which causes relaxation after meals when gut motility and gastrin levels are high and closure when colonic distension occurs. This allows time for the colon to achieve its absorptive functions and also prevents colonic bacteria entering the normally aseptic small bowel. At the ICV the cellular architecture switches from villous mucosa to colonic columnar.

The pouch-like caecum, transverse colon and sigmoid are all intraperitoneal structures and attached to a mesentery, which makes them mobile. By contrast the ascending colon, descending colon and rectum are retroperitoneal and more fixed. The distal 12 cm of the rectum lies below the peritoneal reflection. The anal canal is 2.5-4 cm long running from the ano-rectal junction to the anus and is not part of the colorectum. The anus consists of an internal and external sphincter. The colonic inner circular muscle thickens to form the internal anal sphincter, under involuntary control, and is held in continuous contraction. The external anal sphincter is formed of striated muscle and is under voluntary control.

1.1.2. Histology

The innermost layer of the colorectum is the mucosa. It is lined with simple columnar epithelium and appears smooth as there are no villi present. Instead, the mucosa is shaped into many straight tubular glands (crypts of Lieberkuhn), *Figure 1.1*. Throughout the mucosa there are abundant absorptive enterocytes that actively transport sodium (and with it water) and goblet cells that secrete mucus. The epithelium of the crypts also contains stem cells, which replace the epithelium every few days, along with enteric endocrine cells.

The lamina propria separates the crypts and contains loose connective tissue, along with numerous lymphoid cells. The muscularis mucosa lies deep to the bottom of the crypts and is composed of a thin layer of circular and longitudinal muscle. The submucosa is a relatively unspecialised thin layer of connective tissue.

Between the muscularis mucosa and submucosa are numerous organized lymphoid nodules, Peyer's patches. These are found throughout the colon and have a role in immune surveillance of the intestinal lumen and in facilitating the generation of the immune response against pathogenic microorganisms.

Beneath the submucosa lies the important muscularis propria. This is composed of an inner circular and outer longitudinal muscle layer, with the Auerbach plexus (a part of the enteric nervous system, providing motor innervation to both layers) scattered between. The longitudinal layer lies just beneath the serosa, but doesn't cover the entire bowel wall; instead it runs as three bands (teniae coli). Between the teniae coli bands, the wall bulges out to produce the three haustral folds. The three muscle bands converge at the appendix and at the rectosigmoid junction, where they merge to form a singular longitudinal muscle layer. When the teniae coli contract lengthwise, then the colon folds in on itself to produce the distinctive semilunar folds. Finally, the outer layer of the colorectum is the serosa, which is attached to mesentery.

Arterial supply of the colon is from branches of the superior and inferior mesenteric arteries. The

superior mesenteric artery supplies the colon up to the splenic flexure, from where the inferior mesenteric artery takes over. Venous drainage mirrors the arterial supply, with the superior mesenteric vein joining the splenic vein to form the portal vein. The inferior mesenteric vein also joins the splenic vein.

Lymphatic drainage of the colorectum follows the vascular supply. The colon and proximal two-thirds of the rectum drain via the paraaortic lymph nodes. The distal third of the rectum and anus has lymphatic drainage to the paraaortic nodes as well as the inguinal and internal iliac lymph nodes. Small lymph nodes run alongside the mesenteric vessels, with larger groups present at the root of the superior and inferior mesenteric arteries. Lymph fluid then passes to the cisterna chyli, which ultimately leads to the thoracic duct.

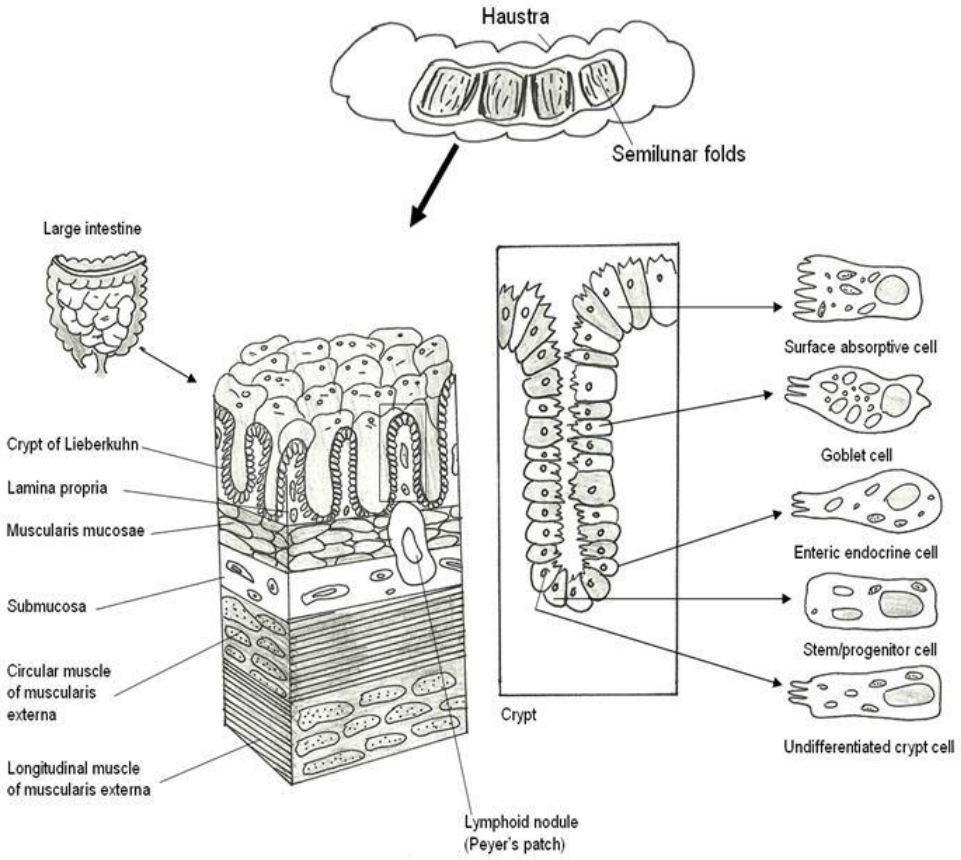


Figure 1.1 The anatomy and histology of the colorectum. Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 41-3, page 885.

1.1.3. Physiology

The primary role of the colon is to process the undigested chyme into more solid and bulky faeces before it enters the rectum ready for infrequent excretion. This is achieved by absorbing most of the water across the mucosa. Following the active absorption of sodium by enterocytes, water follows by obligatory osmosis, while potassium is secreted into the lumen. This predominantly occurs in the ascending and transverse colon. At the same time, viscous mucus is secreted to help the passage of stool. Meanwhile the descending colon, sigmoid and rectum are predominately used for storage.

Transit within the large bowel is relatively slow, taking several days instead of the several hours taken in the small bowel. Movement within the colon is achieved through three mechanisms; segmentation, peristalsis and mass movement. Segmentation traps colonic contents between contracted haustra and churns the contents to facilitate sodium and water absorption. Peristalsis causes waves of slow and regular contractions, transporting stool to the descending colon for storage. Mass movement occurs in the descending colon and sigmoid, where strong peristaltic waves force a large mass of stool into the rectum. These contractions occur several times a day, normally after meals. Distention of the rectum activates defecation via the defecation reflex, which causes the simultaneous contraction of the sigmoid and rectum and relaxation of the anal sphincters. In adults the defecation reflex can be inhibited voluntarily.

Colonic motility and the defecation reflex are controlled by the myenteric (Auerbach) plexus, which is part of the enteric nervous system, and extrinsic parasympathetic innervation. The upper large intestine is controlled by the vagus nerve and lower colon, rectum and anus by sacral nerves. Segmentation and peristalsis are predominantly controlled by the myenteric plexus (but also affected by parasympathetic drive), while mass movements, although initiated by the myenteric plexus, receive input from the central and parasympathetic nervous systems to regulate rate and intensity.

1.1.4. Gut flora

Gut flora are the microorganisms (microbiota) that live in the intestinal tract. There are an estimated 10 trillion organisms in the large bowel, 10 times the number of human cells(13,14). Within the large bowel most of the flora is bacterial, with up to 1,000 different species present and bacteria and their products accounting for 60% of the dry weight of faeces. It is clear that flora is not merely commensal but actively involved in a diverse range of processes including: adapting the immune system and excluding pathogenic bacteria; creating vitamins and hormones and fermenting energy substrates. Furthermore, the intestinal microbiota is intrinsically linked with overall health and the in particular with the risk of developing CRC(15). There is still much to learn about the host microbiota interaction, including how CRC risk can potentially be modified by alterations in dietary components and eating behaviors(16).

1.2. Colorectal cancer

Colorectal cancer refers to a cancer originating in the large intestine, including the colon and rectum, but excluding those derived from the anus. Cancers of the colon and rectum are considered a single disease, with the rectum defined as the 15 cm closest to the anal margin. Importantly CRCs do not include adenomas, where the basement membrane and muscularis mucosae are intact. However, most cancers develop at the mucosa from adenomas, through the acquisition of genetic changes. Beneath the mucosa lie the submucosa, muscularis propria and the serosa. The submucosa contains blood and lymphatic vessels and so once breached by a cancer can lead to distant spread.

1.2.1. Pathological sub-types of colorectal cancer

Table 1.1 shows the classification of CRCs as proposed by the World Health Organization(17). Approximately 95% of CRCs are adenocarcinomas deriving from the glandular epithelium. The majority of adenocarcinomas are mucinous (meaning the cells secrete mucus and are surrounded by a pool of mucus), while a small proportion (2%) are Signet-Ring adenocarcinomas, where the mucus is trapped within the cells. Other histological types account for an estimated 2% to 5% of CRCs and are shown in *Table 1.2* (18). The prognostic impact of the histological subtype is not fully understood, but is not considered a major factor. Instead the tumour grade has greater prognostic implications. In the case of adenocarcinomas this is based on the proportion of the tumour that is gland forming. The higher the percentage of gland formation, the more differentiated the tumour and better the prognosis, even when adjusted for stage(19).

Table 1.1. The WHO classification of CRCs

Adenocarcinoma
Medullary carcinoma
Mucinous (colloid) adenocarcinoma (>50% mucinous)
Signet-ring cell carcinoma (>50% signet-ring cells)
Squamous cell (epidermoid) carcinoma
Adenosquamous carcinoma
Small-cell (oat cell) carcinoma
Undifferentiated carcinoma
Other (e.g., papillary carcinoma)

Table 1.2 A full description of colorectal tumour types.

Epithelial tumours;
- Adenoma
  - Tubular
  - Villous
  - Tubulovillous
  - Serrated
- Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases
  - Low-grade glandular intraepithelial neoplasia
  - High-grade glandular intraepithelial neoplasia
- Carcinoma
  - Adenocarcinoma
  - Mucinous adenocarcinoma
  - Signet-ring cell carcinoma
  - Small cell carcinoma
  - Adenosquamous carcinoma
  - Medullary carcinoma
  - Undifferentiated carcinoma
- Carcinoid (well-differentiated neuroendocrine neoplasm)
  - Enterochromaffin (EC)-cell, serotonin-producing neoplasm.
  - L-cell, glucagon-like peptide and pancreatic polypeptide/peptide YY (PYY)-producing tumour
  - Others

Non-epithelial tumours;
- Lipoma
- Leiomyoma
- Gastrointestinal stromal tumor
- Leiomyosarcoma
- Angiosarcoma
- Kaposi sarcoma
- Melanoma
- Others

Malignant lymphomas;
- Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type
- Mantle cell lymphoma

1.2.1.1. Sporadic and hereditary cancer

CRC is a multifactorial disease, but causality can broadly be categorised as either sporadic or inherited. Sporadic cancers are the commonest type and occur when there is no family history of the disease. These cancers develop from the accumulation of mutations over a lifetime(20). By contrast, inherited cancer accounts for approximately 5%-10% of cases, and is caused by inherited high penetrance mutations and usually presents at an earlier age.

The commonest type of hereditary cancer is the autosomal dominant Hereditary Non-Polyposis Colorectal Cancer (HNPCC), which accounts for 2-5% of CRC cases, and can be divided into Lynch syndrome I (familial colon cancer) and Lynch syndrome II (HNPCC associated with cancers in other gastrointestinal sites and gynaecological cancers). In HNPCC, mutations are found in the mismatch repair genes, hMLH1 and hMSH2, which leads to microsatellite instability(21). The lifetime risk of colon cancer in HNPCC is 80%, with a mean age of 44 at diagnosis and two-thirds of cancers are found

in the proximal colon.

The second commonest hereditary form is Familial Adenomatous Polyposis Coli (FAP), an autosomal dominant syndrome, responsible for 1% of CRC cases. This leads to mutations in the tumour suppressor gene Adenomatous Polyposis Coli (APC). In FAP, hundreds of adenomatous polyps develop from puberty onwards, which inevitably develop into CRC. Variants of FAP include Turcot and Gardner syndromes. Other rare autosomal dominant disorders causing CRC include; Juvenile Polyposis syndrome, Cowden syndrome, MUTYH-associated Polyposis (MYH) and Peutz-Jeghers syndrome. In addition to these distinct syndromes, independent familial cancer predispositions also exist.

1.2.1.2. Polyp–carcinoma sequence

The pathogenesis of adenocarcinoma was described by Fearon and Vogelstein in 1990(22). It describes carcinogenesis as a multistep process from adenomatous polyp to carcinoma, which is characterised by DNA instability. Mutations in the APC gene (as seen in FAP) are also found in the majority of sporadic cancers and cause the activation of oncogenes including c-myc and cyclin D1, which leads to the development of the malignant phenotype(23). Further mutations include, abnormal DNA methylation, which either activates other oncogenes or disrupts tumor suppressor genes. This accumulation of mutations can eventually lead to malignant transformation.

Polyps initially form as simple aggregations of epithelial cells caused by the proliferation of crypt cells that then fail to differentiate and trigger the changes described above. Over time these adenomas grow and develop increasing dysplasia with the composition changing from tubular to villous components. Malignant transformation occurs when local invasion develops. However the majority of polyps do not develop into carcinomas and not all adenocarcinomas develop via this sequence. Recently, alternate pathways have been described, including the sessile serrated adenoma (SSA) pathway(20). SSAs are similar in morphology to hyperplastic polyps, which are serrated but non-dysplastic and mostly innocuous. However SSAs do have malignant potential via mutations in the BRAF and KRAS oncogenes and may account for up to 20% of sporadic CRCs(24,25). These cancers are predominantly right-sided colon lesions and predominantly affect middle-aged women(26).

1.2.2. Epidemiology of colorectal cancer

1.2.2.1. Incidence and prevalence

In 2008, the Office of National Statistics (ONS) found the annual incidence of CRC was 33,604 in England and 40,695 in the whole of the UK (2). In the UK, 13% of all new cancers are colorectal, making it the third most common cancer after breast (n=49,961) and lung cancer (n=42,026), *Figure 1.2*. Among male patients, prostate cancer is the most common, while there are roughly equal numbers of lung cancer cases and CRC. In females, breast is by far the most common cancer with similar numbers of lung and CRC cases. ONS data shows there has been a 3% increase in CRC between 1999-

2001 and 2008-2010, *Figure 1.3*. In 2006, there were an estimated 143,500 prevalent cases in the UK(27).

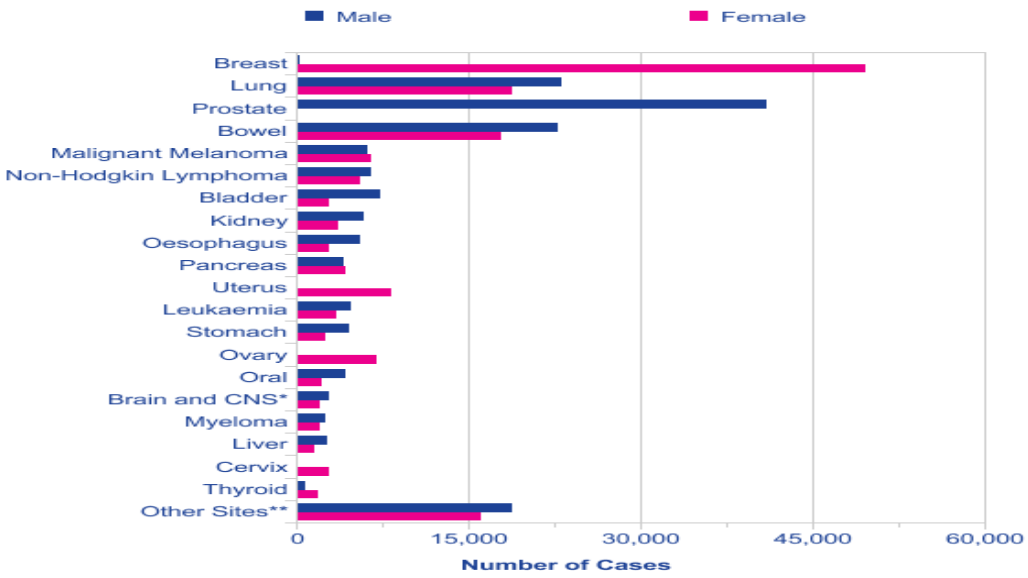


Figure 1.2 The 20 most commonly diagnosed cancers in the United Kingdom in 2010 (excluding non-melanoma skin cancer)(28).

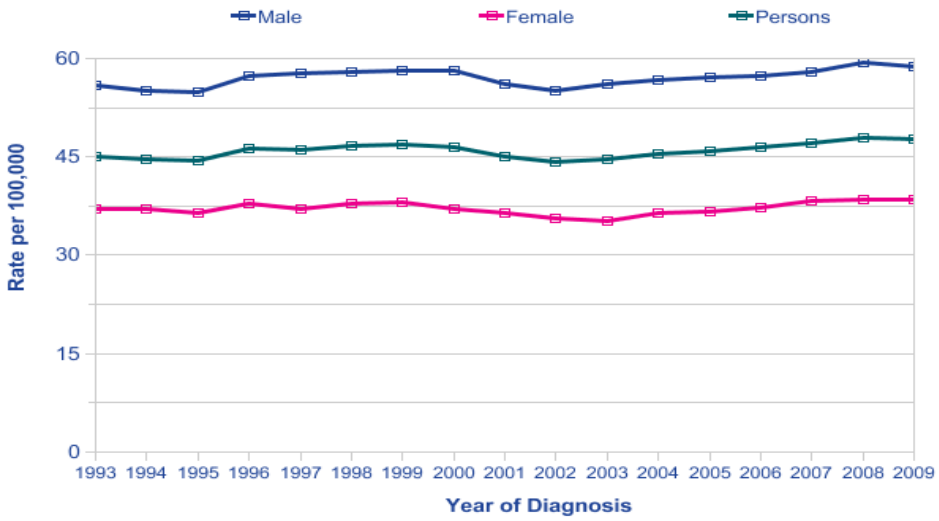


Figure 1.3 CRC incidence rates have marginally increased in United Kingdom since the mid-1990s(28).

1.2.2.2. Age

CRC risk increases markedly with age and 84% of cases occur in patents aged 60 years and over(2). Incidence begins to rise noticeably over 50 years of age and peaks in patients over 80 years, *Figure 1.4*. There is a higher incidence in male patients at all ages but this is widest between 65-74 years and

thereafter the gap falls modestly. At younger ages, there are more male than female patients, but over 80 years this reverses in accordance with higher overall survival rates among females.

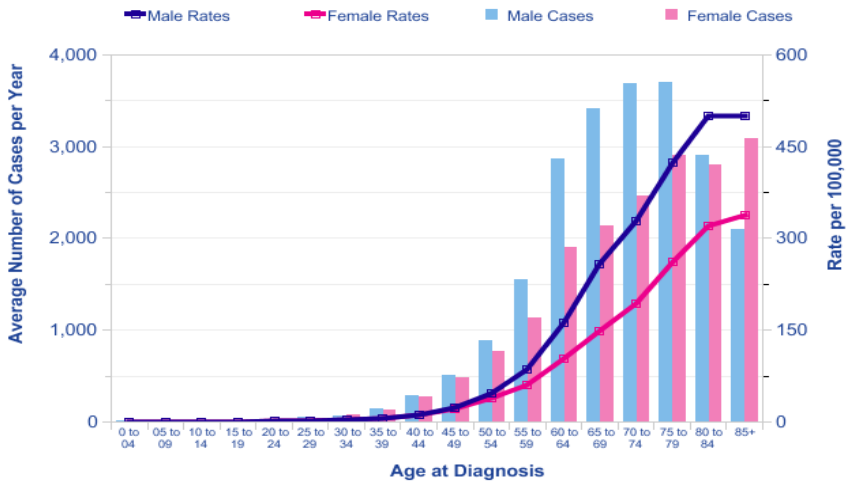


Figure 1.4 The average number of new CRC cases per year and age-specific incidence rates per 100,000 population in the UK in 2007 (for colorectal and anal cancer). Chart taken directly from Cancer Research UK (28).

1.2.2.3. Gender

Gender influences on cancer risk, with a higher incidence in men (69 per 100,000 cases a year) compared to women (46 per 100,00 cases a year) (29). In England from 1999-2006 there were 186,977 CRCs diagnosed. Of these, 102,772 (55.0%) were male patients and 84,205 (45.0%) females(30).

1.2.2.4. Site

There are two common sets of terminology used to describe cancer site distribution. The first uses a proximal (up to and including the splenic flexure) and distal division. The second splits the large bowel into three sites; colonic, rectosigmoid and rectal. In the UK around 60% of CRCs are distal (and 40% proximal), while using the alternative division of sites finds that 64.4% are colonic, 7.4% are at the rectosigmoid and 28.2% are rectal(2).

There are marked gender differences in the site distribution of CRC, with more rectal cancers seen in male patients and more proximal colon cancers seen among females(31). Among females, 42% of all CRCs are proximal, compared to only 31% in males(32). The reason for this difference is unknown but may be due to different levels of exposure to risk factors and their response to them. This difference has a major impact on the diagnostic strategies used and the effectiveness of screening programmes, across the UK.

It has been suggested that, over the last few decades, there has been a shift towards more proximal cancers (33). However recently it has been demonstrated that this is not a true shift but rather a reflection of effective prevention of distal cancers through screening and an increasing aged population, where proximal cancer is more common(34).

1.2.2.5. Deprivation

There is a paucity of readily comparable date to study the impact of deprivation on CRC rates. The latest available ONS data for England covers the period 2000-2004 and reports no statistically significant differences in rates dependent on deprivation. However, one study found men in the most deprived areas had a 11% higher age-stratified risk of CRC compared to the least deprived areas (35). Another study from England during a similar time period (1996-2004), found no clear relationship between the frequency of CRCs and deprivation levels, even when separately analysing for site and gender(30).

1.2.2.6. Co-morbidity

Apart from the disease-specific risk described above, co-morbidities do not appear to affect the incidence of CRC(36). Co-morbidity does, however, have a significant impact on survival and this is discussed below.

1.2.2.7. Ethnicity

There are difficulties in identifying ethnic minorities correctly in the UK cancer databases which makes it hard to accurately identify rates and outcomes (37). The main ethnic minorities in the UK are catergorised as African, Caribbean or South East Asian. Earlier studies have shown CRC incidence and survival to be lower in ethnic minority groups. However, some evidence suggests that incidence is increasing in these groups towards that of the Caucasian population. This maybe a consequence of adopting a more western lifestyle(38,39).

1.2.3. Risk factors for colorectal cancer

A risk factor is defined as 'an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic which on the basis of epidemiological evidence is known to be associated with health-related condition(s) considered important to prevent.'(40).

1.2.3.1. Genetic factors

In addition to the hereditary cancers syndromes described above, certain ethnic groups have a greater risk of CRC. In particular, Ashkenazi Jews have a much greater lifetime risk of between 9-15%(41).

1.2.3.2. Environmental factors

Acquired environmental factors are very important and modulate the risk of the genetic mutations, which can ultimately lead to cancer. There are large variations in age standardised incidence rates across the world, with a 15-fold difference seen between the highest and lowest risk populations(42). Risk is highest in developed countries, especially in the USA and Europe, although incidence rates seem to have stabilised. Incidence rates are now increasing in the developing world, driven by the adoption of western lifestyles(43). Specific risk factors include; reduced physical activity(44), a diet low in fibre,

fruit and vegetables and high in red meat(45), and specific risk factors such as alcohol consumption and cigarette smoking (46).

1.2.3.3. Other disease risk factors

1.2.3.3.1. Inflammatory Bowel Disease (IBD)

IBD predisposes patients to CRC, although the risk is difficult to quantify. IBD comprises of Ulcerative Colitis (UC), Crohn's disease and Indeterminate Colitis. Early studies into UC overestimated the risk, by including patients with predominately severe disease, while later studies may have underestimated the risk by including patients with proctitis or following colectomy. Overall 2% of CRC cases have IBD and the cancer risk begins to increase 8 years after diagnosis. After 10 years of UC, the risk is 2%, at 20 years 8% and after 30 years the risk is 18%(47). The crude annual incidence rates is between 0.06%-0.16% and the relative risk is 1-2.75 that of the general population. Recently the cancer risk in UC patients has actually been falling, due to 5-aminosalicylic acid (5-ASA) maintenance therapy and possibly endoscopic surveillance(48).

Patients with longstanding Crohn's colitis as opposed to those with small bowel involvement only, are thought to have a similar cancer risk as UC patients(49). CRC in IBD follows a sequence from no dysplasia, through to indefinite dysplasia, low-grade and high-grade dysplasia and finally carcinoma. This is driven by inflammation, with the risk of CRC directly linked to the severity of inflammation(50).

1.2.3.3.2. Previous adenomatous polyp

Most adenocarcinomas are derived from adenomatous polyps, which become more common with advancing age(51). Between the ages of 50-54 years, an average risk individual has an 11% risk of having an adenoma. This increases to 33-50% in individuals aged 65-75 years(52,53). Despite this the majority of polyps do not result in cancer. The risk of progression to cancer depends on the number of adenomas found, the size and histological components. The strongest predictor of adenoma recurrence (and subsequent cancer) is the number of adenomas detected at the index colonoscopy. When three or more adenomas are detected, the risk of recurrent adenomas at three-year follow-up is 6%, compared to only 3% in patients with one or two(54). Size is also relevant and patients with a polyp over 1 cm have a significantly higher chance of recurrent adenoma at three-year follow-up(55). Finally adenomas with tubulovillous or villous features or high-grade dysplasia are associated with the development of further advanced adenomas during follow-up(56,57).

It has been clearly demonstrated that removing polyps reduces the risk of CRC (58,59). A study following 1,418 patients for a mean of 5.9 years following polypectomy for one or more adenomas, found the CRC incidence was 76%-90% lower than expected. However despite polypectomy these patients are at a greater risk of both adenoma recurrence and CRC than the general population and may need ongoing colonoscopy surveillance.

1.2.3.3.3. Previous CRC

Patients diagnosed with CRC are at increased risk of having another lesion at the time of diagnosis (synchronous lesions) and subsequently (metachronous lesions). Synchronous carcinomas are defined as two or more lesions, detected either before surgery, intra-operatively, or within 6 months following surgery. By definition, these lesions should be separated by 4 cm of normal bowel and not represent submucosal spread or a satellite lesion. Metachronous lesions are diagnosed 6 months after the primary lesion, and away from the site of the original lesion, thus not representing recurrence of the primary lesion(60).

Synchronous carcinomas are detected in 2% of cases, which supports the practice of perioperative colonoscopy assessment(61). The cumulative risk of metachronous carcinomas was 2% among 5-year survivors and 7% among 20-year survivors and therefore justifies the long-term follow-up of CRC patients(62).

1.2.3.3.4. Other diseases and operations

Patients with diabetes and acromegaly are at increased risk of CRC(63,64), as are those who have received an organ transplant (65,66).

1.2.4. Clinical presentation of colorectal cancer

The majority of CRC patients are diagnosed electively after presenting with symptoms to their primary care doctor. The commonest presentations are rectal bleeding, a change in bowel habit or symptoms of anaemia(6). These patients are then referred on to secondary hospital care for investigations. A second group will present as an emergency directly to secondary care. This is commonly because of significant constitutional symptoms, a large rectal bleed or with symptoms related to bowel obstruction or perforation, *Table 1.3*. Internationally, rates of emergency presentation range from 3-34%(67-71). The UK has a high rate at around 30%(69,72). The reasons for this are explored later in the chapter and forms the basis of my thesis.

A small group of patients will be diagnosed during a surveillance programme for conditions such as IBD or following a history of colorectal neoplasia. Some cancers may be identified during bowel cancer screening programmes. In the UK, currently 3% of patients are diagnosed through the NHS-implemented national Bowel Cancer Screening Programme (BCSP)(73), *Figure 1.5*. A similar proportion of patients are diagnosed through national screening programmes in countries with comparable health systems(74).

1.2.4.1. Signs and symptoms

Patients commonly present with rectal bleeding, a change in bowel habit, anaemia or constitutional symptoms depending on the cancer site and whether metastases are present, *Table 1.3*. Distal cancers more commonly present with overt rectal bleeding and symptoms caused by luminal obstruction. Symptoms of proximal cancer are often absent or vague until the cancer is advanced and the diagnosis is

often made following the identification of anaemia. As CRC is common and curable if detected early, any patient especially over 40 years of age should be thoroughly investigated if their symptoms suggest CRC. See Table 1.4 for a full description of which patients should be urgently referred according to UK guidelines.

Rectal bleeding is an important symptom, but is also non-specific. Most patients with new onset rectal bleeding will initially attend primary care (75). The overall risk of CRC in isolated rectal bleeding is between 1.0% and 2.4% (76,77). Patients over 40 years with new or persistent rectal bleeding should be investigated. The positive predictive value of rectal bleeding representing CRC is less than 1 in 1000 in the community setting, 1 in 50 in primary care and 1 in 3 in patients referred to secondary care (78). This shows how patients themselves and then general practitioners act as gatekeepers to secondary care. In patients with rectal bleeding, the presence or absence of other symptoms will alter the probability of a cancer diagnosis, but no additional factor will shift the probability in such a way to refute the need to investigate further(79).

Bleeding from proximal cancers is less likely to be noticed by the patient, as degradation of the blood and mixing in the stool often makes this unnoticeable (occult). Instead proximal cancers more commonly present with symptoms caused by the ensuing anaemia or following blood tests(80). The positive predictive value of anaemia is between 2.3% and 7.4%(81,82). Anaemia tends to be more insidious as a presenting symptom, compared with rectal bleeding, and is associated with a lower overall survival(83). Other symptoms such as weight loss, abdominal pain, diarrhoea and constipation all have a lower predictive value, however the presence of multiple symptoms is associated with an increased probability of CRC and therefore should be investigated(82).

Luminal obstruction from cancer encroachment leads to symptoms such as a change in bowel habit (predominantly constipation, although partial obstruction can cause diarrhoea), abdominal pain, distention and nausea and vomiting. It is more common in the distal colon, which is narrower and at this point the stool is harder due to water reabsorption in the proximal bowel. Once cancers become advanced, more generalised cachexia symptoms such as anorexia, weight loss and weakness become apparent.

Apart from anaemia, the signs that should alert the clinician to CRC include an abdominal or rectal mass and their presence increases the probability of a diagnosis of CRC. Specifically, one study found over a third of patients with CRC had a palpable mass on rectal examination(84).

Table 1.3 Common presenting features of CRC

Abdominal pain, including symptoms of bowel obstruction
Change in bowel habit
Rectal bleeding or melaena stool
Abdominal mass
Iron deficiency anaemia

1.2.4.2. Referral pathways to diagnosis

As illustrated above there are four pathways to diagnosis; a) an elective admission following a primary care referral, b) an emergency hospital presentation, c) bowel cancer screening and d) routine endoscopic surveillance, *Figure 1.5*. Currently in the UK, most patients present electively through primary care or as an emergency directly to secondary care. Only a minority of cancer diagnoses are made by the BCSP or through surveillance programmes.

Figure 1.5 shows how each of the referral pathways can be affected by delays differently. This time period is comprised of a combination of patient delay, primary care delay and secondary care delay. The patient delay occurs from time taken to decide to access primary care once symptoms appear, the primary care delay is the time a general practitioner takes to arrange referral and secondary care delay is made up of the time waiting for outpatient appointments and appropriate diagnostic investigations. Beyond the time to make the diagnosis, patients will face further delays while preoperative staging investigations are performed and then treatment (usually surgical) is arranged.

The NHS BCSP selects patients with a greater risk of malignancy, because of the age cut-off used (currently screening 60-74 years). This programme relies on the sensitivity of the Faecal Occult Blood test (FOBt) to decide which patients are offered a colonoscopy, the gold standard test for diagnosing CRC. Patient uptake rates, and to a lesser extent colonoscopy quality, also affect the effectiveness of the BCSP. The effectiveness of endoscopic surveillance is based on identifying high risk patients in the first place. This includes patients with a family history or previous CRC or IBD. Surveillance also relies on patient motivation, accurate colonoscopy and ensuring the correct follow-up is carried out.

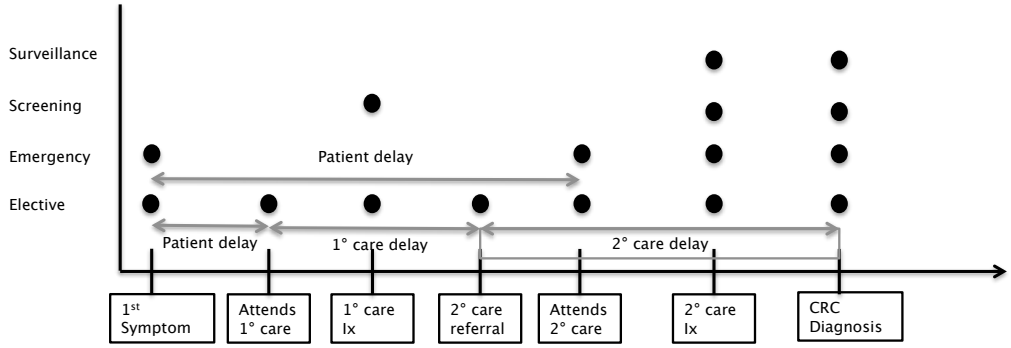


Figure 1.5 The four possible diagnostic routes for any patient with CRC. The total delay for each of the four routes may include; patient, primary care or secondary care (system) delay.

Between 5% and 20% of CRC patients present asymptomatically as a result of surveillance or screening (85-87). Screened patients are diagnosed with an earlier stage of cancer and as the volume of screening increases within a country, the rate of emergency presentation appears to fall(88). This will be discussed in more detail in chapter 4 (11,88). However, within the UK the majority of patients still present with symptoms to their GP or as an emergency directly to hospital. Earlier diagnosis of patients would likely reduce the number of emergency presentations and improve outcomes by diagnosing earlier stage disease and avoiding the high morbidity and mortality associated with subsequent emergency operations(85).

As longer delays are associated with worse outcomes, resources could be used to target the causes of delays and reduce detrimental outcomes caused by cancers presenting at a late stage. To this end the 'National Awareness and Early Diagnosis Initiative' (NAEDI) was created in the UK. The aim of which was to support activities which lead to the earlier diagnosis of cancer and so improve cancer survival rates. The NAEDI used routinely collected data to interrogate the pathways leading to the diagnosis, and linked relative survival at 12 months, for CRC in England between 2006 and 2008. The study found 26% of CRC patients presented as an emergency, 67% through an elective route (including 2% as screen detected) and 7% were unknown. There was dramatically lower survival following diagnosis through the emergency route, with 12-month survival in only 50% of patients identified through the emergency route compared with 80-84% for elective routes and 98% in the screen detected group. Emergency routes were commoner with increasing age, accounting for 45% of diagnoses in the over 85 years age group. Deprivation was also associated with emergency diagnoses, accounting for 32% of the most deprived quintile of patients compared to 22% of the least deprived. Of note, in 2006 there were 0% screen detected cancers, increasing to 5% by 2008, due to the BCSP roll out. In total there were 2,086 screen detected cancers over the 2-year period. This demonstrates the need to understand the causes of emergency presentation and poses the question that I address in my thesis and discuss in depth in chapter 4(89).

1.2.4.2.1. Elective presentation (primary care referral)

Primary care has an important role in identifying patients who may have CRC and ensuring they are promptly referred for necessary investigations.

The majority of patients with abdominal symptoms present to primary care(82). The difficulty for general practitioners is identifying those which warrant referral to exclude CRC from all the patients presenting with abdominal symptoms(90,91). This is set in the context of each general practitioner seeing only around one new CRC case a year(92). Guidelines have been developed to help identify which patients to refer; these are based on a mixture of evidence and expert agreement. They have an important goal in trying to reduce delays to diagnosis, which is associated with late presentation and poorer outcomes. Equally guidelines allow patients without cancer to avoid unnecessary investigations, which itself will help to control waiting times(93). Table 1.4 lists the clinical scenarios which should necessitate 2-week referral for suspected cancer. These patients are seen in secondary care by a CRC specialist within 2 weeks of presenting to their general practitioner.

Guidelines are useful provided they reduce primary care delay, but not at the expense of secondary care delay. However a substantial minority of patients with CRC fall outside the guidelines for referral. This makes the case for general practitioners to use their clinical judgment and refer any other patients they consider may have cancer(94).

Table 1.4 Referral Guidelines for Suspected Cancer. Department of Health(90).

Refer urgently patients:
• aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting 6 weeks or more
• aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms
• aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding
• of any age with a right lower abdominal mass consistent with involvement of the large bowel
• of any age with a palpable rectal mass (intraluminal and not pelvic; a pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist)
• who are men of any age with unexplained iron deficiency anaemia and a haemoglobin of 11 g/100 ml or below
• who are non-menstruating women with unexplained iron deficiency anaemia and a haemoglobin of 10 g/100 ml or below

1.2.4.2.2. Emergency presentation

An emergency presentation occurs when the initial secondary care episode leading to the diagnosis of CRC was an emergency admission. An emergency admission is one made at short notice at the request of accident and emergency services, general practitioners, bed bureau, or consultant outpatient clinics.

Patients presenting as an emergency with CRC are more often; older, female, from lower

socioeconomic groups and have more advanced disease(11,95-98). Emergency presentations are less likely to have surgical resection with curative intent. Surgical intervention following emergency presentation is associated with high morbidity (45–50%) and mortality (15–45%)(73,99). Many such patients had actually had symptoms for some weeks, and often months, before the presentation. Later in the thesis, I will explore the consequences of emergency presentation and strategies to avoid late presentation.

1.2.5. Diagnosis of colorectal cancer

To confidently confirm or refute the suspicion of CRC an investigation must adequately examine the entire colon and rectum. The options include colonoscopy, sigmoidoscopy, colon capsule, barium enema and Computerized Tomography Colonography (CTC), all of which require some form of bowel cleansing (preparation). All procedures have potential complications and miss rates and multiple procedures may be necessary. The ideal diagnostic strategy is not yet known. However the initial diagnosis is made, a full examination of the large bowel involving colonoscopy or CTC should always take place prior to surgery to identify the 5% of cases that have a synchronous lesion(61).

1.2.5.1. Colonoscopy

Colonoscopy has a high sensitivity and specificity and is the established gold standard investigation(100). It allows visualization of the whole of the large bowel, with the ability to biopsy any suspicious lesions and remove any adenomas by polypectomy. Furthermore it doesn't expose the patient to any ionizing radiation. However some patients have co-morbidities that prevent colonoscopy from being performed or result in an inadequate examination, where the operator fails to reach the caecum. In the UK pre-2005, inadequate examination was a common outcome with at least 23% of procedures being incomplete. Following a quality improvement programme this has improved recently, with caecal intubation rates of 96% recorded nationally in 2013(101,102). Failed examinations may occur due to: poor operator skill; patient's intolerance of the procedure; inadequate bowel preparation or an obstruction to complete colonoscopy (such as a diverticular stricture). In such cases alternative investigations are required. Complications of colonoscopy include bleeding, perforation, readmission to hospital and, very rarely death(103,104).

1.2.5.2. Barium enema

Double contrast barium enema (DCBE) has long been used to diagnose CRC and, although safer than other examinations, it is less sensitive than both colonoscopy and CTC and should not be used routinely(100).

1.2.5.3. CT colonography (CTC)

CTC is a relatively recent innovation and uses 2-D and 3-D image reconstruction techniques to view the abdomen and pelvis in cross-section. It requires laxative preparation and air or carbon dioxide insufflation.

The sensitivity of CTC was thought to lie between that of DCBE and colonoscopy but this was based on the surrogate finding of polyps, as the prevalence of invasive cancer in individual trials was low(105). A recent meta-analysis has, however, shown equivalence between CTC and colonoscopy for the detection of invasive cancer, with overall sensitivity of 96.1% vs. 94.7%(106). A recent, pragmatic multi-centre randomised trial (the SIGGAR trial) compared the two techniques, and found similar sensitivities for the two tests. However patients initially referred for CTC required more additional investigations(107). Finally, CTC offers additional benefits over colonoscopy in being able to image structures outside the bowel lumen(108). CTC should be used when colonoscopy is unsuccessful or inappropriate. In frail and elderly patients that require colonic investigation but cannot tolerate full bowel preparation then minimal preparation CT colonography is an acceptable alternative(109).

1.2.5.4. Sigmoidoscopy

When sigmoidoscopy is used on its own, a negative test can effectively eliminate distal but not proximal cancer(110). Traditionally sigmoidoscopy has been used in combination with barium enema (which can image proximal CRC), however this approach is still less sensitive than colonoscopy. Compared to colonoscopy more cancers are missed overall(111,112).

1.2.5.5. Colon capsule

Specifically designed capsule endoscopy is a new and less invasive way of examining the large bowel. Currently there is not enough evidence to support its general use in diagnosing colon cancer(113). However in the future it may provide an accurate assessment of the large bowel and cancer risk, but without the ability to biopsy any suspicious lesions.

1.2.5.6. Other tests

Carcinoembryonic antigen (CEA) is a tumour marker that has no role in diagnosing CRC, but can be used in the follow-up of patients after surgery. If the CEA falls immediately after surgery, then monitoring levels can identify patients with early recurrence, which may be treatable. Recent advances in molecular technology have identified many putative biomarkers relevant to the diagnosis of CRC. Currently, most are in the discovery phase and few have undergone clinical evaluation. Therefore at present biomarkers are not part of the diagnostic algorithm(114).

1.2.6. Colorectal cancer staging

Tumour staging is the most important prognostic predictor of clinical outcome for patients with colorectal carcinoma. This requires the assessment of local spread and detection of the presence or

absence of distant metastases. The original staging system was developed by Cuthbert Duke in 1932(115), *Table 1.5*. A cancer limited to the submucosa is defined as a Dukes A stage and by definition has no lymph node or distant metastases and has excellent prognosis. Further progression into and through the muscular layers is defined as Dukes B, while Dukes C defines cancer that has spread to regional lymph nodes with a corresponding worse prognosis. Despite being revised over the years, this classification's prognostic accuracy suffers from not assessing the extent of lymph node involvement or tumor grade. The Tumour, Nodes and Metastases (TNM) classification was introduced to address these weaknesses and provide greater accuracy and standardisation. The TNM staging can be used to estimate prognosis, *Table 1.6*. The T-stage describes the depth of tumour infiltration into the bowel wall, the N-stage the extent of regional lymph nodes involvement and the M-stage the presence of distant metastases or residual tumour following treatment. In Table 1.7, a comparison is made between the two staging systems as well as showing the relative percentage of cases in each stage and their 5-year relative survival.

Table 1.5 Description of the Dukes stage classification(116).

Dukes Stage	**Description of CRC spread**
Stage A:	Limited to mucosa
Stage B1:	Extending into muscularis propria but not penetrating through it; nodes not involved
Stage B2:	Penetrating through muscularis propria; nodes not involved
Stage C1:	Extending into muscularis propria but not penetrating through it. Nodes involved
Stage C2:	Penetrating through muscularis propria. Nodes involved
Stage D:	Distant metastatic spread

Table 1.6 TNM classification (version 5, 1997) with sub-classifications.

TNM	Stage	Extension to
Tis N0 M0	0	Carcinoma *in situ*: intraepithelial or invasion of lamina propria
T1 N0 M0	I	Submucosa
T2 N0 M0	I	Muscularis propria
T3 N0 M0	IIA	Subserosa/perirectal tissue
	Sub-staging	
	T3a	<1 mm
	T3b	1–5 mm
	T3c	5–15 mm
	T3d	15+ mm
T4 N0 M0	IIB	Perforation into visceral peritoneum (b) or invasion to other organs (a)
T1–2 N1 M0	IIIA	1–3 regional nodes involved
T3–4 N1 M0	IIIB	1–3 regional nodes involved
T1–4 N2 M0	IIIC	≥4 regional nodes involved
T1–4 N2 M1	IV	Distant metastases

Table 1.7 A comparison of the Dukes and TNM staging classifications, showing the proportion of cases with each stage disease and their 5-year survival. The table is UK data from the ONS between 1996 and 2006(2)

Dukes stage	TNM stage	% of cases*	5-year relative survival (%)
A	T1N0M0 or T2N0M0	13.2	93
B	T3N0M0 or T4N0M0	36.9	77
C	Any T, N1M0 or any T, N2 M0	35.9	48
D	Any T, any N, M1	14.0	7

*excluding patients with an unknown stage

1.2.6.1. Colonic cancer

Staging is less important in colonic cancer compared to rectal cancer, as surgery is not usually stage dependent. Most patients will undergo the same operation whether for curative or palliative intent. The single most sensitive test for local spread or distant metastases is contrast-enhanced Computerized

Tomography (CT) of the chest, abdomen and pelvis. CT assesses for synchronous lesions, contiguous organ involvement and metastases. The ability of CT to identify locally stage disease was addressed in a recent meta-analysis, which showed a T staging sensitivity of 77%, N staging sensitivity of 76% and M staging sensitivity of 85%(117). CT is particularly good for identifying invasion beyond the muscularis propria (stage T3+), with a sensitivity of 86%(118). If the CT demonstrates an indeterminate lesion in the liver, then an MRI is more sensitive than contrast-enhanced US to further characterise the lesion. This is especially important if a metastectomy (removing the metastasis) is being considered(119).

1.2.6.2. Rectal cancer

Rectal cancer staging is more complex due to the high recurrence risk. The risk of disabling local pelvic recurrence needs to be assessed preoperatively. CT can help stage distal disease, while MRI is superior for staging the tumour (T), nodes (N) and circumferential resection margin (CRM). Endoscopic ultrasound is also used selectively to assess early stage tumours (T1-T2) and can be used to compliment MRI in establishing the tumour depth(120).

The risk of local recurrence is dependent on the CRM, which can be predicted by careful staging before surgery. Staging is used to select patients for neoadjuvant chemotherapy and radiotherapy(121). When total mesorectal excision surgery is performed, the mesorectal fascia forms the plane of dissection and any tumour within 1mm of the potential circumferential resection margin makes local recurrence and poor survival more likely. Positron emission tomography-computed tomography (PET/CT) is based on identifying abnormal metabolic activity in the body. It has not yet established a role in diagnosing or staging CRC, but may occasionally be used to investigate recurrence, especially before metastectomy(122).

1.2.7. Treatment options for colorectal cancer

There are a number of different ways to describe CRC treatments, based on:

-The aim of treatment: either to remove the cancer entirely (curative intent) or to palliate a patient to maximise the length and quality of a patient's life. At the beginning of treatment it is often unclear which pathway the patient will follow.

-The timing of treatment: either planned (elective) or required urgently due to pressing clinical need (emergency). Treatment performed as an emergency is usually associated with higher mortality and morbidity rates(72).

-Treatment modalities: including surgery, the commonest and most effective therapy by far, endoscopic resection, chemotherapy and radiotherapy. Surgery can be a resection with anastomosis, involve a defunctioning stoma either as a fully open procedure or laparoscopically assisted. Early stage CRC can occasionally be successfully treated by endoscopic resection and with obstructing cancers palliated with a self-expanding metal stent (SEMS). For patients with

advanced cancer, chemotherapy and/or radiotherapy are also frequently used(6).

1.2.7.1. Surgical resection

The primary treatment modality for CRC is surgical resection. The aim is to resect the tumour with a wide local excision, including the removal of associated regional lymphatics and lymph nodes, while avoiding the creation of a stoma.

Local recurrence usually occurs following a full thickness radial extension of the tumour. This means recurrence is more often seen in the peritoneum, omentum and surrounding organs, such as ovaries, bladder or spleen. For this reason, the surgeon will usually attempt en bloc resection, including the removal of all or part of any involved structures. On the other hand, proximal or distal mucosal spread is less common and recurrence at the site of anastomosis is rare.

Surgery alone is used for Dukes A and B cancer. Once a tumour has spread to the lymph nodes (Dukes C), then chemotherapy is required to optimise outcomes. Adjuvant chemotherapy usually means 6 months of treatment, using 5-fluorouracil (5-FU) and leucovorin following surgery. Patients with metastatic disease commonly receive palliative chemotherapy including 5-fluorouracil, leucovorin and ironotecan(123).

Most surgery is performed via an exploratory laparotomy, although laparoscopic surgery is becoming more common. A meta-analysis of 33 randomised clinical trials showed there was no significant differences in survival, recurrence or complications between open and laparoscopic surgery(124). Guidance is available from the National Institute for Health and Care Excellence (NICE) and advice depends on the lesion's suitability for resection, patient preference and the surgeons experience of each procedure(125).

1.2.7.1.1. Colonic surgery

Radical resection of a colonic tumour includes complete mesocolic excision with flush ligation of the colonic vessels; it is associated with reduced local recurrence and improved survival, especially in stage III cancers(126,127).

The main types of surgical operation for colonic cancer are:

-Right hemicolectomy: for caecal and right colonic cancers.

-Extended right hemicolectomy: for cancers in the proximal or middle transverse colon.

-Transverse colectomy: for certain cancers in the transverse colon.

-Left hemicolectomy: for cancers at the splenic flexure and left colon.

-Sigmoid colectomy: for sigmoid cancers.

-Total abdominal colectomy with ileorectal anastomosis: for hereditary nonpolyposis colon cancer (HNPCC), attenuated familial adenomatous polyposis (FAP), metachronous cancers in separate colon segments, or acute malignant colon obstruction (sometimes).

-Panprotcocolectomy: for FAP and UC with high grade dysplasia or carcinoma, *Figure 1.6*.

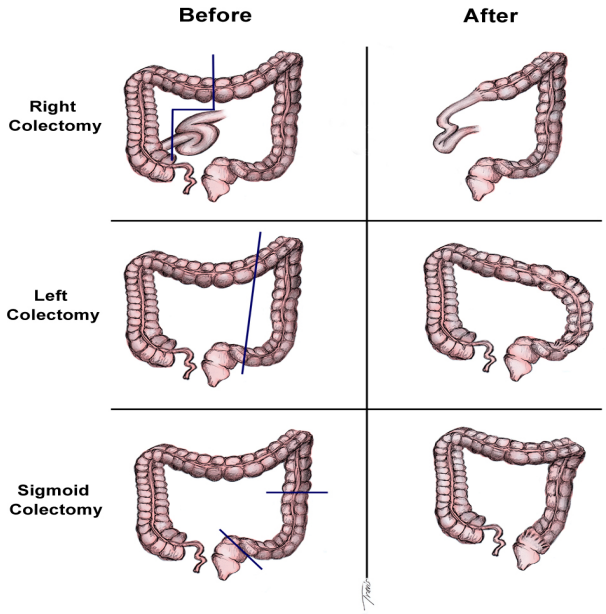


Figure 1.6 A schematic representation of the major types of colonic resections.

1.2.7.1.2. Rectal surgery

The primary goal of rectal surgery is to entirely remove the cancer, as local recurrence is associated with a poor survival and quality of life. Secondary goals include restoration of bowel function with acceptable anal continence and the preservation of genitourinary functions. For cancers in the middle and lower thirds of the rectum, the surgical technique of total mesorectal excision (TME) reduces the risk of local recurrence and improves survival(128). This is because a clear circumferential resection margin is more reliably achieved. Efforts should be made to preserve the autonomic nerves in the pelvis to minimise bladder and sexual dysfunction, but not at the expense of tumour clearance. Cancers in the upper third of the rectum do not need total excision of the mesorectum, providing careful resection is performed(129).

The main types of surgical operations for rectal cancer are:

-Lower Anterior Resection (LAR); cancers of the proximal two thirds of the rectum, leaving the rectal sphincter intact.

-Abdominoperineal Excision of the Rectum (APER); cancers of the distal third of the rectum. This involves the removal of the rectum, anus and part of the sigmoid colon, through incisions

in the abdomen and perineum. The end of the remaining sigmoid colon is brought out as a permanent stoma.

The LAR operation is more successful than APER in preventing local recurrence due to the higher rate of clear circumferential resection margin achieved. Some low rectal tumours still require an APER or if an anterior resection is used, then a defunctioning stoma should be considered to reduce the risk of an anastomotic leak(130,131).

1.2.7.1.3. Other procedures

Metastatic CRC may still benefit from surgery to improve symptoms and overall quality of life. Options include a palliative resection and anastomosis or a simpler defunctioning ileostomy or colostomy. An alternative to surgery is to insert a Self Expanding Metal Stent (SEMS) which can be used to reestablish luminal patency and continence(132). There is also some evidence that carefully selected patients with isolated metastatic disease may benefit from hepatic and pulmonary resections(133).

1.2.7.1.4. Surgical complications

Complications can be divided into intraoperative and postoperative complications. Intraoperative complications include bleeding and bowel, ureteral and bladder injuries. The main postoperative complications include wound infection, anastomotic leakage, prolonged ileus and bleeding. Patients may also suffer from infective complications at other sites (e.g. pneumonia), decompensation of cardiovascular disease (e.g. heart failure) or thrombotic complications (e.g. deep vein thrombosis or pulmonary embolus)(134).

1.2.7.2. Chemotherapy and radiotherapy

Chemotherapy usually kills fast growing cells within the body, targeting malignant cells but also normal tissues such as skin, gut and bone marrow leading to the commonest side effects. Chemotherapy in CRC can be used as mono-therapy or in combination and delivered either orally or intravenously. Radiotherapy uses ionizing radiation to destroy malignant tissue and may act synergistically when combined with chemotherapy.

Colonic cancer is predominately treated with chemotherapy. Rectal cancer is treated with a combination of chemotherapy and radiotherapy. However the treatment decision is complex, needing a Multi-Disciplinary team (MDT) to discuss the balance between the benefits of treatment and the likelihood and severity of side effects. The use of preoperative magnetic resonance imaging (MRI) staging to risk-stratify patients helps the assessment process. When there is mesorectal fascia involvement the combined use of chemotherapy and radiotherapy can usefully downstage tumours.

Below is a simplified stratification of the use of chemotherapy dependent on the stage of CRC;

-Stage I: chemotherapy in not required.

-Stage II: this covers T2-T4 tumours with no nodal or metastatic disease. Adjuvant chemotherapy may be worthwhile in patients with greater tumour burden (e.g. T4), that are otherwise free from co-morbidities which would make them less tolerant of chemotherapy and its attendant side effects(135).

-Stage III: all patients should be considered for adjuvant chemotherapy as survival is improved(136).

-Stage IV: when metastases are confined to the liver, long-term survival is possible if resection is undertaken along with perioperative chemotherapy. Average 5-year survival after resection is 40%(123). In patients with metastatic disease not restricted to the liver or where liver resection is not appropriate, then the standard of care is systemic chemotherapy which significantly improves survival(137). 5-FU with the addition of either leucovorin or oxaliplatin and possibly irinotecan plus bevacizumab is the current standard of therapy in patients with a good performance status(138).

1.2.7.3. Palliative treatment

Patients with advanced disease will frequently experience multiple symptoms. These commonly include pain, fatigue and emotional distress, with the number and severity of symptoms increasing as the cancer advances. Treatments include analgesics, anti-emetics and anti-secretory drugs as well as nasogastric suction and parenteral nutrition in patients with obstruction. There is also a need to provide psychological and social support to patients and their families, with evidence suggesting palliative care services improve quality of life(139).

1.2.8. Prognosis in the UK and other counties with comparable health systems

Survival is the primary outcome measure for how a healthcare system manages its patients with cancer. Survival is strongly linked to the stage of disease at diagnosis and treatment thereafter(27). In the UK, the current 5-year relative survival rate for CRC is 51%. In patients with Dukes A cancer, survival is 93%, compared to 7% with Dukes D. At present only 13% of patients in the UK are diagnosed with Dukes A and any intervention that could increase this proportion should greatly reduce preventable deaths and improve national cancer outcomes(140).

Currently survival rates vary considerably across Europe, including between the UK's 5-year survival rate and the European average of 57%. Countries of comparable wealth such as Germany (62.2%), Austria (61.2%) and France (59.7%) all have markedly better survival that the UK (51%). It is estimated that if the UK could match the best results in Europe, then around 1,700 deaths per year would be avoided(7).

The first comparative data studies on cancer survival in countries with similar health systems and wealth began in the mid-1990s. The relative survival for CRC was approximately 10% lower in the UK at both 1 and 5 years(141). These results were used to create the political imperative to develop the NHS

Cancer Plan for England (2000) that focused on improving cancer services and in particular raising the 5-year survival to the levels of the best-performing countries in Europe by 2010. The plan emphasized the need to act quickly when symptoms and signs of potential cancer were identified and to improve screening and treatment options.

Over the next seven years until 2007 relative survival increased in the UK, especially after the full implementation of the plan in 2006-2007(142). Despite this, because improvements in other countries kept pace, the survival gap between UK and other countries remained at 10% by 2007, *Figure 1.7*(27). The finding that the survival difference is the same at 1 and 5 years is important, as it shows most of the difference arises soon after diagnosis.

In the UK patients on average present later, with later stage disease, than in Europe. The reasons for this may include: failure to diagnose cancer before symptoms occur (due to inadequate screening and surveillance programmes); lower public awareness of cancer symptoms and diagnostic delay. All of these potential weaknesses will be explored later in this thesis. Poorer survival may also be caused by differences in overall health variables between countries including obesity and physical activity rates, population co-morbidity, deprivation and suboptimal treatments(143).

	Australia			Canada					Denmark	Norway	Swedish regions	UK			
	Australian registries	New South Wales	Victoria	Canadian registries	Alberta	British Columbia	Manitoba	Ontario				UK registries	England	Northern Ireland	Wales
Colorectal cancer															
1 year															
1995–99	80·0%	80·3%	79·6%	79·1%	77·6%	80·7%	79·8%	78·7%	71·7%	78·6%	81·8%	70·2%	70·2%	74·3%	68·3%
2000–02	82·5%	83·2%	81·6%	81·5%	79·8%	82·4%	80·4%	81·7%	73·9%	78·7%	82·8%	73·0%	72·9%	76·8%	72·3%
2005–07	84·9%	84·7%	85·1%	83·5%	80·4%	84·3%	82·1%	83·9%	77·7%	82·4%	83·8%	74·7%	74·7%	76·2%	73·6%
5 years															
1995–99	60·0%	61·2%	58·4%	58·1%	56·3%	59·8%	57·6%	58·0%	48·2%	56·9%	58·5%	47·8%	47·8%	51·1%	45·9%
2000–02	63·4%	65·1%	61·1%	60·9%	58·0%	61·5%	59·6%	61·3%	51·7%	58·8%	60·6%	51·3%	51·2%	54·3%	50·3%
2005–07	65·9%	66·4%	65·5%	63·7%	58·3%	64·0%	63·3%	64·9%	55·8%	62·0%	62·6%	53·6%	53·7%	55·2%	52·3%
Conditional 5-year															
1995–99	75·0%	76·2%	73·4%	73·6%	72·5%	74·2%	72·2%	73·8%	67·3%	72·3%	71·6%	68·1%	68·2%	68·8%	67·2%
2000–02	76·7%	78·2%	74·9%	74·7%	72·5%	74·8%	74·0%	75·2%	70·1%	74·7%	73·3%	70·3%	70·3%	71·1%	69·7%
2005–07	77·7%	78·4%	76·8%	76·4%	72·3%	75·9%	77·1%	77·4%	72·1%	75·4%	74·8%	71·8%	71·8%	73·0%	71·1%

Figure 1.7 Age-standardised relative survival for CRC in countries with similar health systems and wealth, to the UK(27).

1.2.9. Reasons for poorer survival in the UK; late diagnosis

Poor CRC survival in a population is caused by late diagnosis and inferior treatment. Identifying which factor is more significant may be determined by assessing if survival improves more in;

a) the total series of cases (due to earlier diagnosis)
b) stage specific analyses (due to better treatments)

Interestingly, survival between the UK and the best performing countries are comparable once stage had been accounted for. This suggests that the main reason for the low survival in the UK is late diagnosis and not inferior treatment(143).

In the remainder of this chapter, I will outline evidence to support this *late diagnosis* theory. I will then show how UK outcomes (including earlier presentation) have improved over time, but not narrowed the survival gap with other countries. Lastly, I will discuss how variation in outcomes within the UK itself, may explain some of the challenges with the national results.

Deaths within one-year of a diagnosis are usually from patients with late stage disease. Thus relative survival rates at one-year is a useful indicator of the proportion of early and late cancer diagnoses. Compared to other countries, many more UK deaths occur in the early post diagnosis period(9). In fact almost all the excess mortality in the UK is accounted for by early (one-year) mortality. In colon cancer, the majority of the UK excess mortality (the difference between UK and European mortality) occurs in the first 3 months after diagnosis(140). Emergency presentation, which is associated with a high early death rate and low rates of elective surgery, is also more common in the UK (7).

In England access to better treatments and earlier diagnoses have improved over time. Between 1971 and 1975 the one-year survival rate was 39% for men and 40% for women. This has risen to 73% for men and 72% for women between 2005 and 2009. This implies that along with improvements in surgery and chemotherapy, there has also been a reduction in the rate of late presenting cancers(2,144).

Variations in practice are present at all levels within the NHS; between different GP practices, primary care trusts, hospitals and region of the country. This has been shown in every annual Care Quality Commission (CQC) report so far and in the NHS Atlas of Variation in Healthcare(145,146). These differences affect many aspects of healthcare provision from referral rates from primary care through to the type and volume of surgery in a given area(147,148). This is illustrated most dramatically in variations in survival across the UK, with areas of the north-east of England and east London having 5-year survival of less than 25%(2). These variations hold even when adjusting for other risk factors such as deprivation(149). Another marker of quality is the permanent stoma rate for rectal cancer. The national average was at least 34%, but there was a wide variation between cancer networks ranging from 3% to 51%(150). These findings imply there is variation in the provision and quality of services across the country. Other known confounding factors affecting survival include age, gender, co-morbidity, deprivation, cancer site and mode of presentation (Emergency or Elective) and are discussed elsewhere in the thesis in more detail in sections 2.5.3 and 3.5.6.

Late presentation and variation in healthcare delivery across England appear to explain some of the poorer outcomes compared to other countries. In the next two sections, I will list some of the reasons for late presentation and then explore strategies that may reduce delays in presentation.

1.2.10. The causes of late presentation in the UK

Late presentation leads to increased emergency presentations, higher costs and poorer survival. The reasons for late presentation are complex and multifactorial with limited data currently available.

Many studies have looked at whether patient or doctor delay causes late presentation. To date no clear conclusion has emerged(151,152). Certain factors are however associated with patient delay, and these include; a failure to recognise the seriousness of symptoms(153), denial about the potential cause of the symptoms(154), a lack of knowledge about CRC itself or how screening can benefit patients(155,156) and those patients who self-medicated their symptoms(153). Finally, patients who recognised symptoms but did not deem them important were also more likely to delay their presentation to primary care(157). Studies have identified several reasons why primary care doctors delay the referral of a patient with underlying CRC; the most obvious reason being attributing the symptoms to benign conditions, i.e. misdiagnosis of the cancer(158,159). Linked to this is a failure of the practitioner to carry out a full examination of the patient(160). One study found that many patients subsequently diagnosed with CRC believed that their GP had delayed their referral by acting as an over-influential gatekeeper(161). Reassurance from falsely negative investigations was also a factor linked to delayed referral and this is especially important for patients with suboptimal investigations, such as barium enema and flexible sigmoidoscopies(162).

Some authors believe reduced awareness of CRC symptoms in the UK population affects outcomes(163). Others believe that reducing the time delay between the onset of symptoms and the beginning treatment improves survival(164). However studies so far have failed to show any association between the overall duration of symptoms and the stage of the tumour or outcomes(165-167).

In an era of robust referral guidelines for GPs and rapid access to secondary care clinics, there is evolving evidence that patients with delays between referral and diagnosis may paradoxically have a trend toward less aggressive tumours and better subsequent long-term survival. The use of these same guidelines and rapid access clinics appear to have only a minimal effect on aggressive cancers (168). The reason for this paradox is likely to be in the biological nature of different CRCs. Aggressive tumours with poor outcomes will present quickly, while slow growing tumours may be diagnosed after a longer duration of symptoms and still have better outcomes(85). This suggests cancers do not move to more advanced stage (TNM or Dukes) during the symptomatic phase. This makes sense when we recall that the adenoma to cancer development may take from 5-15 years and the symptomatic phase is typically very late in the natural history, presenting in the last few months(169). Thus the assumption that the symptomatic phase of cancer is sufficiently long that earlier referral (e.g. through rapid access clinics) leads to mortality improvements may be implausible(170).

At present there are no studies to show that reducing symptom delay actually improves outcomes; possibly due to the fact that the symptomatic phase is late in the disease process or because the studies were too small to show a difference. This suggests that further speeding up referral from primary care and/or access to secondary care is unlikely to lead to significant improvement in outcome. Instead delays appear to be due patients not seeking healthcare early in the course of their symptoms, GPs not referring these early vague symptoms and healthcare professionals not identifying enough high risk

patients either through screening programmes or enrolling at risk patient such as those with a family history into surveillance programmes.

It may be that in order to reduce late presentations a dual approach is required. Firstly, to diagnose more patients before symptoms occur and secondly to ensure patients present as soon as symptoms to appear. This idea is explored in more detail in the thesis justification section below. In the next section 1.2.11, I discuss some of the strategies for improving survival.

1.2.11. Strategies to improve CRC survival in England

Few CRC patients are currently diagnosed asymptomatically and in the majority that present with symptoms, the CRC is often advanced (89). Earlier in this chapter, in sections 1.2.2 and 1.2.3, I presented some of the known associations between patient characteristics and survival. Many of these factors cannot be changed and so to see improvements in outcomes then modifiable factors need to be identified and targeted for interventions. These include improving the health-seeking behaviour of patients with symptoms, the speed of referral of suitable patients from GPs, the uptake of the BCSP and the diagnostic and treatment capabilities in secondary care(6).

Currently too many UK patients are diagnosed late(89). Delay can be reduced by: improving awareness of symptoms and reducing barriers to accessing services; encouraging GPs to refer patients for diagnostic tests when they have symptoms possibly linked to CRC (sometimes called opportunistic screening); increasing diagnostic availability (most importantly access to colonoscopy) and involving appropriate patients in national screening and surveillance programmes.

Finally, BCSP and other surveillance programmes have a role in identifying patients with pre-symptomatic cancer and maximising population participation is very important in optimising outcomes(171). Identifying the impact of the BCSP on CRC and emergency presentations is important and in chapter 4, I will present the first national data looking at this.

1.2.11.1. UK government initiatives; NHS Cancer Plan for England (2000)

The NHS Cancer plan for England (2000) set out ways to reduce death rates and improve the prospects of survival based on improving prevention, promoting early detection, effective screening practice and guaranteeing high quality treatment and care throughout the country. It was particularly committed to addressing health inequalities by reducing waiting times and the establishing national standards for cancer services. There is evidence showing the plan has been at least partially successful, especially after the full role out in 2006, when one-year survival began to improve(27).

1.2.11.2. Public awareness

The goal of improving public awareness is two-fold; firstly to encourage individuals to visit their doctor if they have symptoms potentially attributable to CRC and secondly to take part in regular screening. These two positive public health messages may be linked. Currently, there is low awareness of the signs

and symptoms of CRC in the public and also widely held negative beliefs about cancer(172). These beliefs discourage early presentation and uptake of screening. If there are perceived or real barriers to accessing primary care then delayed presentations occur and patients are more often left to access healthcare as an emergency admission straight to secondary care.

To improve the situation various forms of awareness campaigns have been studied. These range from simple leaflet distribution in GP surgeries and community centres, to postal campaigns right through to mass media including newspaper articles, billboard and television adverts. Any campaign needs to be aware of barriers to reaching certain populations, including those lacking English language skills or with literacy problems. Most studies to date have been small with minimal follow-up time and it is difficult to draw any firm conclusions. For example, one study from the UK found that after volunteers took the message about cancer awareness to pubs and community halls and the proportion of new cancer cases diagnosed through the urgent 2-week referral route increased significantly (from 43% to 51%). However there was no significant decrease in the stage of cancer at diagnosis(173). This is the pattern for many of the awareness campaigns to date; they seem able to demonstrate an increase in surrogate markers such as patient symptom awareness or 2-week referral rate, without conclusively showing an improvement in outcomes such as survival. The 'UK bowel awareness campaign' aimed to increase public awareness of CRC and prompt symptomatic individuals to seek medical attention. Two pilot sites in the South West and Yorkshire studied results after a seven-week campaign in 2011. The campaign message was:

"If you have (1) A persistent change in normal bowel habit, such as going to the toilet more often and diarrhoea, especially if you are also bleeding from your back passage, or (2) Bleeding from the back passage without any reason, particularly over the age of 55, then it's important to go and see your GP. The sooner you see your doctor to have it checked, the better."

The medium included regional TV, print media (regional/local press etc.), and inserts into regional editions of national press, online, regional/local radio, and shopping centres campaign. The results failed to demonstrate either an increase in CRC diagnoses, nor earlier stage or improved survival, despite a significant rise by 55–60% of 2-week referral(174). The only randomised controlled trial (RCT) on improving awareness comes from The Netherlands and involved distributing an information leaflet. The study reported an increase in patient knowledge and a change in their intentions but no survival advantage(175).

1.2.11.3. Introduction of the 2-week referrals route

In another attempt to tackle late diagnosis, NICE published a report entitled 'Improving Outcomes in Colorectal Cancer' in 2004. Its aim was to improve all aspects of CRC care from disease prevention to referral to secondary care management(6). Its recommendations included standardising referral guidelines, with the aim of increasing appropriate referral rates, and reducing waiting times for

diagnostic tests.

One of the report's suggestions was to introduce the "2-week referral" route, designed to reduce delays between presentation, diagnosis and treatment. The idea being that these fast-tracked patients would be been seen within 2 weeks of presentation by a secondary care specialist. If there was underlying CRC then the outcomes would be improved by earlier diagnosis and treatment and adverse outcomes such as emergency hospital admission avoided, *Figure 1.8*. However 2-week referrals still only diagnose 25-50% of CRCs and can lead to an increase in routine appointments(176,177). It has also been estimated that 30% of CRC cases don't meet current 2-week referral guidelines(177). This report coincided with an effort to increase national endoscopy capacity, to prevent increasing waiting times for endoscopy. This is particularly important given that a study from 2000 found over one-third of patients waited over three months from seeing their GPs with symptoms to their first hospital appointment(178). There is particular concern for delays in patients presenting to GPs with only anaemia, which can result in substantial delays(179). Overall the report recommended reducing the threshold to investigate patients with potential CRC. To accomplish this, GPs were encouraged to take up any opportunity for opportunistic screening and reduce any delay in the referral of patients to appropriate tests.

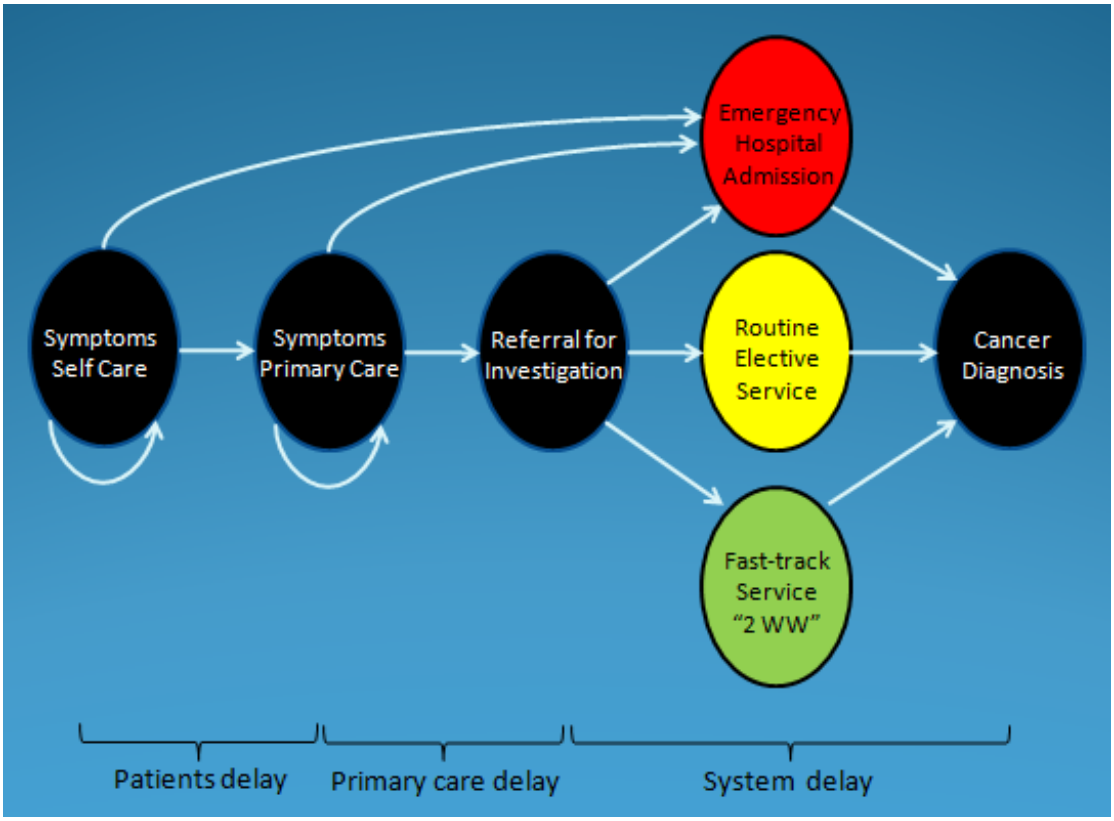


Figure 1.8 This flowchart shows the route and potential delays for patients presenting with CRC.

1.2.11.4. Referral rate and colonoscopy volume

Most patients are diagnosed electively after presenting to their GP with symptoms of concern. Those patients with symptoms caused by partial intestinal obstruction or significant bleeding would immediately warrant referral for colonoscopy. However in other cases where the patient is minimally symptomatic, then they might only be referred for colonoscopy if their GP was a "colonoscopy enthusiast". It might be argued that these GPs are taking part in informal optimistic screening. In a Canadian study, GPs with the highest discrepancy colonoscopy referral rate (referring patients beyond the strict interpretation of guidelines) had the lowest CRC incidence and mortality. Outcomes in the study improved incrementally from the lowest to highest referrers(180).

In conclusion, while it seems credible that poor outcomes are linked to late diagnosis, it is less obvious what is behind the delay. In particular, whether the delay is a function of patient delay once symptoms are apparent or a delay in either primary or secondary care. This is because studies to date have not accounted for the impact of cancer aggressiveness on both the speed of presentation and survival. Secondly there is a lack of long term data on awareness campaigns aimed at improving patient presentation and GP attitudes towards optimistic referral. Further work is required into understanding how more pre-symptomatic and early symptomatic cancer patients can be referred for diagnostic tests at a cost that is sustainable by the NHS, *Figure 1.9*. I will explain in my justification for the thesis, section 1.5, how my work attempts to address this knowledge gap.

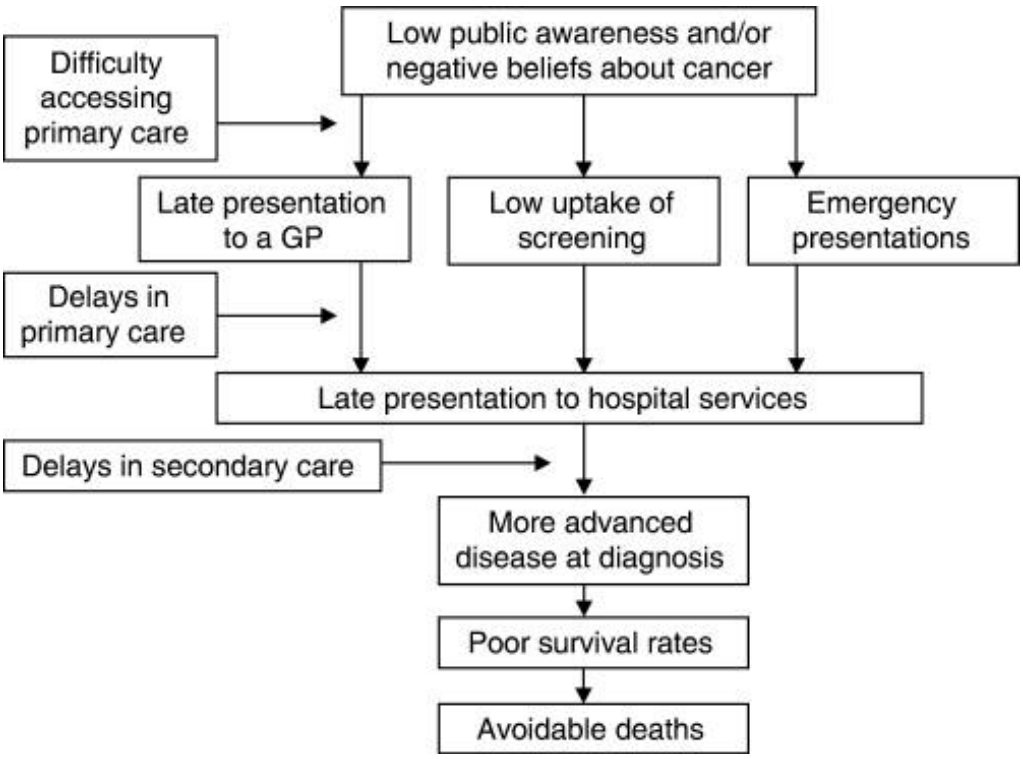


Figure 1.9 A model describing the reasons patients with CRC present late to hospital; including the hypothesised role of screening uptake.

1.3. NHS Bowel Cancer Screening Programme

Despite the interventions described above, the continuing poorer prognosis for UK patients, makes the case for further large scale efforts to improve CRC survival. Since 2006, the biggest single intervention has been the introduction of the NHS national Bowel Cancer Screening Programme (BCSP). The evidence supporting its introduction comes from screening programmes in other countries and RCTs that have shown CRC related mortality can reduce by 25% after introducing a national programme(11).

Four randomised controlled trials, involving 327,043 participants, have shown guaiac-based faecal occult blood test (gFOBt) screening results in a Relative Risk Reduction (RRR) in CRC related mortality of between 11% and 33%(11,96,98,181). A meta-analysis of the same trials showed FOB testing of asymptomatic individuals reduces deaths from CRC by 16% [odds ratio (OR) 0.84; confidence interval (CI) 0.78–0.89](182).

The principle of bowel cancer screening is to detect cancer at a pre-symptomatic stage, leading to earlier diagnosis and thereby improving clinical outcome(183,184). Screening also enables the detection and excision of adenomas, thereby reducing CRC risk. Following a review of all screening options, the National Health Service (NHS) adopted a gFOBt screening programme.

The NHS Bowel Cancer Screening Programme (BCSP) in England began offering biennial gFOBt screening to men and women aged 60–69 years (approximately 10% of the population) in July 2006. An invitation to participate in the BCSP requires an individual to be in the defined age range and be registered with a GP. Individuals are called throughout the two-year period, with the next round invitation going out two years after the previous round is closed. The phased roll-out achieved national coverage in January 2010 and from 2008 the screening age range was extended to 74 years. An early analysis of the first 2.1 million subjects invited to screening showed uptake was 55-60%. Of all subjects tested, 2% were gFOBt positive and 8% of these were found to have cancer(185). From its inception to December 2013, the BCSP had diagnosed 17,893 cancers (personal communication from National Office), with a higher proportion of Dukes' A cancers compared with non-screened patients (35% vs. 13%)(73,185). Currently around 3% of patients with CRC are diagnosed through the NHS BCSP(73) and a similar figure is seen in countries with similar health systems(74,143).

The BCSP uses the gFOBt (hema-screen; Immunostics, New Jersey, USA), which is designed to identify subjects at a higher risk of colonic neoplasia by detecting intraluminal bleeding from vascularised CRCs and adenomas. The amount of bleeding is related to the size, stage and site of the neoplasia(186). Subjects perform the test at home by placing two faecal samples from three separate stools onto each one of six windows in turn. The gFOBt test relies on the pseudoperoxidase activity of haem (from haemoglobin). Each window is impregnated with guaiac and the presence of the haem component of haemoglobin in blood present in faeces releases oxygen from hydrogen peroxide and converts colourless guaiac to a blue colour in the screening laboratory(187).

The BCSP in England is co-ordinated by five regional Hubs; screening kits are returned to one of the five accredited Hub laboratories where stool samples in all six windows are analysed by a manual qualitative process. A kit is reported as 'normal' if none of the six windows (spots) is positive. A kit with five or six positive spots is deemed 'abnormal' and further investigation, usually colonoscopy, is recommended. A kit with between one and four positive spots is deemed 'unclear' and a second kit is sent out to the subject. If the second kit result is normal, a third kit is sent out. If either the second or third kits contain one or more positive spots then the outcome is described as 'weak positive' and colonoscopy is recommended. Following an unclear result in kit one, if both kits are normal then patients are returned to the screening programme for repeat testing in two years' time.

Subjects with abnormal and weak positive test results are referred for colonoscopy. If this is normal the subject is returned to the screening programme for a repeat gFOBt in two years' time. Subjects diagnosed with CRC are referred to their local CRC multidisciplinary team (MDT). If polyps or adenomas are found then surveillance follows the British Society of Gastroenterology (BSG) guidelines(188). In chapter 6, I will explore the performance of the programmes algorithm for determining whether a given result should lead to colonoscopy. The aim is to identify if more cancers and adenomas can be diagnosed without substantially increasing the cost of the programme. To date no other work has analysed the BCSP algorithm in this way.

Broadly speaking, there are two distinct ways a screening programme can improve outcomes. Firstly, the direct effect of diagnosing pre-symptomatic CRCs in patients undergoing screening. This has been the focus of almost all the research in this area. Such patients will have their cancer diagnosed earlier (and possibly at a lower stage) than had they waited until symptoms developed. These patients will have also avoided many of the potential delays in the current pathways. The second potential impact has been much less studied and involves the issue of raising public awareness of CRC. This impact relates to how the introduction of the programme affects the population as a whole. Introducing a screening programme has given a clear message to the population that the healthcare system is determined to identify and treat CRC quickly, as a priority. This itself gives the message to the public of the need to be aware of CRC symptoms and act quickly if they occur. This may lead to a change in population attitudes regarding CRC. A population "exposed" to a screening programme may believe more strongly in the "treatability" of CRC. This would reduce nihilistic attitudes and encourage patients to report symptoms. It is important to realize the two effects affect different populations differently. Patients in the screening age group can benefit from both direct and indirect effects while those outside the screening age group can only benefit from the indirect effect. Further work is required to address causality and eliminate confounding variables. This is explained further in my justification section below and in chapter 4.

Screening can diagnose patients pre-symptomatically and may encourage other symptomatic patients to present sooner. Both of these effects could reduce delay and also potentially reduce the variation in outcomes throughout the country. However, the effectiveness of a programme is reliant on the uptake

rate(189). Uptake of screening is known to be worse in areas with high deprivation, which already have worse CRC outcomes (164). A consequence of which, more deprived patients will still present as an emergency to hospital, *Figure 1.9*.

1.4. Determining variation in practice of CRC care

Clinicians and healthcare providers rely on accurate information to provide safe and effective care to their patients. Information is used to determine which services need to be commissioned and then to measure the service performance and identify how improvements can be made. This is done by comparing quality indicators, such as length of stay and overall survival. It can also highlight trends in healthcare to enable changes to be implemented. For example, if there was increasing incidence of a certain condition then increased resources can be allocated. To allow fair comparison between different providers, confounding variables such as age and co-morbidity need to be adjusted for. Being scrupulous with data quality and making the necessary adjustment means the information supplied to be trusted by those using it.

My thesis studies how methodological changes based on clinically derived algorithms can be applied to routinely collected hospital data. This allows more accurate identification of patients with CRC, as well as a better understanding of their clinical pathway including whether they first presented to hospital care as an emergency. Once a cohort of patients has been accurately identified in this way, then the impact of changes in practice, in this case the introduction of the BCSP, can be studied. This can allow the judgments to be made on the impact and relative worth of the programme across the entire country. This requires accurate data and any missing or inaccurate data could introduce bias and invalidate my conclusions. The most useful data for this type of research is routinely-collected prospective data, found in the HES database. HES allows me to determine if there is differing practice and outcomes for CRC across the country.

I identified an important quality indicator in CRC to be emergency admissions. In section 1.4.1, I explore the rationale for choosing this indicator and describe some other possible data sources, along with HES and why this was chosen for the basis of my thesis.

1.4.1. Candidate Quality Indicators; emergency admission at presentation

Quantifying the real-world benefits is a challenging for all cancer screening programmes. Survival benefit takes many years to realise (190,191) and a range of other healthcare advances may occur over this period to confound the interpretation of national trends in cancer incidence or survival. In the case of CRC screening, a recent meta-analysis of trial data estimated that it took 10.3 years before one death from CRC was prevented for 1,000 patients screened(191). Therefore I needed to identify a reliable

quality indicator that acts as a surrogate for survival and is measured routinely and prospectively in HES data.

In general, healthcare quality can be measured by comparing the performance of an individual or a group of individuals with an ideal or benchmark(192). Quality of care can also be defined as *'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.'*(193). This defines quality as a multidimensional concept, which is best described by the use of quality indicators and expressed as standards. Most quality indicators tend to be negative, such as; death, disease, disability, discomfort, and dissatisfaction and can be generic and relevant to all diseases, or disease-specific measures(194). Once quality indicators are established, then the performance of a given organisation or patient identifier (e.g. ethnicity) can be measured and compared to the standard and to other organisations or patient groups. These finding can then be used to identify variation and set priorities to inform a quality improvement programme. Results can also support providers' decision around commissioning and for accountability and accreditation purposes.

It is clearly important to understand the reasons for persistent unwarranted variations in outcomes, as it allows resources to be focused on the areas of greatest need. Despite this, the eradication of all variation is not what health services should aim to achieve. This is because "If all variation were bad, solutions would be easy. The difficulty is in reducing the bad variation, which reflect limits of professional knowledge or failures in its application while preserving the good variation that makes care patient centred."(195). The task is to know what drives bad variation, and to do this we need to be able to identify candidate quality indicators.

Once a variation in practice (such as 5-year survival) has been identified between two or more groups of patients, the next question is: how to improve the outcome for the disadvantaged group. For this, the different steps associated with a poor outcome need to be established and robust markers associated with these steps identified(196). As an example, if outcomes were worse for a particular group, say those with greater deprivation, can quality indicators be identified that are associated with a specified aspect of care more likely to be present in deprived population groups. It is established that screening can improve outcomes by preventing delayed presentation through the diagnosis of asymptomatic patients(11). Therefore it makes sense to look at screening uptake as a potential quality indicator related to late presentation and worse outcomes. If it can be shown that there are lower screening rates in deprived patients then one method for improving overall outcomes in deprived patients might be to improve screening uptake(171).

In addition to survival rates, other quality indicators have recently been shown to be important. These include measures to evaluate the quality of care at a given population level. Assessing care quality is increasingly important as it allows care providers, purchasers (e.g. Clinical Commissioning Groups (CCGs)) and patients to choose services based on optimal clinical practice, especially in the current

climate of increasing demand and constrained resources(197). One problem is that most of the established quality indicators discuss management of treatments following the diagnosis.

The major problem in the UK is not the treatment provided, but late presentation. Therefore the candidate quality indicators of particular interest in my thesis relate to the pre-hospital and pre-diagnostic time period, as this is where most improvement can occur. Emergency presentation is another quality indicator as it is associated with reduced five-year survival compared with elective presentation and is an indicator of the quality of pre-diagnostic care(198). The UK has a high emergency presentation rate at around 30%, compared with international rates (3-30%)(67-71,184). Other indicators looking at delayed diagnosis include early mortality and the proportion of patients not amenable to surgical resection.

Therefore my main candidate quality indicator to identify the impact of the screening programme is emergency admission at presentation. This is because it is strongly associated with poor outcomes, marks pre-diagnosis care pathways and the rate is high in the UK.

1.4.2. Sources of NHS data

There are many different sources of information in the NHS that can be used to study CRC care. Broadly speaking, these can be divided into routinely collected national data and locally collected data.

National data tends to use standardised collection procedures and principally collects data on patient activity, examples include:

-Hospital Episode Statistics (HES)

-Bowel Cancer Screening System (BCSS) database

-National Audits such as the NBOCAP (National Bowel Cancer Audit)

-NHS Performance Statistics

-Office of National Statistics (ONS)

-Hospital activity records

-Primary care records

-Prescribing records

-Insurance claims

-Emergency service records

With the exception of the BCSS and NBOCAP audit, the databases described above are used for measuring overall healthcare activity and are not specific to CRC. The original purpose of these databases was to allocate resources to meet healthcare demands. However relatively recently, researchers have found they can be used to perform observational studies of health care practice(199).

The advantages of using these national, routinely-collected datasets are the prospective nature of the collection (reducing bias), the large size and high case ascertainment rate. Additionally, the data are relatively inexpensive to acquire and the extraction and analysis process is relatively straightforward. These features can be particularly useful when trying to externally validate other studies, especially those published by tertiary units where results may not be directly comparable to the "real world" situation. Such unbiased datasets can also be used to assess the performance of individual clinicians, units, hospitals, specific areas and the whole country(200).

There are also potential weaknesses with using routinely-collected, national data including issues of data quality, a lack of flexibility (the results may not be relevant to the proposed study) and difficultly manipulating such large databases.

There were alternatives to using HES data to describe national standards of clinical care, the most commonly used example was clinical registries, which were purpose built for the disease of interest. These were commonly used in the fields of cancer and surgery and exist for CRC in the form of the National Bowel Cancer Audit Programme (NBOCAP). In contrast to HES, clinical registries can contain more detailed clinical information for individuals; this can help predict risk factors for adverse outcomes and performance variability more accurately(201). However the quality of the data collected in clinical registries can be variable. The major problem is incomplete data capture as clinical registries are usually run voluntarily and rely on motivated clinicians to add data. This may skew submissions towards more complex cases and lead to the omission of routine cases and those with adverse outcomes. Clinical registries are also costly to maintain and often lack the infrastructure to reach their full potential(202).

In the case of the national CRC audit, the NBOCAP is rich in clinical detail but suffers from a limited case ascertainment rate of 69% and only a 50% rate of data completeness. This compromises its use in analysing national interventions(150). The NBOCAP is very useful in identifying variations in quality, for example it has shown a variation in surgical practice across different areas of the country, with abdomino-perineal resection rates varying from 20% to 40%. These types of results are useful in suggesting variations in outcomes across the UK. The problem arises when analysing causation, trying to unpick causes related to care quality, rather than epidemiological and socio-economic factors. It is only by applying further advanced analytical techniques (as performed later in this thesis) that validated clinically useful measures of care can be presented to help front-line teams improve their service.

Recent studies comparing the accuracy of routinely collected data (including HES) with clinical registries confirmed a close correlation between the two. In 2001, Campbell et al, found the accuracy of HES with registry data was 84% for diagnostic codes and 97% for procedure codes(203). A more recent study also reported a good association between the two forms of data capture, with an 80% accuracy for diagnoses and 84% for procedures(204). The same study also found that accuracy had increased since the introduction in 2002 of 'Payment by Results'. Reasons for the discrepancy that still exists between

routine and registry data include the use of different definitions for diagnoses, procedures and even mortality(205).

Locally collected data are more variable in the quality of information recorded and mainly involve audit and registries. Examples of local data sources include: endoscopy reporting systems; local use of Hospital Patient Administration Systems (PAS); electronic and manual clinical records, MDT datasets and clinical notes-based audits. These can be useful in helping with quality improvement programmes in the area conducted but their wider use is limited. Given the aims of my thesis, the reasons above demonstrate why the HES dataset was most appropriate.

1.4.3. Hospital Episode Statistics (HES) Data

HES is a national data warehouse containing the information coded routinely at discharge for all inpatient care episodes occurring in NHS hospitals. This includes elective day case procedures, elective admissions and unplanned (emergency) admissions (15,16). The original purpose of HES was to describe activity in the service and help with the allocation of resources. Over time, the range of uses of the data has widened.

HES was introduced in 1987 as a method of collecting detailed information for every in-patient and day case hospital episode delivered by NHS hospitals including personal, administrative and clinical information, with more than 15 million records collected annually. It is the most comprehensive and inclusive of all NHS datasets and was established in response to the Körner Report, which found that "inaccuracy, a lack of timeliness and certain inherent defects" were leading to poor quality routine hospital statistics(206). HES also records episodes in the private sector commissioned by the NHS.

1.4.3.1. The structure of the HES database

Each hospital episode of care under a single consultant generates a single HES record. Most patients only have a single episode during an admission (or spell) in hospital, but some will have multiple episodes. While the intention of the data is for administrative purposes, important information on a patient's diagnosis, any procedures occurring and outcome is also recorded. The process begins when a patient is first admitted to hospital. At this point their relevant administrative and demographic details are entered into the hospital's patient administration system (PAS). Once discharged, the patient's clinical notes go to the hospitals coding department where staff extract relevant clinical information, assign appropriate codes and enter them onto a database. The data are extracted directly from clinical information held within patients' records, in the same way as many local audits and studies. Patients' hospital notes (written by the patient's medical team), discharge summaries and letters are scrutinised for information regarding diagnosis and procedures. This process is performed by clinical coders and not clinicians. They study the clinical data to translate the medical terms into an alphanumeric code using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) for diagnoses, and the Office

of Population, Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) for procedures performed.

HES is held nationally and data are regularly submitted by local hospitals from their own information systems throughout the year. Selected extracts from PAS are sent from all hospitals to the HES dataset via the Secondary Uses Service (SUS). Once collected centrally, the data are further processed and cleansed to remove inaccurate or nonsensical data and then archived for subsequent use. HES is thus a repository for England's hospital level activity based on episodes of inpatient and day case care, *Figure 1.10*. HES data are based on the financial year, running from 1st April to 31st March.

HES only codes inpatient episodes including day case episodes such as most endoscopy procedures. Any visits to the outpatient department, including radiology, are not captured. The Health and Social Care Information Centre (HSCIC) does hold a separate 'outpatient' dataset, but this outpatient dataset doesn't contain diagnostic or procedure information, and is not currently linked to HES.

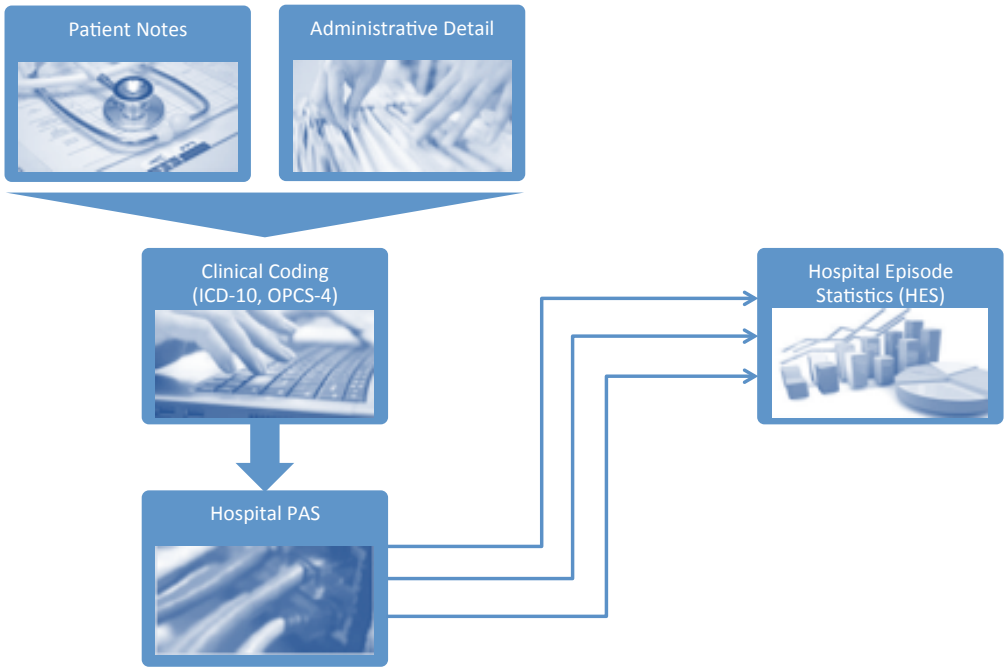
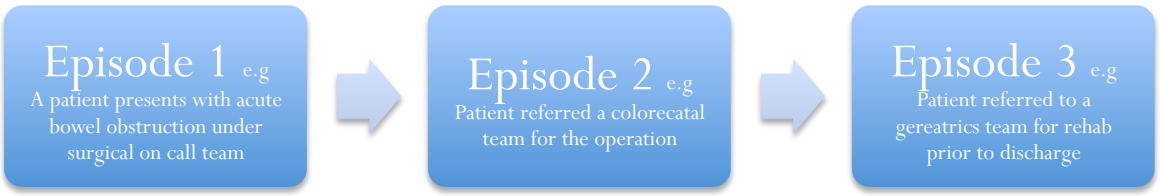


Figure 1.10 The steps taken in the collection and storage of HES data.

The basic unit of the HES dataset is the Finished Consultant Episode (FCE), covering the continuous period of time during which a patient was under the care of one consultant. As a patient may be transferred to the care of other consultants during the same admission (spell), there could be two or more episode records for a single admission. Episodes of care are linked into admissions and those ending in transfer to another hospital will be linked together to avoid multiple counting, *Figure 1.11*.

Each episode contains up to 50 pieces of data. The dataset includes a unique patient identifier (HESID), age, gender, ethnicity, admission time and method (elective or emergency), geographical data for the

area where the patient lives and the treating hospital. Clinical data includes the primary diagnosis (the main reason for admission) and up to thirteen secondary diagnosis fields. In addition there are up to twelve procedural fields and the length of stay and method of discharge are also recorded. Finally, the discharge date and any in-patient deaths are recorded.



Patient A has three episodes of care (each under a different consultant team) and therefore three separate HES records during a single admission.

Patient B has a single episode of care (a single HES record) during the single admission.

Figure 1.11 Illustration of how HES records the number of episodes of care (Finished Consultant Episodes) rather than the number of admissions. Each admission may comprise of one or more episodes.

1.4.3.2. A demonstration of the HES record

Table 1.8 shows the partial HES record for a single patient's pathway of care relating to CRC. Some of the 50 fields in each line of data are not shown due to size constraints but four care episodes covering three admissions to hospital are all shown split across two tables. The tables record the unique hospital identifier (HESID) for the patient (ending as….037F), as well as the beginning (EPISTART) and end (EPIEND) date of each episode. The patient's age (ENDAGE) and sex (SEX) is also recorded. In Table 1.8, the same patient's episodes are shown and describe the different specialties caring for the patient (MAINSPEF). For the 1st, 3rd and 4th episode the code 100 denotes the patient was under the care of a general surgical team. The different types of admission method (ADMIMETH) are recorded, where for example a code 11 denotes an elective admission from a waiting list. The primary diagnostic (DIAG01) and procedural (OPERTN1) codes are recorded (the additional 13 possible diagnostic codes and 11 procedures codes have been removed from this table for simplicity). Finally, there is record of the patient's inpatient death date (DEATHDATE).

Additional data columns and flags for events can be customised for the specific audit or research project. I have added the first episode CRC was mentioned (1stCRC) and when the date was also shown (FIRSTCRCDATE). The column OPERTN1 describes the first procedure that occurred in the episode.

In this case, H244 is a code for the endoscopic insertion of expanding metal stent into lower bowel. Therefore the example shown in Table 1.8 describes a patient whose first episode was on the 02.05.2007 aged 67 years. The patient subsequently had a diagnosis of CRC and metal stent inserted during an episode from the 04-08.06.2007. Unfortunately a more prolonged episode from 20.10.2007-02.11.2007 ended in the patient's death.

Table 1.8 The HES database is configured so each line of data records a single hospital episode of care. Records for one patient's four episodes of care are displayed (not all data is shown).

HESID	EPISTART	EPIEND	ENDAGE	SEX	PROCODE	RELAVENT PRODODE
.....037F	02.05.2007	02.05.2007	67	1	RW6	1
.....037F	04.06.2007	08.06.2007	67	1	RW6	1
.....037F	19.10.2007	19.10.2007	67	1	RW6	1
.....037F	20.10.2007	02.11.2007	67	1	RW6	1

MAINSPEF	ADMIMETH	FIRSTCRC	1st CRC DATE	DEATHDATE	DIAGO1	OPERTN1	OPDATE1
100	11				K529		
301	11	1	08.06.2007		C189	H244	08.06.2007
100	22				C19X	-	
100	28			2.11.2007	C19X	H152	24.10.2007

1.4.3.3. Potential uses of the HES record

Given the size, detail and accuracy of the data, HES has been used extensively as a research tool to define variations in population heath and health delivery across geographic and economic areas. HES can be used to investigate potential causality factors and healthcare trends over time(207). This makes analysis of HES useful for detecting variations in the national provision of CRC care. It also allows reliable markers predictive for this variability to be developed. Finally, it allows the impact of healthcare change (such as the beginning of national screening) to be studied.

1.4.3.4. Quality of HES data and limitations

HES data presents several challenges, including concerns about coding accuracy, coding depth (for example cancer stage is not recorded) and the occasional use of symptom rather than diagnostic codes. Put simply the quality of data reflects the quality of the clinical records and the ability of the coders to interrogate the records. Some of the individual limitations of HES, including identifying the date of diagnosis and accuracy of coding are covered in more detail in chapter 2, where there is also a

comparison with other potential data sources. HES contains no information on outpatient (clinic) attendances and doesn't include a complete capture of some treatments such as chemotherapy and radiotherapy. Finally HES does not contain all useful outcome data, in particular outpatient deaths and quality of life measures (Patient Reported Outcome Measures [PROMs]). However on balance, HES is the single best national database the UK has to offer. Therefore, to determine the impact in England on CRC emergency presentation rates following the introduction of BCSP, it seems appropriate to use HES as the primary data source.

1.5. Justification for the thesis; the direct and indirect effect of introducing the BCSP

Currently the national impact that the introduction of the BCSP has had on CRC care is unknown. Outcomes for CRC in England are worse than other countries and this is largely because patients present later and with more advanced disease. Other national screening programmes have successfully identified a small proportion of patients with pre-symptomatic cancer, so it is important to determine if the BCSP has had this effect, since its roll out in 2006.

Two studies have looked at the impact of bowel cancer screening on overall emergency admissions for CRC. The Nottingham screening study was a randomized controlled trial, comparing 75,253 patients in the screened group (60% response rate) and 74,998 well-matched, unscreened controls (age range; 45 and 74 years). The emergency presentation rate was 23.9% in the screened group, compared to 27.9% in the control group, but the difference was not statistically significant (possibly due to lack of study power)(88). An uncontrolled, observational study from Coventry and North Warwickshire, looked at patients aged 50 to 69 years, as part of a screening programme pilot. The authors reported that 29.4% of CRC patients presented as an emergency in the year before the pilot (1999) but that the local rate had fallen to just 15.8% by 2004. Surprisingly, the proportion of Dukes stage cancers was unchanged over the study period and the annual number of cases did not rise as might be expected if extra screen-detected cases were contributing to the reported totals(208) Expert commentators questioned whether screening itself, or other changes in local or national CRC care over the 5 year period was responsible for the time-trends reported(209). Similar uncontrolled local data for sigmoidoscopy-based colon cancer screening has shown a trend for reduced emergency admissions(210).

However these studies were local, occurring during the screening trials prior to the national programme, with relatively short follow-up. One study failed to show any significant effect and the other was criticized for failing to properly account for confounding variables. Therefore, no study has attempted to understand the nationwide effect of the BCSP.

In my thesis, I begin by reporting the development and validation of methods to analyse HES data to identify a national incident cohort of patients with CRC and then describe their characteristics and a methodology to flag key milestones in the patient journey (Chapter 2). I focus particularly on creating a candidate metric of CRC care, namely *emergency admission during the diagnostic pathway*. Data are

presented to describe the development of a novel, clinically generated algorithm for categorizing all relevant emergency admissions within the coded hospital episodes. Subsequent work establishes the associations between the candidate indicator, patient characteristics and other outcomes (Chapter 3), thereby establishing this specific metric as a surrogate outcome measure for use in comparing services or the impact of interventions. I then deploy this metric as a primary outcome measure in a retrospective, observational study focused on the roll-out of the BCSP across England (Chapter 4). Specifically, I focus on the idea that the launch of the program may have early, population wide and indirect benefits. To support this hypothesis, I examine whether living in an area with a recently activated BCSP is associated with a reduced risk of emergency admission for the population as a whole, and particularly for those of non-screening age. In order to account for various sources of confounding, I use comparable data for oesophagogastric cancer to illustrate that any associations are specific to CRC, rather than reflecting more general features of local services. I next sought to exclude any further confounding factors for the findings in chapter 4 (Chapter 5). Finally, independently from the rest of the thesis, I showed how the BCSP database could itself be analysed. By interrogating the programme, I was able to suggest ways in which the algorithms for referring FOBt results for colonoscopy might be altered in a way to improve the efficiency of CRC diagnosis (Chapter 6).

Chapter 2 - Validation of data extraction from the Hospital Episode Statistics (HES) database for a one-year cohort of incident cases of Colorectal Cancer in England

2.1. Introduction

The HES database is a record of all inpatient hospital activity, including patients seen as a day case and those admitted to a hospital bed. The database covers all NHS hospitals in England and describes the diagnoses and procedures relevant to each episode. HES has been used to study a variety of conditions in an attempt to understand temporal trends of disease incidence, survival, care pathways and results of treatments and other interventions. It has also been used to study the reason for variation in outcomes between healthcare providers(205,211,212).

2.1.1. Hospital Episode Statistics (HES)

The use of routine administrative NHS datasets, such as the HES database, has become increasingly common in the literature. My challenge was to work with data not primarily designed for research in such a way that the results and conclusions were accurate and clinically meaningful.

As reviewed in chapter 1, HES data presents several challenges including concerns about coding accuracy, coding depth and the use of non-specific symptom codes rather than diagnostic terms. Furthermore, HES contains no information on outpatient (clinic) attendances and does not include complete capture of some treatments such as chemotherapy and radiotherapy. Finally, HES does not record any quality of life indices. In addition, two particular concerns with the HES data are addressed here in chapter 2, the methods development chapter. These were a) the lack of a date of diagnosis and b) the accuracy and timing of diagnostic and procedural codes; these two concerns are connected. The lack of recording of a specific date of diagnosis within the routine dataset represents a key obstacle for using HES data to study cancer care. This is because the first time a cancer code appears, may be late in the care pathway and after the clinical diagnosis has been made. Instead at the time of first clinical presentation of the cancer, non-specific diagnostic codes may be recorded. Therefore, to get to the stage of using HES to study national CRC care, considerable manipulation of the raw data was required. In fact, developing novel analytical and linkage methods to overcome or compensate for these issues was a key aim of the thesis.

2.1.1.1. Date of diagnosis

Although HES data contains a number of fields for the recording of diagnostic codes, the actual date of diagnosis is not recorded in the dataset. This presents significant challenges:

Firstly, this creates uncertainty as to when a patient's inpatient journey began. This has implications for understanding how a patient initially presents (electively or as an emergency) and for calculating the timing of important procedures and overall survival time. All studies using routinely recorded data struggle to find the date when patient's symptoms first presented. One study based on comparing hospital records with structured interviews found that hospital records tend to underestimate symptom duration by around 2 months(213). Importantly, patients admitted as an emergency with CRC were less likely to be coded with a cancer diagnosis on their first admission than those presenting electively(214). This may erroneously lead to a patient's pathway beginning at a subsequent elective admission (where the cancer code appears for the first time) and not the presenting emergency admission. Without adjustment, for when these patients actually first presented then these pathways may record an incorrect start date and presentation type, and thus provide unreliable data.

Secondly, the lack of a date of diagnosis presents difficulties in distinguishing new (incident) cases from patients with a previously established diagnosis.

2.1.1.2. Coding of diagnoses and procedures

Coding is the process in which written information in patients' clinical notes is transferred into coded data and recorded into the hospitals information systems. Skilled clinical coders perform the task after the patient has been discharged from hospital. Their primary role is to enable hospitals to be reimbursed for their activity through the 'Payments by Results' (PbR) system. Clinical coders convert diagnostic terms recorded in medical notes into International Classification of Diseases (ICD-10) codes and procedures performed into Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4.5) codes.

The quality of the source documentation, as well as the skill of the coders, therefore determines the accuracy of patients' records. There are well documented concerns regarding coding accuracy, especially incomplete or inaccurate information that lacks sufficient depth to be clinically useful (205,215,216). Most clinical coders are well trained and accurate in converting clinical terms into codes, however they have difficulties identifying the correct information from unstructured clinical notes. This has led to a number of interventions over recent years to improve the recording of medical records and define certain standards(204).

There are other elements to the recording of HES data that need to be acknowledged.

Coding in HES can be vague and lack clinical detail. For example the use of an 'unknown colon cancer site' code instead of a site specific code, such as sigmoid cancer. While it is generally recognised that primary diagnostic codes (diagnostic position 1) are accurately recorded (with a 96% agreement with matched clinical registries), the accuracy of secondary codes is more disputed(204).

Secondly, procedural codes can be underreported, especially when undertaken as a day case(204). This has improved recently, especially following the introduction of PbR. It used to be the case that some

hospitals recorded 'day cases' as outpatient attendances without procedure details (rather than recording them as day cases in HES). This was potentially important in my study cohort, as procedural codes for investigations such as a colonoscopy often identify the beginning of a patient's pathway.

To comply with PbR rules, coding needs to be completed quickly after a patient's discharge from hospital. Patients are often discharged with a probable but not confirmed diagnosis, so in these cases, a cancer code cannot be used. This might occur if a day case colonoscopy identifies a mass with the appearance of cancer but where histological confirmation was still pending.

Between hospital trusts there are different policies and practices for the depth of diagnostic codes recorded. This can create the apparent appearance of higher or lower levels of co-morbidities between trusts and can affect the case-mix adjustments used to compare trust's quality of care. This problem has been described as the 'constant risk fallacy'(207). In practice, it means that highly coding practices generate the appearance of a population with a higher burden of co-morbidity. It is a common problem in all observational studies(217). There is also the theoretical possibility that some units might deliberately use inaccurate codes to maximise reimbursement. Despite this, organisational inaccuracies occur randomly across specific patient characteristics (such as gender) and so should not affect any conclusion based on the HES data nationally.

Overall, the evidence suggests that HES data accurately records the diagnoses and procedures in over 90% of cases(203). Therefore it is useful to study factors associated with disease outcomes nationally, using metrics derived from the available administrative and clinical content of the dataset (e.g. process measures such as emergency hospital presentation). There is the potential for inaccuracy when using HES, but this is addressed by applying the robust methodological approach described in sections 2.5.1-2.5.5. In addition HES can be useful to analyse individual hospital units, although any conclusions must be supported by an alternate source of data that is not influenced by individual coding practices. In the remainder of this chapter, I describe the steps taken to establish my cohort of CRC patients, after briefly setting out some of the main facts regarding CRC in England.

2.1.2. Established associations in Colorectal Cancer (CRC)

CRC is slowly and steadily becoming more common in England, with incidence increasing from 45/100,000 in 1975 to 58/100,000 in 2007(2). This is in part due to an aging population, as 84% of cases occur in patients over 60 years of age, *Figure 2.1*.

The association between CRC and individual patient characteristics, such as age, gender, co-morbidity, deprivation and cancer site have been well described and reviewed in chapter 1. To briefly review, there is a disparity in incidence between the genders, with males more likely to have CRC at all ages(218). The presence of co-morbidity in general is not consistently associated with susceptibility to CRC(219), although certain co-morbidities, such as Primary Sclerosing Cholangitis and Inflammatory Bowel Disease, are associated with an increased susceptibility to CRC(50,220). Furthermore, the risk of CRC

in patients with Ulcerative Colitis increases with the severity and duration of the colitis(47). While the association between deprivation and CRC is not clearly understood, incidence does not appear to be affected(30).

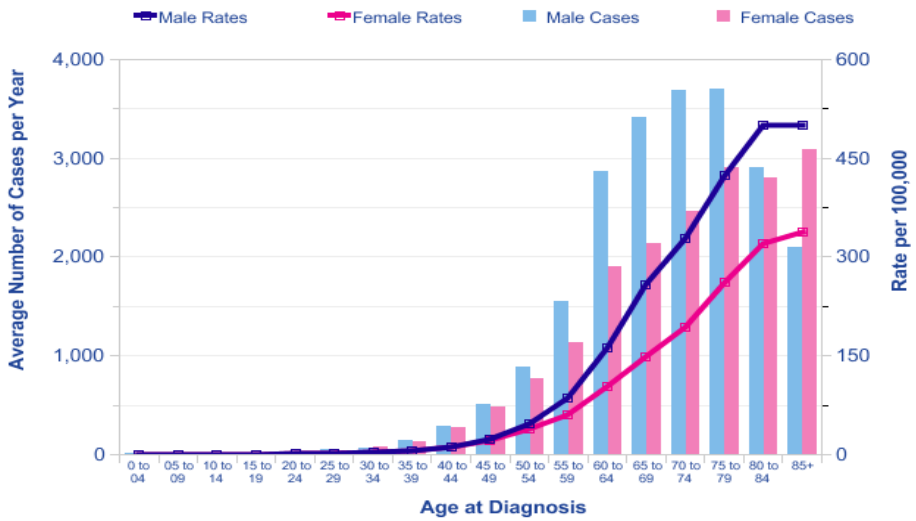


Figure 2.1 Chart taken directly from Cancer Research UK, showing the number of new cases (of colorectal and anal cancer) in different age groups and age-specific incidence rates per 100,000 population in the UK in 2007.

2.1.2.1. Associations between patient characteristics and outcomes

The stage of the CRC at diagnosis has a significant impact on patient outcome(5). In addition, older patients have worse outcomes and are less likely to be referred for major surgery. This may be related to delayed presentation, as a greater proportion of older patients have non-specific symptoms(221). Older patients are also more likely to have colonic cancer, which tends to present later. Other reasons for worse outcomes include the increased likelihood of co-morbidities and general frailty in older patients(222,223). By contrast younger patients tend to present earlier, due the presence of more specific symptoms such as rectal bleeding, and consequently achieve better outcomes(223).

Female patients have poorer outcomes; this is thought to be related to delays in seeking assistance from healthcare providers (224).

The impact of co-morbidity on the outcome of CRC is debated in the literature. Some studies have found that co-morbidity is associated with earlier stage diagnosis and better outcomes. This may be due to patients having more contact with their healthcare providers (related to their co-morbidity) allowing earlier identification of the cancer (225,226). Alternatively, the 'competing demands model' states that co-morbidities may distract healthcare providers attention away from early symptoms of CRC, leading to delayed diagnosis and worse outcomes (222,227). A meta-analysis found that co-morbidity in general does not directly affect the stage of diagnosis or outcomes(219). However, after excluding co-morbidities in general, there are some specific conditions such as diabetes, and dementia that affect CRC

outcomes. Diabetes, especially when poorly controlled, is associated with CRC developing at a younger age and more often in a proximal site. Patients then present at a more advanced stage with subsequent poorer outcomes(228,229). In one study, 7% of CRC patients had dementia and these patients were diagnosed at a more advanced stage and were often under-treated(230).

Deprivation is known to impact adversely on CRC survival, both in countries with universal health care entitlement, such as England, and in countries without, such as the United States(231-233). The reason for this is not entirely clear. Some studies have found that deprived patients are more likely to have advanced local disease and metastasis at presentation(234), while others have shown the stage of disease is unaffected by deprivation. It seems likely that later stage disease at diagnosis is at least partly responsible for the poorer outcomes seen in more deprived patients(235). A number of studies have looked at whether deprived patients have a longer duration of symptoms before seeking medical attention. Findings are inconclusive, with some studies pointing to an association(154,236) and others not(237,238). Even after accounting for differences in stage at diagnosis, deprived patients are more likely to receive no treatment or late treatment following initial first contact with the NHS(235). This is confirmed by the finding that outcomes for individual cancer treatments are unaffected by deprivation(239). One explanation for this may be that physicians perceive deprived patients more negatively leading to inequality in access to treatment(240). Overall, the literature suggests that deprived patients do less well because they have more advanced stage disease at diagnosis and inferior access to treatments.

With regard to cancer site, survival is slightly higher for rectal cancer than colon cancer. However, this predominately reflects the higher rate of rectal cancers diagnosed at a localized stage, with stage-specific survival similar between the two types(241).

The literature suggests that CRC outcomes are negatively associated with increasing age, female gender, deprivation and colonic cancer site. I will use my cohort of patients to explore these findings in more detail.

2.2. Hypothesis

The methodological research described in this chapter is based on the idea that it should be possible to generate clinically meaningful algorithms and linkage techniques that compensate for the limitations of the HES dataset and for variations in how care is coded. Specifically, that by using clinical logic and knowledge of CRC care, it is feasible to develop ways of analysing inpatient coding data to: Accurately identify 'incident' (new) patients diagnosed with CRC in English NHS hospitals over a one-year period; and Link together consecutive inpatient episodes to map the patient journey and determine key milestones (e.g. the first relevant day case or inpatient episode, and whether this was elective or as an emergency). For these methods to be deemed successful, the cohort of incident cases of CRC extracted

from HES data must show face-validity in terms of total numbers, clinical characteristics, mode of presentation and key outcomes when compared with independent published sources of data for CRC (in general, or for England specifically).

2.3. Aims

In this study I aimed:

- To apply clinical knowledge to the analysis of administrative data for English hospitals (Hospital Episode Statistics, HES).
- To develop methods for identifying a cohort of incident cases of CRC over a one-year period.
- Identify all relevant procedures, including lower gastrointestinal endoscopy and surgical resections, within the study cohort.
- To develop a novel procedure for identifying emergency presentation during the CRC pathway for this cohort, allowing me to explore algorithms to screen the full sequence of episodes recorded in HES (including admissions prior to the first coding of cancer) to find all clinically-relevant episodes.
- Identify each patient's **index** admission to hospital with CRC, recognizing that the first coding of cancer may not always coincide with the first clinically relevant admission to hospital.
- Identify whether each patient's first clinically relevant hospital admission was elective or an emergency.
- To compare this new methodology to the traditional analytical approach that focuses solely on episodes coded with a cancer diagnosis.
- To describe the socio-demographic characteristics of the study population (age, gender, co-morbidity, deprivation status and cancer site).
- To use external sources of information to verify the face-validity of case numbers, sociodemographic characteristics and selected outcomes.
- To identify any associations between the patient characteristics, presentation type and outcomes in the study cohort and to compare with existing knowledge in the published literature.

2.4. Methods

2.4.1. Defining my Study Cohort

I extracted a valid one-year cohort of incident CRC cases from England and then mapped their patient pathways. This allowed me to explore associations between patient characteristics, mode of presentation and outcome. My population included all patients aged 16 or over and who were discharged with a diagnosis of CRC from all English National Health Service (NHS) hospitals between October 2006 and September 2007.

In this chapter, I describe the method for correctly identifying a patient's presenting admission and whether it was as an emergency or elective. I also explain the steps taken to validate my cohort against external data sources. In chapter 3, I explore the patient and population associations with an emergency presentation. In chapter 4, I use the new methodologies to study whether the benefits of launching the BCSP extended beyond the minority of individuals actually screened. In particular was there an indirect benefit for the population as a whole, resulting from enhanced public, patient or professional awareness about CRC. This could be suggested if living in an area with a recently activated local BCSP was associated with a reduce risk of emergency presentation for CRC. Chapter 5 challenges whether confounding factors could explain the association between BCSP exposure and a reduced risk of emergency presentation.

2.4.1.1. Study design, data sources and timescales

I used a retrospective observational cohort design, based on data extracted from the HES for England. The source data comprised an extract of HES data for the years 2006-07 and 2007-08. This work formed part of a collaborative project with the NHS Information Centre examining the potential to use routine administrative data to derive clinically meaningful metrics of care for specific conditions ('Engaging Clinicians in their Routine Data') (242,243). The project dataset included data from all acute NHS Trusts, except those exclusively managing paediatric, maternity or psychiatric patients. The data were analysed within the secure University of Liverpool network using the statistical software package SPSS© (Version 18 and 20) as previously described(242,243). Data manipulation and analysis was undertaken mainly in SPSS, although some steps required importing/exporting between SPSS and the spreadsheet application Microsoft Excel©.

I developed methods to extract those patients that presented for the first time with CRC over a one-year period (1st October 2006 – 30th September 2007) from this database, *Figure 2.2*. I excluded patients whose first CRC code was in the 6 months before or after the middle 12 month period. By selecting only cases coded for the first time in the 'middle year' of the data, this ensured there was exactly 12 months of data for each study patient; six months of data before and after the first appearance of the cancer code. This approach ensured that I had the key diagnostic admission data from before the diagnosis was made and also details of treatments in the following six months.

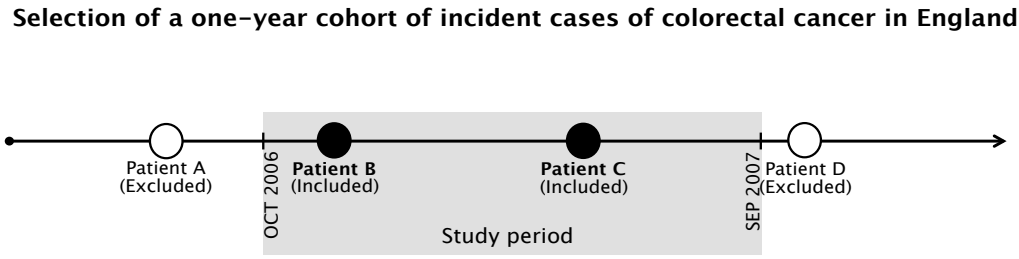


Figure 2.2 The cohort included all patients diagnosed with CRC for the first time within the study period (black circle), thereby excluding cases whose first hospital episode was before or after this period (white circle).

2.4.1.2. Methods to extract incident cases of CRC

Initially, the two separate data years (2006/7 and 2007/8) were merged and all patients with one or more episodes containing a diagnostic code for CRC were identified. Using a unique anonymous identifier assigned to each patient, I extracted all of their 'care episodes' from the main HES dataset and ordered them chronologically. Patients coded with CRC for the first time during the one-year study period (CRC1) were identified as incident cases. Important symptom codes (such as ICD-10 codes for rectal bleeding), procedures (e.g. colonoscopy), operations and outcomes (e.g. death or readmission) were also identified if they occurred within six months either side of CRC1. This allowed me to map a patient's pathway from their initial investigation and presentation (often in the absence of a CRC code) through to their outcome up to a year later, *Figure 2.3*. I then transformed the database from the 'episode' level to the more clinically meaningful 'admission' level. I did this only after extracting the important diagnoses and procedures, to ensure no data was lost. Data can be lost when care is transferred from one consultant to another during an admission, because earlier events can be missed from the final episode record.

Figure 2.4, shows the methodological steps taken to ensure the clinical richness of the database was maintained and that an equal period of data capture was recorded for all patients.

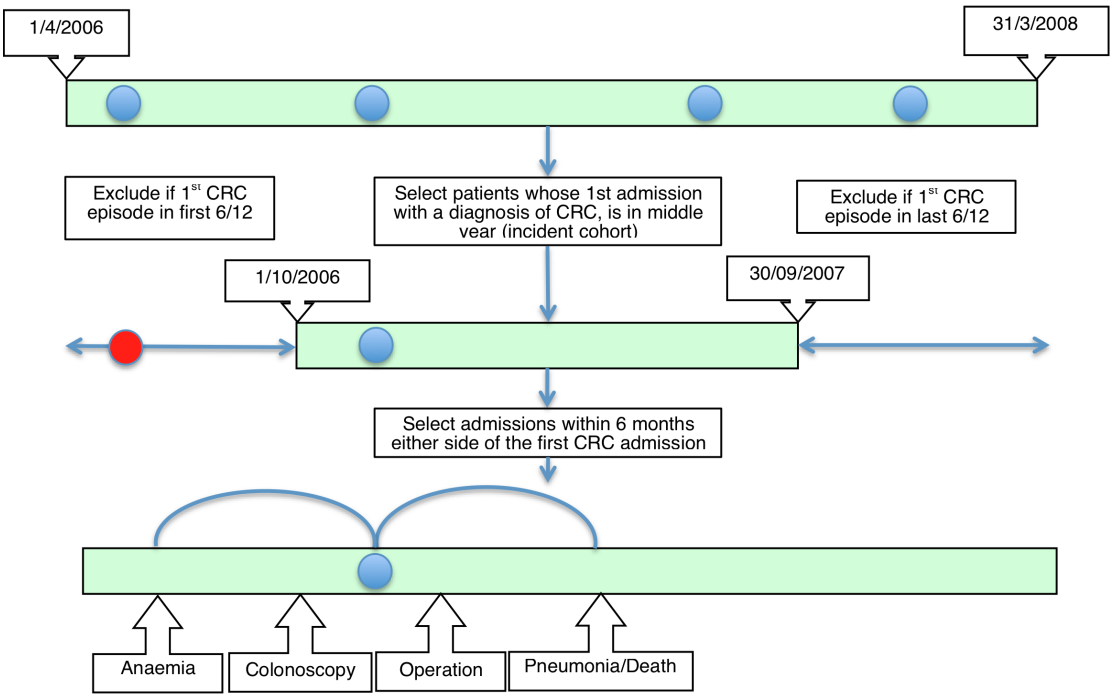


Figure 2.3 The steps taken to identify patients whose first CRC admission (CRC1) fell within the study year and include all admissions within six months. In the first bar, a blue circle represents the CRC1 admission for various patients. In the second and third bars, the 'blue circle' represents a patient retained in the final study cohort and the 'red circle' represents a patient removed because they presented outside the study period.

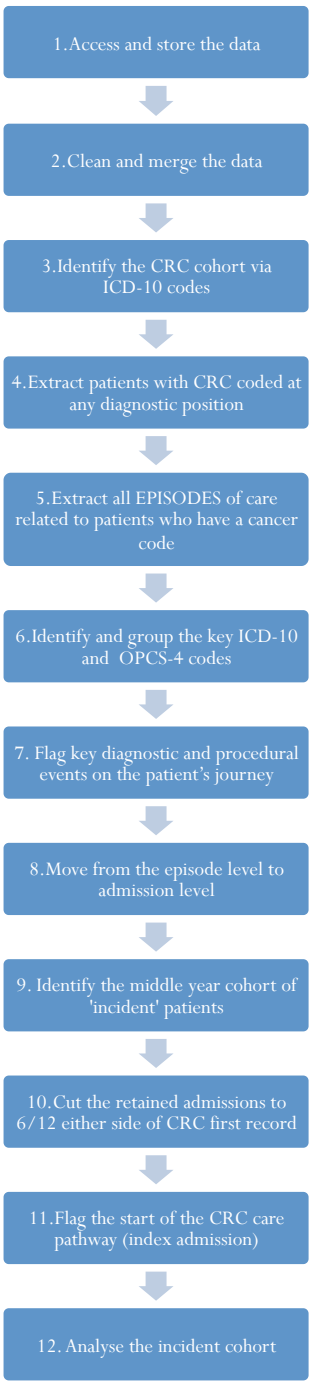


Figure 2.4 A methodological flowchart describing the steps taken to derive the 'incident cohort' patients.

2.4.1.2.1. Clean and merge the data

The two HES database years (2006/07 and 2007/08) were cleaned of irrelevant, invalid and nonsensical data. Examples of excluded data included inputs from maternity and paediatric hospitals and any data with missing or corrupted dates. This ensured that retained episodes referred to patients with a valid age (16 years or over), that care was provided by a medical or surgical team and the admission was to one of the 152 Acute Hospital Trusts in England, *Table 2.1*. The two data years were then merged into a single master file called 'All admissions merged file for 2006/2007 and 2007/2008'.

Table 2.1 The individual HES year datasets were cleaned to include only patients aged 16 years or over, with a valid admission code, under a relevant specialty (medicine or surgery) and managed in a trust treating CRC patients.

	Episodes in 2006/07	Episodes in 2007/08
Dataset containing medical and surgical episodes	**11,580,198**	**12,181,932**
Less;		
excluded admission methods	3,393	3,155
age not shown	5,699	10,296
under 16	404,875	422,100
invalid ages	28,267	30,141
excluded trusts	380,273	560,307
Selected Episodes	**10,757,691**	**11,155,933**

2.4.1.2.2. Identify all CRC patients using coding

Most studies using HES data only include admissions where the disease of interest is coded in position 1 of the database (DIAG01, the 'primary' diagnosis). This approach ignores the diagnostic codes in the other thirteen or more secondary diagnostic fields. This simplistic coding convention assumes that diagnoses coded in lower positions are co-morbidities, although our group has shown that non-specific symptom codes or complications of the disease of interest can appear in position 1 with the key diagnosis coded in a lower order position (242,243). To maximise the chances of capturing all cases of CRC, the methodology required screening of the first seven diagnostic positions (DIAG01-DIAG07) of all episodes in the master file for CRC specific ICD-10 codes, *Table 2.2*. Position seven (DIAG07) accounted for 0.2% (561/252,885) of CRC codes and beyond this position very few CRC codes was recorded at all. I considered it improbable that such an important diagnosis would not be mentioned at a higher position and so judged any CRC code beyond position seven almost certainly reflected a historical diagnosis.

The CRC ICD-10 codes are generally site specific, covering each section of the large bowel from the rectum to the caecum. However, in 14.4% (36,526/252,885) of cases, the code C189 (Malignant neoplasm of colon unspecified) was used, highlighting how HES data can sometimes lack clinical detail.

Using the SPSS, I created syntaxes (the standard programming function in SPSS) to screen for codes representing CRC in the large bowel. The syntax identified a total of 252,885 such episodes from diagnosis position one to seven, *Table 2.3*. Screening at diagnosis position one found 203,770 episodes, thus searching at the other positions identified a further 49,115 episodes or 19.4% of the total. This validates the importance of including episodes beyond position one, which substantially increased the total number of episodes identified and hence identified further CRC cases.

Patients with CRC often have multiple admissions to hospital and so these 252,885 episodes only represent some of the hospital visits. There are also occasions when patients with CRC have a hospital admission that does not lead to a CRC code being recorded in HES due to admissions prior to a formal diagnosis being made (see 2.5.2 for more details) or clinical note keeping not being clear about the CRC diagnosis. I deemed it important to record every hospital admission for patients occurring in the study period. Thus the final step in this process was to record all episodes occurring for patients with at least one CRC code. Using syntaxes based on the unique patient identifier in HES, I identified a total of 360,993 episodes belonging to patients with at least one CRC code in the study period, *Table 2.3*. These steps allowed me to glean as much information as possible from HES on the pathways followed by patients newly diagnosed with CRC.

Table 2.2 A table showing the frequencies of the different site specific CRC ICD-10 codes are shown at each of the first 7 diagnostic positions in the HES master file.

ICD-10	CRC site	DIAG01	DIAG02	DIAG03	DIAG04	DIAG05	DIAG06	DIAG07	Total
C20X	Rectum	58,706	7,290	4,061	2,113	803	438	170	73,581
C19X	Rectosigmoid	20,849	2,458	1,179	519	220	77	40	25,342
C187	Sigmoid colon	39,637	4,238	2,247	836	358	179	78	47,573
C186	Descending colon	4,893	550	264	86	49	17	6	5,865
C185	Splenic flexure	3,485	367	225	112	46	23	18	4,276
C184	Transverse colon	8,609	887	424	198	71	45	16	10,250
C183	Hepatic flexure	4,510	460	177	96	49	30	11	5,333
C182	Ascending colon	12,451	1,034	571	226	94	58	19	14,453
C180	Caecum	24,410	2,728	1,516	595	245	134	58	29,686
C189	Colon unspecified	26,220	4,958	2,981	1,295	649	278	145	36,526
Total		203,770	24,970	13,645	6,076	2,584	1,279	561	252,885

Table 2.3 A table showing how the inclusion of all episodes belonging to patients with a CRC code substantially increased the size of the two year HES database.

Episodes	2006/2007 episodes	2007/2008 episodes	2006-2008 episodes (all)
Total medical and surgical	10,757,691	11,155,933	21,913,624
CRC coded	125,792	127,093	252,885
Extended CRC database	177,147	183,846	360,993

2.4.1.3. Study cohort population

It was important to identify only incident CRC cases. To achieve this, I created algorithms to exclude cases where the CRC code referred to an established diagnosis from a previous data year. I excluded

these patients, as they would have been diagnosed and treated prior to the beginning of the study period and this may have affected outcomes.

2.4.1.3.1. Identify incident CRC patients exclusively

To identify when the first CRC code was recorded, patients had all their admissions placed in chronological order. Patients had already been excluded if their first CRC admission occurred outside of the middle year (1st October 2006 – 30th September 2007). This step identified 34,270 patients with a first CRC code within the study period.

Three further adjustments were then made to ensure only patients with a new diagnosis of CRC were included. Each of these steps therefore led to the exclusion of patients that had a pathway incompatible with a new diagnosis of CRC;

1. Historical cases; Patients with no CRC codes in either position 1 or 2 at any admission within the study period. These patients were judged unlikely to represent a new diagnosis and were removed as the CRC code in all likelihood represented a past diagnosis and thus a co-morbidity.

2. Miscoding (different cancer); When a patient had multiple codes for another gastrointestinal malignancy, such as Oesophageal and Gastric (OG) cancer and only a single CRC code within the study period, it was judged that the CRC code more likely represented a miscoding rather than a second *de novo* cancer.

3. Pre-diagnostic colorectal operations; Patients with a colorectal resection in the six months prior to the study period. In this instance it appeared likely that the diagnosis of CRC had occurred before the study year.

This left a final middle year incident cohort of **32,299 patients**, with **137,498 admissions**, *Table 2.4*.

Table 2.4 Patients were excluded from the cohort when the patient pathway appeared to show the CRC code was either historical (a co-morbidity) or entered by error.

Adjustments to the incident cohort	**No.**
Patients with a CRC code within the 2 years	74,142
-1st year	40,876
-2nd year	33,266
-Middle year	34,270 (137,498 admissions)
Historical	1,673 (4.9%) leaving 32,597
Miscoding (different cancer)	100 (0.3%) leaving 32,497
Pre-diagnostic Colorectal operations	198 (0.6%) leaving 32,299
Incident patient group	**32,299**

2.4.1.4. Exclusion criteria

In this section, I demonstrate that historical cases have been excluded. To do this, I studied the frequency of codes at the first diagnostic (primary diagnosis) and first procedural position (primary procedure) for the admission when the 1st coding for CRC (CRC1) appeared. If the primary codes at CRC1 (the patients first admission with a cancer code at any position) were either CRC codes *per se* or symptoms, diagnoses or procedures closely related to CRC then historical cases were unlikely to have been retained. However if the dataset contained a significant number of non-CRC related codes appearing at the first diagnostic and procedural position, then there was a risk that prevalent cases were retained and unrelated admissions were included where the cancer code appeared as co-morbidity or previously treated condition. While all admissions contained at least one diagnostic code for CRC, not all admissions contained a procedure.

Table 2.5 summarizes the 20 commonest primary diagnosis codes recorded at CRC1 for the cases retained in the study population. In many cases, the primary code was the specific CRC code itself. In some cases, the primary diagnosis recorded was a complication of cancer (e.g. intestinal obstruction) and the CRC code appeared as a secondary diagnosis.

I found that 90.9% of the CRC1 primary diagnoses were for CRC codes, *Table 2.5*. All the other remaining top 20 codes (accounting for 92.7% of patients), coded symptoms or diagnoses strongly linked to a new CRC diagnosis. These included symptom codes such as anaemia and rectal bleeding.

Manual review of all primary diagnostic codes were undertaken to generate a grouping system based on the primary diagnosis recorded. Although there is no systematic coding of symptoms for all patients, I looked at whether the recording of certain R-codes (symptom or sign codes that can be ill-defined, such as rectal bleeding) or specific diagnostic codes compatible with CRC complications were more prevalent. The groups were: a) CRC diagnosis, b) unverified cancer e.g. a malignant polyp, c) a red flag symptom, e.g. rectal bleeding, d) metastases e.g. liver metastasis, e) other gastrointestinal diagnoses e.g. diverticular disease, f) other gastrointestinal symptoms e.g. nausea or g) other non-gastrointestinal related symptoms or diagnoses. Table 2.6 demonstrates the strong predominance of CRC codes and lack of non-CRC related diagnoses among the 20 commonest primary diagnoses. This makes it unlikely that historical CRC cases remained in my cohort.

Table 2.5 The 20 commonest ICD-10 codes in the primary diagnosis position at the CRC1 admission.

Diagnosis	**No. (%)**
Malignant neoplasm of rectum	8,655 (26.8)
Malignant neoplasm of sigmoid colon	5,725 (17.7)
Malignant neoplasm of caecum	3,675 (11.4)
Malignant neoplasm of colon unspecified	3,331 (10.3)
Malignant neoplasm of rectosigmoid junction	2,194 (6.8)
Malignant neoplasm of ascending colon	2,000 (6.2)
Malignant neoplasm of transverse colon	1,318 (4.1)
Malignant neoplasm of descending colon	783 (2.4)
Malignant neoplasm of hepatic flexure	730 (2.3)
Malignant neoplasm of splenic flexure	555 (1.7)
Malignant neoplasm of appendix	185 (0.6)
Other and unspecified intestinal obstruction	116 (0.4)
Malignant neo overlapping lesion of rectum, anus and anal canal	112 (0.3)
Anaemia unspecified	112 (0.3)
Secondary malignant neoplasm of liver	108 (0.3)
Malignant neoplasm overlapping lesion of colon	95 (0.3)
Haemorrhage of anus and rectum	77 (0.2)
Non-infective gastroenteritis and colitis unspecified	65 (0.2)
Polyp of colon	54 (0.2)
Iron deficiency anaemia unspecified	52 (0.2)
Total	29,942 (92.7)

Table 2.6 The 20 commonest primary diagnostic codes at CRC1 merged into clinically coherent groups following manual review. These groups demonstrate the overwhelming majority of primary diagnoses were associated with a new diagnosis of CRC.

Diagnostic & Symptom groups	**No. (%)**
Colorectal cancer	29,358 (90.9)
Pending confirmation e.g. polyp	54 (0.2)
Metastasis	108 (0.3)
Symptom codes (R codes)*	
Red flag symptoms**	422 (1.3)
Anaemia*	164 (0.5)
Non CRC related*	0
Total, top 20 codes	29,942 (92.7)
Cohort total	32,299

*Symptom codes (which can be ill-defined) are given an R prefix within Chapter XVIII of the International Classification of Diseases-10.

** Red flag alarm symptoms included rectal bleeding, change in bowel habit, abdominal mass, abdominal pain and anaemia.

Table 2.7 summarizes the 20 commonest primary procedural codes recorded at the first CRC coded admission (CRC1). All of these codes were relevant to the investigation and management of CRC and the commonest were lower gastrointestinal endoscopies and surgical resections. In 15.7% of patients there was no procedure recorded. I manually reviewed the 20 commonest codes and placed them into clinically related groups, *Table 2.8*. The commonest group was lower gastrointestinal endoscopy (36.8%), followed by major surgical resections (16.6%), radiological investigations (2.8%) and other gastrointestinal procedures e.g. OGD (1.2%). Other colorectal operations (E.g. defunctioning colostomies and ileostomies) were infrequent (2.3%).

I have demonstrated that, at the CRC1 admission, the majority of my cohort had a procedure related to managing CRC. However this did not necessarily mean the CRC1 admission was the first admission in a patient's CRC pathway. The relatively low rate of lower endoscopies and high operative rate made me conclude that there were likely to be earlier relevant admissions – consistent with the hypothesis that the first recording of a cancer code does not always signify the first relevant inpatient episode. In the following section, I will describe which patients' had an earlier relevant admission and whether it was more accurate at marking the start of their CRC pathway. This introduces the new concept of a **'first relevant admission'** (REL1) and the development and testing of methods to identify the true 'index

admission' – the first hospital care episode in the patient's cancer care pathway, when the cancer code may, or may not, be recorded.

Table 2.7 The 20 commonest primary procedures at CRC1. All of these procedures were relevant to the investigation and management of CRC.

OPCS-4	Procedure	No. (%)
H221	Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon	6,019 (18.6)
-	Not recorded	5,087 (15.7)
H251	Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fibreoptic sigmoidoscope	3,721 (11.5)
H201	Fibreoptic endoscopic snare resection of lesion of colon	969 (3.0)
H072	Right hemicolectomy and side to side anastomosis of ileum to transverse colon	897 (2.8)
H073	Right hemicolectomy and anastomosis	780 (2.4)
H229	Unspecified diagnostic endoscopic examination of colon	711 (2.2)
H071	Right hemicolectomy and end to end anastomosis of ileum to colon	660 (2.0)
H333	Anterior resection of rectum and anastomosis of colon to rectum using staples	642 (2.0)
H334	Anterior resection of rectum and anastomosis	615 (1.9)
H335	Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel	598 (1.9)
H336	Anterior resection of rectum and exteriorisation of bowel	503 (1.6)
U081	Computed tomography of abdomen	491 (1.5)
H259	Unspecified diagnostic endoscopic examination of lower bowel using fibreoptic sigmoidoscope	457 (1.4)
U071	Computed tomography of chest	413 (1.3)
H151	Loop colostomy	402 (1.2)
H331	Abdominoperineal excision of rectum and end colostomy	391 (1.2)
G451	Fibreoptic endoscopic examination of upper gastrointestinal tract and biopsy of lesion of upper gastrointestinal tract	374 (1.2)
H412	Peranal excision of lesion of rectum	354 (1.1)
H062	Extended right hemicolectomy and anastomosis of ileum to colon	286 (0.9)
Total		24,370 (75.5)

Table 2.8 The 20 commonest primary procedural codes at CRC1 merged into clinically coherent groups following manual review. The commonest groups were for lower gastrointestinal endoscopy (36.8%) and for major surgical resections (16.6%).

Procedural group	No. (%)
GI endoscopy (lower)	11,877 (36.8)
Major resection	5,372 (16.6)
Other colorectal operations	756 (2.3)
Other GI procedures, inc. OGD	374 (1.2)
Radiological investigation	904 (2.8)
Non recorded	5,087 (15.7)
Total	24,370 (75.5)
Cohort total	32,299

2.4.2. Index admission

I initially considered that a patient's pathway began with the first admission recording a CRC code (CRC1). However, some studies have shown that the first CRC coding admission was not always the patients' first relevant contact with the hospital(2,244). Furthermore, the findings from the section above, made me consider whether on occasions an earlier relevant admission (REL1) marked the cancer presentation. This suspicion was heightened by a line-by-line manual review of the HES records, revealing that some patients had relevant hospital admissions in the weeks prior to their first coding of cancer. Therefore, if an earlier admission (REL1) had a diagnosis or procedure, in keeping with their CRC presentation, then the REL1 and not the CRC1 should be the index admission marking the beginning of a patient's pathway.

REL1 admissions prior to the CRC1 admission may occur when an outpatient colonoscopy is performed to investigate red flag symptoms such as rectal bleeding. In these patients, a CRC code will not be recorded until the histology is known, at the subsequent hospital admission.

To identify relevant admissions prior to CRC coding; I created a steering group that comprised of three clinical specialists (gastroenterologists), two NHS data specialists and as a general physician with experience of NHS data analysis. This was consistent with the original wider project whereby clinical engagement in the analysis of the data was seen as a means to extract greater value from HES (242,243). They used their combined skills and knowledge to identify all diagnoses and procedures considered relevant in the presentation of CRC. Codes were agreed by consensus. Examples included symptoms such as constipation, signs compatible with underlying cancer such as iron deficiency anaemia and lower gastrointestinal endoscopic procedures. **A full list of the included codes is found in *Appendices 1 and 2*.**

2.4.2.1. Definition and Identification

To identify a patient's index admission I searched for the presence of a 'relevant' hospital admission

(REL1) prior to the CRC1. I screened all the admissions in the six months prior to CRC1 for primary diagnoses and procedures relevant to the CRC pathway. A patient's presentation date (index admission) was therefore defined as the CRC1 admission date unless there was a REL1 admission within in the preceding 6 months, in which case this was the index admission date.

2.4.2.1.1. Identification of ICD-10 codes relevant to clinical presentation of CRC

The stages involved identifying all diagnostic codes that might represent CRC presentation were as follows;

1. I used pivot tables in Microsoft 'Excel®' to interrogate diagnostic positions 1-7 for all episodes during the study period. I then calculated the number of times each diagnosis appeared.
2. The steering group then interrogated each diagnostic code that appeared in 10 or more episodes, selecting codes for inclusion, which were deemed clinically relevant. Initially, the steering group selected diagnostic codes from two groups; 'red flag' codes (e.g. rectal bleeding), shown in *Appendix 1.1* and 'anaemia codes' (e.g. iron deficiency), shown in *Appendix 1.2*. The list was expanded to include a group of gastrointestinal type diagnoses and symptoms including, for example, diverticulosis or nausea respectively, shown in *Appendix 1.3*. This was because HES coding tends initially to be vague and rely heavily on symptom codes. The merged group was called 'Gastrointestinal type diagnoses and symptoms'.

2.4.2.1.2. Identification of OPCS-4 procedure codes relevant to clinical presentation of CRC

I identified all procedures that strongly indicated a diagnosis of CRC. These procedures comprised of three groups that occur at different stages of the CRC pathway;

- Those that make the diagnosis (endoscopic procedures)
- Those that stage the CRC (radiological investigations)
- Those that treat the CRC (surgical resection, stoma formation)

Only admissions in the first two groups were selected to screen for earlier relevant admissions (REL1). The third group (treatment options) identified the treatment options that patients had received.

The stages involved in identifying all procedural codes that might represent CRC presentation were as follows;

1. Pivot tables in Microsoft 'Excel'® were used to interrogate procedural positions 1-14 for all episodes in my study cohort.
2. The steering group interrogated all procedural codes that appeared in 10 or more episodes and selected codes that were deemed 'clinically relevant'. They selected gastrointestinal endoscopies, shown in *Appendix 2.1*, as well as radiological imaging such as Computer

Tomography, Ultrasound and Magnetic Resonance Imaging of the gastrointestinal tract, shown in *Appendix 2.2*. The merged group was named 'Gastrointestinal type procedures'.

The main treatment modalities that were identified separately include surgical resections (e.g. anterior resection) and palliative defunctioning procedures (e.g. colostomy), shown in *Appendix 3.1*.

The codes for 'Gastrointestinal type diagnoses and symptoms' were merged with the investigative procedures 'Gastrointestinal type procedures' to form a group called **'Gastrointestinal relevant episodes'**. Using this group of codes I was able to determine if an earlier relevant admission existed for an individual patient. I did this by creating a syntax to search for the first admission containing any 'Gastrointestinal relevant episodes' in the six months prior to the CRC1. This admission was called the first relevant admission (REL1) and created a milestone, when present, denoting the beginning of the patient's cancer pathway (index admission). When there was no earlier relevant admission in the six months prior to first coding of cancer then the index admission was CRC1. Further detail of how this approach was applied to describe the patient pathways is explained later in the chapter.

2.4.2.2. Validating the "first relevant admission" (REL1)

23.2% (7,503/322,99) of patients were identified as having a REL1 admission prior to the first CRC coding admission (CRC1). The mean time interval between the two admissions was 52 days (SD 41.3) with 74.2% of REL1 admissions occurring less than three months before CRC1.

The reasoning for identifying earlier relevant admissions was based on the assumption that these would more accurately reflect the *starting point* for a patient's journey. For this methodological approach to be valid, the diagnostic and procedural codes for REL1 admissions needed to be consistent with the beginning of a CRC pathway. In this section, I have identified the types of diagnoses and procedures at the REL1 and compared them to CRC1 admissions.

At the REL1 admission there were by definition no CRC codes. Instead, the 20 commonest primary diagnostic codes (representing 60.7% of patients) were all relevant to the presentation of CRC. The commonest codes were either for signs or symptoms related to CRC (e.g. anaemia) or other lower gastrointestinal symptoms, as shown in *Table 2.9*. In *Table 2.10,* the codes were grouped according to clinical themes: the commonest groups were red flag symptoms (20.5%), anaemia (16.1%) and codes where CRC confirmation was pending (e.g. *uncertain neoplasm*) (15.4%), all of which potentially identify the start of a CRC pathway.

Table 2.9 The 20 commonest primary diagnostic codes at the REL1 admission were predominately for red flag symptoms, such as rectal bleeding and for anaemia.

Diagnoses	**No. (%)**
Anaemia unspecified	613 (8.2)
Haemorrhage of anus and rectum	518 (6.9)
Iron deficiency anaemia unspecified	369 (4.9)
Polyp of colon	357 (4.8)
Other and unspecified abdominal pain	276 (3.7)
Other iron deficiency anaemias	225 (3.0)
Diverticular dis of large intestine without perforation or abscess	222 (3.0)
Benign neoplasm of rectum	184 (2.5)
Neoplasm uncertain or unknown behaviour colon	184 (2.5)
Rectal polyp	183 (2.4)
Non-infective gastroenteritis and colitis unspecified	178 (2.4)
Other and unspecified intestinal obstruction	169 (2.3)
Constipation	165 (2.2)
Benign neoplasm of sigmoid colon	156 (2.1)
Change in bowel habit	117 (1.6)
Pain localized to other parts of lower abdomen	117 (1.6)
Gastritis unspecified	113 (1.5)
Diaphragmatic hernia without obstruction or gangrene	105 (1.4)
Diverticular disease without perforation or abscess	94 (1.3)
Neoplasm uncertain or unknown behaviour rectum	93 (1.2)
Total	4,551

Table 2.10 The 20 commonest primary diagnostic codes at the REL1 admission were placed into clinically related groups. This showed codes related to red flag symptoms, anaemia as well as those stating confirmation of CRC was pending were most frequently found.

Diagnostic & Symptom groups	**No. (%)**
Pending confirmation e.g. polyp	1,157 (15.4)
Metastasis	0
Red flag symptoms	1,540 (20.5)
Anaemia	1,207 (16.1)
Other Gastrointestinal diagnosis e.g. Diverticular disease	534 (7.1)
Other Gastrointestinal symptoms	113 (1.5)
Other symptoms & diagnoses	0
Total from Table 2.9	4,551 (60.7)
Cohort total	32,299

The 20 commonest primary procedural codes were all consistent with the start of a CRC pathway, *Table 2.11*. Putting the codes in clinically related groups, showed that over half of patients had a lower

gastrointestinal endoscopy, *Table 2.12*. The rate of lower gastrointestinal endoscopy was significantly higher at the REL1 admission than at the CRC1 admission (52.5% vs. 36.8%, P<0.001). Lower GI endoscopy was the investigation that most commonly diagnosed CRC, validating the methodology for identifying the index admission.

If I had used only the CRC1 admission (as is standard practice for HES studies) rather than the more sophisticated method of identifying the REL1, then 7,503 patients or 23.2% of the cohort would have been assigned a later presentation date (an error rate of almost 1 in 4). This is important as the presentation type (elective or emergency) was used as an important outcome measure in later chapters and inaccuracy at this stage would introduce errors.

In conclusion, evidence has been presented to support my assertion that the REL1 admission was a more accurate starting point than CRC1. In particular, the higher rate of lower gastrointestinal endoscopy codes implies this milestone is a more accurate. Henceforth in this thesis, when a REL1 admission is present, it is used instead of the CRC1 admission to denote presentation (index admission).

Table 2.11 The 20 commonest primary procedural codes at the REL1 admission.

Procedure	**No. (%)**
Non-recorded	2,214 (29.5)
Fiberoptic endoscopic examination of upper gastrointestinal tract and biopsy of lesion of upper gastrointestinal tract	1,066 (14.2)
Diagnostic fiberoptic endoscopic examination of colon and biopsy of lesion of colon	717 (9.6)
Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fiberoptic sigmoidoscope	563 (7.5)
Unspecified diagnostic endoscopic examination of lower bowel using fiberoptic sigmoidoscope	425 (5.7)
Unspecified diagnostic fiberoptic endoscopic examination of upper gastrointestinal tract	369 (4.9)
Unspecified diagnostic endoscopic examination of colon	278 (3.7)
Fibreoptic endoscopic snare resection of lesion of colon	215 (2.9)
Unspecified other blood transfusion	206 (2.8)
Computed tomography of abdomen	172 (2.3)
Unspecified diagnostic endoscopic examination of sigmoid colon using rigid sigmoidoscope	112 (1.5)
Endoscopic snare resection of lesion of lower bowel using fiberoptic sigmoidoscope	74 (1.0)
Computed tomography of chest	67 (0.9)
Intravenous blood transfusion of packed cells	55 (0.7)
Computed tomography of head	54 (0.7)
Fibreoptic endoscopic cauterisation of lesion of colon	44 (0.6)
Unspecified endoscopic extirpation of lesion of colon	30 (0.4)
Computerised tomography NEC	25 (0.3)
Endoscopic cauterisation of lesion of lower bowel using fiberoptic sigmoidoscope	24 (0.3)
Peranal excision of lesion of rectum	24 (0.3)
Total	6,734 (89.8)

Table 2.12 At the REL1 admission, the 20 commonest procedures were placed into clinically related groups. The most prevalent group was GI endoscopy (lower) (52.5%).

Procedural group	No. (%)
GI endoscopy (lower)	3,941 (52.5)
Other procedures, inc OGD	261 (3.5)
Radiological test	318 (4.2)
Non-recorded	2,214 (29.5)
Total from Table 2.11	6,734 (89.8)
Cohort total	7,503

2.4.3. Patient characteristics

The baseline patient characteristics described in my patient population included patient age, gender, co-morbidity, deprivation and the cancer site. Establishing how frequently these characteristics occurred was important for a number of reasons. Firstly, it allowed me to gauge how well I had identified the full national cohort of patients. I did this by comparing the crude totals with other externally validated national data sources. Secondly, it allows others to assess the applicability of my study results compared with the populations they are studying. Finally, as individual characteristics, such as age and co-morbidity were important prognostic factors, knowing how frequently they occurred, helped understand the outcomes data.

These same characteristics were used throughout my thesis to describe the presentation and outcome findings. In my study cohort, a patient's age and gender were recorded from the CRC1 admission record.

2.4.3.1. Co-morbidity

Co-morbidity describes the presence of one or more additional disorders (or diseases) co-occurring with the CRC. It is important to identify all relevant co-morbidities as they may have a large impact on a patient's presentation and their outcome.

The Charlson co-morbidity index predicts the ten-year mortality for a patient by taking into account a range of comorbid conditions, such as heart disease and cancer. Each condition is assigned a weighted score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are then summed to provide a total score to predict mortality(245-247). I used the Charlson co-morbidity index in this thesis and calculated a patient's co-morbidity from their CRC1 admission. The first seven diagnostic positions were scored appropriately and added together to create the total Charlson score. There are 14 fields available for diagnostic codes in each episode. However co-morbidities in position 8 or above were only recorded in <1% of patients and so not recorded in this thesis. I assigned co-morbidity based on the weighted Charlson score after excluding the score for the CRC diagnosis. This categorized

patients into one of three groups (None, score of 1 or ≥2) (2,30,244,247). I restricted the number of co-morbidity groups to three to partially control for variations in the case-mix adjustment caused by a number of trusts taking different policies regarding the depth of coding. See the description of the 'constant risk fallacy' in section 2.2.1.2 for more information.

2.4.3.2. Deprivation

I have already described how relative deprivation is associated with poorer outcomes in CRC(248). It is therefore important that any CRC outcome study measures individual patient deprivation. Unfortunately there was no direct record of a patient's level of deprivation in HES. Instead, a deprivation score is derived from where the patient lives, their Lower Super Output Area (LSOA). The LSOA is a geographical area specifically designed for the analysis of small area statistics and contains approximately 400 houses. The LSOA score is based on 10 sets of data that include income, employment, education, health and disability indices within that area. These 10 sets of data were then individually weighted and summed to provide an Index of Multiple Deprivation (IMD) score. This allows deprivation levels to be compared between small geographical areas and, by inference, between their populations. A patient's recorded level of deprivation was therefore based on their IMD score at the CRC1 admission. A rank of 1 is the most deprived and 32,482 the least deprived. In my study cohort, as with previous studies, patients were divided into five quintiles to allow comparison between the different 'relative' deprivations(30,244).

2.4.3.3. Cancer site

The incidence of cancer at the different sites varies depending on age and gender. Cancer presentation and outcomes also depend on the site involved. Rectal cancers tend to present earlier and, when matched for stage, stage C and above rectal cancers do better(241). The cancer site used in this thesis was based on the coding used at the CRC1 admission. HES codes exist for each anatomical section of the large bowel (for example cancer of the caecum). To follow the approach used by the majority of cancer registries and so allow comparison with external data sources I merged the individual codes for large bowel cancer into three groups; colonic, rectosigmoid and rectum. This also allowed me to include colonic cancers that had been given a non-site specific code.

2.4.4. Patient Presentation

Knowing the admission type when the patient first presented with CRC enabled me to understand whether the overall patient pathway began as an emergency or electively. As emergency presentation was associated with adverse outcomes and it was very important that all such cases were accurately recorded. In subsequent chapters the causes and implications following emergency presentations will be described in more detail.

In the analysis described in this section, I made further checks on the validity of my methodological approach as well as describing the consequences of different presentations identified at the index admission.

2.4.4.1. Emergency Vs. Elective Admission

This defines whether the individual patient's pathway was elective or an emergency, to do this I identified the admission method (ADMIMETH field) at their index admission (16).

Patients with ADMIMETH field terms "emergency admission via A and E, via the GP, the bed bureau, out-patient clinic or from another hospital" were identified as an emergency admission. All other admission codes recorded in the ADMIMETH field were recorded as an elective admission.

2.4.4.2. The six presentation pathways

A patient's index admission was found by screening all admissions in the six months prior to the CRC1 for the earliest 'Gastrointestinal relevant admission'. For many patients there were no earlier relevant admissions (REL1), so CRC1 was used. However, when an earlier relevant admission (REL1) existed, it was recorded as the index admission. This approach created six distinct pathways based on the type of presentation at the REL1 and CRC1 that describe the beginning of a patient's journey, *Table 2.13*.

Table 2.13 The six potential presentation pathways based on the mode of admission (elective or emergency) at the first relevant admission (REL1) and first coding with CRC admission (CRC1).

Pathway	**No. of patients**	**Percentage of patients**	**Description**
1. El	16,430	50.9%	Patients for whom the CRC1 code was given after an elective admission, and had no earlier gastrointestinal related admissions.
2. ElEl	3,584	11.1%	Represents patients with an elective gastrointestinal related admission before the first CRC coded elective admission
3. EmEl	1,954	6.0%	Represents patients with an emergency gastrointestinal related admission before elective CRC1 admission.
4. Em	8,366	25.9%	Represents patients for whom the CRC1 code was given during an emergency admission and who had no earlier gastrointestinal related admissions.
5. EmEm	1,331	4.1%	Represents patients with an emergency gastrointestinal related admission before the CRC1 emergency admission.
6. ElEm	634	2.0%	Represents patients with an earlier elective gastrointestinal related admission before the emergency CRC1 admission.

This approach allowed a patient's pathway to be identified as fully elective, fully emergency or switching between emergency and elective care, *Figure 2.5*. The key question was: "are patients whose presentation type has switched based on the REL1 admission truly more like the presentation group they have joined than the group they have left?" That is, are the rates of diagnostic and procedural codes for patients in the EmEL pathway really closer to other patients with emergency presentations, i.e. Em and EmEm?

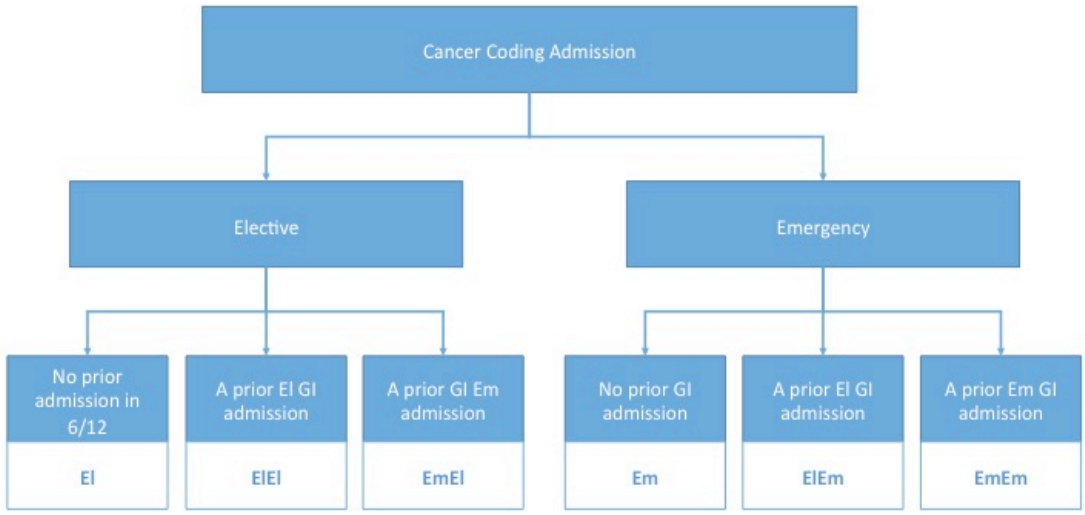


Figure 2.5 This flowchart demonstrates the six pathways that patients with CRC can take

El= elective admission type, Em= emergency admission type

2.4.4.3. Validating the pathways

In this section I presented evidence suggesting my methodological approach had correctly identified patients presenting as an emergency or electively. I have already shown that, compared to CRC1, a REL1 admission more accurately reflected the patient's presentation (index admission) to hospital care (methods; section 2.5.2.2).

If my methodological approach was correct then the three pathways that began electively (El, ElEm, ElEl) would have rates of diagnostic and procedural codes distinct from the three pathways that begin as an emergency (Em, EmEl, EmEm).

For most patients (n=24,796, [76.8%]), the index admission was also their CRC1 admission (i.e. the patient belonged to the group El or Em). The remaining patients (n=7,503 [23.2%]), all had an earlier REL1 admission. This encompassed two pathways (EmEm and EmEL) with an earlier emergency admission (n=3,285 [10.2%]) and two pathways (ElEl and ElEm) with an earlier elective admission (n=4,218 [13.1%]).

I found the three elective groups (El, ElEl and ElEm) had similar rates of primary procedure codes at the index admission. These code profiles were distinct from the three emergency groups (Em, EmEm and EmEl), which also shared similar profiles to each other, *Figure 2.5*.

Looking at the frequency of procedure rates, the elective groups (El, ElEl and ElEm) all had high rates of lower gastrointestinal endoscopy codes (61.0%, 85.5% and 75.9%). This was not the case for the EmEl group (18.5%), whose lower gastrointestinal endoscopy rate was closer to the other emergency groups (Em 12.8% and EmEm 12.2%), *Figure 2.6*. This was an important finding because it suggested that changing the presentation type based on identifying an earlier relevant admission has allowed patients with similar diagnoses and procedures at presentation to be grouped together. In other words it identified when patients had actually presented. Finally, I found that the procedural rates for the ElEm and EmEl groups were markedly different. This demonstrated that it was not the presence of an emergency admission at any point in the pathway that makes the difference, but its presence at the start.

Accepting that the index admission was actually the start of the patient's pathway, led to an increase in the number of cases defined as an emergency from 32.0% to 36.1%. This was because the EmEl group (n=1,954) was larger than the ElEm group (n=634). This was an important observation, as it shows my methodology identified more patients as having an emergency presentation than would be identified using traditional methods. Furthermore, this approach lengthens these patients' diagnostic journeys and thus slightly increases overall projected survival.

In summary, the groups El, ElEl and ElEm are similar to each other, as are the groups Em, EmEm and EmEl, *Figure 2.5, 2.6*. This supports the hypothesis that, when present the index admission should be the REL1 admission.

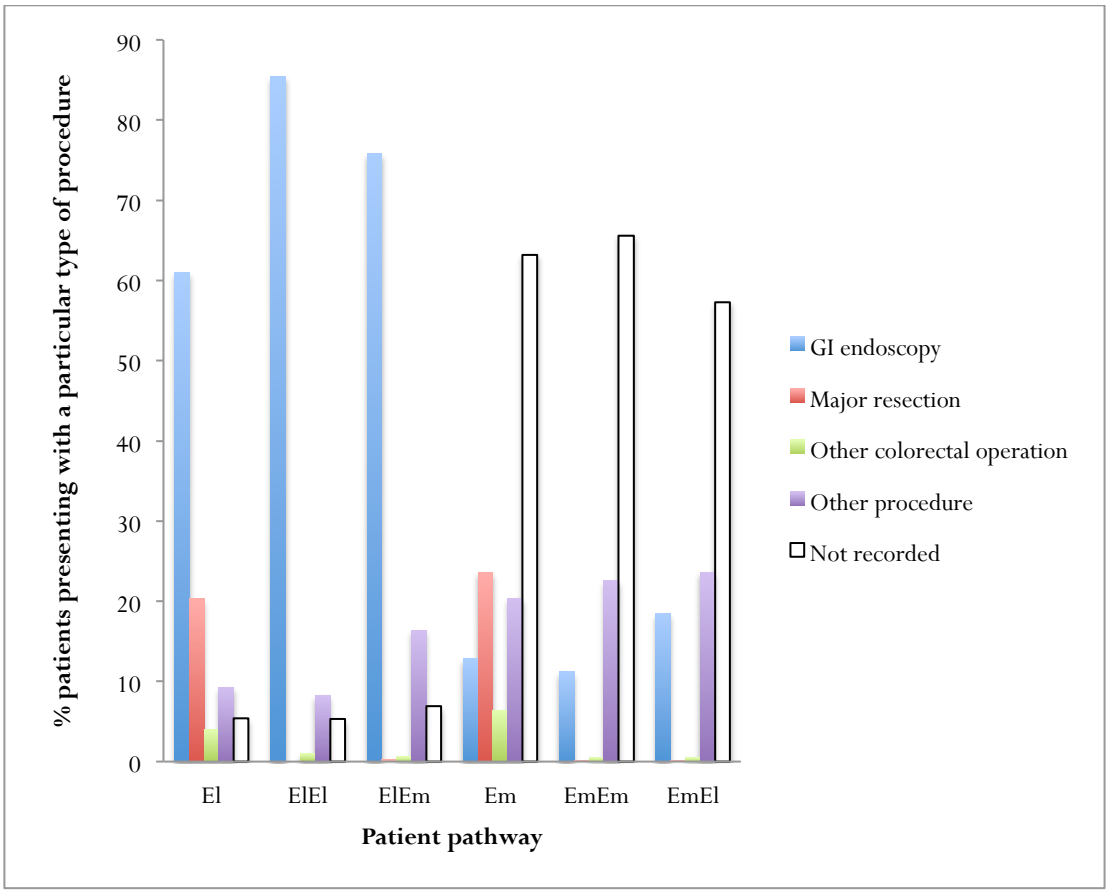


Figure 2.6 The rates of clinically related types of procedures in the six presentation pathways.

2.4.5. Patient outcomes

To validate my study population against external data sources, my primary outcome measures were major surgical resection and one-year mortality taken from the index admission. These outcomes are commonly described in the literature and thus allowed me to compare my results to external data sources later in the chapter. Secondary outcome variables included: any colorectal operation; the timing of surgery; length of stay and readmission after surgery, all of which are validated measures of care quality(150).

2.4.5.1. Primary outcome measures

2.4.5.1.1. Major surgical resections

Major surgical resections were classified as operations that removed a segment of the colorectum either with direct anastomosis or with a temporary or permanent stoma. This was the most important intervention for most patients with CRC and offers the greatest chance of cure. A syntax was run, to search for surgical resection codes at every admission including and following the index admission. I also defined the operation type and whether it involved a laparoscopic approach or required stoma formation.

2.4.5.1.2. One-year mortality

To identify patients dying within one-year of presentation HES data was combined with data from the Office of National Statistics (ONS). HES records deaths during an in-patient episode and not those occurring out of hospital, therefore, HES did not capture some deaths amongst my patient population. To capture all deaths occurring during follow-up, out of hospital deaths were added by external linkage to the statutory register of deaths held by the ONS, using the unique patient identifier. The one-year mortality was calculated from the date of the index admission.

2.4.5.2. Secondary outcome measures

I identified secondary outcome measures that were all widely accepted quality markers(150). Secondary outcomes were classified as:

1. All colorectal operations; this was a broader definition of colorectal surgery than the outcome 'major surgical resection' and included all the above mentioned resections, along with defunctioning ileostomies and colostomies. These operations are often reserved for palliative patients or those with co-morbidities that precluded more aggressive surgical management.
2. The length of stay, where I described the number of nights in hospital after the index admission and at the admission when major surgical resection occurred.
3. Hospital re-admission in the 30-days following discharge from hospital, after a major surgical resection.

2.5. Results

2.5.1. Overview of my study cohort

There were 32,299 incident cases of CRC in my one-year cohort and patient characteristics are summarized in *Table 2.14*. Patients were allocated to the following age groups: <55 yrs, 55-64 yrs, 65-74 yrs, 75-84 yrs and ≥85 yrs. Co-morbidity was defined with Charlson scores (None, score of 1 or ≥2). Finally, cancer site was split into three distinct areas; rectal, rectosigmoid or colon. In most patients with colon cancer, the anatomical site was accurately defined (i.e. ascending or transverse colon cancer) however unlike in the rectal cancers, it can be difficult to describe the exact site of a colon cancer endoscopically. For this reason, some patients were given the code 'malignant neoplasm of colon unspecified'. Patients were given a deprivation score, from 1-32,482 and then split into equally matched quintiles. These groups of categorical variables have been described in the literature extensively(212,244,249).

The mean age at diagnosis was 71 years (sd 12.1) and 55.7% of patients were male. At the CRC1 admission, 67.6% of patients had no co-morbidities, 7.4% had one and 25.0% had two or more. A lower proportion of my CRC cohort of patients lived in deprived areas; there were 17.1% of cases in the most deprived quintile, compared to 20.4% in the least deprived quintile. Colon cancer accounted

for 62.6% of cases, rectosigmoid 7.6% and rectal 29.8%, *Table 2.14*.

Table 2.14 Characteristics of CRC patients diagnosed in English NHS hospitals over a one-year period (October 2006 to September 2007).

Patient characteristics	Total cases, N (%)
No.	32,299
Age group	
<55 yrs	3,044 (9.4)
55-64 yrs	5,872 (18.2)
65-74 yrs	9,474 (29.3)
75-84 yrs	10,080 (31.2)
≥85 yrs	3,829 (11.9)
Gender	
Male	17,981 (55.7)
Female	14,318 (44.3)
Co-morbidity	
0	21,847 (67.6)
1	2,383 (7.4)
≥2	8,069 (25.0)
Deprivation	
IMD not recorded	322 (1.0)
1 (most deprived)	5,516 (17.1)
2	6,044 (18.7)
3	6,844 (21.2)
4	6,980 (21.6)
5 (least deprived)	6,593 (20.4)
Site	
Rectal	9,631 (29.8)
Rectosigmoid	2,440 (7.6)
Colon	20,228 (62.6)

2.5.1.1. Patient presentation

In my cohort the emergency presentation rate was 36.1% at the index admission. This was higher than the 32.0% found at the CRC1 ($p<0.001$). Therefore, the index admission methodological approach increased the number of patients regarded as having presented as an emergency, *Table 2.15*. Clearly a proportion of patients were experiencing an emergency admission early in their cancer journey, before the cancer code was first recorded. This is a key finding of this methodological work and crucial to the accurate study of factors associated with emergency presentation for cancer care.

Table 2.15 Presentation mode and outcomes for the 32,299 CRC patients diagnosed in English NHS hospitals over the one-year period October 2006 to September 2007.

Patient outcomes	Total cases, N (%)
Index admission	
Elective	20,648 (63.9)
Emergency	11,651 (36.1)
First colorectal cancer coding	
Elective	21,968 (68.0)
Emergency	10,331 (32.0)
Outcomes	
Any colorectal operation	20,674 (64.0)
Major surgical resection	16,332 (50.6)
1-year mortality (index admission)	9,469 (29.3)
1-year mortality (CRC1 admission)	9,637 (29.8)

2.5.1.1.1. Short stay emergency admission

I challenged the assumption that all patients with an emergency presentation should be treated equally. In particular, that patients whose initial emergency admission length of stay was <1 day, should be treated as "true emergency presentations". I have termed such cases "short stay emergency admissions".

In the emergency presentation group, 777 of the 11,651 (6.7%) patients had a short stay emergency admission at their index admission. If these patients had much better outcomes than other emergency admission patients, it would raise the question of whether these were truly emergencies. The short stay emergency group had a slightly lower one-year mortality rate than longer stay emergencies (43.9% versus 49.8%; p=0.001) but both were substantially higher than that of the elective group (18.0%). Resection rates for the short stay emergency group was actually inferior to those presenting with a longer stay emergency (31.0% vs. 35.7%; p=0.009) but rates for elective presentations were much high (59.1%). Taken together this showed it was reasonable to include patients whose initial length of stay was <1 day within the overall emergency group.

2.5.1.2. Patient outcomes

Overall, 50.6% of patients had a major surgical resection and the one-year mortality from the index admission was 29.3%, *Table 2.15*.

2.5.2. Comparison between my study cohort and external CRC data sources

In this section I explore the validity of my study cohort by comparing the patient characteristics, presentation type and outcomes with matched external sources of data. My aim was to show that my cohort contained all incident CRC patients with characteristics similar to other published population-based cohorts. The external data sources used include the National Bowel Cancer Audit Programme (NBOCAP), Office for National Statistics (ONS) cancer registration data and key studies from England

and elsewhere(2,150). Stringent efforts were made to match the time period and populations as closely as possible. Where there are differences in the populations or time period between my data and external sources, they are stated in the text. The patient characteristics and outcomes of my study cohort are shown in *Tables 2.14 and 2.15* and were compared with external sources in *Table 2.24*.

I identified 32,299 incident CRC cases in England during my study year, which was comparable to an independent estimate of 33,604 new cases for England in 2007(2). The external source for this estimate was the Office for National Statistics (ONS), which publishes annual data on CRC registrations in England, compiled from regional cancer registries, *Table 2.24 (External data 1).*

2.5.2.1. Patient characteristics

2.5.2.1.1. Age

In my study cohort the mean age was 71 years and the median age 77 years. CRC was rare among younger patients and steadily increased with age, especially above 55 years, with the highest numbers of cases occurring among 60-85 year olds and falling thereafter, *Figure 2.7*. In my study cohort 83.4% (n=26,952) of patients were aged 60 years and over. The closest external age specific data came from the ONS for 2007 where a closely comparable 84.0% (n=33,970) of cases were 60 and over, *Table 16, 24 (External data 2)*(2). This age distribution was consistent with other similar studies(2,30).

Next I compared the number of patients in my study cohort at the extremes of age, with matched external data. In my cohort: 1.5% (n=493) of cases were aged <40 years compared to 1.4% (583/40,440) in the ONS data for 2007. At the other end of the age spectrum, 11.9% (n=3,829) of my cases were aged ≥85 years compared to 12.8% (5,187/40,440) in the 2007 ONS data for the UK(2). The similarity of the age profile data, between my cohort and a closely matched external data source reassured me that my methodology was not excluding any group of patients based on age.

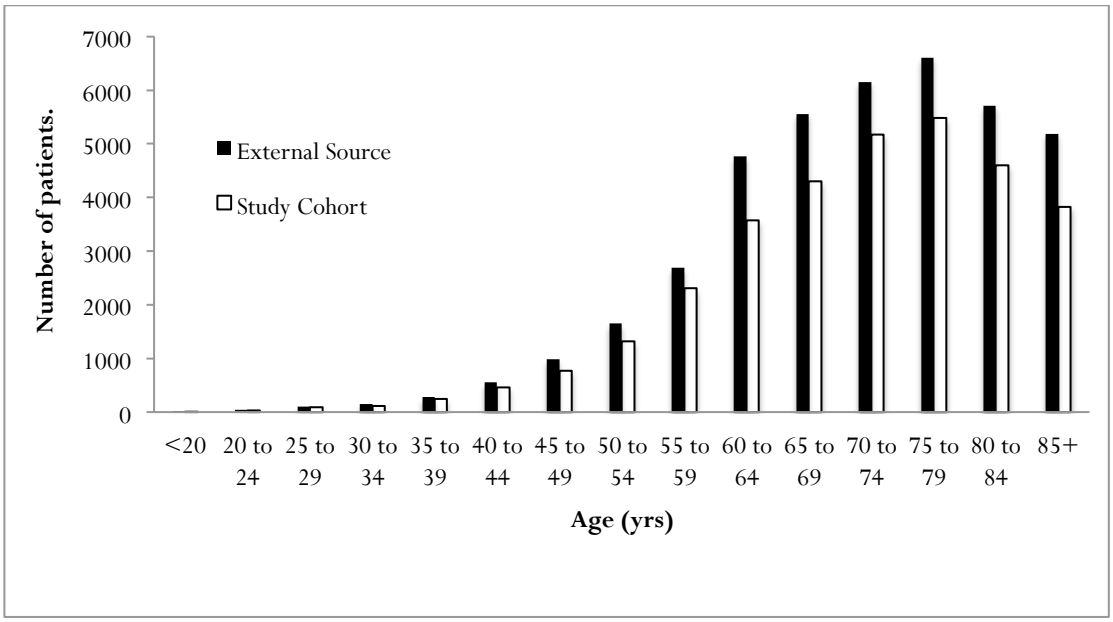


Figure 2.7 My study cohort showed similar trends in crude cancer cases according to age, as a matched external source (ONS 2007, colorectal and anal cancers in the UK)(2).

2.5.2.1.2. Gender

In my study cohort 55.7% of cases were male and 44.3% female. Similar findings were reported in the 2007 ONS data, with 55.2% of cases males and 44.8% female, *Table 2.16, Table 2.24 (External data 1)*(2). This gender ratio was also found in comparable international studies(218).

In the study cohort, there were more male patients at all age ranges, except for those aged over 85 years, *Figure 2.10.* This finding was exactly matched by external sources from Cancer Research UK data, *Figure 2.8*.

Table 2.16 The Office for National Statistics annual incidence data for 2007 in England was comparable to my cohort, in terms of total incident cases reported and gender distribution(2).

Cases	**Study cohort, N (%)**	**ONS, N, (%)**
Total	32,299	33,604
Male	17,981 (55.7)	18,538 (55.2)
Female	14,318 (44.3)	15,066 (44.8)

*Adapted from ONS for 2007.

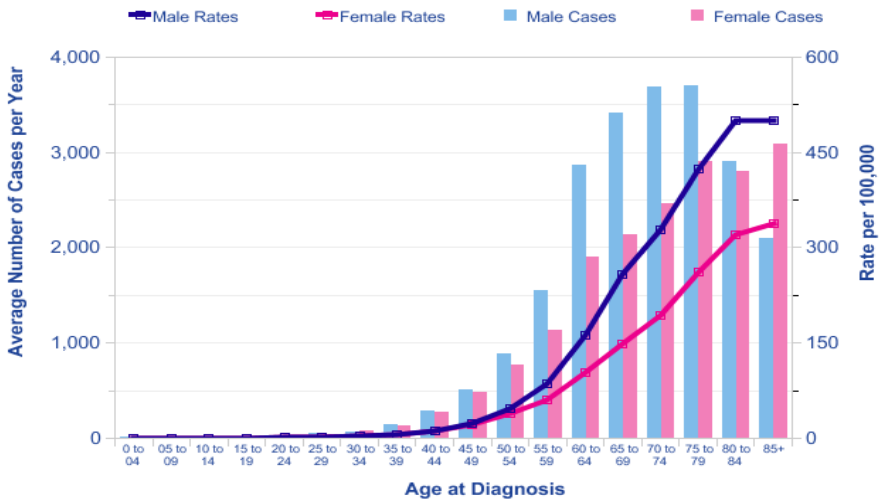


Figure 2.8 Chart taken directly from Cancer Research UK 2007, showing the number of new cases by age group and age-specific incidence rates per 100,000 population in the UK (for colorectal and anal cancer).

2.5.2.1.3. Co-morbidity

In my study cohort, the weighted Charlson co-morbidity score was 0 for 67.6% (n=21,847) of patients, one for 7.4% (n=2,383) and ≥2 for 25.0% (n=8,069). In one study of 246,469 patients, in England, undergoing a colorectal resection between 2000 and 2008, 144,518 (58.6%) had CRC, 64.2% had a Charlson score of 0, a further 9.4% had a score of 1-4 and 26.4% had a score ≥5 (150 had the score missing)(212). A similar Danish study found 53% of patients had a score of 0, 37% a score of 1-2 and the remaining 10% a score of 3 or more(250). A study of 11,524 patients in New Zealand was perhaps the most closely matched, finding a Charlson score of 0 in 67.1%, 1 in 17.5% and ≥2 in 15.1%, *Table 2.17, 24 (External data 3)*(36). Overall, these data showed that in most studies, including my own, around two-thirds of patients have no co-morbidities. There was less agreement between the studies, on the frequency of either single or multiple co-morbidities. This was likely to be due to differences in coding strategies between the groups.

Table 2.17 A comparison of the frequency of co-morbidities in my study cohort and a matched population from New Zealand (36).

Co-morbidity score)	**Study cohort,** N (%)	**Sarfati et al,** N (%)
0	21,847 (67.6)	7,732 (67.1%)
1	2,383 (7.4)	2,013 (17.5%)
≥2	8,069 (25.0)	1,740 (15.1%)

2.5.2.1.4. Deprivation

My study cohort found slightly more patients belonging to the least deprived quintiles (20.4%), compared with the most deprived quintile (17.1%), the other quintiles were equally populated. These data showed the crude numbers of cancer cases across the deprivation quintiles – and not the 'rate' (i.e. cases per unit population per year). However as each LSOA contains a similar number of patients dividing the country into 'fifths' according to LSOA based deprivation scores was also crudely dividing the population into five equal groups. Because of this it was reasonable to compare the crude annual number of cases in England to external published estimates. There were no directly comparable data of CRC cases in deprivation quintiles across England between 2006 and 2007. However, a cross sectional study from England (1999-2006) showed no relationship between the level of deprivation and the crude number of CRC cases, *Table 2.18, 24 (External data 4)*(30). The closest ONS data for England covered the period 2000-2004 also reported no significant association between CRC rates and deprivation. However, in common with our findings, the crude rate for the least deprived quintile was slightly higher than for the most deprived, *Table 2.19*(35). Another study from England during a similar time period (1996-2004), found no clear relationship between the CRC frequency and deprivation levels, *Table 2.20*(251). A Scottish study for the period covering our cohort (2006-2010) showed similar crude rates, but with age-standardised rates higher among more deprived patients, *Table 2.21*(252).

Overall, the external data agrees with our findings that, in England, there was no substantial variation in crude rate of CRC across categories of socioeconomic deprivation.

Table 2.18 The proportion of CRC patients in each deprivation quintile; comparing my study cohort against a cross sectional study from England (1999-2006).

Deprivation	**Study cohort, N (%)**	***Raine et al*** (30)**, N (%)**
Missing	322 (1.0)	0 (0)
1 (Least deprived)	6,593 (20.4)	37,041 (19.8)
2	6,980 (21.6)	39,753 (21.3)
3	6,844 (21.2)	39,309 (21.0)
4	6,044 (18.7)	36,470 (19.5)
5 (Most deprived)	5,516 (17.1)	34,404 (18.4)

Table 2.19 A study comparing the crude and age-adjusted rates of CRC in each deprivation quintile in England between 2000-2004(35).

Deprivation	N	Crude rate	ASR*	95% CI
1 (Least deprived)	27,402	55.3	41.2	40.7-41.6
2	30,545	61.6	42.3	41.8-42.8
3	30,821	62	42.9	42.4-43.4
4	28,953	58	43.4	42.9-43.9
5 (Most deprived)	24,976	49.8	43.8	43.3-44.3

*Age standardised rate

Table 2.20 A study from England during the period 1996-2004, found no clear association between CRC frequency and the level of deprivation (251).

Deprivation	Male Colon	Female Colon	Male Rectum	Female Rectum	Total, N (%)
1 (Least deprived)	16,346	15,492	10,782	6,927	49,547 (19.3)
2	17,563	17,687	11,866	7,964	55,080 (21.5)
3	16,971	17,774	11,611	8,203	54,559 (21.3)
4	15,916	16,469	11,315	7,918	51,618 (20.1)
5 (Most deprived)	14,205	13,888	10,869	6,734	45,696 (17.8)

Table 2.21 The association between deprivation and the frequency and age-standardised incidence rates (ASR) of CRC in Scotland between 2006-2010(252).

Deprivation	N	ASR	Confidence Interval (CI)
1 (Least deprived)	3,638	50.8	49.1-52.5
2	3,655	48.6	47.0-50.2
3	3,972	52.9	51.2-54.6
4	4,147	56.7	54.9-58.6
5 (Most deprived)	3,654	56.5	54.6-58.4

2.5.2.1.5. Cancer site

My study cohort was comprised of 9,631 (29.8%) rectal cancers, 2,440 (7.6%) recto-sigmoid cancers and 20,228 (62.6%) colonic cancers. The ONS data for 2007-2008, with 38,091 cases, was comparable to my study cohort, *Table 2.22*. There were 10,740 (28.2%) rectal, 2,807 (7.4%) recto-sigmoid and 24,544 (64.4%) colonic cancers, *Table 2.22, 2.24 (External data 2)*(2). In both my cohort and the ONS data, overlapping or unspecified colonic site codes were included in the colonic cancer group. The fact

that these figures are closely matched suggests that it is unlikely that my cohort had systematically failed to record cancer from a particular site.

Table 2.22 A comparison of the frequency of CRC cases at different anatomical sites between my cohort and the ONS cohort for the United Kingdom in 2007(2).

Cancer site	**Study cohort, N (%)**	**ONS data N (%)**
Rectal	9,631 (29.8)	10,621 (27.9)
Rectosigmoid	2,440 (7.6)	2,807 (7.4)
Colon	20,228 (62.6)*	24,663 (64.7)**
Total	32,299	38,091

*contains 3,538 overlapping and unspecified colonic case, **contains 3,323 overlapping and unspecified colonic cases

2.5.2.2. Patient presentation

In my cohort, 63.9% of patients presented electively and 36.1% as an emergency. In Scotland between 1991 and 1994 comparable proportions of patients presented as elective (69.2%) and emergency (30.8%) admissions(198). More recently between 1999 and 2006, an English study of 186,977 CRC patients showed 32.5% (n=60,684) of presentations were an emergency, *Table 2.24 (External data 5)*(30).

Many studies only reported on whether surgery was during an elective or emergency admission. In a large study of CRC surgery in England 76.8% (n=111,025) of operations were elective and 23.2% (n=33,493) emergencies(212). By comparison, I found 74.7% (n=12,284) of operations were during elective admissions and 25.3% (n=4,152) during emergency.

2.5.2.3. Primary outcomes

2.5.2.3.1. Surgical resection rates

In my study cohort, 64.0% of patients had operative management, with 50.6% having a major resection. This contrasts with the NBOCAP report for 2006/07, which covered most trusts in England (135 out of 152) and a smaller number of trusts from elsewhere in the British Isles (n=16, including one from the Republic of Ireland), *Table 2.23* (150). This report found 73.7% of patients received some form of operative management and 59.6% had a major resection. Although the NBOCAP study reported a higher operative rate, it had identified far fewer patients (21,170 vs. 32,299). The age, gender and cancer site rates were all very similar between the two groups, *Table 2.24 (External data 5)*.

Table 2.23 A comparison of data between my study cohort and the NBOCAP report (2006/07), which contained 21,170 CRC patients from the UK and Republic of Ireland. The NBOCAP response rate was 61.5%.

Variable		Study cohort, N (%)	NBOCAP, N (%)
Cases	Total	32,299	21,170
	Surgically treated	20,674 (64.0)	15,670 (73.7)
	Major resections	16,332 (50.6)	12,612 (59.6)
Gender	Male	17,981 (55.7)	11,785 (55.7)
	Female	14,318 (44.3)	9,351 (44.2)
	Not reported	0	34 (0.2)
Age	≤ 60	6,053 (18.7)	4,020 (19.0)
	61-70	8,171 (25.3)	5,535 (26.1)
	71-80	10,686 (33.1)	7,121 (33.6)
	>80	7,389 (22.9)	4,492 (21.2)
	Unknown	0	2 (0.0)
Site	Colon	20,228 (62.6)	12,478 (58.9)
	Rectosigmoid	2,440 (7.6)	1,786 (8.4)
	Rectum	9,631 (29.8)	6,698 (31.6)
	Unknown	0	208 (1.0)

2.5.2.3.2. One-year mortality

The one-year mortality rate in my study cohort was 29.3% (28.7% in men and 30.1% in women). This was marginally higher than the ONS figures that, between 2004 and 2008, reported rates of 23.7% for men and 26.9% for women(253). The ONS one-year mortality rate for 2007 alone was 24.0% for men and for 25.0% women, *Table 2.24 (External data 1)*. In another study in England between 2005 and 2007 the one-year mortality was 25.3%(27).

2.5.2.3.3. Conclusions

In conclusion, the external data sources results closely match those of my own cohort. This was particularly the case for patient characteristics and presentation. In terms of outcomes, I found the operative rate was lower in my study cohort and the one-year mortality was higher than the external data.

Table 2.24 A comparison of the patient characteristics, procedure types and outcomes between my study cohort and matched external data sources.

Variables	**Total cases**	**External data 1** (2)	**External data 2** (253)	**External data 3** (36)	**External data 4** (35)	**External data 5** (150)
Total	32,299	33,604	40,440	11,524	186,977	21,170
Time period	1 year	1 year	1 year	7 years	7 years	1 year
Gender, N (%)						
Male	17,981 (55.7)	18,538 (55.2)				
Female	14,318 (44.3)	15,066 (44.8)				
Age group, N (%)						
<55 yrs	3,044 (9.4)		3,784 (9.4)			
55-64 yrs	5,872 (18.2)		7,452 (18.4)			
65-74 yrs	9,474 (29.3)		11,701 (28.9)			
75-84 yrs	10,080 (31.2)		12,316 (30.4)			
≥85 yrs	3,829 (11.9)		5,187 (12.8)			
Site, N (%)						
Rectal	9,631 (29.8)		10,740 (28.2%)			
Rectosigmoid	2,440 (7.6)		2,807 (7.4%)			
Colon	20,228 (62.6)		24,544 (64.4%)			
Co-morbidity, N (%)						
0	21,847 (67.6)			7,732 (67.1)		
1	2,383 (7.4)			2,013 (17.5)		
≥2	8,069 (25.0)			1,740 (15.1)		
Deprivation, N (%)						
IMD missing	322 (1.0)				0 (0)	
1 (most deprived)	5,516 (17.1)				37,041 (19.8)	
2	6,044 (18.7)				39,753 (21.3)	
3	6,844 (21.2)				39,309 (21.0)	
4	6,980 (21.6)				36,470 (19.5)	

5 (least deprived)	6,593 (20.4)			34,404 (18.4)	
Start diagnostic journey, N (%)					
Elective	20,648 (63.9)			126,293 (67.5)	
Emergency	11,651 (36.1)			60,684 (32.5)	
Outcomes, N (%)					
Operation ever	20,674 (64.0)				15,670 (73.7)
Major resection	16,332 (50.6)				12,612 (59.6)
One year mortality	9,469 (29.3)	males 25.0%, females 26.0 %			

2.5.3. Associations between patient characteristics and outcomes

In this section associations between patient characteristics (age, gender, co-morbidity, deprivation and cancer site) are described, as well as those between patient characteristics and outcomes. By confirming known associations, I again tested the cohort validity.

2.5.3.1. Age

2.5.3.1.1. Age and other patient characteristics

In my study cohort older patient groups contained a higher proportion of colon (proximal) cancers. 56.5% of patients aged <55 years had colon cancer; this increased to 67.7% in those aged over 85 years ($p<0.001$), *Table 2.25, Figure 2.9*. Overall, the mean age of rectal cancer patients was 69.7 years (sd 12.2), which was lower than for rectosigmoid cancer patients at 70.2 years (sd 11.7) and colon cancer patient at 71.6 years (sd 12.1)($P>0.05$). This association has been found in other studies(254).

I found that patients over 55 years old, had a significant increase in co-morbidity scores of one or higher, compared to younger patients, ($p<0.001$), *Table 2.26*. This has also been shown in a systematic review of 28 studies(255).

In older age groups, there were progressively fewer patients from deprived quintiles. Compared to the other quintiles in patients over 74 years there were significantly fewer patients in the most deprived quintile ($p<0.001$), *Table 2.27*. Once again this finding has been reported previously (252).

Table 2.25 A table showing the association between age and cancer site my study cohort.

Site	Total, N (%)	<55, N (%)	55-64 yrs, N (%)	65-74 yrs, N (%)	75- 84 yrs, N (%)	≥85 yrs, N (%)
Rectal	9,631 (29.8)	1,077 (35.4)	2,030 (34.6)	2,841 (30.0)	2,680 (26.6)	1,003 (26.2)
Rectosigmoid	2,440 (7.6)	246 (8.1)	473 (8.1)	778 (8.2)	709 (7.0)	234 (6.1)
Colon	20,228 ›2.6)	1,721 (56.5)	3,369 (57.4)	5,855 (61.8)	6,691 (66.4)	2,592 (67.7)

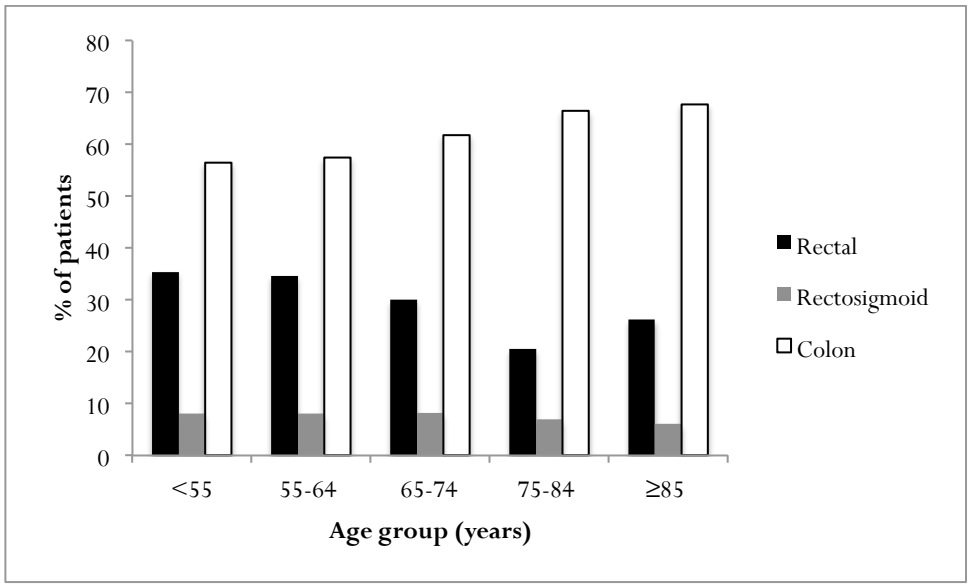


Figure 2.9 Increasing age was associated with a proportionally more proximal cancers in the study cohort.

Table 2.26 A table showing the association between age and co-morbidity my study cohort.

Co-morbidity score	Total, N (%)	<55, N (%)	55-64 yrs, N (%)	65-74 yrs, N (%)	75-84 yrs, N (%)	≥85 yrs, N (%)
0	21,847 (67.6)	2,221 (73.0)	4,160 (70.8)	6,500 (68.6)	6,550 (65.0)	2,416 (63.1)
1	2,383 (7.4)	100 (3.3)	324 (5.5)	699 (7.4)	906 (9.0)	354 (9.2)
≥2	8,069 (25.0)	723 (23.8)	1,388 (23.6)	2,275 (24.0)	2,624 (26.0)	1,059 (27.7)

Table 2.27 A table showing the association between age and deprivation in my study cohort.

Deprivation	**Total, N**	**<55, N (%)**	**55-64 yrs, N (%)**	**65-74 yrs, N (%)**	**75-84 yrs, N (%)**	**≥85 yrs, N (%)**
IMD missing	322 (1.0)	67 (2.2)	74 (1.3)	92 (1.0)	69 (0.7)	20 (0.5)
1 (most deprived)	5,516 (17.1)	608 (20.0)	1,004 (17.1)	1,665 (17.6)	1,599 (15.9)	640 (16.7)
2	6,044 (18.7)	580 (19.1)	1,068 (17.1)	1,729 (18.2)	1,948 (19.3)	719 (18.8)
3	6,844 (21.2)	580 (19.1)	1,219 (20.8)	2,010 (21.2)	2,178 (21.6)	857 (22.4)
4	6,980 (21.6)	574 (18.9)	1,302 (22.2)	2,035 (21.5)	2,220 (22.0)	849 (22.2)
5 (least deprived)	6,593 (20.4)	635 (20.9)	1,205 (20.5)	1,943 (20.5)	2,066 (20.5)	744 (19.4)

2.5.3.1.2. Age and outcomes

In my study cohort, older patients (≥85 years) were significantly less likely to have a major surgical resection ($p<0.001$), *Table 2.28*. In patients under 65 years old the rate was over 50%, this fell to 31.4% in patients over 65 years ($p<0.001$). Furthermore, older patients had a higher chance of death within one year. Amongst the oldest age group (≥85 years) one-year mortality was 50.5%, compared with 18.0% in the youngest age group (<55 years). Other studies have also found that age was a negative predictor for survival(256).

Table 2.28 A comparison between age and outcomes (surgical resection and one-year mortality). In my cohort, the oldest age group had significantly fewer operations and lower one-year survival.

Age groups (years)	**Surgical Resection,** N (%)	**One-year Mortality,** N (%)	**P value**
<55	1,662 (54.6)	548 (18.0)	
55-64	3,367 (57.3)	1,164 (19.8)	
65-74	5,243 (48.2)	2,301 (24.3)	
75-84	4,856 (48.2)	3,522 (34.9)	
≥85	1,204 (31.4)	1,934 (50.5)	**<0.001**

2.5.3.2. Gender

2.5.3.2.1. Gender and other patient characteristics

In my study cohort, female patients were on average older at presentation than male patients (71.9 years vs. 70.2 years, [$p<0.05$]). Males made up a larger proportion of cases up until 80 years, after that improved female life expectancy reversed the trend, *Figure 2.10*. Patients aged 80 and over accounted for 31.2% of female patients, but only 22.0% of male patients, *Table 2.29*. One consequence of the

different age distributions was the proportion of male and female CRC patients that could be "exposed" to the Bowel Cancer Screening Programme (BCSP). At the time of my study, the BCSP recruited patients aged 60-69 years. This age range covered 27.0% of male and 21.0% of female CRC patients ($p<0.001$), *Table 2.29*. According to the census in 2011, there are 6,824,000 individuals aged 60-69 years in the UK. This equates to 10.8% of the population. The Cancer Reform Strategy announced that from April 2010, the NHS BCSP would increase its screening age up to the 75th birthday for both men and women. According to the 2011 census this equated to 14.7% of the total population. In my cohort, this covers 44.3% of male and 35.4% of female CRC patients, *Table 2.30*. Numerous other studies have shown that women present at an older age than men(257,258).

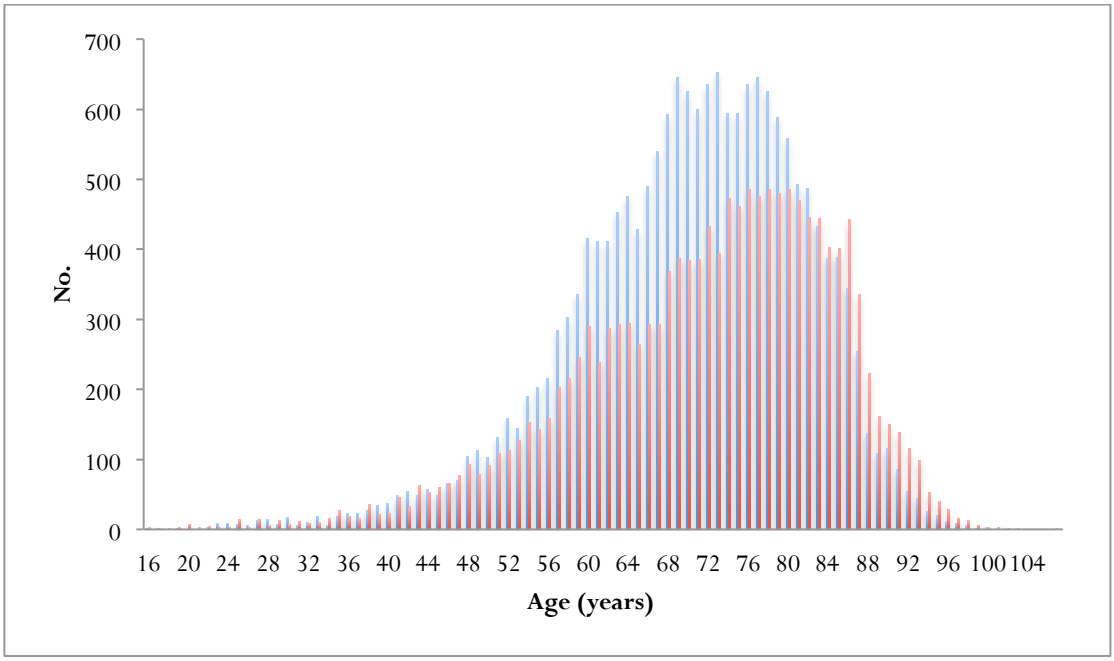


Figure 2.10 A chart describing the number of male (blue) and female (red) CRC patients at different ages. Male patients were more numerous and on average were diagnosed at a younger age.

Table 2.29 The number of male and female patients in different age groups in my study cohort. In particular this highlights that a significantly higher proportion of male patients (27% vs. 21%) were in the BCSP age range (60-69 years).

Age groups (years)	**Male, N (%)**	**Female, N (%)**	**P value**
<60	2,962 (16.5)	2,385 (16.7)	
60-69*	4,861 (27.0)	3,007 (21.0)	**<0.001**
70-79	6,196 (34.5)	4,455 (31.1)	
>79	3,962 (22.0)	4,471 (31.2)	

*The screening age group.

Table 2.30 The number of male and female patients in different age groups in my study cohort, after the age extension of the BCSP to include 70-74 year old patients (from April 2010). A significantly higher proportion of male CRC patients were within the screening age group.

Age groups (years)	**Male, N (%)**	**Female, N (%)**	**P value**
<60	2,962 (16.5)	2,385 (16.7)	
60-74*	7,969 (44.3)	5,074 (35.4)	**<0.001**
75-84	5,446 (30.3)	4,634 (32.4)	
>84	1,604 (8.9)	2,225 (15.5)	

*The screening age group.

Male patients were more likely to have rectal cancer (32.9%, [5,915/17,981]) than female patients (26.0% [3,716/14,318]), *Table 2.31*. This may be another reason for the superiority of screening men, as rectal cancer is more often picked up by FOBt than colon cancer(73). At all three cancer sites (rectal, recto-sigmoid and colon) male patients are diagnosed at an earlier age, *Table 2.32*.

Gender did not appear to have any significant impact on the level of co-morbidity reported at the first CRC coded admission, *Table 2.33*. There were almost identical rates of male and female patients having a Charlson co-morbidity score of 0 (67.3% vs. 68.1%, P=0.149). Finally, male and female patients had almost identical levels of deprivation, *Table 2.34*.

Table 2.31 A comparison of cancer site and gender identified that male patients were significantly more likely to present with rectal cancer.

Site	**Total, N (%)**	**Male, N (%)**	**Female, N (%)**	**P value**
Rectal	9,631 (29.8)	5,915 (32.9)	3,716 (26.0)	<0.001
Rectosigmoid	2,440 (7.6)	1,429 (7.9)	1,011 (7.1)	
Colon	20,228 (62.6)	10,637 (59.2)	9,591 (67.0)	

Table 2.32 A comparison of cancer site and the age of presentation for male and female patients. At all sites male patients were diagnosed at a younger age

Site	**Total, N (sd)**	**Male, N (sd)**	**Female, N (sd)**	**P value**
All	71.0 (12.1)	70.2 (11.5)	71.9 (12.8)	<0.001
Rectal	69.7 (12.2)	69.1 (11.5)	70.7 (13.3)	<0.001
Rectosigmoid	70.2 (11.7)	69.8 (11.0)	70.7 (12.6)	0.056
Colon	71.6 (12.1)	70.9 (11.6)	72.4 (12.6)	<0.001

Table 2.33 A comparison of co-morbidity and gender.

Co-morbidity	Total, N (%)	Male, N (%)	Female, N (%)	P value
0	21,847 (67.6)	12,102 (67.3)	9,745 (68.1)	0.151
1	2,383 (7.4)	1,370 (7.6)	1,013 (7.1)	
≥2	8,069 (25.0)	4,509 (25.1)	3,560 (24.9)	

Table 2.34 A comparison of deprivation and gender.

Deprivation	Male, N (%)	Female, N (%)
IMD missing	181 (1.0)	141 (1.0)
1 (most deprived)	3,139 (17.5)	2,377 (16.6)
2	3,285 (18.3)	2,759 (19.3)
3	3,772 (21.0)	3,072 (21.5)
4	3,898 (21.7)	3,082 (21.5)
5 (least deprived)	3,706 (20.6)	2,887 (20.2)

2.5.3.2.2. Gender and outcomes

In my cohort, gender did not have a significant impact on the crude surgical resection rate. The crude one-year mortality rate was higher among females but this was not adjusted for females presenting on average later, *Table 2.35*.

Table 2.35 A comparison of the surgical resection and one-year mortality rates between male and female patients in my cohort.

Gender	Surgical Resection, N (%)	One-year Mortality, N (%)
Male	9,142 (50.8)	5,156 (28.7)
Female	7,190 (50.2)*	4,313 (30.1)**

*P=0.264, **P=0.005

2.5.3.3. Co-morbidity

2.5.3.3.1. Co-morbidity and other patient characteristics

I have already confirmed the expected increase in co-morbidity with advancing age (section 2.6.3.1). In this section, I demonstrate an association between co-morbidity and colon cancer. Amongst patients with colon cancer 27.5% had ≥2 co-morbidities, compared with 18.3% of rectal cancer patients ($p<0.001$). This can be partially explained by the increased proportion of colon cancers with advancing age. As already shown, the mean age of presentation with colon cancer was higher than for rectal cancer (71.6 yrs vs. 69.7 yrs vs. $p<0.05$), *Table 2.36*.

There was a moderate association between increasing levels of co-morbidity and increasing deprivation. The most deprived quintile had more patients with one or more co-morbidities than the other quintiles combined (p=0.003), *Table 2.37*.

Table 2.36 A comparison of co-morbidity and cancer site. Patients with colon cancer had higher co-morbidities than those with rectal cancer (p<0.001).

Co-morbidity	Total, N (%)	Rectal, N (%)	Rectosigmoid, N (%)	Colon, N (%)	P value
0	21,847 (67.6)	7,149 (74.2)	1,550 (63.5)	13,148 (65.0)	
1	2,383 (7.4)	720 (7.5)	150 (6.1)	1,513 (7.5)	
≥2	8,069 (25.0)	1,762 (18.3)	740 (30.3)	5,567 (27.5)	<0.001

Table 2.37 A comparison of deprivation and co-morbidity. More patients in the most deprived quintile had a co-morbidity than in the other quintiles (p=0.003).

Deprivation	Total, N (%)	Co-morbidity 0, N (%)	Co-morbidity 1, N (%)	Co-morbidity ≥2, N (%)	P value
IMD missing	322 (1.0)	183 (56.8)	20 (6.2)	119 (37.0)	
1 (most deprived)	5,516 (17.1)	3,644 (66.1)	461 (8.4)	1,411 (25.6)	0.003*
2	6,044 (18.7)	4,015 (66.4)	478 (7.9)	1,551 (25.7)	
3	6,844 (21.2)	4,626 (67.6)	537 (7.8)	1,681 (24.6)	
4	6,980 (21.6)	4,736 (67.9)	477 (6.8)	1,767 (25.3)	
5 (least deprived)	6,593 (20.4)	4,643 (70.4)	410 (6.2)	1,540 (23.4)	

*excluding IMD missing.

2.5.3.3.2. Co-morbidity and outcomes

I found the presence of even a single co-morbidity led to significantly lower surgical resection rates (49.9% vs. 57.3%, p<0.001). Equally, a single co-morbidity was associated with a higher one-year mortality rate (20.4% to 30.0%, p<0.001), *Table 2.38*. This finding is supported by a study from Denmark that used a similar definition of co-morbidity and found that increasing co-morbidity and proximal site interacted to reduce major surgical resection rates(250).

Table 2.38 A comparison of the surgical resection and one-year mortality rates between patients with different levels of co-morbidity.

Co-morbidity	Surgical Resection, N (%)	One-year Mortality, N (%)	P value
0	12,511 (57.3)	4,452 (20.4)	
1	1,189 (49.9)	715 (30.0)	
≥2	2,632 (32.6)	4,302 (53.3)	>0.001

2.5.3.4. Deprivation

2.5.3.4.1. Deprivation and other patient characteristics

In my cohort, I have already shown that increasing deprivation is associated with an earlier age of CRC diagnosis and increased likelihood of co-morbidity (section 2.6.3.1 and 2.6.3.3). The mean age of patients in the most deprived quintile was 70.2 years (sd 12.7), compared to 71.1 years (sd 12.0) among patients from other quintiles ($p<0.001$]), *Table 2.39*.

Table 2.39 Showing the age of CRC presentation for patients in the different deprivation quintiles.

Deprivation	Age, yrs. (sd)
IMD missing	65.2 (14.3)
1 (most deprived)	70.2 (12.7)
2	71.0 (12.2)
3	71.4 (11.9)
4	71.3 (11.8)
5 (least deprived)	70.9 (12.0)

2.5.3.4.2. Deprivation and outcomes

I found surgical resection rates were lower, and one-year mortality rates higher, in patients in the most deprived quintile, *Table 2.40*. The crude surgical resection rate fell from 54.1% in the least deprived quintile to 41.0% in the most deprived quintile ($p<0.001$), while the one-year mortality rate increased from 26.9% to 32.2% ($p<0.001$).

Table 2.40 A comparison of the surgical resection and one-year mortality rates between patients with different levels of deprivation.

Deprivation	**Surgical Resection,** N (%)	**One-year Mortality,** N (%)	**P value**
Missing	132 (41.0)	58 (18.0)	
1 (most deprived)	2,566 (46.5)	1,775 (32.2)	
2	2,959 (49.0)	1,905 (31.5)	>0.001
3	3,495 (51.1)	1,991 (29.1)	>0.001
4	3,614 (51.8)	1,965 (28.2)	>0.001
5 (least deprived)	3,566 (54.1)	1,775 (26.9)	>0.001

2.5.3.5. Cancer site

2.5.3.5.1. Cancer site and other patient characteristics

I have already shown the association between cancer site and age (colon type cancer appears more commonly in older patients), gender (rectal cancer was commoner among males) and co-morbidity (colon cancer patients had greater co-morbidity). In the final comparison between CRC site and other patient variables I found no association between site and the level of deprivation. This included a comparison of the most deprived quintile to the other quintiles that showed no significant difference in the proportion of colon site cancers to rectal and rectosigmoid cancers (p=0.215), *Table 2.41*. There was limited data in the literature regarding CRC site and deprivation, although one study from the USA reported a higher incidence rate of proximal cancer among patients from deprived areas(259).

Table 2.41 A comparison of deprivation and the site of CRC.

Deprivation	**Total, N (%)**	**Rectal, N (%)**	**Rectosigmoid, N (%)**	**Colon, N (%)**	**P value**
IMD missing	322 (1.0)	94 (29.2)	22 (6.8)	206 (64.0)	
1 (most deprived)	5,516 (17.1)	1,684 (30.5)	419 (7.6)	3,413 (61.9)	0.215
2	6,044 (18.7)	1,856 (30.7)	459 (7.6)	3,729 (61.7)	
3	6,844 (21.2)	1,993 (29.1)	539 (7.9)	4,312 (63.0)	
4	6,980 (21.6)	2,060 (29.5)	542 (7.8)	4,378 (62.7)	
5 (least deprived)	6,593 (20.4)	1,944 (29.5)	459 (7.0)	4,190 (63.6)	

*excluding IMD missing.

2.5.3.5.2. Cancer site and outcomes

In my cohort, I found that rectal cancers had a lower resection rate than colon cancer. I also found that one-year mortality was lower for rectal cancers, *Table 2.42,* as shown in other studies(241).

Table 2.42 A comparison of the surgical resection and one-year mortality rates between patients with CRC at different sites. Compared to colon cancer, distal cancer site was associated with significantly lower surgical resection rates and lower rates of one-year mortality.

Cancer site	Surgical Resection, N (%)	One-year Mortality, N (%)	P value
Rectal	4,647 (48.1)	2,488 (25.8)	
Rectosigmoid	1,164 (47.7)	756 (31.0)	
Colon	10,531 (52.1)	6,225 (30.8)	>0.001

2.5.3.6. Summary

2.5.3.6.1. Summary of the associations between patient characteristics

This section summarizes the relationships found in my cohort between fixed patient characteristics and the findings from other studies.

1. *Increasing patient age and a shift to more colon cancers*

   I found a proximal shift in CRC site with increasing age, as has been described in other comparative studies(254,260).

2. *Increasing age and increasing co-morbidity*

   I found increasing co-morbidity was associated with increasing age, as has been described previously(254,255). In fact age has often been used as a surrogate marker for co-morbidity.

3. *Male patients were diagnosed at a younger age and a higher proportion were in the BCSP age range*

   I found men develop CRC at an earlier age than women and this can affect access to the BCSP. Other comparative studies support this finding (257,258,261).

4. *Male patients have a higher incidence of rectal cancer*

   I found male patients are more likely to have distal cancers, with the gender disparity increasing steadily from the caecum to the rectum. Other comparative studies support this finding(254,262,263).

5. *Increasing co-morbidity and prevalence of colon cancer site*

   I found patients with increasing levels of co-morbidity are more likely to have a proximal CRC. This is supported by a comparative study(264).

6. *Increasing co-morbidity and increasing deprivation*

Among my cohort, I found an association between patients with higher levels of co-morbidity and increasing levels of deprivation. As expected, levels of co-morbidity were higher among people living in more deprived areas, consistent with known population trends (265).

7. *Increasing deprivation and diagnosis at a younger age*

   I found that that deprived patients are diagnosed at an earlier age. I also showed they had higher emergency presentation rates and lower resection rates, which is supported by another UK CRC cohort

   (235).

2.5.3.6.2. Summary of the associations between patient characteristics and outcomes

This section summarises the relationships I found in the study cohort between the fixed patient characteristics and the primary outcomes (surgical resection and one-year mortality). I found statistically significant associations between:

- Increasing age and reduced surgical resection and higher one-year mortality.
- Women and increased one-year mortality (likely confounded by age at presentation).
- Increasing co-morbidity and reduced access to surgical resection and higher one-year mortality.
- Proximal cancer and reduced surgical resection and higher one-year mortality.
- Increasing deprivation and reduced surgical resection and higher one-year mortality.

2.6. Discussion

2.6.1. Overview

This chapter demonstrated my novel methodological approach to creating a dataset from HES could accurately identify patients diagnosed with CRC in England in the one-year period from October 2006 to September 2007. I applied clinically sound algorithms to the HES data to identify when patients first presented with CRC (index admission), how they presented and what their outcome was.

My approach allowed me to capture all incident CRC patients and exclude the prevalent ones. My database contained all patient admissions and gave me access to: the important patient characteristics; the date and mode of initial presentation (elective or emergency) and outcomes (major surgical resection and one-year mortality). I recorded other important milestones such as the date of lower gastrointestinal endoscopy.

I demonstrated a novel methodology to identify the date patients first presented to hospital along with data to suggest that this approach was an improvement upon the standard approach to analysing HES data. I called this first relevant admission the 'index admission'. Importantly, this allowed me to identify a patient's mode of presentation; elective or an emergency. This mode of presentation is strongly associated with CRC outcome and is discussed in more detail in chapter 3. My method of identifying the

index admission did not rely only on the first coding of CRC, but on establishing the first relevant admission. I believe this better identifies the earliest point of secondary care contact for patients. This approach established that there was a substantial group of patients (23.1%) with a relevant admission before CRC had first been coded, which I believe represents the beginning of the patient journey. I substantiated this by showing that the coded procedures at the earlier 'index admission' were more predictive of a CRC presentation than those at the first CRC coding. In fact, the first coding of cancer admission was often the second cancer related admission. It was particularly striking that at the 'index admission'; the proportion of patients having a lower gastrointestinal endoscopy (the key diagnostic tool) was substantially higher than at the first CRC coding (the admission used in most of the published literature in the field).

This novel methodological approach identified more patients with an emergency presentation than traditional methods. This was because CRC codes were often lacking at the index admission, especially when the presentation was as an emergency(214). This was important because, as I describe in chapter 3, the presentation method is highly correlated with outcomes such as access to major resection and one-year mortality. Once we can accurately identify how a patient presents, we can study how changes in healthcare delivery affect the rate of emergency presentations. For example, a reduction in emergency presentation with the introduction of the BCSP might suggest more positive outcomes would be likely to occur downstream, such as overall survival at five years. I hope my approach may provide a model for future studies.

I compared the results in my study cohort with comparable and matched external studies. The relative equivalence of these results provided further evidence supporting my methodology. Having established the validity of the methodological approach, I further investigated the associations between the key patient characteristics and looked at the rates of the different presentation types (elective or emergency) and outcomes (surgical resection and one-year mortality rates).

2.6.2. Discussion of the methodological approach

I took a number of steps to identify all incident cases of CRC in the study period. Firstly, I identified all patients with a code for CRC at any position in the HES record. Next, I identified all admissions to hospital for these patients, even if a given admission did not code for CRC. Finally, I removed patients that appeared to have the CRC code as co-morbidity and not as an incident case.

I showed that identifying cases that had a CRC code at any position, rather than just the primary diagnosis (or first position code) was a good way of capturing the maximum number of patients through the HES system. The advantage of this was especially apparent for emergency cases and patients that presented in extremis with a short survival from presentation. Identifying such patients was obviously important in attempting to understand the full spectrum of disease in England. Yet these cases could be missed if a presentation initially coded a symptom code such as rectal bleeding or obstruction at position

one, with CRC at a later coding position. In particular, patients presenting as an emergency are coded poorly, as are those who died during the presenting episode or shortly afterwards and did not have further elective admissions where the coding may have been more accurate. Therefore my methodological approach was likely to have made two significant adjustments not seen in traditional approaches; a) to identify a proportion of patients whose earliest contact with secondary care is with an emergency presentation that was not previously recognised because the CRC code was lacking and b) to include a group of patients not previously identified, those lacking a CRC code at position one. These patients will tend to have worse outcomes with a lower rate of surgery and higher one-year mortality rate than patients identified from primary diagnosis code alone. I believe this was one reason why the cohort study outcomes were slightly worse than similarly matched external reports (e.g. the NBOCAP report for 2006/7) - I was identifying some patients not picked up by other analyses of HES data and cancer registries. When considering the reverse possibility, that I had included patients with a CRC code as co-morbidity or coded incorrectly one needs to understand the steps taken to mitigate this risk. Identifying patients with the worst outcomes is important because they are the group with most to benefit from interventions. By reducing this variation in outcomes, the overall care of English patients with CRC will be improved.

By identifying all admissions for patients with one or more CRC codes, I maximised the information obtainable for each patient. Recording only episodes where CRC was coded would create a database of around 250,000 episodes, while my approach identified 360,000 episodes. This was especially important for identifying when the index admission was from an earlier relevant admission (see section 2.5.2.2). Without this analysis a day case admission for a diagnostic colonoscopy before the CRC1 admission would not have been identifiable as the 'index admission' despite its obvious relevance to the CRC pathway.

I also demonstrated methodological rigour by firstly searching for important codes at the episode level. This eliminated the possibility of missing a code only recorded in a finished consultant episode that was not recorded in the final episode for that admission.

Prevalent cases and cases incorrectly coded with CRC would initially have been captured by my approach. I needed refinement to remove these cases and to do so I made three adjustments to the cohort. Firstly, for any patient without a CRC code in the first two diagnostic positions at any admission I judged it unlikely that the case was active or new and these were excluded. Secondly, patients with a miscoding were removed; these were taken to be patients with more than one non-CRC gastrointestinal malignancy code and only a single CRC code. If there were two or more CRC codes then the patients was retained with the presumption this referred to synchronous cancers. Lastly, patients with a colorectal operation before the CRC1 were removed. Again the justifiable assumption was made that this was more likely to represent an operation for a cancer diagnosed before the start of the study period (i.e. a prevalent CRC case).

I incorporated other strategies to try and improve the study cohort's accuracy. For example, I was aware that some hospitals have a policy of coding many more co-morbidities than others. This creates the 'constant risk fallacy' whereby patients of comparable health appear to have more co-morbidity in highly coding units. The effect of this is to imply these highly coding units have better outcomes for matched co-morbidity, compared to units that code less thoroughly. To mitigate against this, I restricted co-morbidity to three groups (0, 1 and more than 1) thus reducing the effect of case mixed adjustment caused by some units recording a much greater number of co-morbidities(244).

2.6.3. How to accurately identify the admission when the patient first presents

As mentioned in the introduction (section 1.4.3), HES data does not contain a date of diagnosis. Yet knowing the date when a patient first presents is vital for understanding a patient's journey as well as mortality outcomes (such as death within one-year of presentation). Previous studies have tended to mark the diagnosis date as the same admission when the cancer code first appeared. This is despite evidence showing the first coding of a disease is often not the patient's first presentation with the condition (2,244). This was why I went to lengths to identify if there was an earlier relevant admission (REL1). I identified the REL1 as the first admission within six months of the CRC1, with a diagnosis or procedure code consistent with CRC presentation. If no such admission was found, I retained the CRC1 as the 'index admission'. Codes were only defined as relevant after appraisal by a steering group with experience in CRC and large database analysis. I used a broad inclusion criterion for relevant diagnoses and procedures, as my entire cohort would eventually be diagnosed with CRC. These admissions with a relevant diagnosis code, but not a CRC code, were more likely to mark the beginning of the patient's journey. Put another way, if a patient presents with a symptom or sign of cancer but the cancer is not recorded, the admission was still caused by the underlying cancer.

I next set out to show that these REL1 admissions more accurately identified a patient's presentation than the CRC1. To do this I compared the procedures recorded at the REL1 and CRC1 admissions. The most important observation was the rate of lower gastrointestinal endoscopy codes (the primary method of diagnosing CRC) were significantly higher in the REL1, rather than CRC1 admission (52.5% vs. 36.8%, $P<0.001$).

Having demonstrated the improved accuracy of using REL1 as the index admission I next described how the rates of elective and emergency admissions were affected by a change in presentation date. By accepting the REL1 admission as the start of the patient's pathway, the number of cases defined as an emergency increased from 32.0% to 36.1%. This was because the EmEl group (n=1,954) was larger than the ElEm group (n=634). This was an important observation, as it showed my methodology had identified more patients as having an emergency presentation, than using traditional methods. This approach also lengthens these patients' diagnostic journeys and slightly increases overall survival.

The final evidence supporting the use of the first relevant admission comes from comparing the rates of procedural codes for all six possible cancer pathways. I showed that the three pathways starting with an elective presentation (El, ElEl and ElEm) all had very similar rates of lower gastrointestinal endoscopies. Likewise those from the three emergency pathways (Em, EmEm and EmEl) all had similar rates of lower gastrointestinal endoscopies to each other. In conclusion, patients that started their care pathway electively were distinct from those starting with an emergency.

2.6.4. Proving the accuracy of the study cohort

Before accepting the findings from my study cohort, I needed to further test its validity, by comparing the findings to accurate and comparable external data sources. After this I would be justified in using the cohort data to explore standard and novel associations in this chapter and in the rest of the thesis.

In terms of the number of case identified and patient characteristics the study cohort was very close to other external data sources. The total number of patients in my cohort (n=32,299) closely matched other data sources for the annual incidence of CRC in England. Furthermore, the basic demographic profile for age, gender, cancer site and deprivation closely matched other published findings(150). The exception was for co-morbidity, it was difficult to find closely matched studies for comparison(36). The fact that the overall number of cases identified was so similar, and that the majority of characteristics were matched, made it unlikely there was any systematic failure to identify any specific group of patients.

With regards to presentation type, my cohort had a slightly higher emergency presentation rate than comparable studies. I believe this was actually the result of better patient identification, for one reason, emergency admissions are more poorly coded than elective admissions. This meant it was more likely that a CRC code will not appear at an emergency index admission than an elective one(214). Secondly, emergency patients are often sicker patients, more likely to die without a full investigation and certainly before definitive surgery. Therefore cancer registries fail to identify more of these types of patients. Both of these reasons suggest that traditional methodological approaches will have tended to underreport the emergency presentation rate. Patients with an elective CRC1 admission and an earlier emergency REL1 admission provided supporting evidence for this observation. This group of patients had rates of diagnoses and procedures (in particular red flag symptoms and lower endoscopies) at the REL1 admission that more closely matched those of other patients presenting as an emergency.

My study cohort had lower rates of major surgical resection than recorded in the NBOCAP during the same time period. This report may have under-reported non-surgically managed cases due to selection bias(202). This may be because data entry relies on input from colorectal surgeons who may not be closely involved in the care of patients unsuitable for any operative intervention (e.g. palliative cases). The NBOCAP report estimated a data capture rate of 61.5%, based on analysis from the cancer registries that inform ONS data(150). It is therefore possible that the operative rate in the unrecorded

patients was considerably lower. Under-reporting of operations in HES was unlikely because it is such an important intervention and results in a large PbR tariff. Similarly, recordings of procedures in HES is known to be very high(203).

In my cohort the one-year mortality rate was 29.3% compared to 25.3%, in the most closely matched external data (27). As with the surgical resection data the slightly worse outcome in my cohort made me consider whether I had included in my cohort a population of patients normally missed from other registries. In these groups there would be more emergency presentations, less accurate coding, at least at the start of the pathways, and worse overall outcomes. Therefore reasons for the disparity may be the exclusion of some advanced CRC cases from the cancer registries databases or potentiality the retention of some prevalent cases in our cohort.

Overall the distributions of patient characteristics were similar to those from comparative data sources. There were differences in the rates of emergency presentation, surgical resection and to a lesser degree one-year mortality. However, the reasons for this may relate to better data capture of advanced cancer cases in my cohort.

As explained above (in sections 2.5.1, 2.5.2), I took a number of additional steps to ensure accuracy and completeness of my cohort. This level of scrutiny has not normally been described by groups using HES data in general(266) and specifically in using HES to investigate CRC(267). Some HES based studies have used a similar approach to my own but not in the context of CRC or screening(244).

Most of the published work on CRC outcomes arise from single centres or are based on evaluating specific treatments(72). There is less work on unexplained variation in the quality of care delivered at the national level, despite this having been identified as a significant issue(268). The annual report from the NBOCAP is the most comprehensive and highly regarded report and should be used to benchmark any new analysis of CRC care in England(150). It is a clinical database and as such it was relevant to consider the differences between information obtained from a clinical registry and that from routinely collected data, such as HES.

Firstly, although HES-based studies have been criticized in the past for having poor data quality, this tended to come from studies from a decade or more ago(269). The latest evidence shows that routinely collected hospital data are improving and of sufficient quality to be used for both research and clinical decision making purposes (203,204).

Only one study has looked at the accuracy of HES data against a CRC specific clinical registry (NBOCAP)(211). Garout *et al,* a decade ago compared CRC patients undergoing surgery and found HES recorded 53% more patients than the ACPGBI audit(211). This discrepancy was partly due to some units not returning any outcomes to the NBOCAP, however even in units returning data, the rate was 12% lower than HES. On average the NBOCAP reported 13 fewer cases per unit. Interestingly the difference in surgical rates between the two databases was lowest for the more for complex operations

(e.g. anterior resection) usually performed by dedicated colorectal surgeons and highest for simpler emergency operations (e.g. Hartmann's procedure, often performed as an emergency by the on-call non-specialist surgeon on the sickest patients). This supports my view that my methodology for data capture was robust for capturing more CRC patients and especially those patients that were sickest and potentially received substandard or limited hospital care. These patients are often the oldest patients and it is interesting to note that patients in the NBOCAP audit (2007/8) were younger (21.2%; of patients aged >80 years) compared with my cohort (22.9%). In the same study, the mortality rates following surgery were comparable (with a <1% difference), but this study did not identify out of hospital deaths in the HES database. I could safely assume that including "out of hospital deaths" would increase the 30-day mortality rate in the NBOCAP cohort and bring the result closer to the rate identified in my cohort. One final thought is that combining both data sources could be a useful way of monitoring outcomes in units. If both analyses identified concerns with performance, then a more enhanced assessment of quality could be instigated.

Finally, compared with the cost of maintaining a clinical registry the cost of a single HES patient record is far cheaper, estimated at £1 compared to £60(270).

2.6.5. Associations between patient characteristics

I found that older patients were more likely to be diagnosed with colon cancers. This proximal shift in CRC site with increasing age has been described in other studies(254,260). This was important as compared with distal CRC proximal CRC tends to present with more advanced disease and has worse outcomes (264). This may be another reason why there are more emergency presentations and worse outcomes in older patients and another reason why flexible sigmoidoscopy alone is not an acceptable way to investigate symptoms in older patients.

Unsurprisingly I found that older patients (over 74 years) were significantly more likely to have one or more co-morbidities than younger patients. Increasing co-morbidity has previously been associated with older patients diagnosed with CRC(254,255). This was unsurprising, as age is commonly perceived to be a surrogate marker for co-morbidity. It needs to be remembered that older patients with CRC are a heterogeneous group that include patients with an otherwise excellent health status. If age is solely used instead of co-morbidity then there is a risk of undertreating older patients, because of biased clinician preferences. I have shown that increasing age is associated with worse outcomes. This is reported in other studies, especially when the patient is unmarried and living alone(256).

I found male patients were diagnosed on average earlier than females. This finding has been replicated in other studies (257,258,261). This has a number of potential implications; firstly it means any data looking to see if outcomes differed by gender would need to be matched for age and secondly that a higher proportion of males are in the BCSP age range. This will be discussed in chapter 4 but could create bias in the potential effect of screening irrespective of different uptake rates of screening based on

gender. Along with gender variation in screening test sensitivity, the age distributions for males and females may be one reason for the apparent superiority of screening for male patients(271). Some authors have even suggested this is should mean CRC screening should be offered at different age ranges depending on gender (261).

In my cohort male patients have a higher rate of rectal cancer than females, with proximal CRC being found more commonly in women. It has been described previously how the proportion of CRC cases that are men increases steadily on moving from the caecum to the rectum (254,257,262,263,272,273). This maybe another reason for the apparent better outcomes for men. Finally, it has been shown that proximal CRC becomes more common as women get older but not for men(272). This again has implications for CRC screening (as screening for proximal cancer is less accurate) and especially for the roll out of one-off flexible sigmoidoscopy screening, which is less effective for older women.

Cardiovascular diseases, hypertension and previous cancers are the main co-morbidities found in patients with CRC. Patients with co-morbidity were more likely to have a proximal CRC in the study cohort(264). It may be that some common co-morbidities such as diabetes and cardiovascular disease are associated with common risk factors or pathophysiological pathways that increase the risk of proximal cancer. These might include factors such as dietary or the presence of micro-vascular disease, which themselves increase the risk of cancer at a proximal site (274).

My cohort also demonstrated a relationship between increasing co-morbidity and deprivation, which has been previously described(265). I also found deprivation was associated with a CRC diagnosis at a younger age. A search of the literature failed to identify any other study from the UK has shown that deprived patients are diagnosed at an earlier age(235). If patients from deprived areas were more likely to be diagnosed at a younger age it is especially important that these patients are targeted for preventative strategies such as the screening programme because this is a difficult group to reach with health promotion strategies and they have a lower uptake of screening (171).

Looking at the associations between patient characteristics and outcomes the main route to long-term survival is through a successful surgical resection of the cancer. If I could identify unexplained low rates of resection for a particular patient characteristic then this opens up the possibility of preventing under-treatment. If the rationale for the under-treatment could not be backed up by clinical evidence of inferior outcomes then the argument could be made that there was some bias with in the healthcare system preventing access to surgery for these patients.

In my cohort I found that increasing age was associated with a reduced crude surgical resection rate and higher one-year mortality, which is backed up by other studies(256). This main reason for this was that the stage of cancer is higher in older patients(8,275). However over the last few decades survival differences based on age has reduced substantially. The predominant reason for this is thought to be the increased resection rates among the elderly(276). Unfortunately, my patient cohort does not have a

record of the patient's cancer stage so I cannot directly challenge whether there is under treatment based on age bias or simply that older patients had more advanced disease that would not benefit from surgical resection.

In my study cohort there was no significant difference in the resection rate based on gender. This was interesting because while most other studies have reported rates approximately equal between the genders (258,272), a small number of studies have reported more women undergoing an attempt at curative surgery(257). The crude one-year mortality rate was higher among females, but this was likely to be a confounding effect caused by age.

Increasing co-morbidity was associated with reduced surgical resection and higher one-year mortality in my study cohort. In other studies, increased co-morbidity was negatively associated with short-term survival(277). This association was especially strong for older male patients(274). I showed co-morbidity was strongly associated with poor outcomes. This was in agreement with the "competing demands" model, which argues that co-morbidity is associated with delayed diagnosis and also other work showing poorer survival in patients with co-morbidity(250).

Increasing deprivation was associated with reduced surgical resection and higher one-year mortality. This was supported by other studies which found that the most socioeconomically deprived patients had higher mortality rates, largely explained by excess early mortality especially in the first month after diagnosis(251).

I found that a proximal cancer site was associated with reduced surgical resection and higher one-year mortality. Other studies support this finding in particular that outcomes tend to be better in patients with rectal cancer(223).

There are some weaknesses in my methodological approach. Several of these are common to all HES related studies and the most significant of these are associated with missing clinical information. Important omissions from the database include, as already mentioned, a date of diagnosis. Also missing are the stage of cancer, which is of course of great prognostic impact, and patient ethnicity. There will always be some problems associated with the accuracy of clinical recordkeeping and transposition into codes by clinical coders. Other problems include under-reporting of co-morbidity in some hospitals and maybe missing codes for some day case procedures such as colonoscopy.

I acknowledge that the codes included to define the REL1 admission were somewhat subjective, however I mitigated this by using an expert panel to select those included. Only a separate analysis of the patients' medical records at the time of the REL1 admission could determine for certain if all the included codes were truly relevant.

Finally, while I was able to identify some risk factors, such as increasing age, to explain variation in outcomes. I was not able to exclude all potential cofounding factors. Therefore I could not directly

apply causality to the outcomes. I will however look into the causes for variations in outcome in subsequent chapters and especially the impact of the introduction of the BCSP.

In conclusion, I believe my methodological approach is superior to traditional analytical approaches that focus solely on episodes coded with a cancer diagnosis. This was because it contained more patients with incident CRC, including patients with advanced CRC and those not suitable for surgical resection. These cases are possibly excluded from other cancer registry databases. Furthermore for each patient, I identified more of the relevant episodes of care and therefore increased the completeness of the patients journeys compared to other studies. In particular, I believe I have captured a more accurate start date for the patient's journey, by identifying the first relevant admission (REL1). Almost a quarter of patients had an earlier relevant admission and this process identified a higher rate of emergency presentation than was previously believed to be the case. This is very important as it creates a target to focus resources on, which will hopefully lead to improvements in CRC outcomes.

I then validated my cohort against external data sources to show already established associations and also describe some new findings. My study cohort is therefore an accurate representation of CRC across England, and forms my main data source in the subsequent chapters of this thesis.

Chapter 3 - Emergency presentation: establishing my primary outcome measure

3.1. Introduction

In the United Kingdom the mean five-year survival for CRC is 50%. This is significantly lower than other countries of comparable wealth(140,171). The rate of emergency presentations in the UK is approximately 30%,(69,72,99) which is high compared with international rates of between 3-34%(67-71,184). The five-year survival after an elective presentation is 58%, but following an emergency presentation it is only 39%(198). Therefore any strategy to prevent emergency presentations is also likely to improve overall survival.

3.1.1. What is an emergency presentation?

I have defined an emergency presentation as one where the presenting admission was an unplanned hospitalisation. These should be avoidable in the majority of cases. This is because symptoms will usually have been present for some time and the NHS is now geared towards providing rapid access to diagnostic services (endoscopic and radiological) for patients with potential CRC. Therefore any patient with slowly progressive symptoms that presents as an emergency could be described as an 'avoidable emergency presentation', while those presenting as an acute deterioration with an event such as obstruction or perforation could be described as 'unavoidable emergency presentation'. Either way a high rate might imply inappropriate delays either in seeking medical attention or in the diagnostic process.

I identified the patient's admission type, according to the ADMIMETH field in the HES database (*Table 1.8*, chapter 1). HES defines an emergency admission as one that is unpredictable and at short notice because of clinical need. In practice, this means presenting;

- directly via the Emergency Department
- as an emergency GP referral
- as an emergency admission from the out-patient department
- or as an emergency transfer from another hospital

All other admission types were defined as elective admissions. Several studies have used this approach (89,244,278) while others have used more clinically defined metrics, such as presentation with large bowel obstruction, perforation or significant rectal bleeding(97,279).

3.1.2. Possible causes of emergency presentation

Symptoms caused by CRC include rectal bleeding, a change in bowel habit or weight loss and are usually slowly progressive. These symptoms eventually reach a threshold that compels patients to attend

primary care. Therefore most patients present electively via their GP(6,95,97). There are also some patients diagnosed asymptomatically following a primary care consultation, for example following investigation of anaemia. Once CRC is suspected, the NHS aims to ensure that patients are speedily referred through to hospital care for rapid assessment and diagnosis, using a two week wait referral pathway(280). As already described in chapter 1, patients can also be diagnosed electively, as part of surveillance programmes and more recently through the BCSP.

The remaining patients present as an emergency and are more likely to be acutely unwell(72). At the most serious end of the spectrum patients may have severe and immediately life-threatening symptoms, resulting from large bowel obstruction, often requiring emergency surgical interventions. This may lead to perforation or severe haemodynamic derangements. Patients may also present directly to secondary care with significant bleeding(97). However, not all emergency patients are acutely unwell and the reason these patients present as an emergency directly to secondary care is not fully understood. Table 3.1 describes where in the care pathway, delays may occur, that lead to emergency presentations.

Despite the attractive mechanistic idea that delay causes emergency presentation, so far the supporting data are mixed. Some studies have described longer delays in the patient's pathway for those presenting as an emergency, especially when the delays are caused by primary care and secondary care(281). *Scott et al* found that, on average, symptoms in elective patients were present for three weeks before diagnosis compared to eleven weeks for emergency patients(72). This doesn't however explain why the delay occurred and symptom delay on its own (regardless of the presentation type) has not been shown to effect CRC stage or prognosis(167). However a small study looking at patient delay found no significant difference in the time between the onset of the first CRC symptom and first medical visit, in emergency or elective patients (27 vs. 30 days)(214).

Primary care delay may contribute to emergency presentation for some patients as studies have found around two-thirds of emergency patients had visited their general practitioner with symptoms of CRC before being admitted(282). There may also be poor integration of services between primary and secondary care and within secondary care. Together this creates the so called 'waiting iceberg' of delays between outpatient appointments and investigations(160,283).

Aggressive tumours, which have poorer outcomes, will tend to present soon after symptoms appear. By contrast, slow growing tumours may be diagnosed after a longer duration of symptoms and still have better outcomes(85). This may complicate the association between delay and outcomes as some patients with significant delays from first symptom to diagnosis may have a nonaggressive and ultimately treatable cancer, while an aggressive cancer may be rapidly diagnosed but still resistant to effective treatment.

Overall, there is no convincing data yet that shows delay in a given part of the patient pathway is responsible for emergency presentations.

Table 3.1 The type and cause of different delays that can lead to the breakdown in the elective care pathway.

Type of delay	Description	Cause
Patient	The time between noticing a symptom and consulting a GP	The non-specific nature of early CRC symptoms The patient ignoring symptoms until a crisis is reached A failure to understand how to access elective care (e.g. not being registered with a GP).
Primary care	The time between a patient's first GP consultation and referral	Delay in accessing a primary care appointment Receiving false assurances regarding their symptoms.
Secondary care	The time between referral and cancer diagnosis	Delay in accessing a secondary care appointment Delay in the investigation of their symptoms Receiving false assurances regarding their symptoms.

3.1.3. Differences between emergency and elective presentations

There is some evidence to suggest symptom patterns differ between elective and emergency presentations, notwithstanding there being a significant overlap. Patients admitted as an emergency more often present with the 'constitutional syndrome' (weakness, anorexia and weight loss) along with intestinal-specific symptoms such as diarrhoea, vomiting and abdominal pain(214). This may be because these symptoms are more associated with bowel obstruction. Additionally, patients with acute complications from their CRC such as a major bleed, colonic perforation or obstruction are much more likely to present as an emergency(97). Elective patients more commonly present with specific lower gastrointestinal symptoms, such as rectal bleeding or a change in bowel habit(72,214,282). There is some evidence that presenting to hospital over the weekend is associated with worse outcomes(284). What is less well understood is whether patients presenting electively or as an emergency are affected differently depending on the day of the week(284).

3.1.4. Factors known to be associated with emergency presentation

In addition to particular symptoms previous studies have suggested that certain patient characteristics are associated with emergency presentation. These include patients that are: older, have co-morbidities, are female and from lower socioeconomic groups. Emergency presentation is also more likely in patients with colonic rather than rectal cancer and in patients with advanced stage disease (69,97,219,285). However, these studies are either from single centres or from different countries, with a different healthcare model to the UK. There are currently no robust national studies from the UK, which identify the patient characteristics most associated with emergency presentation.

3.1.5. Outcomes following an emergency presentation

Importantly for my thesis there is already some evidence showing that emergency presentation is associated with adverse outcomes. Emergency presentation has been linked to reduced access to major resection and reduced survival at one-year. Furthermore these patients have on average a longer length of stay in hospital and more postoperative complications (285,286). These findings are partly explained by the characteristics of the patients themselves, who are more likely to be older, female, poor and have co-morbidities(72,85,287). However these studies are again either from single centres, from countries with different healthcare models or were conducted over 25 years ago. This means that while there is evidence to suggest an association between emergency presentation and poorer outcomes, there is still a need to study the results in an up-to-date English population of CRC patients.

3.2. Hypothesis

My hypothesis is that even after adjusting for patient characteristics, emergency presentation is a strong independent predictor of poor CRC outcomes. Patients presenting as an emergency, have reduced access to surgical resection and reduced one-year survival. Therefore emergency presentation can be used as a used as a metric in studies to examine factors associated with variation in CRC outcomes.

3.3. Aims

My aims in this chapter are to:

- Describe differences in the types of presenting symptoms and initial management between emergency and elective patients.
- Identify the characteristics associated with emergency presentation of CRC.
- Describe how outcomes following emergency presentation differ from those of elective patients; primarily in terms of mortality and access to surgical resection. Secondary quality indicators including the length of stay during the operative admission and readmission rate following surgery are also described.
- Demonstrate that emergency presentation is an independent predictor of adverse outcomes.

3.4. Methods

Chapter 2 described how I identified my patient cohort and the methodology for identifying a patient's index admission. I have produced evidence to support the use of the presentation mode (emergency or elective) at the index admission to define how a patient's journey begins. Therefore I can use my cohort to look at differences between the two groups.

This chapter will compare the characteristics and outcomes of patients with an emergency or elective presentation. The characteristics compared include: age, gender, co-morbidity, cancer site and deprivation. The primary outcomes measured were surgical resection and one-year mortality. Groups were compared using the chi-square test and binary logistic regression (univariate and multivariate). I

used Kaplan-Meier survival curves to demonstrate the impact of an emergency admission at presentation on survival. The secondary outcomes include: the length of stay at the presenting admission and during the admission for surgery and the readmission rate following surgery.

3.5. Results

3.5.1. Characteristics of patients presenting as an emergency

In this section I describe the correlation between patient characteristics and emergency presentation. Overall in my cohort 11,651 (36.1%) patients presented as an emergency, with 20,648 (63.9%) presenting electively, *Table 3.2*.

Patients presenting in an emergency were significantly older with an average age of 73.1 years (sd 12.8), compared with 69.8 years (sd 11.6, $p<0.001$) for elective patients. The proportion of patients with emergency presentation in the oldest group (>85 years) was 56.3%, compared with 28.8% in the 55-64 year group ($p<0.001$). Women were more likely to present as an emergency (38.6% vs. 34.1%, $p<0.001$).

Increasing co-morbidity was associated with emergency presentation. In patients with a Charlson co-morbidity score of ≥2 the emergency rate was 58.3%, compared to only 27.0% in patients without co-morbidities ($p<0.001$).

Proximal CRC was also associated with emergency presentation. In patients with colon cancer, the emergency rate was 42.4%, compared with only 23.4% in rectal cancer ($p<0.001$). Finally, patients in the most deprived quintile had an emergency presentation rate of 42.0% (2,319/5,516), compared with 31.9% (2,104/6,593) in the least deprived quintile, *Table 3.2*. Each of these patient characteristics will be examined in greater depth below.

Table 3.2 Characteristics of patients presenting electively and as an emergency.

Patient characteristic	Total cases, N (%)	Elective, N (%)	Emergency, N (%)	P value
No.	32,299	20,648 (63.9)	11,651 (36.1)	
Age groups				
Mean age yrs (sd)	*71.0 (12.1)*	*69.8 (11.6)*	*73.1 (12.8)*	
<55 yrs	3,044 (9.4)	2,043 (67.1)	1,001 (32.9)	
55-64 yrs	5,872 (18.2)	4,183 (71.2)	1,689 (28.8)	
65-74 yrs	9,474 (29.3)	6,564 (69.3)	2,910 (30.7)	
75-84 yrs	10,080 (31.2)	6,186 (61.4)	3,894 (38.6)	
≥85 yrs	3,829 (11.9)	1,672 (43.7)	2,157 (56.3)	<0.001
Gender				
Male	17,981 (55.7)	11,853 (65.9)	6,128 (34.1)	<0.001
Female	14,318 (44.3)	8,795 (61.4)	5,523 (38.6)	
Co-morbidity				
0	21,847 (67.6)	15,941 (73.0)	5,906 (27.0)	<0.001
1	2,383 (7.4)	1,340 (56.2)	1,043 (43.8)	
≥2	8,069 (25.0)	3,367 (41.7)	4,702 (58.3)	
Site				
Rectal	9,631 (29.8)	7,375 (76.6)	2,256 (23.4)	
Rectosigmoid	2,440 (7.6)	1,613 (66.1)	827 (33.9)	
Colon	20,228 (62.6)	11,660 (57.6)	8,568 (42.4)	<0.001
Deprivation				
IMD missing	322 (1.0)	193 (59.9)	129 (40.1)	
1 (most deprived)	5,516 (17.1)	3,197 (58.0)	2,319 (42.0)	
2	6,044 (18.7)	3,770 (62.4)	2,274 (37.6)	
3	6,844 (21.2)	4,363 (63.7)	2,481 (36.3)	
4	6,980 (21.6)	4,636 (66.4)	2,344 (33.6)	
5 (least deprived)	6,593 (20.4)	4,489 (68.1)	2,104 (31.9)	<0.001

3.5.2. Associations between emergency presentation and patient characteristics

3.5.2.1. Age

Table 3.3 shows that emergency presentation rates generally increase with age. However amongst the relatively small group of patients aged 54 years and younger, the rate is actually higher than in patients aged 55-74 years. Emergency rates then rise sharply and significantly in the elderly group (over 85 years), *Figure 3.1*.

Looking at the data in more detail; emergency rates are highest at both extremes of age, with the lowest rates between 50-70 years. Patients under 30 years and over 80 years, had rates up to 70%, while those in the middle of the age distribution were around 30%.

Binary logistic regression confirmed that patients under 55 years have a greater chance of an emergency presentation than patients aged 56-75 years. Above 75 years the odds of emergency presentation increased and were highest in the oldest patient group (over 85 years) with an Odds Ratio (OR) of 2.63 (2.39-2.91) compared to patients <55 years, *Table 3.3*.

Table 3.3 A binary logistic regression analysis showing the association between a patients age group and the risk of emergency presentation.

Age groups	Emergency presentations/ total (%)	Univariate OR	CI	P value
<55 yrs	1,001/3,044 (32.9)	1	-	-
55-64 yrs	1,689/5,872 (28.8)	0.82	0.75-0.91	<0.001
65-74 yrs	2,910/9,474 (30.7)	0.91	0.83-0.99	0.025
75-84 yrs	3,894/10,080 (38.6)	1.29	1.18-1.40	<0.001
≥85 yrs	2,157/3,829 (56.3)*	2.63	2.39-2.91	<0.001

*p<0.001

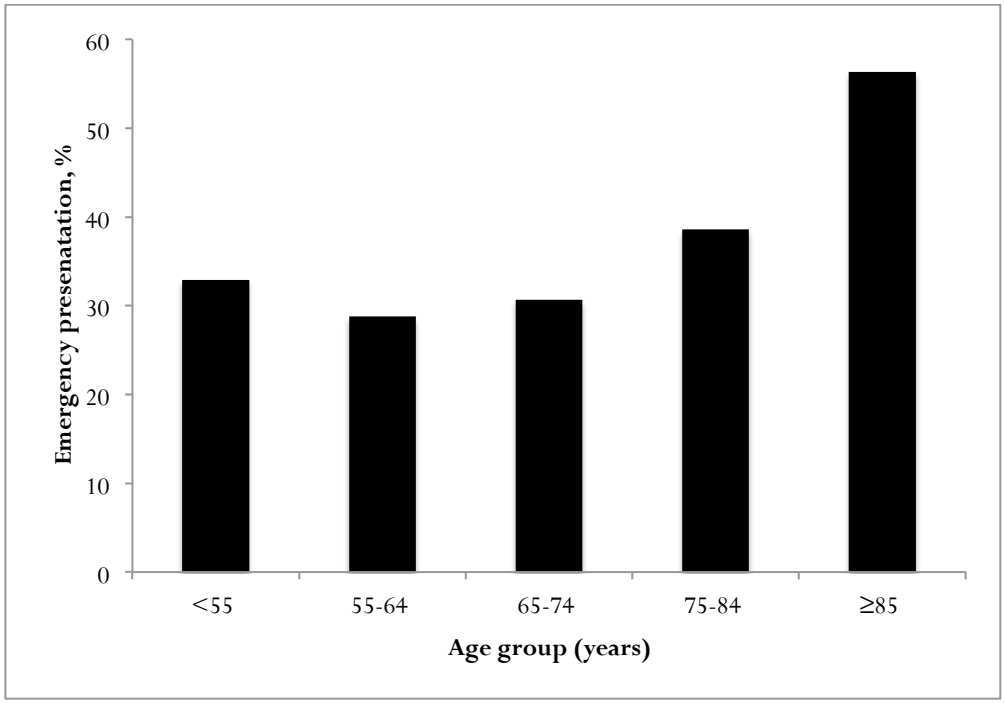


Figure 3.1 The relationship between age and emergency presentation. Over the age of 55, emergency presentation became more common with increasing age.

3.5.2.2. Gender

A higher proportion of female patients presented as an emergency (38.6% vs. 34.1%, p<0.001). This association was supported by univariate regression analysis, which showed female patients have an OR of 1.22 (1.16-1.27), *Table 3.4*.

Table 3.4 The risk of emergency presentation in male and female patients.

Gender	Emergency presentations/ total (%)	OR	Univariate CI	P value
Male	6,128/17,981 (34.1)	1	-	-
Female	5,523/14,318 (38.6)*	1.22	1.16-1.27	<0.001

*p<0.001

3.5.2.3. Co-morbidity

Compared to no co-morbidity, the presence of even a single co-morbidity was associated with a near doubling of the emergency presentation rate (43.8% vs. 27.0%, p<0.001). This is supported by binary logistic regression analysis with an OR of emergency presentation of 2.10 (1.93-2.29) with a single co-morbidity, *Table 3.5*.

Table 3.5 The risk of emergency presentation in patients with different levels of co-morbidity.

Co-morbidity	Emergency presentations / Total (%)	OR	Univariate CI	P value
0	5,906/21,847 (27.0)	1	-	-
1	1,043/2,383 (43.8)*	2.10	1.93-2.29	<0.001
≥2	4,702/8,069 (58.3)*	3.77	3.57-3.98	<0.001

* p<0.001

3.5.2.4. Site

Colon cancers are significantly more likely than rectal cancers to result in an emergency presentation (42.4% vs. 23.4%, p<0.001). Taking rectosigmoid cancers as the baseline for binary logistic regression analysis, rectal cancers have a smaller chance of presenting as an emergency (OR 0.60 [0.52-0.66]) and colon cancer a greater chance (OR 1.43 [1.31-1.57]), *Table 3.6*.

Table 3.6 The risk of emergency presentation in patients with cancer at different sites.

Site	Emergency presentations / Total (%)	OR	Univariate CI	P value
Rectosigmoid	827/2,440 (33.9)	1	-	-
Rectal	2,256/9,631 (23.4)	0.60	0.52-0.66	<0.001
Colon	8,568/20,228 (42.4)*	1.43	1.31-1.57	<0.001

3.5.2.5. Deprivation

The risk of an emergency presentation is associated with increasing deprivation. There was a 10.1% difference in emergency presentation rates between the most and least deprived quintiles. This was supported by binary logistic regression analysis, which showed that compared to the most deprived

quintile, the risk of emergency presentation in the least deprived was 0.65 (0.60-0.70, p<0.001), *Table 3.7.*

Table 3.7 The risk of emergency presentation in patients with different levels of deprivation.

Deprivation	Emergency presentations/ Total (%)	Univariate OR	CI	P value
IMD missing	129/322 (40.1)			
1 (most deprived)	2,319/5,516 (42.0)*	1	-	-
2	2,274/6,044 (37.6)	0.83	0.77-0.90	<0.001
3	2,481/6,844 (36.3)	0.78	0.73-0.84	<0.001
4	2,344/6,980 (33.6)	0.70	0.65-0.75	<0.001
5 (least deprived)	2,104/6,593 (31.9)	0.65	0.60-0.70	<0.001

3.5.3. Multivariate analysis of patient characteristics

The multivariate model in Table 3.8 shows that all included patient characteristics showed significant and independent associations with emergency presentation.

The strongest associations with emergency presentation were increasing co-morbidity, followed by increasing age and deprivation. An analysis of links between deprivation and emergency presentation, showed a near perfect social gradient from least to most deprived, with significance shown across the entire gradient (p <0.001). Female gender and proximal cancer had a weaker association.

Interestingly, increasing age, co-morbidity and female gender were less strongly associated with emergency presentation in the multivariate model than in the univariate model.

Table 3.8 A univariate and multivariate analysis of factors associated with emergency presentation.

Variable	Emergency presentations/ Total (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	P value	OR	CI	P value
Age group (years)							
<55	1,001/3,044 (32.9)	1	-	-	1	-	-
55-64	1,689/5,872 (28.8)	0.82	0.75-0.90	<0.001	0.79	0.72-0.88	<0.001
65-74	2,910/9,474 (30.7)	0.89	0.82-0.98	0.016	0.83	0.75-0.91	<0.001
75-84	3,894/10,080 (38.6)	1.28	1.17-1.39	<0.001	1.15	1.04-1.26	0.004
≥85	2,157/3,829 (56.3)	2.61	2.37-2.89	<0.001	2.44	2.19-2.71	<0.001
Gender							
Male	6,128/17,981 (34.1)	1	-	-	1	-	-
Female	5,523/14,318 (38.6)	1.22	1.16-1.27	<0.001	1.10	1.04-1.15	<0.001
Co-morbidity groups							
No co-morbidity	5,906/21,847 (27.0)	1	-	-	1	-	-
1 co-morbidity	1,043/2,383 (43.8)	2.10	1.93-2.29	<0.001	1.99	1.82-2.18	<0.001
≥ 2 co-morbidity	4,702/8,069 (58.3)	3.81	3.61-4.02	<0.001	3.71	3.51-3.92	<0.001
Site							
Rectosigmoid	827/2,440 (33.9)	1	-	-	1	-	-
Rectal	2,256/9,631 (23.4)	0.60	0.54-0.66	<0.001	0.67	0.61-0.74	<0.001
Colon	8,568/20,228 (42.4)	1.45	1.32-1.58	<0.001	1.48	1.35-1.63	<0.001
Deprivation							
IMD missing	129/322 (40.1)	-	-	-	-	-	-
1 (most deprived)	2,319/5,516 (42.0)	1	-	-	1	-	-
2	2,274/6,044 (37.6)	0.83	0.77-0.90	<0.001	0.80	0.74-0.87	<0.001
3	2,481/6,844 (36.3)	0.78	0.73-0.84	<0.001	0.75	0.69-0.81	<0.001
4	2,344/6,980 (33.6)	0.70	0.65-0.75	<0.001	0.66	0.61-0.71	<0.001
5 (least deprived)	2,104/6,593 (31.9)	0.65	0.60-0.70	<0.001	0.63	0.58-0.68	<0.001

3.5.4. Risk tables for predicting emergency presentation

Risk tables were created to better demonstrate how patient characteristics influenced the risk of an emergency presentation. Rates of emergency presentation ranged from 11.9%, in females aged 55-64 years with rectal/rectosigmoid cancer and no co-morbidities, up to 77.2% among female patients aged ≥85 years with co-morbidities and colon cancer, *Table 3.9, 3.10.*

Table 3.9 Risk tables for emergency presentation (%) based on age, co-morbidity and site (male patients).

Age Group	Co-Morbidity 0		Co-Morbidity ≥ 1	
	Rectal/ Rectosigmoid	Colon	Rectal/ Rectosigmoid	Colon
<55	15.7	38.4	37.9	62.0
55-64	13.5	27.1	36.8	52.1
65-74	13.3	27.2	38.2	55.3
75-84	20.1	30.8	46.0	59.1
≥85	34.7	47.7	64.4	72.5

Table 3.10 Risk tables for emergency presentation (%) based on age, co-morbidity and site (female patients).

Age Group	Co-Morbidity 0		Co-Morbidity ≥ 1	
	Rectal/ Rectosigmoid	Colon	Rectal/ Rectosigmoid	Colon
<55	14.4	32.5	38.2	55.9
55-64	11.9	28.8	37.8	54.7
65-74	14.2	28.2	43.9	53.9
75-84	23.6	34.8	47.2	64.0
≥85	42.8	53.0	66.0	77.2

3.5.5. Diagnoses and procedures recorded at presentation

3.5.5.1. The frequency of diagnostic codes at position one at the index admission

At the presenting (index) admission, the commonest primary diagnostic codes were, unsurprisingly, for CRC itself. Of interest, only 58.2% of emergency presentations had a primary CRC code at presentation, compared to 75.7% of elective presentation. This implies a greater degree of diagnostic uncertainty at presentation in the emergency group. This is depicted in Figure 3.2, which also shows that in place of CRC codes, there were significantly higher rates of red flag symptoms (11.8% vs. 2.6%, $p<0.001$) and anaemia (5.0% vs. 3.6%, $p<0.001$) codes, among the emergency group.

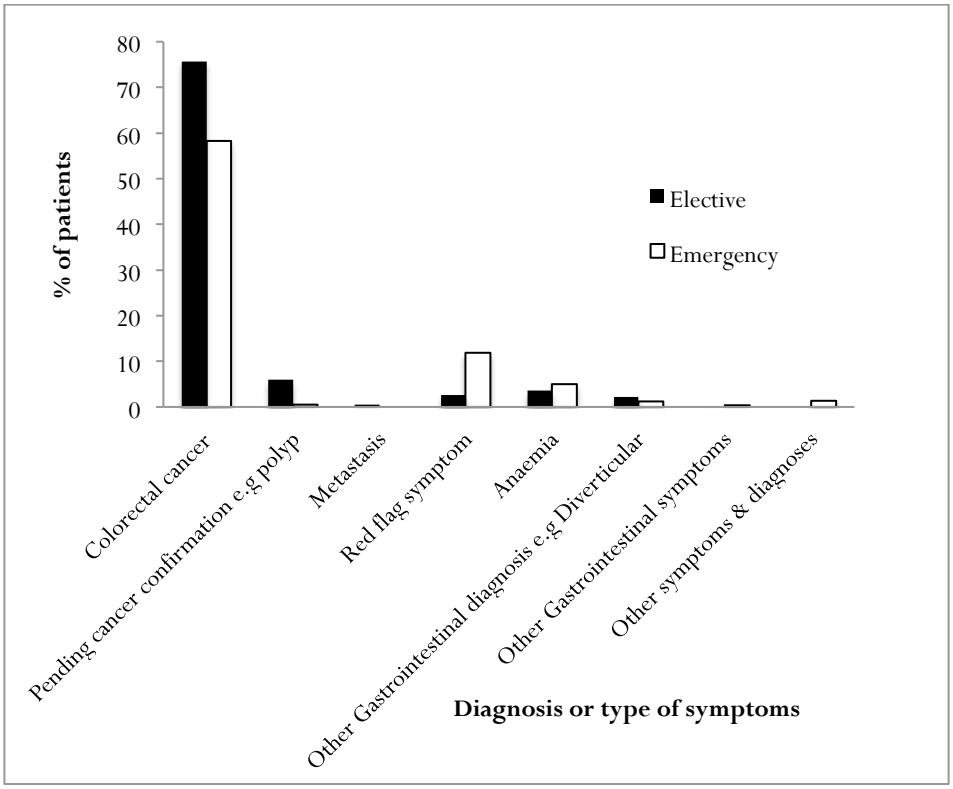


Figure 3.2 A chart showing the frequency of diagnostic codes at position one at the index admission for elective and emergency patients.

3.5.5.2. The frequency of procedural codes at position one at presentation

For elective patients, a lower gastrointestinal endoscopy was the commonest primary procedure recorded at presentation (65.7%). However in the emergency group only 13.6% of patients had a lower gastrointestinal endoscopy recorded at presentation. Instead patients presenting as an emergency more often had 'no procedure' (43.5%) or 'other procedure' (21.2%) recorded. The rates of major surgical resections during the index admission were similar for both emergency (16.9%) and elective (16.1%) groups, *Figure 3.3*.

These results unsurprisingly show that elective patients are more likely to follow an optimal management pathway with early access to the key diagnostic procedure, a lower gastrointestinal endoscopy.

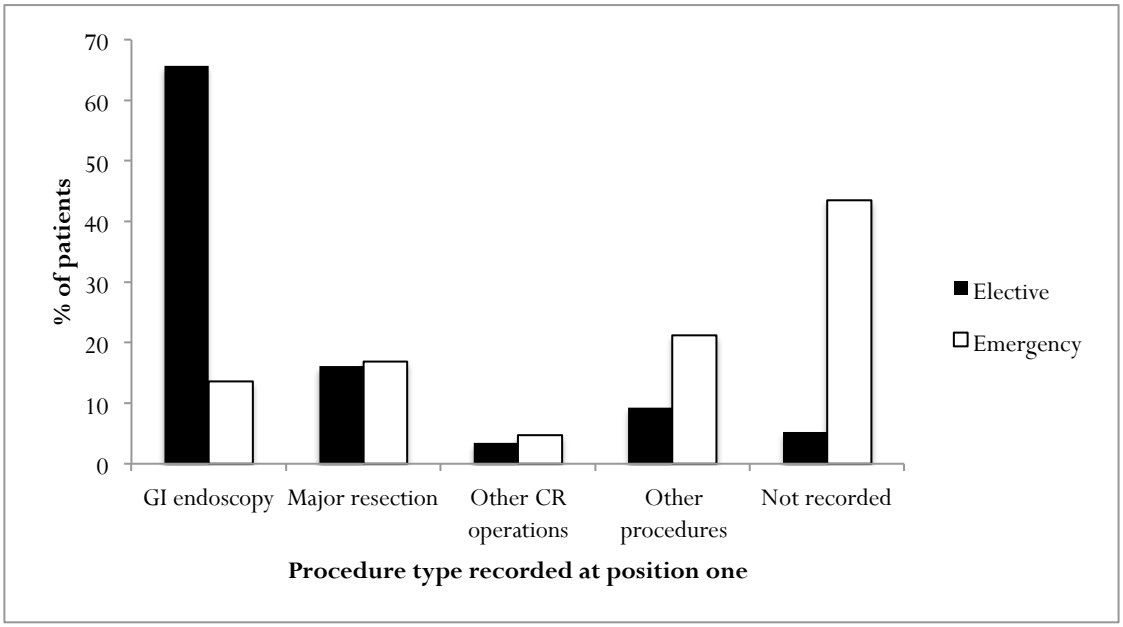


Figure 3.3 A chart showing the frequency of procedural codes at position one at the index admission for elective and emergency patients.

3.5.5.3. Selected symptoms, signs and complications at presentation; 'unavoidable' versus 'avoidable' emergencies

I next looked at whether selected symptoms, signs and acute CRC complications were more prevalent in either group at presentations, *Table 3.11, Figure 3.4*. Together, anaemia was recorded in 12.3% of patients, rectal bleeding in 5.2%, while the complications I stated would lead to an 'unavoidable emergency presentation'; obstruction and perforation were present in 2.1% and 0.9% of patients respectively. The emergency group had a much higher rate of CRC complications. In particular perforation was twentyfold more frequent (2.4% vs. 0.1%, $p<0.001$) and obstruction four times higher (4.1% vs. 1.0%, $p<0.001$). Thus the proportion of 'unavoidable emergency presentations' (with either

an obstruction or perforation) was 6.5%. This suggests the majority of emergency presentations remain 'avoidable', *Table 3.11*.

Table 3.11 A table showing the rates of selected symptoms, signs and complications at CRC presentation for elective and emergency patients.

Symptoms/Signs	Total	Elective, N (%)	Emergency, N (%)	P value
Total	32,299	20,648 (63.9)	11,651 (36.1)	
Rectal bleeding	1,656	910 (4.4)	746 (6.4)	<0.001
Large bowel obstruction	691	208 (1.0)	483 (4.1)	<0.001
Perforation	296 (0.9)	15 (0.1)	281 (2.4)	<0.001
Anaemia	3,966 (12.3)	2,124 (10.3)	1,842 (15.8)	<0.001

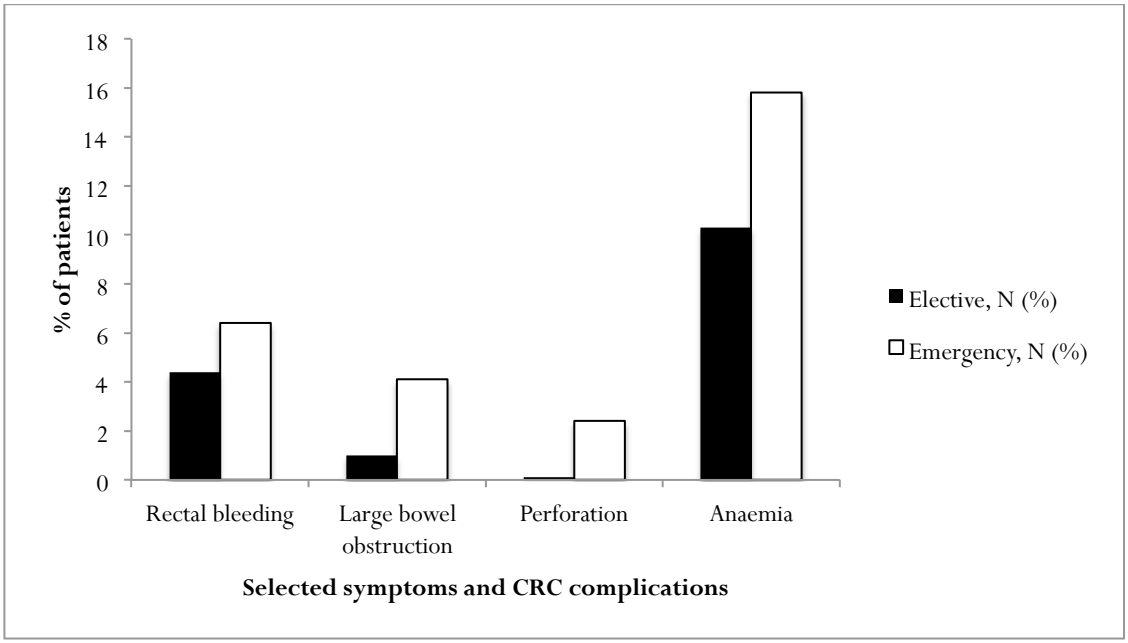


Figure 3.4 A chart showing the frequency of selected symptoms and CRC complications at presentation for the elective and emergency groups.

3.5.6. Outcomes for patients presenting as an emergency

The key primary outcomes studied were access to surgical resection and survival at one-year. Secondary outcome measures included length of stay at presentation and following surgery, the presence of complications and readmissions following surgery.

3.5.6.1. Primary outcomes

3.5.6.1.1. Access to surgical resection

There was a considerable difference in rates of surgery between the two groups. Emergency patients were significantly less likely to have surgical resection within six months of presentation (35.4% vs. 59.1%, p<0.001). The same association was seen for 'any colorectal operation', a definition that included de-functioning procedures (e.g. colostomies and ileostomies), with 71.0% of elective patients and 51.6% of emergency patients receiving an operation, *Table 3.12*.

Out of a total of 20,674 (64.0%) colorectal operations, 8,702 (42.1%) occurred in the presenting admission. In elective patients the rate was 26.5% (5,469/20,648) and among emergency patients the rate was 27.7% (3,233/11,651, p=0.015).

Patients in the emergency group were significantly less likely to have a laparoscopic assisted resection (6.2% vs. 17.4%, p<0.001), to receive an anterior resection (9.8% vs. 41.7%, p<0.001) or Abdomino-Perineal Excision of the Rectum (APER) (2.4% vs. 9.6%, p<0.001). Patients in the emergency group were more likely to receive a Hartmann's procedure (11.7% vs. 5.2%, p<0.001), *Table 3.13*.

In patients undergoing a major resection within six months of presentation, the majority of the elective group also had their surgery performed electively (96.8%). Conversely, in patients with an emergency presentation and resection, just over half (56.7%) of these patients going on to resection, had the surgery during an emergency admission, *Figure 3.5*.

Table 3.12 A comparison of the rates of surgery for patients presenting electively and as an emergency.

Outcomes	Total cases, N (%)	Elective, N (%)	Emergency, N (%)	P value
Any colorectal operation	20,674 (64.0)	14,658 (71.0)	6,016 (51.6)	<0.001
Major resection	16,332 (50.6)	12,204 (59.1)	4,128 (35.4)	<0.001
Laparoscopic	2,377 (14.6)*	2,121 (17.4)*	256 (6.2)*	<0.001

*proportion of major resections

Table 3.13 A comparison of the types of surgical operations for patients presenting electively and as an emergency.

Operations	Elective, N (%)	Emergency, N (%)	P value
Major resections	12,204	4,128	<0.001
Anterior resection	5,083 (41.7)	403 (9.8)	<0.001
APER	1,167 (9.6)	101 (2.4)	<0.001
Hartmann's	630 (5.2)	485 (11.7)	<0.001
Other resection operations	5,324 (36.3)	3,139 (52.2)	<0.001

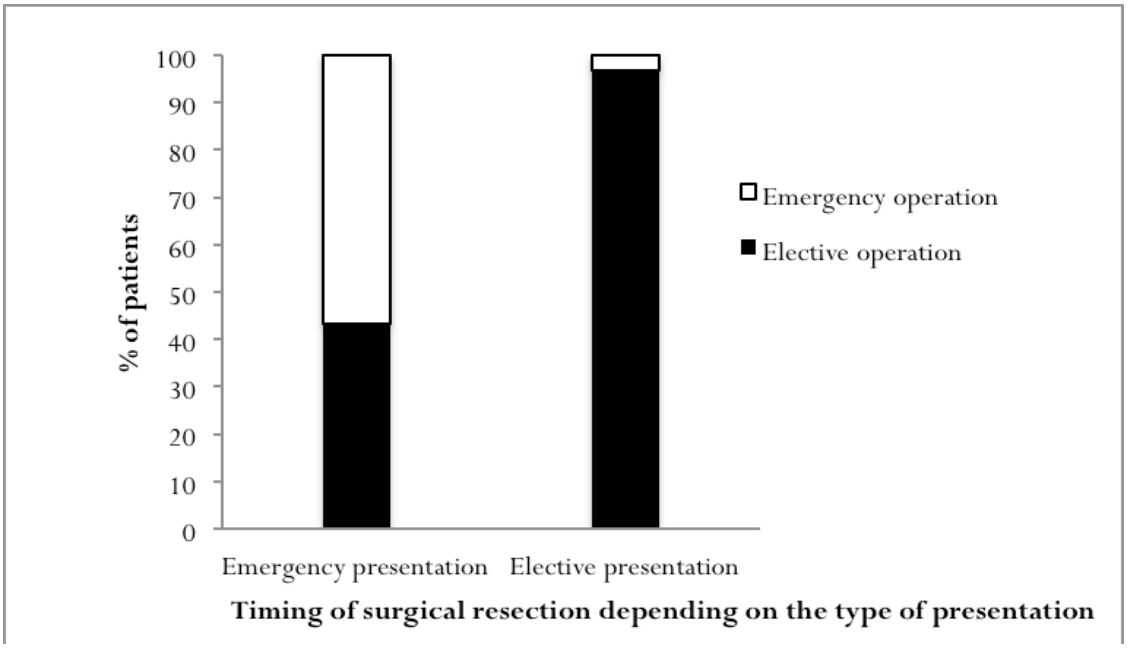


Figure 3.5 A chart illustrating the risk that operated patients will require an emergency (or elective) operation depending on whether the initial presentation was elective or an emergency. Following an elective presentation, the likelihood of elective surgery is very high, with only 3.2% requiring an emergency operation ($p<0.001$). However patients with an emergency presentation are more likely to have an emergency rather than elective operation ($p<0.001$).

3.5.6.1.2. One-year mortality

Emergency patients had a significantly higher mortality rate at one-year (49.4% vs. 18.0%, $p<0.001$), *Table 3.14*. This discrepancy in survival was even greater within the first 30 days of presentation, where the mortality rate was almost four times higher in emergency patients (6.5% vs.1.7%, $P<0.001$).

This early and continued survival advantage associated with an elective presentation is clearly demonstrated by Kaplan-Meier survival curves, *Figures 3.6, 3.7*. The curves begin to diverge soon after the index presentation and are widely separated after 100 days. Beyond 100 days the curves separate to a much lesser degree, implying that most of the difference in mortality is due to excess early deaths in the emergency group. As a total of all deaths in the first year after presentation 30.4% of emergency group deaths appeared within the first 30 days compared to 9.6% in the elective group.

The mortality rate 30 days after a surgical resection was significantly associated with the mode of presentation. Emergency presentations had a significantly higher mortality rate (10.8% vs. 2.8%, $p<0.001$). This difference persisted in the year following surgery (25.6% vs. 9.4%, $p<0.001$), *Table 3.14*.

Table 3.14 A comparison of 30-day and one-year mortality following presentation and major resection for patients presenting electively and as an emergency.

Outcomes	Total cases, N (%)	Elective, N (%)	Emergency, N (%)	P value
30 day mortality following index admission	2,106 (6.5)	357 (1.7)	1,749 (15.0)	<0.001
One-year mortality following index admission	9,469 (29.3)	3,712 (18.0)	5,757 (49.4)	<0.001
30 day mortality following major resection	791 (4.8)	345 (2.8)	446 (10.8)	<0.001
One-year mortality following major resection	2,208 (13.5)	1,152 (9.4)	1,056 (25.6)	<0.001

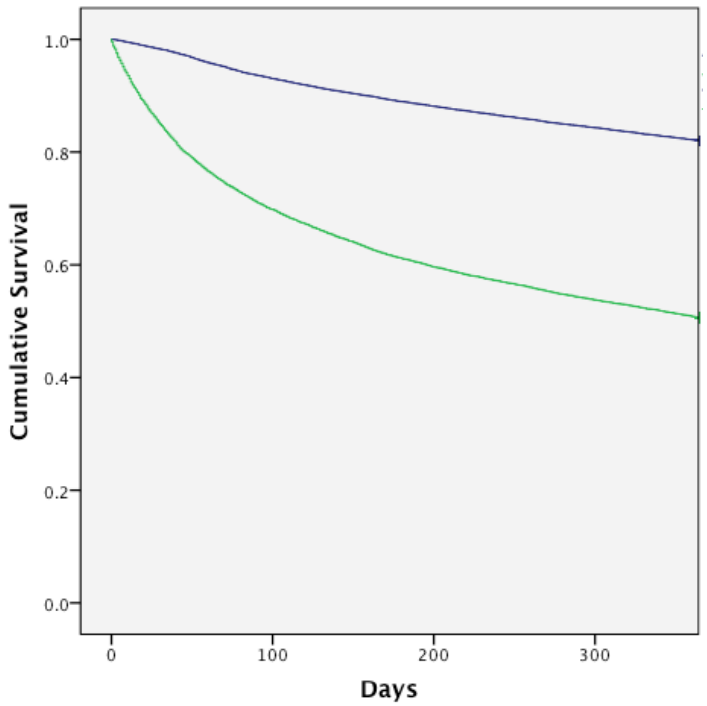


Figure 3.6 Kaplan-Meier survival curves demonstrating cumulative survival out to one year following presentation for elective (blue line) and emergency (green line) patients. The discordance in survival began early in the post-presentation period with most of the separation in survival curves established in the first 100 days (log rank test p<0.001).

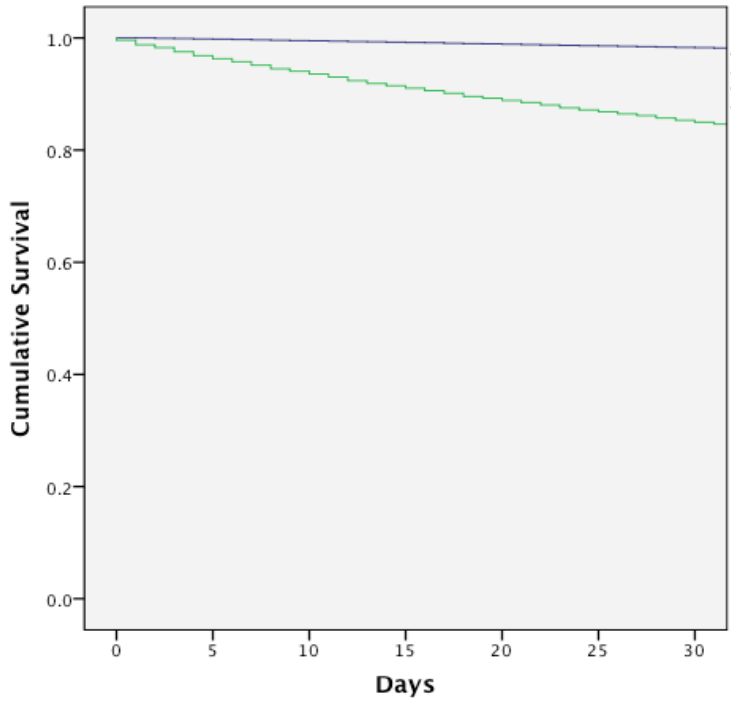


Figure 3.7 Kaplan-Meier survival curves demonstrating cumulative survival for the 30 days after presentation for elective (blue line) and emergency (green line) patients. There was early diverge in survival between the curves (log rank test p<0.001).

3.5.6.2. Secondary outcomes

3.5.6.2.1. Length of stay at the index admission and at the major resection admission

In this section I looked at whether emergency patients had a different length of stay at their initial presenting admission. The mean length of stay was considerably longer for emergency patients (14.6 days [sd 18.5] vs. 3.5 days [sd 10.5], p<0.001). This was largely explained by the higher number of day case index admissions in the elective group. There were 14,203 (68.8%) elective day case presentations, compared with just 777 (6.7%) short stay emergency admissions. Even if all these admissions were excluded, then the mean length of stay for emergency patients was still significantly longer (15.6 days vs. 11.2 days, p<0.001).

I also addressed the question of whether patients who present as an emergency experience a longer (more complicated) period of hospitalisation for their subsequent surgery. I found when the index admission was elective, the surgical length of stay was 12.4 (sd 10.2) days, compared to 20.3 (sd 16.5) days in emergency presentations (p<0.001), *Figure* 3.8.

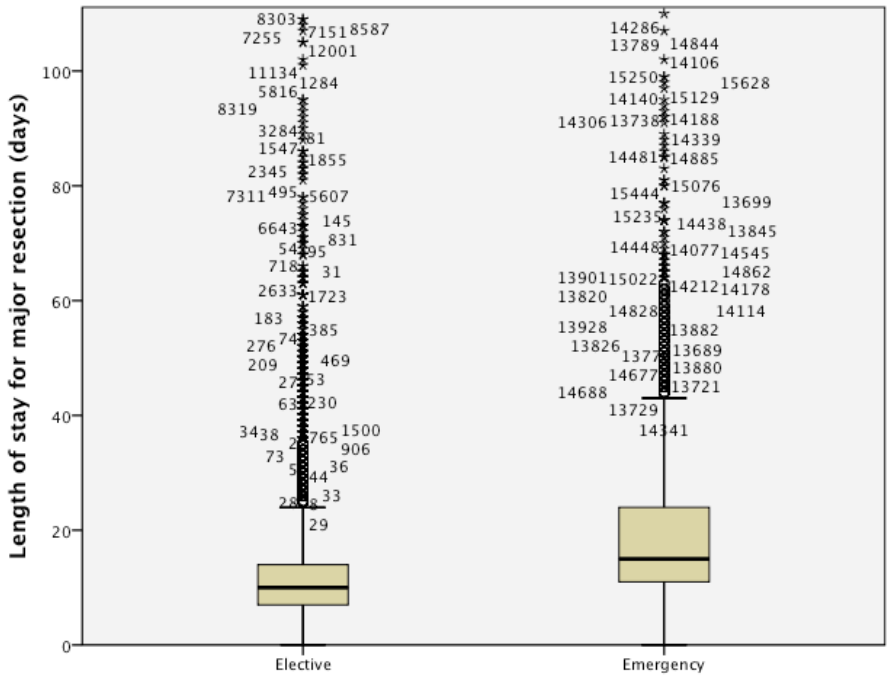


Figure 3.8 A box and whisker plot showing the length of stay following a major resection for elective and emergency presentation type (the numbers denote individual patient data points).

3.5.7. Emergency presentation as an independent risk factor for one year mortality

After adjusting for available patient case-mix factors (age, gender, co-morbidity and socioeconomic deprivation) emergency presentation was a strong independent predictor of one-year mortality. Patients with an emergency mode of index admission had a four-fold increased risk of death compared to adjusted elective cases (OR=4.11, CI: 3.88-4.35, $p<0.001$). The next strongest association with one-year mortality was an age of over 85 years (OR 4.05) and having a Charlson co-morbidity score of ≥ 2 (OR 3.14) *Table 3.15*.

Table 3.15 A univariate and multivariate analysis showing the associations between patient characteristics and presentation type and survival at one-year.

Variable	One-year mortality/ Total (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	P value	OR	CI	P value
Age group (years)							
<55	548/3,044 (18.0)	1	-	-	1	-	-
55-64	1,164/5,872 (19.8)	1.12	1.00-1.25	0.059	1.17	1.03-1.32	0.014
65-74	2,301/9,474 (24.3)	1.44	1.30-1.60	<0.001	1.53	1.37-1.72	<0.001
75-84	3,522/10,080 (34.9)	2.41	2.17-2.66	<0.001	2.49	2.23-2.78	<0.001
≥85	1,934/3,829 (50.5)	4.57	4.08-5.11	<0.001	4.05	3.58-4.58	<0.001
Gender							
Male	5,156/17,981 (28.7)	1	-	-	1	-	-
Female	4,313/14,318 (30.1)	1.07	1.02-1.13	0.004	0.94	0.89-0.99	0.025
Co-morbidity groups							
No co-morbidity	4,452/21,847 (20.4)	1	-	-	1	-	-
1 co-morbidity	715/2,383 (30.0)	1.67	1.52-1.83	<0.001	1.21	1.09-1.34	<0.001
≥ 2 co-morbidity	4,302/8,069 (53.3)	4.52	4.28-4.77	<0.001	3.14	2.95-3.33	<0.001
Site							
Rectosigmoid	756/2,440 (31.0)	1	-	-	1	-	-
Rectal	2,488/9,631 (26.3)	0.78	0.71-0.86	<0.001	1.03	0.92-1.15	<0.001
Colon	6,225/20,228 (30.8)	1.00	0.91-1.10	0.999	0.88	0.79-0.97	<0.001
Deprivation							
IMD missing	58/322 (18.0)						
1 (most deprived)	1,775/5,516 (32.2)	1	-	-	1	-	-
2	1,905/6,044 (31.5)	0.97	0.90-1.05	0.447	1.00	0.91-1.09	0.921
3	1,991/6,844 (29.1)	0.87	0.80-0.93	<0.001	0.89	0.82-0.97	0.009
4	1,965/6,980 (28.2)	0.83	0.77-0.89	<0.001	0.87	0.79-0.95	0.001
5 (least deprived)	1,775/6,593 (26.9)	0.78	0.72-0.84	<0.001	0.86	0.79-0.94	0.001
Presentation							
Elective	3,712/20,648 (18.0)	1	-	-	1	-	-
Emergency	5,757/11,651 (49.4)	5.76	5.47-6.07	<0.001	4.11	3.88-4.35	<0.001

3.6. Discussion

For the first time in a national cohort of English CRC patients I have shown that emergency presentation has very significant prognostic implications. Having adjusted for other prognostic factors, the Odds Ratio for mortality at one year following emergency presentation was 4.11. This is the single strongest predictor of adverse outcomes, even more than age, co-morbidity, site or deprivation. This is especially important given my finding that many emergency presentations are likely to be avoidable. Because of these findings; emergency presentation can be used as the primary outcome measure in my thesis, and to assess the impact of interventions on national CRC care.

The emergency presentation group had a one-year mortality rate of 49% (5,757/11,651) compared to 18% (3,712/20,648) in the elective group. It was also associated with much lower rates of major surgical resection, a higher percentage of emergency operations, a longer length of stay, more readmissions and suboptimal types of operations (e.g. Hartmann's procedure).

Increased mortality was apparent just 30 days following presentation. This implies not only that emergency presentation is an adverse quality indicator, but that it is associated with late presentation and late stage disease. Therefore interventions to reduce emergency presentations should reduce late presentation CRCs and so, reduce early mortality. That fact that mortality after emergency presentation rises so soon after the presentation, makes it a useful early outcomes metric for assessing the impact of interventions, such as a CRC awareness campaign. This is especially helpful as other markers used to measure quality and variations in CRC care take a long time to be measurable e.g. five-year CRC specific mortality. Overall the risks associated with an emergency presentation are substantial and strategies to reduce its occurrence warrant serious attention.

In my cohort emergency presentation was common, occurring in 36.1% of cases. This is in line with other studies from the UK and Ireland(70,72). Patient characteristics associated with emergency presentation included; female gender, older patients, those with co-morbidity and greater deprivation. Patients with colon cancer (as opposed to rectal cancer) also had a higher risk. Therefore all of these factors need to be adjusted for when using emergency presentation rates as a quality indicator, for example when comparing care between different units or studying tends over time.

There has been little attempt so far to firstly understand why emergency presentations occur and secondly why they are associated with such negative outcomes. To do this requires an understanding of why some patients and primary and secondary care physicians delay accessing the appropriate services, which would lead to an elective diagnosis. Some of this requires information not available for my thesis. I have, however, explored patient and cancer characteristics, that appear more commonly in emergencies. This chapter also shines light on two other interesting factors applicable to emergency presentation patients. Firstly, that emergency presentation is associated with early deaths suggesting many of these patients are presenting late, with advanced malignancy. Secondly the finding that rates of

presentations with severe complication such as a perforation or obstruction were low (6.5%) and that only a minority of emergency patients (27.7%) needed surgery in the presenting admission. This suggests that only a small percentage of emergency presentations were truly 'unavoidable'. In turn this allows me to speculate that reducing 'avoidable' emergency presentations can make substantial outcome gains. Increasing patient awareness of the symptoms of CRC and ensuring their flow through to diagnosis and definitive treatment is rapid might do this. This hypothesis is developed further in later chapters.

I have shown that increasing age was generally associated with more emergency presentations. Many studies have confirmed this (97). *Waldron et al*, found that patients over 70 years had a higher rate compared to younger patients (58% vs. 43%, $p<0.001$), while *Scott et al*, found that the median age was 74 years for emergency patients, compared to 72 years in the elective group and *Bass et al*, found the median age was 72 and 69 years respectively(70,72,288,289). However, one study of 273 patients found emergency presentation was not commoner among those patients aged 70 and above(223). I found emergency presentations were more common among the small number of patients under 40 years of age as well as among the elderly. This was a new finding and requires further study. Taken with the increased emergency rate among the elderly, I have shown higher emergency rates at both extremes of age. The reasons are unclear but may be because at extremes of age, both patients and medical professionals fail to consider CRC until symptoms and the disease are more advanced. It also bears consideration that patients within the BCSP age range have some of the lowest rates, which will be discussed further in chapter 4.

There are a number of reasons why older patients are more likely to present as an emergency(97). Elderly patients tend to have more advanced stage cancer at diagnosis (275) and some but not all studies have shown a longer delay in making the diagnosis(223,290). Age is also associated with social isolation and being widowed is certainly a factor behind emergency presentation(72). One study showed that elderly patients more commonly present with symptomatic anaemia and nonspecific symptoms, such as falls, and it is likely that this uncertainty creates delays for both patients and in primary care(223). There is also a trend for elderly patients to report lower rates of specific symptoms such as a rectal bleeding or change in bowel habit. Finally, it has been shown that there are more missed opportunities for diagnosing CRC among older patients, such as uninvestigated iron deficiency anaemia and rectal bleeding(291).

I found many young patients (<40 years) presented as an emergency. Some studies do show an increasing incidence of CRC among younger patients. The same studies also describe an association with later-stage and higher-grade tumours, but equivalent or better 5-year cancer specific survival(5,292). Younger patients are also more likely to be male and to have colon (as opposed to rectal) cancer(293,294). It is not known whether there are differences in the duration of symptoms at diagnosis based on the age of the patient. Some studies have found comparable times between younger and older

patients(294) and others that patients under 65 are more likely to delay seeking medical attention(221). The type of symptoms reported (e.g. rectal bleeding or change in bowel habit) appear to be similar between younger and older patients(294). Young age was not a poor prognostic factor in itself, but familial CRC risk factors were and this demonstrates the need for screening and surveillance of those at risk(295).

The association between younger age and emergency presentation may due to a reduced public and health professional awareness of the possibility of cancer in younger patients, a more aggressive cancer phenotype (especially in patients with cancer syndromes) or even the impact of bowel cancer screening between the ages of 60-69 years (covered in detail in chapter 4).

I found female patients had a greater risk of emergency presentation and this is supported by other studies and applies especially to widows and those living on their own (72,97,198). A study with a similar population to my own found comparable results, with 35.3% (n=29,751) of females and 30.1% (n=30,933) of males presenting as an emergency(30). The reason for this is unknown, but it has been suggested that women are more reluctant to present with symptoms, as they are more reluctant to undergo lower endoscopy. Women experience more embarrassment and fear related to having an endoscopic procedure, especially if performed by a male endoscopist and that this can be strong enough to cause delay(296,297). It is also established that women experience more pain than men during lower endoscopy(298). However women are more likely to respond to an invitation to join a bowel cancer screening programme(171). I found that women are more likely to present with proximal cancer and this is itself associated with emergency presentation. Therefore increased emergency presentations among women may relate more to proximal CRC predominance and to more negative attitudes towards invasive investigations. These associations may partially explain why the female OR for emergency presentation is 1.22 on univariate analysis but only 1.09 when multivariate analysis is performed.

There was a strong association between co-morbidity and emergency presentation. Even a single co-morbidity increased the OR to 2.10, while two or more increased the OR to 3.81. It has previously been shown that patients with poorer overall health and specific co-morbidities are more likely to present as an emergency(72,97,291). The reasons for this are not completely understood. Interestingly, increased co-morbidity does not appear to be associated with delays to diagnosis, which might otherwise explain a greater propensity to emergency presentation(219). One explanation may be that patients with co-morbidities are more likely to develop proximal cancer, which is itself a risk factor for emergency presentation(274). Finally, it has been shown that there are more missed opportunities for diagnosing CRC among patients with co-morbidities, such as uninvestigated iron deficiency anaemia or rectal bleeding(291).

In my cohort and others, colonic or right-sided cancers are more likely to present as an emergency. In my study the odds ratio was 1.48 (1.35-1.63, $p<0.001$) in a multivariate analysis, while in another

study it was 1.70 (1.57-1.84)(69,97,198,214). Right-sided lesions tend to present with less specific symptoms, such as abdominal pain, malaise and vomiting. Patients and clinicians can easily misinterpret these symptoms. By comparison, patients with rectal cancer report more localised symptoms, such as rectal bleeding(223). While more colon cancers present as emergency, their survival at one year is actually higher than for rectal cancer(69).

There was a trend between increasing deprivation and emergency presentation. In the most deprived quintile, 10.1% more patients presented as an emergency than in the least deprived quintile, which had a multivariate OR of 0.63 (0.58-0.68). Deprivation has previously been associated with emergency CRC presentation(97). In the UK, between 1992 and 1995, the emergency presentation rate was 56% for the tenth most deprived decile compared to 35% in the most affluent decile, equating to an OR of 2.29 (2.09-2.52)(299). Deprivation is also associated with mortality following colorectal surgery and early readmission post operatively(267). Deprivation appears to have a greater effect on emergency presentation than on one-year mortality, where the OR is 0.86 (0.79-0.94). The greater use of Accident and Emergency by deprived patients might be because these patients tend to be more unwell at presentation (248). Equally, on the whole patients with greater levels of deprivation tend to make less use of primary care and present more often directly to secondary care(300). Another reason may be that deprived patients are perceived more negatively by health professionals and offered fewer comprehensive investigations and treatments (235,240).

I next analysed the types of symptoms and diagnoses that appeared more commonly for patients with an emergency presentation. Emergency patients were less likely to be coded with CRC at presentation, which suggests greater diagnostic uncertainty. Emergency patients were also less likely to have the optimal diagnostic test (lower gastrointestinal endoscopy) at presentation, again signifying uncertainty at the outset of hospital care.

Anaemia caused by CRC might be considered an insidious problem, more likely to be investigated in an elective pathway. However, it was more likely to be coded in the emergency group than the elective group (15.8% vs. 10.3%). Predictably, bowel obstruction was four times more common and bowel perforation twenty times more common with emergency presentation. Although large bowel obstruction and perforation were recorded significantly more often among emergency patients, coding for these specific acute emergency events accounted for only a small proportion of total emergencies. Of this selected group of codes, anaemia was by far the most frequent. This observation would support the possibility that a significant proportion of emergency hospitalisations are 'avoidable' and not predominantly for acute emergency complications of CRC. As many emergency presentations are potentially avoidable this again raises the possibility that interventions could be introduced that will reduce this risk and potentially improve overall CRC outcomes.

On the whole, when a CRC patient presents initially as an emergency it appears that patients and medical teams are less certain about what is happening. This may be because the symptoms that emergency patients more commonly present with are not those classically considered to be caused by CRC. One study that looked at the different presentations for emergency and elective patients, found that abdominal pain was more common [interaction odds ratio 2.3 (1.6-3.3); P=0.047] and rectal bleeding less common [0.30 (0.08, 1.0); P=0.040] in the emergency group(282). Therefore perhaps both patient and medical teams are unclear how to manage symptoms that they don't consider likely to be caused by CRC. This could be improved by raising awareness of CRC symptoms for both patients and health professionals.

In summary, the codes and procedures recorded at emergency presentations hint at more uncertainty for the patient and primary and secondary care teams. If medical professionals place more focus on particular symptoms (e.g. abdominal pain) and particular types of patients (e.g. the elderly) then emergency presentations could be reduced and patients diagnosed earlier. However at present HES is not yet detailed enough for detailed symptom-level analysis.

In order to use emergency presentation as my primary outcome measure in subsequent studies, I had to establish its association with adverse outcomes. Specifically this meant reduced surgical intervention and one-year mortality.

It is well established that CRC patients have the greatest chance of long-term survival if they undergo elective surgical intervention. I found emergency patients were less likely to have surgical resection (35.4% vs. 59.1%, $p<0.001$). This was supported by findings from a large UK series, which found resection rates of 64% for emergency patients and 72% for elective patients(198).

When surgical resection follows an emergency presentation both morbidity (45–50%) and mortality (15–45%) are high(69,73,89,99,214). In my cohort, emergency and elective patients having major surgical resections had significantly different mortality rates. Only 2.8% of elective group patients died in hospital following the operation. This compared with 11% of emergency patients (data not shown in the results section). These differences were also seen with both 30-day (10.8% vs. 2.8%) and one-year (25.6% vs. 9.4%) mortality rates. At 30-days following surgery, the mortality rate is 3.9 times higher in the emergency presentation group. At one-year, it is 2.7 times higher. This shows there is an early excess of deaths following surgery in emergency patients. However, it also shows that after the initial period, differences in survival rates do not get progressively worse. The danger for patients could be mostly related to their acute clinical health and not to more advanced cancer. This is supported by studies that have shown that the inferior survival following emergency surgery is limited to the early postoperative period, representing the danger in operating following acute presentation and uncorrected medical complications (71,301). However further work would be required with a longer follow-up period to definitively show this.

The reasons for the poorer outcomes relate to the patient factors described above and also the fact the surgery is more likely to be performed by a non-specialist(302). I found that when patients presented as an emergency then any subsequent surgery was also much more likely to be as an emergency operation. In contrast, only 3% of elective presentations had emergency surgery. The type of surgery is also affected by admission type, with much higher rates of Hartmann's procedure in emergency presentations and a much lower rate of laparoscopy use.

I found significantly higher mortality following an emergency presentation. This is partially related to adverse patient and disease factors but even adjusting for these factors, including disease stage, my study and others have shown mortality was higher following an emergency presentation(214). It seems that emergency presentation was especially associated with early mortality. I found striking differences in the 30-day mortality between the presentation types (7% vs. 1%). Similarly, a UK study found the in-hospital mortality rate following CRC diagnosis was 19% for emergency patients and 8% for elective patients(72).

One study found the median survival was 8 months after an emergency presentation and 30 months following a elective admission. Even after adjusting for age, gender, site and stage, the excess risk of death was 61%(214). In my cohort, one-year mortality was 49.4% in the emergency group compared to 18.0% in elective patients. While another study found, survival at 5 years was 46% in the elective group and 28% in the emergency group(214). This effect is seen even after case adjustment and in emergency patients having attempted curative resection. It has been hypothesised that the later excess of deaths is due to presence of residual occult disease(198). Certainly, the type of disease explains some of the difference, with metastatic disease rates higher rates at the time of presentation in emergency cases (40% vs. 28%)(69).

It seems that the majority of excess mortality is confined to the early period following presentation and the early postoperative period. Therefore, although emergency patients had worse outcomes at one-year, most of the difference was accounted in the few first months following presentation. This suggests emergency presentation is an adverse prognostic marker because patients have presented following an unspecified delay, with more advanced disease.

In my cohort, length of stay (LOS) of the presenting hospital admission was longer for emergency patients. This group stayed a mean of 16 days compared to 11 days for elective patients (after excluding day case admissions). Another study found the average emergency stay was 24 days compared with 11 days for elective patients(285). This substantially increases costs and also exposures patients to additional complications associated with prolonged hospital admissions(71). These include clostridium difficile infection and venous thromboembolism. One study found that after the presenting admission, discharge to a long term care facility was needed for 25% of emergency patients compared with 2% of elective patients(285).

The negative impact of emergency route to diagnosis has already been established in upper gastrointestinal cancers(278), other cancers (89) and in other major surgical disciplines(303). I have now shown that emergency presentation is an independent predictor of adverse CRC outcomes. The next challenge is to study why this is the case. The answer is likely to be multifactorial. Clearly, some patients presenting as an emergency will be sicker, often with significant metabolic abnormalities increasing the likelihood of early morbidity and mortality. In addition, patients are often older and with more co-morbidity, which will reduce the chance of surgery being offered and increase the risk associated with it. The cancer itself is likely to be more advanced with a reduced chance of successful treatment. This will affect the decision to operate and offer other treatment modalities and therefore influence medium to long-term survival. However beyond this there appears to be a large group of patients that present as an emergency because either: they do not understand how to access the health service electively or the elective services are not available. These patients are somehow excluded from the standard primary care referral model and subsequently fail to be optimally managed. They then present later with vague, slow to be diagnosed symptoms, with delays to important investigations and reduced access to surgery. The challenge is to implement changes in healthcare that allow these patients to access diagnostic services quicker. Some strategies have been discussed already in chapter 1 and include: rapid referral policies, such as two-week wait referrals, and speedy access to diagnostic services for all cases. Other solutions include raising public awareness of CRC symptoms and the introduction of the BCSP, which is discussed in chapter 4. In countries with an established screening programme, there are lower rates of emergency presentations (6-19%) compared to countries without a national programme (22-34%)(67,68,70,71,286,304). Additional resources could be given to tackle specific subgroups with the worst outcomes. Examples include changing the current cancer referral guidelines for patients at the extremes of age or direct advertising campaigns to target hard to reach groups, such as the most deprived and socially isolated. Changes could be made to further extend the screening age range and also to ensure young patients with a family history are screened. Other technological solutions include the wider use of computed tomographic colonography or the colon capsule endoscopy to help screen more elderly and frail patients with co-morbidities. A significant proportion of emergency presentations could be avoided if patients had a greater awareness of symptoms and medical teams referred more quickly when alerted to the possibility of CRC.

The main weaknesses in using emergency presentation as the primary outcome measure is that it has not yet been confirmed to predict long-term survival (past one-year). It could also be argued that for many patients we don't understand why the patient presented as an emergency, was it the severity of the symptoms or an inability to access primary care.

In conclusion, in this chapter I have shown that an emergency presentation is independently an adverse prognostic marker, associated with one-year mortality and lack of surgical resection. More specifically, it is associated with an excess of early deaths after presentation, suggesting it is associated with the late

presentation of cancer. I also offered evidence to suggest that most emergency presentations are avoidable. Most importantly I have shown that emergency presentation can be used in my thesis as a quality indicator and as my primary outcome measure.

Chapter 4 - Introduction of the Bowel Cancer Screening Program (BCSP) in England and its association with emergency presentations for colorectal cancer

4.1. Introduction

The NHS BCSP began in 2006 with the aim of reducing CRC mortality in screened individuals. In this chapter, the cohort of CRC patients derived using my novel methodological approach was used to test whether the early benefits of launching a BCSP might have extended beyond the minority of individuals who are targeted by the screening program.

4.1.1. How CRC presents

Most patients present electively with symptoms or signs to their primary care doctor. Patients may also present as an emergency directly to secondary care or be detected asymptomatically through routine surveillance or since 2006 by the BCSP.

4.1.2. The NHS Bowel Cancer Screening Programme (BCSP)

As discussed in chapter 3 it is thought that the poor outcomes for UK CRC patients is largely the result of late presentation and consequent advanced stage of the disease, which reduces the chance of curative surgical resection(143,305). The national BCSP aims to detect cancers at a pre-symptomatic stage, leading to the earlier elective diagnosis of less invasive cancers(184). The secondary aim of screening is to remove adenomas that can develop into cancer, with the expectation that this will reduce the national incidence of CRC. This is supported by a number of large studies from the United States showing colonoscopy screening can reduce CRC incidence (306,307).

Prior to the introduction of the UK programme, pilot studies between 2000 and 2005 in Scotland (Tayside, Grampian and Fife) and England (Coventry and North Warwickshire) established that the performance of the FOBt in randomised controlled trials could be replicated in a UK setting(308,309). In the English pilot, uptake was between 50% and 60% in line with the randomised trials. Cancer was detected in 2.3/10,000 screened subjects(310). In randomised trials this screening strategy reduced CRC mortality by 16% in those invited for screening and by 25% in those accepting screening(11,96,98). This provided positive evidence driving the British government to implement a national screening programme. However, there have been criticisms of the effectiveness of these screening trials, most importantly that they failed to show any difference in all-cause mortality(182,311).

National screening began in July 2006 with a phased roll out, achieving national coverage by January 2010. There were three waves of rollout for the BCSP. Screening centres in the first and second waves became operational prior to April 2008 while the third wave, covering the rest of the country, became operational from April 2008, with complete coverage achieved by January 2010, *Figure 4.1*.

Screening involves biennial Faecal Occult Blood tests (FOBt), initially inviting all men and women aged from 60–69 years. From 2010, this was extended up to 75 years. Approximately 10% of the UK population is aged 60–69 years, with half the invitations sent out in year one of the screening round and the remainder in year two. The latest UK figures show that 26% of CRCs occur in this age group(312).

In England, the BCSP is coordinated through five programme hubs, each with a population of roughly 10 million in total, *Figure 4.2*. These hubs provide a call and recall service to patients, supply the FOBt kits and despatch test results. Beneath the screening hubs are the local screening centres, in England there are 56, each serving a population of 500,000 to 2 million people. These centres see people who have presented with positive test results through the screening programme. Most people (approximately 98%) will have a negative test result, with no positive FOBt results. These subjects will be invited to participate again in two years' time(171). Those participants with a positive FOBt result are invited to the local screening centre and offered a colonoscopy as the investigation of choice. Depending on the findings they are then offered screening again in two years' time, entered into the polyp surveillance programme or referred for CRC treatment at a local hospital following a multi-disciplinary team (MDT) assessment, *Figure 4.3*.

Screening would be most effective if all individuals took a test which was 100%, sensitive to CRC. This is not the case with the current programme for a number of reasons. Firstly, many cancer patients don't have access to screening, as only 25% of cancers are currently diagnosed in the screened age group of 60-69 years and uptake in this group is only 50%(30). Even with the age extension of the screening programme to 75 years, a large proportion of patients with CRC still won't be screened and furthermore the FOBt sensitivity for CRC is poor. A systematic review found its sensitivity ranged from 6.2% to 83.3%. This variability is due to the different test thresholds, study populations and study design used in the trials(313).

Therefore the current screening programme will fail to identify many cases of CRC. However it could be speculated that a fortunate byproduct of the screening programme is a greater awareness of CRC among all individuals and healthcare providers. This may alter health seeking behaviour and result in a reduction in late presenting cancers. I speculate that this 'indirect effect' will operate by increasing awareness and reducing barriers for patients to come forward. Secondly general practitioners will have a lower threshold for referral for investigation, both leading to improved outcomes.

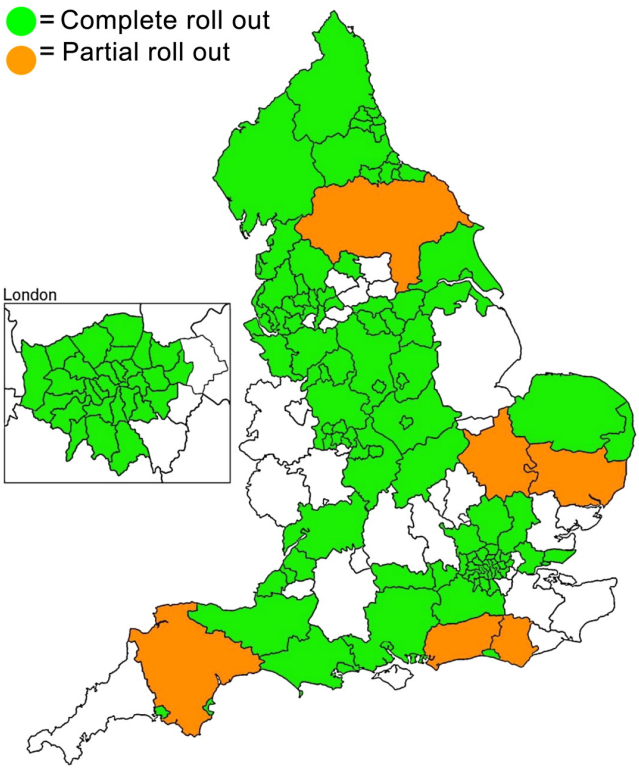


Figure 4.1 Uptake of the BCSP in late 2008, according to primary care trusts(314).

Figure 4.2 Areas of England covered by the five regional Bowel Cancer Screening Programme hubs.

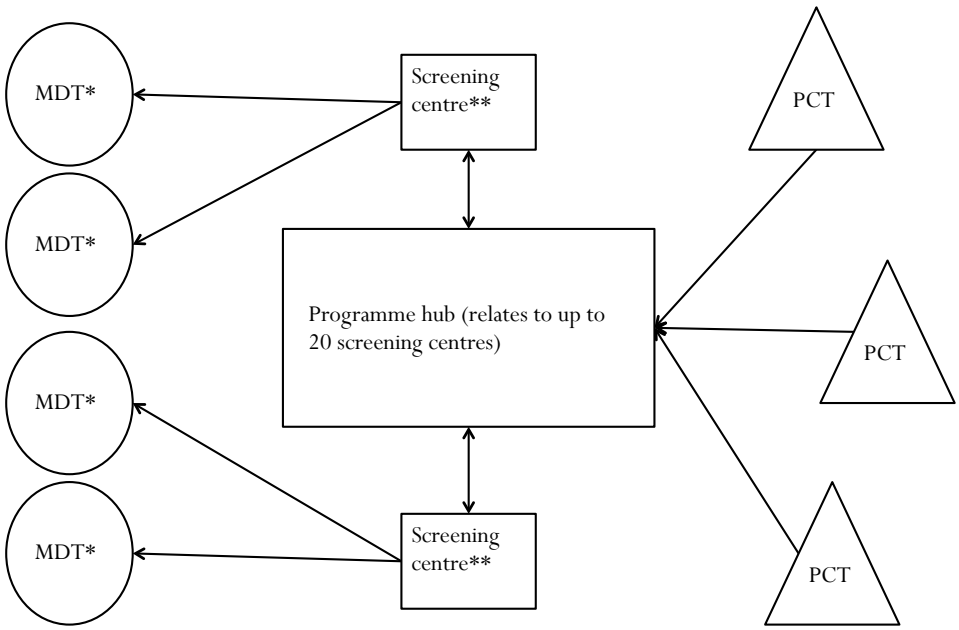


Figure 4.3 Configuration of programme hubs, screening centres and multidisciplinary teams (MDTs). *MDT at the treating hospital, ** a screening centre more have one or more colonoscopy sites

4.1.3. Evidence for the effectiveness of the BCSP in screened individuals

Screening success relies on individual participation and this varies according to age, gender, co-morbidity, ethnic background, and deprivation status(305). An early analysis of the first 2.1 million subjects invited to screening showed the overall uptake was 55-60%, but in London was only 40%. This resulted in 1,772 cancers being diagnosed, 70% of which were early stage (Dukes A or B)(171). The proportion of Dukes A cancers among the screened group was significantly higher than among non-screened patients (35% vs. 13%)(73).

It is estimated that if uptake remains at 60% then over the next 20 years, there would be 20,000 fewer CRC deaths in the UK (315). With CRC screening there is the extra potential benefit from removing adenomatous polyps, and so prevent cancer from ever developing(58). However, the case for the UK BCSP has not yet been conclusively proven. In particular it will take many years before we can establish long-term mortality benefits. This is partially because patients responding to a screening invitation are on average healthier than those that don't participate(305). It is also unclear whether screen-detected cancers behave in the same way as symptomatic cancers and whether they are as dangerous for patients. This demonstrates the problem at the heart of understanding the effectiveness of any screening programme. It is tempting to assume that the 'progressive disease model' can be used. This is where a disease fits neatly into three stages; a) a disease free state, where no existing technology could identify the cancer, b) the pre-clinical disease stage, where the patient does have cancer but is symptom free and

where a screening test can identify the cancer and c) the clinical stage, where the cancer causes symptoms that instigate investigation and diagnosis of the cancer.

Screening effectiveness is predicated on cancer being detectable in the pre-clinical stage and that this time is long enough to allow treatments to occur earlier and improve patient outcome (i.e. to reduce cancer-associated mortality). The critical time period is therefore between a cancer being screen detected (in the pre-clinical phase) and death. The problem with this approach is that early end points (such as disease stage and early survival) rely on false assumption that the natural history of screen detected (asymptomatic) and symptomatic cancers are the same. In reality, screen detected cancers are often more benign and readily treatable(316).

To understand the effectiveness of screening, the cancer mortality rate in the screening population is required. This is the number of cancers deaths in a given time for a given population(317). Reducing cancer mortality in a population is the best indication of the programmes effectiveness as it is derived not only from the ability to detect cancer but the effectiveness of the treatment given. However this requires costly long-term follow-up on large populations.

Using short-term surrogate markers, such as one-year mortality and surgical resection rates, poses four main problems:

1) **The "healthy volunteer effect"** relates to the fundamental differences between people who participate in screening programs and those that do not. On average participants are more affluent, more educated, healthier and have a longer life expectancy(316). CRC screening participants have markedly lower mortality rates compared to the general population(11).
2) **Lead-time bias:** Lead-time is the time period that exists between when the cancer was diagnosed by screening, to the time when it would have presented without screening. As survival is measured from the date of diagnosis, this creates "lead-time bias". This means that the apparent duration of the disease and by that, the survival is lengthened. This does not mean the patient lives any longer and it is why case survival rates in screening programmes should be assessed with care.
3) **Length-bias** relates to differences in the cancers found in screen detected and clinically detected groups. Cancers that are screen detected have a longer pre-clinical duration than clinical cases. These cancers are slow growing and not only have a longer pre-clinical stage, but also a longer clinical phase than clinical detected cancers. Furthermore, these indolent cancers are more likely to have a favourable outcomes even without screening, because they are less likely to have spread to lymph nodes and metastasised(318).
4) The final bias, **"over-diagnosis bias"**, is linked to the lead-time and length biases mentioned above and relates to a subset of cancers that are either non-progressive or even

regress in the pre-clinical stage. Therefore this group of cancers can be detected by a screening test but would not progress to clinical disease and would not negatively affect a patient's quality or quantity of life. These non-progressive cancers remain pre-clinical for a long time and are therefore more likely to be detected by a screening programme.

Due to all of these biases simply identifying lower stage cancers or an increase in survival is not evidence of screening efficacy. Conclusive proof will not be seen until trends in CRC and overall mortality data can be shown and this will take many years and is beyond the scope of this thesis. Although the concept of screening is straightforward, screening for some cancers has proved controversial (e.g. breast and prostate cancer), with doubts whether the overall gains from specific programmes warrant the cost or harms(190,319,320). In practice, quantifying the real-world benefits of population-based cancer screening is difficult. Survival benefit takes many years to realise (190,191) and a range of other healthcare advances may occur during this period to confound the interpretation of national trends in cancer incidence or survival. In the case of CRC screening, a recent meta-analysis of trial data estimated that it took 10.3 years before one death from CRC was prevented for 1,000 patients screened(191). By studying the association between start-up of local screening and risk of presentation as an emergency for CRC, it may be possible to generate evidence of the early and population wide benefits of launching the programme.

4.1.4. Evidence for the effectiveness of the BCSP in non-screened individuals

In the United Kingdom awareness of CRC symptoms is poor, with 24% of adults unable to correctly name any warning signs and over half (58%) unable to correctly recall any risk factors(163). By contrast, the BCSP has been very proactive in advertising the benefits of screening and improved outcomes with early detection. Information is supplied to participants through their kits and also spread by word of mouth to friends and family. There is prominent advertising both in GP surgeries and by local and national media campaigns. Therefore, additional benefits from the BCSP may include increased awareness of CRC among all individuals and healthcare providers. This will heighten the general public's understanding of the disease and thus may contribute a general benefit to the whole population reflected in fewer emergency presentations and a reduction in late presenting cancers.

The most direct way that screening raises awareness is through the postal invitation that is sent to the participants. This initial letter explains that they will shortly be invited to take part in the programme and encloses a booklet called 'Bowel Cancer Screening – The Facts' (*Appendix 4*). There is then an opportunity to opt out by contacting the screening hub on a free telephone number. Otherwise, one week later a screening kit, which includes leaflets, sample sticks and a foil-lined envelope are dispatched to the participant's address. Following a positive test, participants are invited to a nurse-led clinic. At the clinic appointment the patient will receive; counselling, a health questionnaire, information, consent for colonoscopy and a leaflet about the test. Other forms of awareness promotion include posters designed for GP surgeries and local community centres (*Appendices 5,6*), media campaigns including

posters on billboards and buses and local and national media campaigns. More direct approaches were used in some areas, such as creating community clinics in each Primary Care Trust. These were held so that participants could easily access screening assessment clinics locally, with the aim of increasing uptake.

Once members of the public have an increased awareness of screening programmes they are more likely to be screened themselves and encourage their peers to be screened(69,72,172). Standard advertising methods are less likely to be reach individuals that are: older, male, from ethnic minorities, suffering from mental health problems or learning disabilities and living in deprived areas(321). To try and improve awareness in these groups, targetted advertising was used. This included leaflets especially designed for men, that were specifically designed around a sports theme (*Appendix 7*) and also used spouse encouragement to increase the likelihood of participation (*Appendix 8*). To reach ethnic minorities the booklets were made available in 20 languages and outreach clinics were provided in community centres. Pictorial booklets, including all the steps required to complete the stool test, were used to support patients with learning difficulties (*Appendix 9*). Finally, specific DVDs were designed for black and racial minorities, patients who are deaf and hard of hearing and those with low literacy skills and learning difficulties.

To raise awareness within primary healthcare before each Primary Care Trust (PCT) went live with the programme the key members of the PCTs were invited to education sessions. The education sessions highlighted the public health issues of CRC including health inequalities, the background to the screening programme and its impact on Primary Health Care Teams, the process of screening, and the signs and symptoms of CRC.

In conclusion, the BCSP in raising awareness of CRC, will not only improve screening uptake among invited subjects but also encourage patients with symptomatic CRC, to present earlier (73,322). Such a benefit would reduce the risk of emergency presentation for both "screened" and "non-screened" CRC patients living in an area with an active BCSP.

4.1.5. Evidence screening programmes reduce emergency presentations

Chapter 3 demonstrated that emergency presentation with CRC was a marker of poor outcomes. Interventions that reduce emergency presentations and emergency surgery lead to increased survival for patients and reduced costs to healthcare providers(323). Therefore, one early sign that screening is beneficial to an area could be a reduction in the risk of emergency presentations, following the introduction of screening.

The Nottingham screening study ran from 1981 to 1991 and involved 75,253 patients in the screened group (60% response rate) and 74,998 well-matched, unscreened controls. The emergency presentation rate was 23.9% in the screened group, compared to 27.9% in the control group, which was not a statically significant difference(88). Interestingly, a study from Coventry and North Warwickshire as

part of the English pilot study reported 29.4% of patients presented as an emergency in 1999 (the year before bowel screening began) and by 2004, the end of the pilot, the rate had fallen to 15.8%, which was statistically significant (p=0.001). Surprisingly, the proportion of Dukes stage cancers was unchanged over the study period and the number of cases did not rise as would be expected with the finding of "additional" screened cases(324). It is therefore unclear whether screening itself, or other changes in CRC care over the 5 years, caused the reduction in emergency presentations. Interestingly, one study showed how introducing a fast-track, flexible sigmoidoscopy service for patients with any of six high-risk criteria for CRC could potentially reduce emergency presentations. Before the service began in the area, the emergency rate was 36%, while in the three years after this had reduced to 26% (p= 0.059)(210).

4.2. Hypothesis

I believe my cohort of CRC patients derived from HES data and refined using clinical logic and algorithms can be used in a retrospective, observational study to investigate the roll-out of the BCSP across England. Using emergency presentation as my metric of outcome, I will investigate whether there was an early, population wide and indirect benefit, particularly for those of non-screening age.

I consider the risk of emergency presentation with CRC may be reduced among people living in an area with an active BCSP. My exposure of interest was "living in an area with an active BSCP". This was not the same as a patient actually taking part in the screening programme, simply that they lived in an area where the BCSP was active. This reduction in risk may be due to both direct and indirect effects. The "direct" effect applies only to a small number of screened individuals, where their asymptomatic cancer will be detected. The "indirect" effect is due to a heightened awareness of the symptoms of CRC among patients and health professionals in areas with an active BCSP.

I am unable to tell how an individual case was affected by the programme; whether it was increased personal awareness of CRC symptoms due to the BCSP that lead to the patient seeking help sooner (reduced patient delay) or whether it was because the patient was seeing a GP who had heightened awareness of CRC, because of the programme, and therefore a lower referral threshold (reduced practitioner delay). It may of course also be a combination of factors that lead to a quicker referral for definitive diagnostic tests.

I also aim to quantify the "dose of exposure", in terms of the duration of time that the programme has been active in an area and whether this was associated with a reduced risk of emergency presentation. Therefore, I propose that the longer the exposure to screening a patient has, the lesser the risk of an emergency presentation.

I consider that no part of the non-screening population will be adversely affected by the introduction of the BCSP.

4.3. Aims

My aim is to study whether "living in an area with an active BSCP" was associated with a reduced risk of emergency presentation for CRC. Specifically in this chapter, I will;

1) Identify whether screening exposure was associated with a reduced risk of emergency presentation in patients within the screening age group.
2) Identify whether screening exposure was associated with a reduced risk of emergency presentation in patients within the non-screening age group.
3) Investigate the effects of screening exposure on patient characteristics.
4) Identify whether the dose of exposure (the duration of time that BCSP had been active locally) was associated with a reduced risk of emergency presentation.

I cannot, at this stage, know whether any association was causal or related to a confounding factor. For example, was living in an area with an active BCSP just a surrogate for parts of the country where risk of emergency was "already lower", perhaps because of better diagnostic services. Therefore, I will compare the effects of screening exposure on outcomes for CRC against a control group. I selected oesophageal and gastric cancer (OG cancer) as the most appropriate disease control, since these are gastrointestinal tumours that have similarities to CRC in terms of clinical presentation (patients can present with non-specific gastrointestinal symptoms, plus or minus alarm features, with considerable overlap with common benign conditions) and pathway of diagnosis (a major emphasis on referral from primary care for diagnostics, in this case gastroscopy). As with CRC, there are similar concerns in the UK regarding diagnostic delay and potentially 'avoidable' emergency presentations for OG cancer(244).

My goal was to demonstrate that there was no association between a locally active BCSP and the risk of emergency presentation for OG cancer. This would make it less likely that there was a general confounding effect caused by local factors unrelated to the programme. Hence, the study aimed to determine whether living in an area with an active BCSP was associated with a reduced risk of emergency presentation for CRC but without any such association apparent for OG cancer.

4.4. Methods

To address the aims in this chapter I needed to identify two separate populations. My primary population was the one-year (October 2006 to September 2007) CRC cohort derived in chapter one. The secondary population contained patients presenting with OG cancer during the same time period.

As my original database in chapter 1 covered the period April 2006 to March 2008, I restricted inclusion in this chapter to patients that presented with a minimum of 6 months admission data before and after their index admission. Therefore, my cohort in this chapter is termed the "middle year cohort" as it encompassed those patients whose initial index admission occurred between October 2006 to

September 2007, (*Figure 2.2, chapter 2).*

In order for me to be able to determine a patient had been "exposed" to screening at presentation I needed to know when a) the patient first presented with CRC and b) when their local screening centre started screening. Therefore, any patient without these dates was excluded from the study. I used this information to study the association between screening exposure and emergency presentation in patients in the screening age and also those outside the screening age, the non-screening population. My primary outcome was emergency presentation of CRC and secondary outcomes were surgical resection and one-year mortality.

The second population contained all patients presenting with OG cancer from October 2006 to September 2007 that also had a date for when their local screening centre started screening.

4.4.1. Identifying the Primary Care Trusts (PCTs) in England

During the study period general practices in England were grouped administratively and geographically into primary care trusts (PCTs). These PCTs were responsible for commissioning services for the local population of registered patients. PCTs decided which screening centre to refer to and, once the centre became operational, individuals within the PCT become liable for enrollment in the programme.

At the beginning of the middle year cohort in October 2006, the BCSP was active in only a few parts of England. During the year, it became active in other areas but not all, *Figure 4.1*. Hence, there was variation in exposure to start-up of BCSP between PCTs during the period of study, *Figure 2.2, chapter 2*. *Appendix 10* shows the date that each screening centre became operational and which PCTs it covered. This provided an opportunity to develop logistic regression models to estimate the association between start-up of BCSP in a patient's area and the risk of emergency presentation during the diagnostic pathway. This information was obtained from the BCSP(325). I thus generated a list identifying each PCT in England and the date when screening began. On 1st October 2006 there were 152 PCTs in England, with an average population of just under 330,000 each. There was one trust (North East Lincolnshire), which used two identification codes and this required reconciliation of the data.

The decision to refer which population to which screening centre, was made by the Strategic Health Authorities (SHAs). To eliminate uncertainty of screening exposure, I excluded 10 PCTs that referred patients to more than one screening centre, when the start-up dates of the screening centres were different. This was because it was not possible to allocate the entire PCT population to a single screening start-up date. Following removal of all patients belonging to those 10 PCTs my study cohort comprised of 142 PCTs. The number of CRC patients was reduced from 32,299 to 27,640(2).

Of the 142 PCTs included in my study 17 had commenced screening prior to the start of the study period, therefore all these patients were placed in the "exposed" group. 48 PCTs began active screening during my study year so some of these patients were in the "exposed" group and others were in the

"non-exposed " group. Finally, 77 PCTs had not yet started screening by the end of my study cohort and all of these patients were in the "non-exposed" group. There were 7,142 patients in the "exposed" group and 20,498 patients in the "non-exposed" group.

4.4.2. Identifying the time period that patients were exposed to the BCSP

Each patient was first assigned a variable to indicate whether or not they were living in a PCT that had active BCSP at the date of presentation, *Figure 4.4*. For those cases in which the BCSP was active, I calculated the duration that screening had been active in the area, relative to the patient's presentation. I categorised patients according to exposure status into three groups: (1) No active local screening at the time of presentation (the control or "non-exposed" group); (2) "Exposed" to screening for less than six months (<6 months); and (3) "Exposed" to screening for more than 6 months (≥6 months). I split the exposed patients into two groups, in order to look for an early effect from screening introduction. This was because such a finding would have been very unlikely to come from the direct effect alone.

I categorized patients according to age, gender, co-morbidity and deprivation to correct for case-mix in the overall analysis and also to explore whether any risk reduction for emergency presentation was different among particular sub-groups of patients. To further evaluate any 'dose-response' effect from screening exposure, I undertook sensitivity analysis using an alternative continuous exposure variable (duration of locally active BCSP, expressed in months).

Exposure status based on the start-up date of the local bowel cancer screening programme

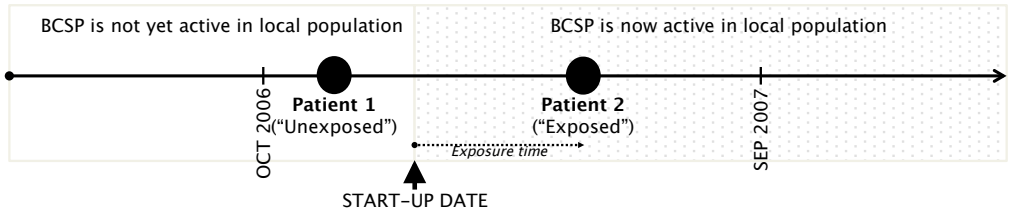


Figure 4.4 Screening exposure status for each patient in the cohort was determined relative to the startup date of the BCSP in his or her PCT. The black dot represents a patients index admission.

4.4.3. Identifying a comparative group of patients (OG cancer)

I examined whether there was any relationship between screening programme exposure and emergency presentation rates for OG cancer, using data from our group's recent study. The development and validation of this dataset was undertaken by Shawihdi et al and has been reported (16). The OG cancer data was extracted from the same national HES database as I used for the CRC cases. The methods for extracting the OG cancer data were comparable to those described for CRC (see section 2.5.1) and the study covered the same time period (October 2006 to September 2007). In total there were 9,319 patients with OG cancer compared with 27,640 patients with CRC.

I determined exposure status of each OG cancer patient based on the start date of screening in their PCT of residence and the date of their presentation. I selected the same patient characteristics for the OG cancer cases as for the CRC cohort. These were; age group, gender, co-morbidity, deprivation and each patient had their presentation defined as elective or emergency.

4.5. Results

4.5.1. Association between locally active bowel cancer screening program and emergency presentation of CRC

My study cohort contained 27,640 CRC patients belonging to the 142 included PCTs. Out of this group 7,142 (25.8%) were living in an area with an active BCSP at the time of presenting with CRC ("exposed" group) and for each patient I was aware exactly how long the programme had been active for. The remaining 20,498 patients (74.1%) were classed as "non-exposed" and were living in an area where the BCSP had not yet started.

The characteristics of these patients were comparable to the original cohort of 32,299 patients in 152 PCTs, described in chapter 1, *Table 4.1*. In my study cohort the mean age at diagnosis was 70.9 years, 55.9% of cases were male and 67.9% had no co-morbidities. The level of deprivation was relatively evenly spread across the cohort, with 18.8% in the most deprived quintile and 19.6% in the least deprived quintile. Overall, in my study cohort, 36.5% of patients presented as an emergency.

In patients "exposed" to screening for any length of time the crude emergency presentation rate was significantly lower at 34.9% (2,492/7,142) than the 37.0% (7,599/20,520) in the "non-exposed" group (p=0.002). In the screening age only group (60-69 years), the crude emergency presentation rate was significantly lower in the "exposed" group 27.2% (515/1,893), compared to the "non-exposed" group at 30.3% (1,460/4,825)(p=0.013). In the non-screening age only group (all others), the crude emergency presentation rate was not significantly lower in the "exposed" group 37.7% (1,977/5,248), compared to the "non-exposed" group at 39.1% (6,135/15,673)(p=0.060), *Figure 4.5*.

Table 4.1 Characteristics of CRC patients presenting in English NHS hospitals over a one-year period (October 2006 to September 2007).

Patient characteristics	**Total, N (%)**	**Study cohort, N (%)**	**Non-exposed, N (%)**	**Exposed <6 months, N (%)**	**Exposed ≥6 months, N (%)**
Number of cases	32,299	27,640	20,498	4,151	2,991
Age, mean (sd)	71.0 (12.1)	70.9 (12.1)	71.0 (12.3)	70.8 (11.6)	70.7 (11.8)
Age groups					
< 60	5,347 (16.6)	4,583 (16.6)	3,435 (16.8)	684 (16.5)	464 (15.5)
60 to 69	7,868 (24.4)	6,719 (24.3)	4,825 (23.5)	1,078 (26.0)	816 (27.3)
70 to 79	10,651 (33.0)	9,134 (33.0)	6,748 (32.9)	1,374 (33.1)	1,012 (33.8)
>79	8,433 (26.1)	7,204 (26.1)	5,490 (26.8)	1,015 (24.5)	699 (23.4)
Gender					
Male	17,981 (55.7)	15,437 (55.9)	11,337 (55.3)	2,387 (57.5)	1,713 (57.3)
Female	14,318 (44.3)	12,203 (44.1)	9,161 (44.7)	1,764 (42.5)	1,278 (42.7)
Co-morbidity groups					
1 (No co-morbidity)	21,847 (67.6)	18,760 (67.9)	13,933 (68.0)	2,781 (67.0)	2,046 (68.4)
2 (1 co-morbidity)	2,383 (7.4)	2,067 (7.5)	1,513 (7.4)	323 (7.8)	231 (7.7)
3 (2 or more co-morbidity)	8,069 (25.0)	6,813 (24.6)	5,052 (24.6)	1,047 (25.2)	714 (23.9)
Patient deprivation					
IMD missing*	322 (1.0)				
1 (Most deprived)	5,516 (17.1)	5,197 (18.8)	3,567 (17.4)	1,012 (24.4)	618 (20.7)
2	6,044 (18.7)	5,324 (19.3)	3,851 (18.8)	873 (21.0)	600 (20.1)
3	6,844 (21.2)	5,794 (21.0)	4,279 (20.8)	846 (20.4)	669 (22.4)
4	6,980 (21.6)	5,897 (21.3)	4,472 (21.8)	823 (19.8)	602 (20.1)
5 (Least deprived)	6,593 (20.4)	5,428 (19.6)	4,329 (21.1)	597 (14.4)	502 (16.8)
Emergency admission	11,651 (36.1)	10,087 (36.5)	7,595 (37.1)	1,513 (36.4)	979 (32.7)

*Patients from the original cohort with a missing IMD were excluded from the other columns

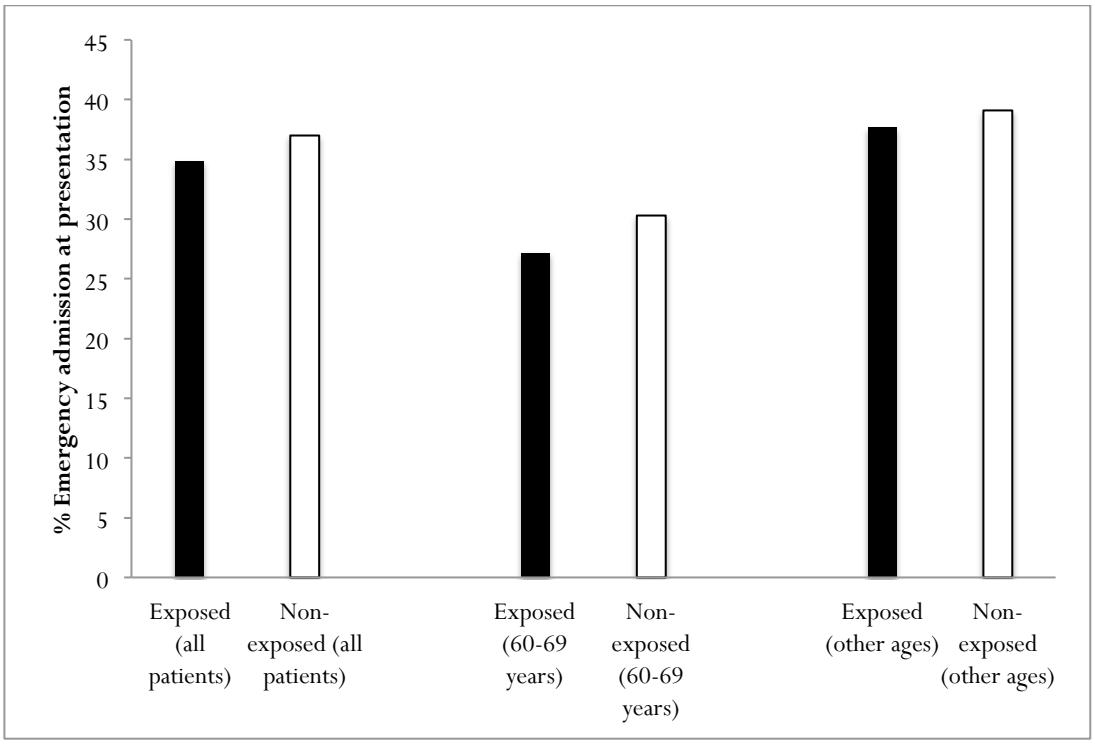


Figure 4.5 A chart comparing the rates of emergency presentations, in patients exposed and non-exposed to the BCSP in all ages and then split into those in screening (60-69 years) and non-screening (other ages) ages.

Of the "exposed" group, 4,151 patients presented within the first six months of the local start-up date (<6 months) and 2,991 patients presented six months or more after screening had started in their area (≥6 months). The mean exposure time was 5.7 months (ranging from 0.1 to 15.2 months). It should be noted that only approximately half the target population of 60-69 year olds would have been offered screening within the first year of activation of the programme. Hence, few cancers within this population-based study of all ages are likely to have been screen-detected.

There was a small but significant difference in mean age of patients across the three groups ("non-exposed": 71.0 yrs; <6 months exposure: 70.8 yrs; ≥6 months exposure: 70.7 yrs; $p<0.01$ ANOVA), *Table 4.1*. This may be explained by the predictable finding that the proportion of CRC patients in the screening age group (60-69 years) was higher for "exposed" than "non-exposed" groups, thereby bringing down the mean age by a small amount. Comparing areas where the screening had been active for 6 months or more to the "non-exposed" group; significantly more patients are aged within the screening age (60-69 years) (27.3% vs. 23.5%, $p<0.001$). This suggests that there was enhanced detection of CRC among people of screening age either within the programme (asymptomatic, screen detected cases) or via normal diagnostic routes.

There was no difference in gender mix or levels of co-morbidity across the exposure groups.

The crude rate of emergency presentations was lowest in the "exposed" group when the BCSP had been

active in their local population for over 6 months (32.7%) and highest in the "non-exposed" group of patients diagnosed before screening began in their area (37.1%, p<0.001), *Table 4.1, Figure 4.6*. Those cases of CRC diagnosed within six months (<6 months) of local start-up of BCSP had an intermediate rate of emergency admission.

In binary logistic regression, the adjusted odds ratio for emergency presentation in patients presenting ≥6 months in the "exposed" group was 0.83 (CI: 0.76-0.90, p<0.001) compared to "non-exposed" (control) cases. Those patients with less than 6 months exposure, had an odds ratio between the two other groups, at 0.95 (CI: 0.88-1.02, p=0.170), *Table 4.2*. Hence, after adjusting for patient characteristics I was able to confirm that exposure to locally active screening was an independent patient-level factor associated with emergency admission for CRC in England.

As expected from my earlier work, increasing age, especially 80 years and over (2.09, CI: 1.93-2.27), female gender (1.17, CI: 1.11-1.24) and two or more co-morbidities (4.06 CI: 3.83-4.31) were associated with increased odds of emergency admission for CRC patients. Patients in the lowest quintile of deprivation had the lowest risk of emergency presentation (0.64, CI: 0.59-0.70). Therefore patients that were: over 80 years of age; female; afflicted with multiple co-morbidities or from the most deprived quintile were all more likely to present with an emergency presentation. The strongest independent predictor was two or more co-morbidities.

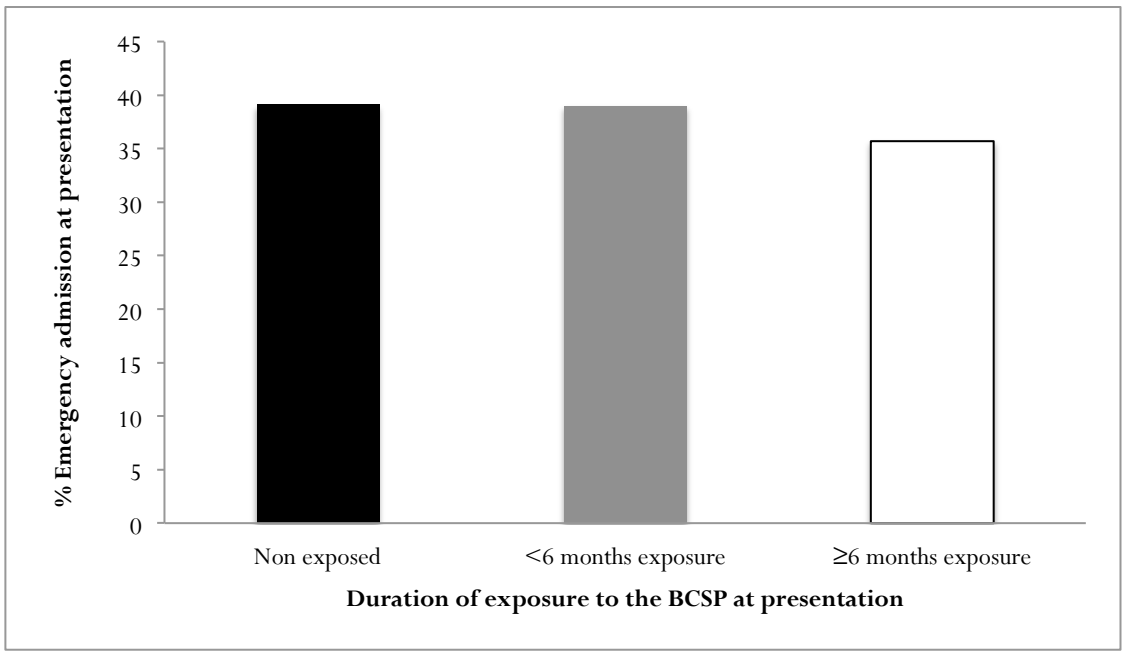


Figure 4.6 A chart showing emergency presentation rates, in patients with different levels of exposure to the BCSP. The unadjusted emergency rate is significantly lower in the group with more than 6 months exposure to the BCSP than the control group (p<0.001).

Table 4.2 A binary logistic regression analysis of 27,640 CRC cases diagnosed between October 2006 and September 2007, showing factors associated with emergency presentation.

Variable	Emergency presentations / total cases (%)	Unadjusted (univariate) OR	CI	p value	Adjusted (multivariate) OR	CI	p value
Age group (years)							
<60 years	1,440/4,583 (31.4)	1	-	-	1	-	-
60-69 years	1,975/6,719 (29.4)	0.91	0.84-0.99	0.021	0.90	0.83-0.98	0.019
70-79 years	3,087/9,134 (33.8)	1.11	1.03-1.20	0.005	1.08	1.00-1.17	0.063
>79 years	3,585/7,204 (49.8)	2.16	2.00-2.34	<0.001	2.09	1.93-2.27	<0.001
Gender							
Male	5,320/15,437 (34.5)	1	-	-	1	-	-
Female	4,767/12,203 (39.1)	1.22	1.16-1.28	<0.001	1.17	1.11-1.24	<0.001
Co-morbidity groups							
No co-morbidity	5,085/18,760 (27.1)	1	-	-	1	-	-
1 co-morbidity	914/2,067 (44.2)	2.13	1.94-2.34	<0.001	2.02	1.84-2.22	<0.001
≥ 2 co-morbidity	4,088/6,813 (60.0)	4.03	3.81-4.28	<0.001	4.06	3.83-4.31	<0.001
Deprivation							
1 (most deprived)	2,194/5,197 (42.2)	1	-	-	1	-	-
2	2,013/5,324 (37.8)	0.83	0.77-0.90	<0.001	0.80	0.73-0.87	<0.001
3	2,122/5,794 (36.6)	0.79	0.73-0.85	<0.001	0.76	0.70-0.83	<0.001
4	2,012/5,897 (34.1)	0.71	0.66-0.77	<0.001	0.67	0.62-0.73	<0.001
5 (least deprived)	1,746/5,428 (32.2)	0.65	0.60-0.70	<0.001	0.64	0.59-0.70	<0.001
BCSP Exposure							
Control	7,595/20,498 (37.1)	1	-	-	1	-	-
BCSP <6 months	1,513/4,151 (36.4)	0.97	0.91-1.04	0.463	0.95	0.88-1.02	0.170
BCSP ≥6 months	979/2,991 (32.7)	0.83	0.76-0.90	<0.001	0.83	0.76-0.90	<0.001

4.5.1.1. Association between risk reduction for emergency admission and duration of screening exposure

My results showed that living in an area where the BCSP had been active for more than 6 months was associated with a significantly lower rate of emergency presentations. In addition, patients with more than 12 months exposure to local screening had substantially lower rates of emergency presentations than those with 6-12 months exposure (26.6% vs. 33.7%, p=0.005). Both groups had substantially lower rates than the "non-exposed" group (37.1%), *Table 4.3, Figure 4.7*. This suggests that the

magnitude of risk reduction is greater when the BCSP has been active for a longer time period, at least over the first 1-2 years.

I next studied whether the impact of screening was incremental, such that each additional period of time was associated with progressively lower rates of emergency presentations. To do this, I substituted the categorical exposure variable ("non-exposed"; <6 months "exposed"; ≥6 months "exposed") with a continuous exposure variable (the duration in months) that BCSP had been active at the time of the patient's presentation. Exposure was thus expressed as the number of months that screening was active at the time of the patient's diagnosis. Using this continuous exposure variable, the adjusted OR provided an estimate of risk reduction per month of exposure. For every month of exposure, the OR was 0.98 (CI: 0.97-0.99, p<0.001), thus representing a 2% reduction in relative risk of emergency presentations for every month "exposed" to local screening. Among those "screened" patients (60-69 years) the effect was slightly higher, with an OR of 0.97 (CI: 0.96-0.99, p<0.001), while for patients "non-screened" (not of screening age), the OR was 0.98 (CI: 0.97-0.99, p<0.001). These analyses confirmed an independent association between incrementally increasing exposure time and risk of emergency presentation for patients overall. This association was seen for both those in the screening and non-screening age-groups, *Table 4.4*.

Table 4.3 The emergency presentation rate for patient groups depending on their length of exposure to the BCSP at time of presentation. Compared to other groups, those exposed for >12 months had the lowest rate of emergency presentation (p<0.001).

Exposure	**Emergency presentations/total (%)**	**P value**
Non Exposed	7,595/20,498 (37.1)	
<6 months exposure	1,513/4,151 (36.4)	0.170
6-12 months exposure	870/2581 (33.7)*	<0.001
>12 months exposure	109/410 (26.6)**	<0.001

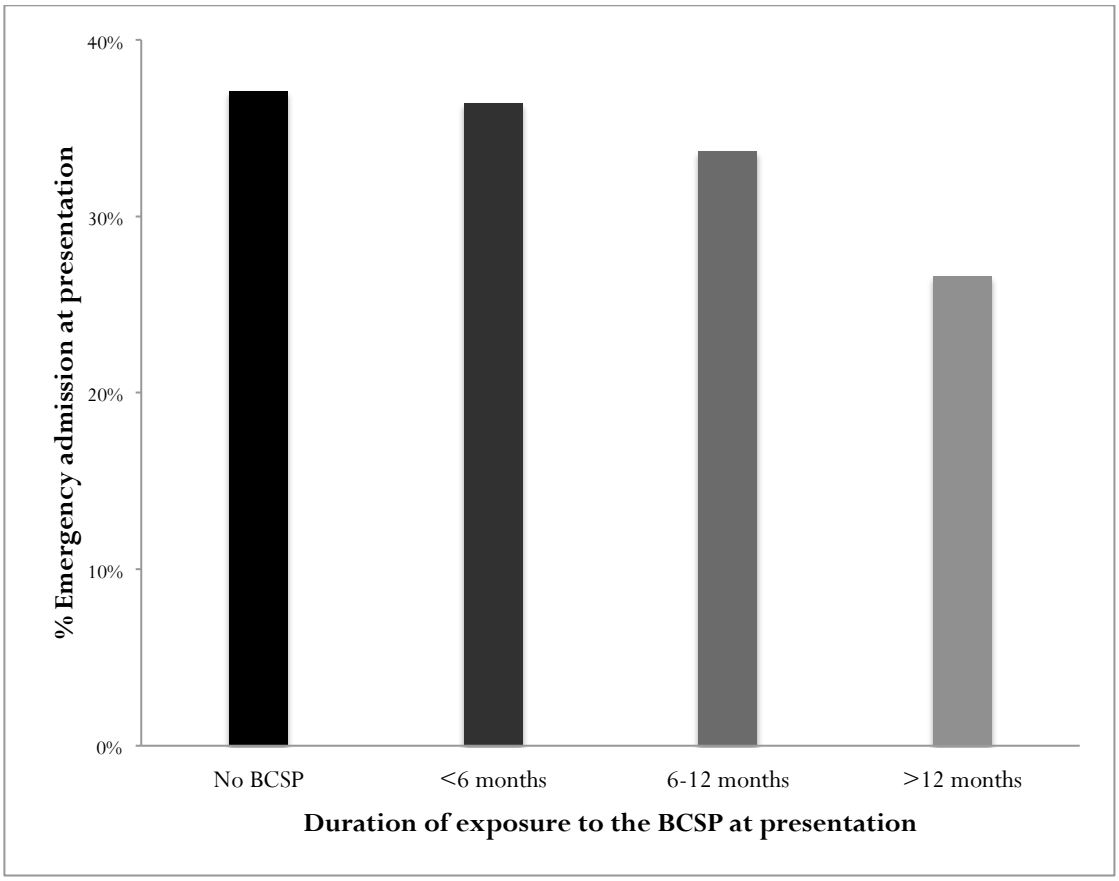


Figure 4.7 A chart of emergency presentation rates for patients with different lengths of exposure to the BCSP.

Table 4.4 A continuous variable analysis of exposure to the BCSP. The table showed the impact that each month of exposure to screening had on all patients and those specifically in the screening and non-screening age groups. Results were shown before and after adjusting for age, gender, co-morbidity and deprivation in multivariate logistic regression.

Variable	Emergency presentations / total cases (%)	Unadjusted (univariate) OR	CI	P value	Adjusted (multivariate) OR	CI	P value
BCSP exposure (months)							
All age-groups							
Non exposed	7,599/20,520 (37.0)	1	-	-	1	-	-
Exposed (per month)	2,488/7,120 (34.9)	0.98	0.97-0.99	<0.001	0.98	0.97-0.99	<0.001
Screening age only (60-69)							
Non exposed	1,460/4,826 (30.3)	1	-	-	1	-	-
Exposed (per month)	515/1,893 (27.2)	0.97	0.96-0.99	0.002	0.97	0.96-0.99	0.003
Non-screening age groups							
Non exposed	6,135/15,673 (39.1)	1	-	-	1	-	-
Exposed (per month)	1,977/5,248 (37.7)	0.98	0.97-0.99	<0.001	0.98	0.97-0.99	<0.001

4.5.1.2. The direct and indirect effect of screening exposure

The patients with the greatest reduction in risk of emergency presentation were those of screening age (60-69 years) who were potentially "exposed" to screening directly. However, there was also a significantly lower risk of emergency presentation for patients outside the age targeted by the screening programme, *Tables 4.5, 4.6, Figures 4.6, 4.7*. This is a key finding of the study, as it suggests that both the direct and indirect effects contribute to any reduction in emergency rates.

4.5.1.2.1. Risk reduction for emergency presentation according to age group

The section aims to examine whether the risk reduction for emergency presentation associated with an active BCSP was different for those of screening age (60-69 years) compared to those of non-screening age. This is at the heart of my hypothesis that sought to produce evidence that there is both a direct effect of screening and an indirect effect, caused by increased awareness of CRC in the local population and healthcare system.

To determine whether the exposure variable (active BSCP) was associated with reduced risk of emergency presentation for screening age and non-screening age patients, I constructed two models (Tables 4.5 & 4.6), one that included only the 6,719 CRC patients of screening age (60-69 years) and another that included the remaining 20,921 non-screening age cases.

For the 6,719 screening age cases, the crude emergency presentation rate was lower in those patients presenting with ≥6 months exposure than in the "non-exposed" controls (24.8% vs. 30.3%, $p<0.001$), *Table 4.5, Figure 4.8*. The adjusted odds ratio for emergency admission in patients diagnosed ≥6 months after screening started was also reduced at 0.75 (CI: 0.63-0.90).

The same pattern was observed in the unadjusted emergency presentation rates for patients in the non-screening age. Patients with ≥6 months screening exposure had lower rates than those that were "not exposed" (35.7% vs. 39.1%, $p<0.001$), The adjusted OR for emergency presentation in patients with ≥6 months screening exposure was 0.85 (CI: 0.77-0.94), *Table 4.6, Figure 4.9*.

These findings are consistent with my hypothesis that the start-up of BCSP resulted in indirect, general benefits across the whole local population during this period. It also showed, as expected, that the magnitude of risk reduction were greatest for those that were of screening age.

Table 4.5 A binary logistic regression analysis of 6,719 CRC cases of screening age (60-69 years) diagnosed between October 2006 and September 2007, showing factors associated with emergency presentation.

Variable	Emergency presentations / total cases (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	P value	OR	CI	P value
Age group (years)							
60-69 years	1,975/6,719 (29.4)	1	-	-	1	-	-
Gender							
Male	1,180/4,142 (28.5)	1	-	-	1	-	-
Female	795/2,577 (30.8)	1.12	1.01-1.25	0.039	1.10	0.98-1.23	0.096
Co-morbidity groups							
No co-morbidity	1,006/4,739 (21.2)	1	-	-	1	-	-
1 co-morbidity	153/453 (33.8)	1.89	1.54-2.33	<0.001	1.87	1.52-2.30	<0.001
≥ 2 co-morbidity	816/1,527 (53.4)	4.26	3.77-4.81	<0.001	4.24	3.75-4.79	<0.001
Deprivation							
1 (most deprived)	444/1,310 (33.9)	1	-	-	1	-	-
2	377/1,271 (29.7)	0.82	0.70-0.97	0.021	0.79	0.67-0.95	0.009
3	409/1,381 (29.6)	0.82	0.70-0.97	0.017	0.80	0.68-0.95	0.011
4	413/1,450 (28.5)	0.78	0.66-0.91	0.002	0.78	0.66-0.93	0.005
5 (least deprived)	332/1,307 (25.4)	0.66	0.56-0.79	<0.001	0.67	0.56-0.80	<0.001
BCSP Group							
Control	1,460/4,825 (30.3)	1	-	-	1	-	-
BCSP <6 months	313/1,078 (29.0)	0.94	0.82-1.09	0.428	0.92	0.79-1.07	0.270
BCSP ≥6 months	202/816 (24.8)	0.76	0.64-0.90	0.001	0.75	0.63-0.90	0.002

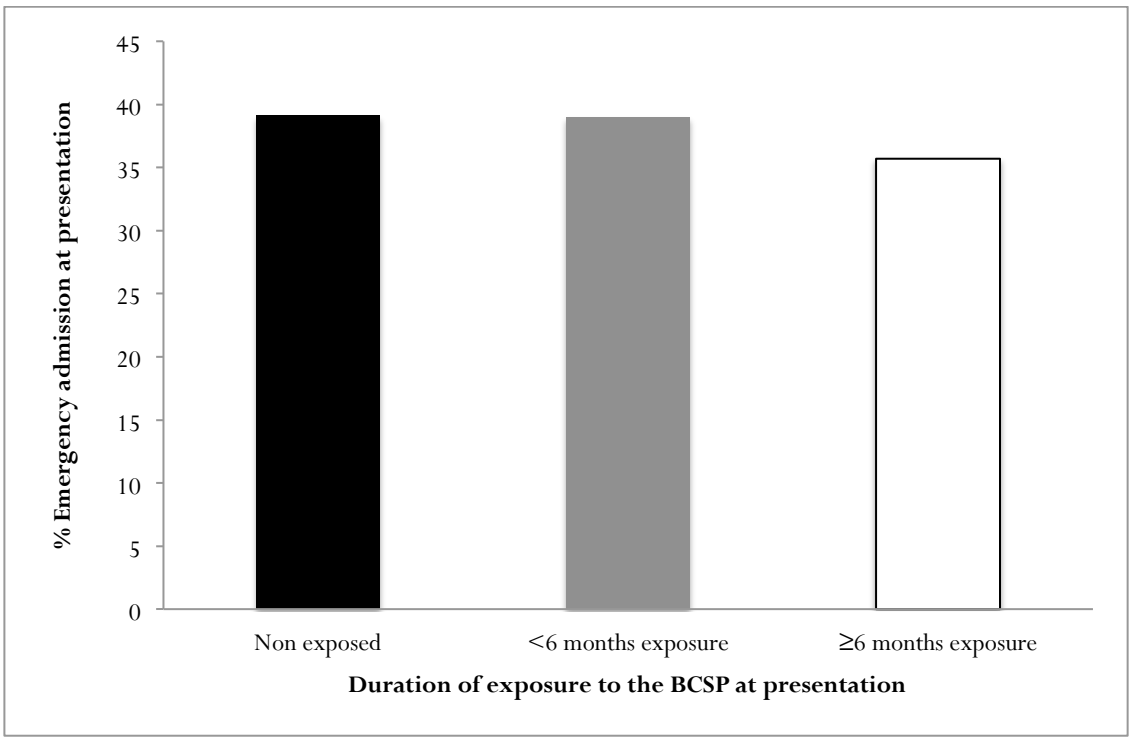


Figure 4.8 A chart showing emergency presentation rates, in screening age (60-69 years) patients, depending on the different length of exposure to the BCSP. The unadjusted emergency rate is significantly lower in the group with more than 6 months exposure to the BCSP than the control group ($p<0.001$).

Table 4.6 A binary logistic regression analysis of 20,921 non-screening age CRC patients diagnosed between October 2006 and September 2007, showing factors associated with emergency presentation.

Variable	Emergency presentations / total cases (%)	Unadjusted (univariate) OR	CI	p value	Adjusted (multivariate) OR	CI	p value
Age group (years)							
<60 years	1,440/4,583 (31.4)	1	-	-	1	-	-
70-79 years	3,087/9,134 (33.8)	1.11	1.03-1.20	0.005	1.08	1.00-1.17	0.063
>79 years	3,585/7,204 (49.8)	2.16	2.00-2.34	<0.001	2.09	1.92-2.27	<0.001
Gender							
Male	4,140/11,295 (36.7)	1	-	-	1	-	-
Female	3,972/9,626 (41.3)	1.21	1.15-1.28	<0.001	1.20	1.13-1.27	<0.001
Co-morbidity groups							
No co-morbidity	4,079/14,021 (29.1)	1	-	-	1	-	-
1 co-morbidity	761/1,614 (47.1)	2.17	1.96-2.41	<0.001	2.07	1.86-2.30	<0.001
≥ 2 co-morbidity	3,272/5,286 (61.9)	3.96	3.71-4.23	<0.001	4.01	3.75-4.29	<0.001
Deprivation							
1 most deprived	1,750/3,887 (45.0)	1	-	-	1	-	-
2	1,636/4,053 (40.4)	0.83	0.76-0.90	<0.001	0.80	0.73-0.88	<0.001
3	1,713/4,413 (38.8)	0.78	0.71-0.85	<0.001	0.75	0.69-0.83	<0.001
4	1,599/4,447 (36.0)	0.69	0.63-0.75	<0.001	0.64	0.59-0.71	<0.001
5 least deprived	1,414/4,121 (34.3)	0.64	0.58-0.70	<0.001	0.63	0.58-0.70	<0.001
BCSP Group							
Control	6,135/15,673 (39.1)	1	-	-	1	-	-
BCSP <6 months	1,200/3,073 (39.0)	1.00	0.92-1.08	0.922	0.96	0.88-1.04	0.337
BCSP ≥6 months	777/2,175 (35.7)	0.86	0.79-0.95	0.002	0.85	0.77-0.94	0.001

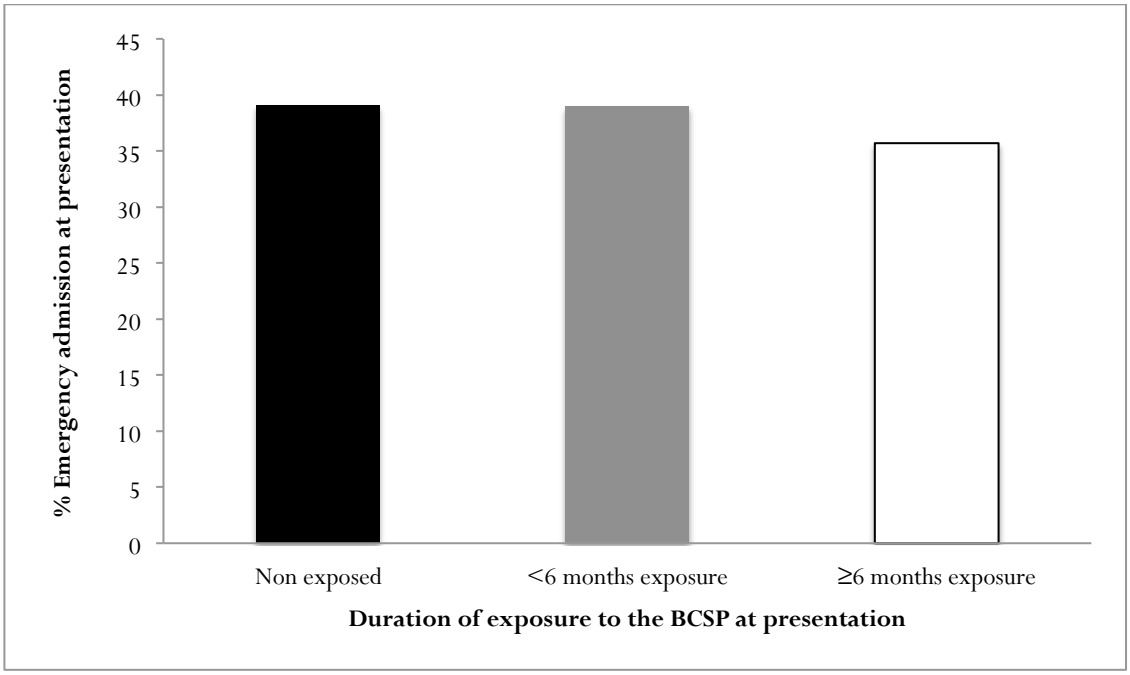


Figure 4.9 A chart showing emergency presentation rates, in non-screening age CRC patients, depending on the different length of exposure to the BCSP. The unadjusted emergency rate is significantly lower in the group with more than 6 months exposure to the BCSP than the control group ($p<0.001$).

4.5.1.3. Secondary outcomes: surgical resection rates and one-year mortality

There was a numerically higher rate of major surgery among patients living in an area with an active BCSP (50.9% vs. 49.5%; p=0.049), *Table 4.7*. In the group with more than 12 months exposure at presentation, the resection rate was 57.2%, *Table 4.8*. This suggested that at least with longer screening exposure, more patients were receiving operations and therefore the best chance of long-term survival.

Among patients diagnosed at a time when the local BCSP was active, the crude one-year mortality rate was non-significantly lower than for those diagnosed before the programme started in their area (29.9% vs. 28.8%; p=0.399) in the main cohort group, *Table 4.9*. However, when patients were split according to the length of screening exposure, the sub-group "exposed" to more than 12 months had a significantly lower one-year mortality rate, compared to the "non-exposed" group (22.1% vs. 29.9%, p=0.002), *Table 4.10*.

Table 4.7 A table comparing the rates of major resection in patients that presented before and after local start up date (LSUD) of screening.

Exposure	**Major resection, N (%)**
Before LUSD	10,150/20,498 (49.5)
After LUSD	3,633/7,142 (50.9)
P=0.049	

Table 4.8 A table comparing the rates of major resection, depending on the length of screening exposure. The rate was significantly higher for people presenting when screening had been active for over twelve months compared to the non-exposed group.

Exposure	Major resection, N (%)
Non exposed	10,150/20,498 (49.5)*
0/12-6/12	2,074/4,151 (50.0)
6/12-12/12	1,324/2,580 (51.3)
>12/12	235/411 (57.2)*

*P=0.002

Table 4.9 A table comparing the one-year mortality rates in patients that presented before and after local start up date (LSUD) of screening.

Exposure	One-year mortality, N (%)
Before LUSD	6,138/20,948 (29.9)
After LUSD	2,055/7,142 (28.8)

P=0.399

Table 4.10 A table comparing the one-year mortality rates, depending on the length of screening exposure. The rate was significantly higher for people presenting when screening had been active for over twelve months compared to the non-exposed group.

Exposure	One-year mortality, N (%)
Non exposed	6,138/20,948 (29.9)*
<6 months	1,209/4,151 (29.1)
6-12 months	755/2,580 (29.3)
>12 months	91/411 (22.1)*

*P<0.001

4.5.2. Control Study To Explore Confounding: Association between locally active bowel cancer screening program and emergency presentation of oesophageal and gastric cancer

To verify that any associations of the BCSP are specific to CRC, rather than reflecting more general features of local services I studied changes in OG cancer presentations with screening exposure. The characteristics of 22,450 cases of OG cancer diagnosed in England over a two year period (2006-2008) have already been described(244). Of these patients 9,319 were diagnosed during the one-year study period (October 2006 and September 2007). Relative to their presentation, 6,787 OG cancer patients were diagnosed at a time when BCSP was not active in their PCT ("non-exposed") and 2,532 (37.3%) were diagnosed after the BCSP had started ("exposed"). Crude rates of emergency presentation during the diagnostic pathway for OG cancer showed no difference between the exposure groups. The emergency presentation rate in the "non-exposed" group was 28.0%, compared to 29.7% in those "exposed" for less than 6 months and 28.0% in these "exposed" for longer.

The results of the binary logistic regression analysis are shown in *Table 4.11*. I found no association between emergency presentation rates of OG cancer and my predictor variable defining exposure of the

local population to BCSP. This suggests that the impact of BCSP exposure was specific for CRC and that outcomes for other gastrointestinal malignancies were unaffected.

Table 4.11 A binary logistic regression analysis of 9,319 OG cancer cases diagnosed between October 2006 and September 2007. The table shows there was no association between BCSP exposure and emergency presentations in either the univariate or multivariate analysis.

Variable	Emergency presentations/ total (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	p value	OR	CI	p value
Age group (yrs)							
<60	293/1,454 (20.2)	1	-	-	1	-	-
60-69	460/2,171 (21.2)	1.07	0.90-1.26	0.451	1.06	0.89-1.26	0.498
70-79	769/3,023 (25.4)	1.35	1.16-1.57	<0.001	1.32	1.12-1.55	0.001
>79	1,110/2,671 (41.6)	2.82	2.43-3.27	<0.001	3.02	2.57-3.54	<0.001
Gender							
Male	1,634/6,090 (26.8)	1	-	-	1	-	-
Female	998/3,229 (30.9)	1.22	1.11-1.34	<0.001	1.10	0.99-1.22	0.070
Co-morbidity							
0	1,345/6,757 (19.9)	1	-	-	1	-	-
1	770/1,744 (44.2)	3.18	2.85-3.56	<0.001	3.14	2.80-3.52	<0.001
≥2	517/818 (63.2)	6.91	5.92-8.06	<0.001	7.72	6.58-9.05	<0.001
Deprivation							
1 (most deprived)	676/2,130 (31.7)	1	-	-	1	-	-
2	551/1,936 (28.5)	0.86	0.75-0.98	0.023	0.87	0.75-1.00	0.052
3	522/1,830 (28.5)	0.86	0.75-0.98	0.028	0.84	0.72-0.92	0.019
4	494/1,840 (26.8)	0.79	0.69-0.91	0.001	0.76	0.65-0.88	<0.001
5 (least deprived)	389/1,583 (24.6)	0.70	0.61-0.82	<0.001	0.65	0.55-0.76	<0.001
BCSP Exposure							
Control	1,900/6,787 (28.0)	1	-	-	1	-	-
BCSP <6 months	417/1,406 (29.7)	1.08	0.96-1.23	0.207	1.07	0.93-1.22	0.350
BCSP ≥6 months	315/1,126 (28.0)	1.00	0.87-1.15	0.989	0.95	0.82-1.11	0.510

4.6. Discussion

This chapter was first and foremost about testing the application of my new methodological approach, which extracts greater value from HES data. I have shown that combining clinical logic and the newly

developed metric of emergency presentation can test associations between exposure and outcomes in large populations. In this case whether living in an area with a (recently) activated BCSP was associated with a reduced risk of emergency admission for CRC. This form of retrospective, observational study, focussed on the roll-out of the BCSP across England, is a useful example of how enhanced HES data can help us to understand complex and important questions of national health policy.

My results suggest that following the introduction of the BCSP across England there was a significant reduction in the risk of CRC patients presenting as an emergency. This effect was greatest among screening age patients. In this group, the risk of emergency presentation in patients presenting more than six months after the local start-up of screening was 0.75 times that of someone "not exposed" to screening. However, the risk reduction was not only confined to the screening age group but also to the non-screening group. In this group, the risk of emergency presentation after 6 months of screening exposure was 0.85 times that of someone "not exposed". This suggests that indirect, population-wide benefits accrued as screening was introduced.

As already mentioned, two smaller studies exploring the impact of bowel cancer screening on emergency presentations for CRC have been carried out in England, which have helped to inform my results.

One was a randomized controlled trial assessing FOBt screening (the Nottingham screening study), which compared 75,253 patients in the screened group (60% response rate) and 74,998 well matched, unscreened controls (age range; 45-74 years)(88). The emergency presentation rate was 23.9% in the screened group, compared to 27.9% in the control group, but the difference was not statistically significant (p-value reported as non-significant, the actual number was not stated in the manuscript). This may have been due to a lack of study power. On initial inspection the baseline rate of emergency presentations appeared to be considerably lower than the overall rate of 36.5% in my cohort. The reason for this was likely to be the age cutoff of 74 years in the Nottingham study. When compared to my screening age patients the results were more comparable. In patients "not exposed" to screening my cohort had a 30.3% emergency rate and in those "exposed" for more than 6 months, the rate was 24.8%. Therefore, there was a 4% reduction in the Nottingham study and 5.5% reduction in my cohort of screening age patients. Of interest was how large the reduction was for both studies compared to the detection of cancer in screened subjects of just 2.3/10,000 (310). This suggests the direct effect of identifying CRC at screening was unlikely to have accounted for the full 4-5% reduction in emergency presentations.

In an uncontrolled observational study from Coventry and North Warwickshire, where the bowel cancer screening pilot targeted patients aged 50 to 69 years, the authors reported that 29.4% of CRC patients presented as an emergency in the year before the pilot (1999) but that the local rate had fallen to just 15.8% by 2004. Surprisingly, the proportion of Dukes stage cancers was unchanged over the

study period and the annual number of cases did not increase as might be expected if extra screen-detected cases were contributing to the reported totals(208). Expert commentators questioned whether screening itself, or other changes in local or national CRC care over the 5 year period, was responsible for the time-trends reported(209). It is difficult to compare these results to my own, especially as my study lacks data on the cancer stage at presentation. However they suggest that factors outside the direct effect of the screening programme were responsible for the changes in emergency presentation.

My study had the advantage of nationwide coverage and a design that sought to control for sources of bias. For example, by studying the results over only a one-year period I eliminated confounding caused by changes in NHS practice over time. I also studied patients presenting with OG cancer over the same time period in order to have a control group. This demonstrated that the impact of screening exposure only affected CRC patients and thus the results for CRC patients were unlikely to have been caused by underlying differences in the quality of care provided by areas that began screening sooner.

The staged roll out of screening across the country meant that simple observation of temporal trends in annual emergency presentation rates would not provide an accurate means of assessing the impact of the programme on unplanned care. Hence I conceived a study design that took advantage of the variation in exposure of local populations to start-up of BCSP during the roll out period. In my analysis there were significantly fewer patients "exposed" to screening than not (7,142 vs. 20,498). Ideally, the groups would have been more evenly matched.

Most patients in my cohort were "not exposed" to the BCSP at the time of their CRC presentation. Furthermore most patients that were "exposed", could only be affected indirectly by screening as only 24.3% of CRC patients were in the screening age. Furthermore, only half of patients are called for screening in the first year of the programme and the average length of exposure to screening was only 5.7 months at presentation. These explanations go some way towards supporting what the baselines figures of my study and the Nottingham and Coventry trials have shown, namely that despite the clear evidence of a role for the screening programme in reducing emergency presentations, there is little evidence that this occurs directly through the early diagnosis of asymptomatic patients. This was very important because it goes to the heart of how a screening programme may reduce the burden of late-presenting CRC. While there may be a role for improving the technical sophistication of the screening test or performance of the colonoscopy, it seems likely that greater benefit will come from increasing the overall population's awareness of CRC symptoms and the need to seek urgent medical attention.

The first key finding in my results was the significant association between any exposure to screening in patients of all ages and a reduced risk of emergency presentation. In patients "exposed" to screening for any length of time, the rate was 34.9% compared to 37.0% in the "non exposed" group. My next finding was that longer exposure, in particular over 6 months, was more strongly associated with improved outcomes. On multivariate analysis, the OR for patients with >6 months exposure was 0.83

compared to the "non-exposed" group. This was a highly significant finding. However, the group of patients "exposed" for less than 6 months had an OR of 0.95 and this was not significantly lower. This supports my hypothesis, which stated that living in an area with an active BCSP was associated with a reduced risk of an emergency presentation, through both direct and indirect effects.

I further studied the effect of screening duration on outcomes by splitting those patients with more than 6 months exposure into "6-12 months exposure" and "more than 12 months exposure". This showed that the longer the duration of exposure, the lower the emergency rates became; the exposure effect was not a one off effect but a continuing positive effect. In fact, every month of exposure was associated with a 2% reduction in the risk of emergency presentation. Showing the same association when exposure was used as a continuous rather than categorical variable supported the incremental (or dose-response) nature of screening exposure.

I next consider what factors may be behind the association between exposure and reduced emergency presentations. Patients of screening age may benefit from the programme both directly through the diagnosis of the asymptomatic cancer and indirectly through enhanced awareness of the need to present their symptoms to medical professional. Meanwhile non-screening patients can only be helped indirectly.

Evidence for the direct effect comes from the higher proportion of screening age group patients in the >6 months exposure group, compared with the "non-exposed" group (27.3% vs. 23.5%). Not knowing which patients were diagnosed directly through the BCSP, meant it was not possible to quantify the direct and indirect effects of screening. However, unsurprisingly this does point to there being a greater increase in CRC detection in screening age patients once screening was established. I also described a greater reduction in the odds of emergency presentation in screening age compared to non-screening age after 6 months exposure (0.75 compared with 0.85). Ultimately, it must also be remembered that some of the patients in the screening age may have benefitted from the enhanced awareness brought about being enrolled in a campaign (and having letters and FOBt kits sent through the post).

While screen-detected cancers will have contributed to the reduced risk of emergency presentation observed in the screening age group, this cannot explain the major risk reduction also seen in the non-screening age group. In this case, increased awareness among patients and health professionals will have been a factor (i.e. the indirect effect). Moreover, I have shown a risk reduction within 6-12 months of start-up, when screening will have been offered to fewer than half of eligible 60-69 year olds and so before the full benefits of the screening programme have been realised.

I was not able to fully quantify the indirect benefits of the programme because HES cannot identify screen-detected cancers. Hence, I cannot know how much of the observed reduction in risk of emergency presentation was attributable to the elective diagnosis of symptomless cancers within the programme itself. I do, however, know the date when a PCT joined the screening programme and

therefore whether screening was available at the time of a given patient's presentation. I also know that any reduction in the non-screening age group must be due to the indirect effect and could only be influenced by the screening programme increasing public and professional awareness. In fact, relative to the total number of new CRC cases diagnosed nationally, the absolute numbers of screen-detected tumours is low. In a report of cumulative findings from the BCSP until October 2008 (a full year after the end of my study period) only 1,772 screen-detected CRC cases had been recorded(171). It follows that our study cohort of 27,640 cases will have contained only a few hundred screen-detected cancer patients. Evidence of this effect can be seen in the 4% increased rate of CRCs diagnosed in screening age patients (60-69 years) in areas where screening had been active for ≥6 months compared to "non-exposed" areas.

Overall my data for major surgical resections and one-year survival was not strong enough to support the claim that these outcomes are improved in the early period after screening was introduced. However the 12-month exposure group data suggests there may be a trend for better outcomes with a longer follow-up period. Despite this, these positive results have to be interpreted with caution, as early outcome metrics such as access to surgery and early survival are liable to be affected by lead time, length time and over-diagnosis bias that has been discussed already. For that reason, I have not studied these outcomes in detail.

In my national cohort I also showed that increasing age, female gender, increased levels of co-morbidity and socioeconomic deprivation are all associated with an increased risk of emergency admission for CRC. This was consistent with previous research(30,36,69,70,72,97,251).

There is a well-established correlation between deprivation and CRC-related mortality, which needs to be addressed(326). A UK study from 1992-95 that also used HES found the emergency rates varied significantly from the least deprived (35%) to the most deprived decile (56%)(299). In trying to understand why this is, one must first exclude data-related artifacts, with patients misattributing deprivation levels. This theory, called the "ecological fallacy", seemed implausible given that studies have demonstrated that excess mortality associated with census designated deprived areas was fully explained by the concentration in those areas of people with adverse personal or household socioeconomic factors(327). A second complication was the exclusion from HES data of operations carried out in private hospitals. As private operations are more common among wealthier patients then the deprivation gradient I found is actually more likely to be an underestimate of the inverse outcomes associated with deprivation. Actual causes for the poor outcomes associated with deprivation are partly explained by the later stage of disease among deprived patients, however this simply begs the question of why they present with later stage disease(248). One reason is the increased prevalence of co-morbidities among deprived patients(328). In addition, deprived patients use health resources less in proportion to need than wealthier patients and are more likely to fail to access primary care at an early disease stage(329). This is, at least partially, due to a lower awareness of CRC symptoms among the most

deprived groups of patients. 20% of the most deprived group couldn't name any cancer symptom compared to 9% of the least deprived. Blood in the stool was mentioned as a cancer symptom by 13% of the least deprived compared to 4% of the most deprived patients. Similarly, tiredness or fatigue by 12% and 5% respectively(330). This has further repercussions, with low CRC knowledge being associated with negative attitudes towards participation in CRC screening(322).

Even when symptoms have been bought to medical attention deprived patients can have a more difficult patient journey, with a breakdown in elective care more likely, leading to delays and emergency presentation. One major problem is related to communication between healthcare workers and patients with low literacy skills. This is the case for CRC screening in the UK, where a lack of literacy skills was associated with increasing levels of deprivation and participants with adequate literacy had a 58% uptake rate, compared to only 48% among those with limited health literacy skills(331). This finding has also been found in cervical screening(332). Deficient health literacy skills affect patients ability to understand health promotion literature, website advice and especially reading and understanding official letters which can lead to missed appointments(333). There are 5.2 million adults the UK with low literacy skills(334). This problem is compounded by the discrepancy between the reading age required to understand important medical information and the average reading age. For example, the average reading age in the UK is nine years old yet the NHS Direct website requires an average reading age of 17 years(335).

I also considered whether the 'inverse equity hypothesis' might explain how the introduction of screening might affect patients of different levels of deprivation. This hypothesis states that after new public health programmes are enacted, they are initially taken up more by the least deprived groups, which causes a short term increase in health inequalities. However, following this first phase the benefits to the least deprived plateau and the more deprived sections of the population take up the health programme leading to a reduction in overall health inequalities. A similar patterns has already been commented on for the more established cervical cancer screening programme where rates of inequality between the least and most deprived areas narrowed over time(336). The follow-up period in this chapter was too short to investigate whether this occurred with the BCSP.

Most of the survival disadvantage associated with deprivation occurs shortly after diagnosis and then reduces or disappears completely over a longer period of time(142). If socioeconomic-based inequality was reduced following the introduction of screening then I might have expected a greater fall in the one-year mortality among deprived patients presenting after screening had begun. Therefore I looked at changes in survival following the introduction of screening using the main cohort based on deprivation level. All deprivation quintiles showed a reduction in mortality in the exposed group of around 2% and this was not dependent on the deprivation level, *Table 4.1*. I am therefore unable to venture whether screening is reducing deprivation-related inequality or even if there is evidence for the 'inverse equity hypothesis'.

My analysis of 9,319 cases of oesophageal and gastric cancer diagnosed during the study period found no association between the risk of emergency presentation for this unrelated tumour type and local roll-out of the BCSP. This made it more likely that any associations are specific to CRC, rather than reflecting more general features of local services.

The full impact of the BCSP will take some years to quantify but this chapter suggests that the introduction of screening has produced benefits that extended beyond those people targeted by and participating in the programme. These indirect benefits are likely to have translated into savings in acute hospital bed days and improvement in cancer outcomes. This strengthens the case supporting the cost-effectiveness of introducing bowel cancer screening in the UK(337). The roll out of national screening based on FOBt has now been completed and services in England are preparing for implementation of screening with flexible sigmoidoscopy. It will be interesting to see whether this next phase is associated with similar population-wide benefits.

In January 2012 the UK launched the first ever cancer awareness campaign 'Be Clear on Cancer' with TV, radio and newspaper advertisements encouraging people to look out for early signs of bowel and other cancers and to seek early help from their GP. Pilot data already shows an increase in the number of patients attending their GP with symptoms and a subsequent increase in the number of urgent hospital referrals(338). It will be interesting to see whether this has further positive population-wide effects on CRC outcomes. This is a poorly understood area and warrants further research.

There were several weaknesses in this chapter. In the study cohort, 20,498 (71.0%) cases occurred before screening was active in their PCT; therefore most patients were "not exposed". This meant that there were comparatively few patients to judge the effect of different lengths of screening exposure. Furthermore, as already mentioned, I was unable to state whether an individual patients was diagnosed through the screening programme or thorough the normal symptomatic service. Part of my thesis hypothesis was to show that the significant improvements in emergency presentation rates following the introduction of screening were beyond what could be achieved through directly diagnosing asymptomatic cases. However among patients in the screening age, I was unable to show which patients were and were not "exposed", simply that it would be approximately one quarter of the screening age population or 7% of the overall population.

I could also not completely determine whether the quality of local services at the time of presentation affected outcomes. However the lack of association between exposure and OG cancer outcomes does at least partially address this question. There is also the general problem with observational studies on screening programmes, which is that the true benefit or not of a programme is only really revealed when long-term cancer mortality or even all-cause mortality is known. The lack of any association between screening exposure and OG cancer outcomes helps to partially refute this possibility. Although my logistic regression models included key potential confounders, I cannot entirely eliminate the

possibility of residual confounding given the observational nature of the work. Nevertheless, I undertook sensitivity and sub-group analyses and found consistent results. I found patients with the greatest potential exposure to screening had the greatest benefit in terms of reduced emergency presentation. Indeed, there was a gradient of improved outcomes, running from those with no exposure through to those with over 12 months exposure. This evidence also makes it less likely that the finding were due to an overall improvement in care driven by 'The NHS Cancer plan for England' (2000). This drive to reducing waiting times and standardise referral practices, co-incidentally achieved full role out in 2006, around the same time as screening began. If this were the driving factor behind the reduction in emergency presentation rates then the results would be seen for all CRC patients, irrespective of screening exposure (27).

Finally, it could also be argued that my assumption about increased awareness only beginning with the introduction of local screening was simplistic. In fact awareness could have increased from the start of screening in the first pilot area and then slowly filtered out nationally. Patients may have become aware of the importance of having CRC symptoms fully investigated through national news reports or from friends and family living in areas of the country that adopted screening sooner.

In conclusion, I have used enhanced HES data and a novel metric of CRC care to show substantial improvements in outcomes for patients presenting after the introduction of screening in their area. This risk reduction extended to cases outside the screening age group and was apparent within just 6-12 months of start-up of the programme. These findings of an early and population-wide reduction in risk of emergency presentation suggest that the launch of the programme was associated with indirect benefits for symptomatic cases diagnosed during the roll out period. I believe that this study provides observational evidence that the benefits of launching a public screening programme for CRC are not limited to people of screening age with asymptomatic cancer but extend to the wider population. This is likely to reflect enhanced public and/or professional awareness of colon cancer leading to more timely clinical presentation and investigation in the symptomatic population.

There are however several important concerns about the applicability of the results presented so far. The most important being whether screening exposure explained the perceived improvement in outcomes. This concern stems from whether areas starting screening sooner had better services already and this caused the apparent association with positive outcomes and adopting screening. This better service hypothesis (BSH) stated that PCTs that starting screening earlier were better and hence this explained the better results. I have shown that the screening effect was only seen in CRC outcomes and that no similar improvements were seen in a matched population of OG cancers. Further work defending the findings presented in this chapter, is presented in chapter 5.

Chapter 5 - Supplementary studies to explore confounding and expand the evidence

5.1. Introduction

In the preceding chapter (*Chapter 4*), I reported the findings of a cross-sectional study designed to examine factors associated with risk of emergency presentation during the diagnostic pathway for a cohort of patients presenting with CRC over a defined one-year period (Oct 2006 – Sept 2007). This was an opportunity to deploy my metric of CRC care (emergency presentation), developed using novel approaches to interrogating hospital discharge coding data (HES). The availability of a dataset spanning 2006-2008 allowed me to test an idea relating to the roll out of the BCSP across England.

My original study suggested that 'living in an area with an active BCSP' was associated with a reduced risk of emergency presentation and that this risk reduction was apparent within six-to-twelve months of local start-up (implying early and indirect, as opposed to direct, benefits to the population). As might be predicted, the magnitude of risk reduction was greater for those patients living in an area where screening had been active for a longer period. Importantly, this 'effect' was observed for both screening age and non-screening age patients – consistent with my idea that the launch of the programme would be associated with population wide benefits that go beyond the minority of people that are actually screened.

To explore confounding in my original study, in *Chapter 4* I compared associations between the exposure variable ('living in an area with an active BCSP') and the risk of patients with OG cancer presenting as an emergency. The logic of choosing this control group was that emergency presentations for another form of GI cancer would be a marker of the overall status of local diagnostic pathways across primary and secondary care within each PCT. If the PCTs in the first wave of roll-out of the program ('early adopters') tended to be those with the 'best' local services, then all the patients from these areas in my original study would have been regarded as 'exposed' to living in an area with an active programme. If these areas already had superior cancer outcomes in general, then this would confound the study. Similarly, 'later adopter' PCTs may have had inferior services. My control group sought to test this idea, examining whether living in an area with an active BCSP during the study time frame was associated with a reduced risk of emergency presentations for OG cancer. By showing no such association I have gone some way to excluding this possible source of confounding (henceforth referred to as the 'better care hypothesis').

In the present chapter, I will report a series of supplementary analyses of the original two-year HES dataset. In this work, I aimed to re-test my main hypothesis on the national data but with the application of more restrictive selection criteria for the PCTs to include in the study. Within the available national dataset (2006-2008), I designed a 'longitudinal' study, extracting data on all CRC patients diagnosed six months before and after local screening start-up within each individual PCT. These supplementary

studies aimed to eliminate or refute potential bias related to the 'better care hypothesis'– the idea that 'early adopter' PCTs were simply places having superior local services at the outset, or 'late adopters' were areas with inferior services.

In addition, I explore variation in rates of emergency presentations across the individual PCTs. I wanted to determine whether any individual PCTs included in the analysis had implausible rates of emergency presentations (i.e. extreme data 'outliers') – as might occur as a result of some systematic local coding problem.

A key finding in *Chapter 4* was evidence to suggest the possibility that the launch of a local BCSP was associated with *population-wide* benefit – reducing the risk of emergency presentation of CRC for people presenting with CRC. This implies a better chance of elective diagnosis for symptomatic patients in the population who presented with CRC during the initial period after the launch of screening.

Colonoscopy is the gold standard investigation for CRC and it has also been shown that a higher discretionary use of colonoscopy is associated with improved outcomes (180). Hence, I was interested to examine whether changes in elective colonoscopy volume or rates were implicated as a mechanism for improved outcomes in the early period following start-up of local BCSP. If there was an expansion of total elective diagnostic capacity in services at the time of the launch of screening, then this may have resulted in easier access to elective diagnostics for the general population. Colonoscopies performed within the BCSP program account for only a small percentage of total colonoscopies and, more importantly, there is a time lag of several months between being called for FOBt screening and attending the colonoscopy. Hence, any significant, early rise in local colonoscopy activity would be among the symptomatic (i.e. not screened) population and not as a result of screening colonoscopies.

5.2. Methods

5.2.1 Grouping of PCTs into 'Early', 'Middle' and 'Later' adopters according to local start-up date of BCSP

The original dataset reported in *Chapter 4* contained CRC patients from 152 PCTs. For the present analysis, I categorized the PCTs into three sub-groups: '**Early adopters**' were those PCTs that had launched their screening program before October 2006; '**Middle year adopters**' were those that commenced screening between October 2006 and September 2007; and '**Later adopters**' where those PCTs that had not yet started screening. Data for CRC patients from the original cohort were then aggregated according to these groupings. This allowed comparison of the basic demographic features and emergency presentation rates of CRC patients according to the three PCT sub-groups. The purpose was to see if there was any systematic difference between crude rates of emergency presentation for patients living in PCTs that were at different stages of adoption of the screening program. The 'better care hypothesis' would predict lower rates of emergency presentation for people living in 'Early

adopter' PCTs and/or higher rates for those living in 'Later adopter' PCTs. Furthermore, by allocating each patient with a new variable to reflect group membership of their PCT of residence, a new binary logistic regression model could be developed to test whether this candidate predictor variable was associated with risk of emergency presentation. In other words, to see whether the patient's PCT sub-group (Early adopter, Middle Year Adopter of Later Adopter) was associated with risk of emergency admission for CRC.

5.2.2 Exclusion of 'Early' and 'Late' adopter PCTs and alternative longitudinal study designs

Next, I focused exclusively on the PCTs that began their screening programme between the October 2006 and September 2007, of which there were forty-eight. Hence, I excluded the so-called 'Early' and 'Later' adopter PCTs entirely. By selecting only those PCTs that began screening within the 'Middle Year', my original 2-year master dataset would allow for analysis of at least six months of HES data before and after the screening start date for each of the 48 'Middle Year' PCTs included in the new analysis. I identified all the patients presenting with CRC from six months before the start date of local screening to up to six months after, *Figure 5.1*. Hence, for each PCT there would be a 'pre-screening' cohort diagnosed in the six months immediately before the launch date of the local programme, and a 'post-screening' cohort of patients diagnosed during the six months after that date. The original cross-sectional study reported in *Chapter 4* included 142 PCTs, with early adopting PCTs contributing mainly patients 'exposed' to screening and later adopting PCTs contributing 'unexposed' patients. This new approach allowed me to remove the potential of bias related to my 'better care hypothesis'. By eliminating this confounding factor, I would be able to re-test my overall hypothesis about the early impact of launching a screening programme and refute the idea that my original results were biased by the cross-sectional study design. The identification of these patient cohorts required identification of each patient's index admission, as per the methodology described in *Chapter 2*, in order to accurately capture only those patients presenting for the first time in the relevant time windows for each PCT. This process identified 7,920 patients. With only six months of observational data available for the 'post-start-up' period for each selected PCT, this alternative study design focused specifically on risk of emergency admission during the earliest phase of local start-up – seeking evidence for early, population-wide, indirect benefits as opposed to direct effects of screening.

As a further variation on PCT selection criteria and study design, I tightened the parameters further by including only 39 PCTs that started screening in the first six months of the middle year (October 2006-March 2007). This involved selecting PCTs with an even closer match in terms of their local launch dates. The available national dataset would then allow for capture of all cases presenting in the 12 months after launch for each of these PCTs, *Figure 5.2*. This identified 8,772 patients. I further divided this group of patients according to those presenting 0-6 months and 6-12 months after the local start-up date (LSUD) of screening. This extended the observation period to cover the first year after local start up for this group of PCTs.

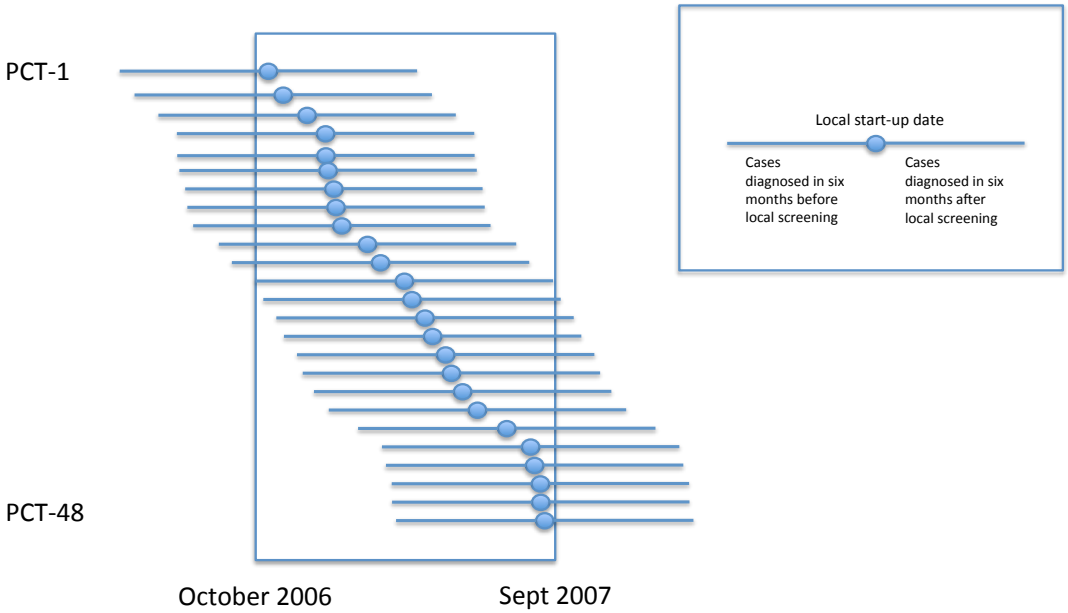


Figure 5.1 Diagram to show how local cohorts of CRC cases were selected for each of the PCTs that launched screening in the 'Middle Year' (n=48). For each PCT two cohorts of incident cases of CRC were identified. The first cohort ('before') contained all CRC cases diagnosed during the six month period before the local start-up date for the BCSP. The second cohort ('after') contained those diagnosed in the six months after this date.

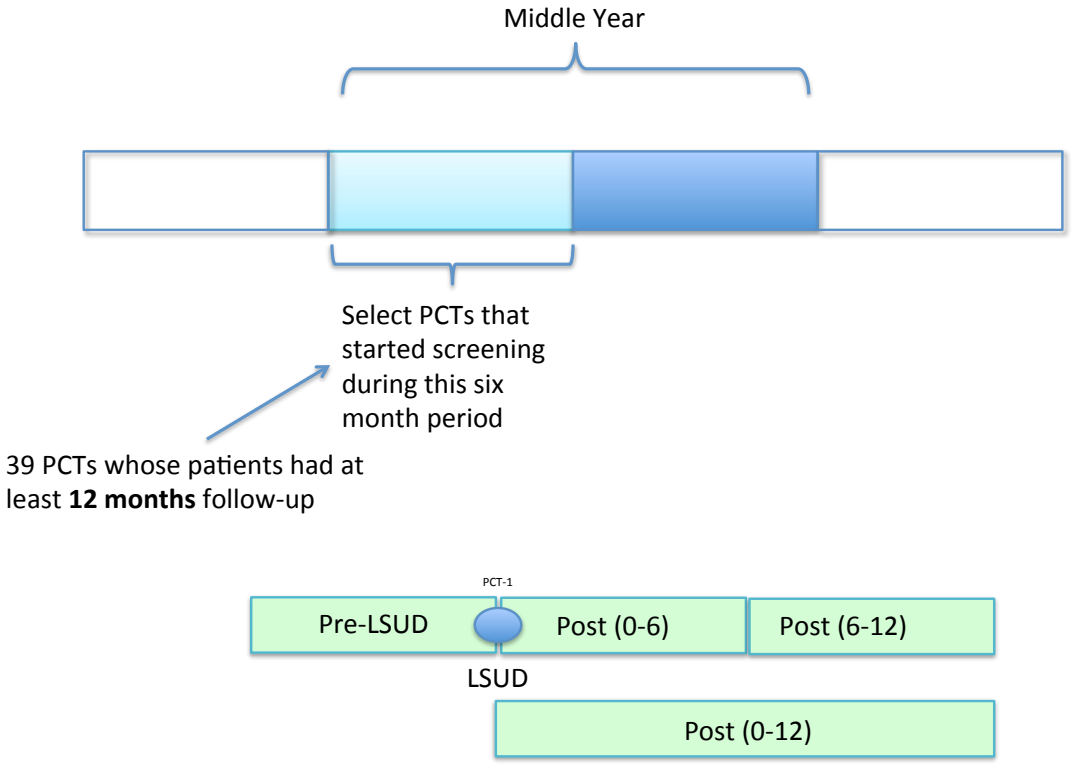


Figure 5.2 Diagram to show how local cohorts of CRC cases were selected for each of the PCTs that launched screening in the first six months of the 'Middle Year' (n=39). For each PCT three cohorts of incident cases of CRC were identified. The first cohort contained all CRC cases diagnosed during the six month period before the local start-up date for the BCSP ('Pre-LSUD'). The second cohort were those diagnosed at 0-6 months (Post 0-6) after start-up, and the third cohort were those diagnosed 6-12 months after this date (Post 6-12). Pooled data for all cases diagnosed in year after LSUD was also analysed (Post 0-12).

5.2.3 Extraction of data for elective daycase colonoscopy

This section describes how I extracted data for *elective day case colonoscopies* for the 48 PCTs that began screening in the middle year. I wanted to investigate what happened to colonoscopy volume in both screening and non-screening age groups following local introduction of screening, using the six month period prior to local start-up ('pre') and the six month period after ('post') for each PCT. I was interested in exploring whether there was evidence for any expansion in overall colonoscopy volume (or rate) in the immediate period after start-up of the program. In the early period after launch of a BCSP, only small numbers of people in the general population would be undergoing colonoscopy as a direct result of screening, and this would be confined to people in the screening age group who tested positive for FOBT. Hence, a significant increase in overall population levels of colonoscopy would suggest that the launch of screening had been coincident with increased activity within the elective diagnostic service for symptomatic patients – especially if the increase was observed among the population outside of the

target age for screening. The impact of launching screening programmes on local service provision and demand has not been reported.

Returning to the original 'All admissions merged file for 2006/2007 and 2007/2008' described in chapter 2, I identified all recorded patients who had received colonoscopies using a syntax that contained all possible OPCS-4 procedural codes for colonoscopy. I excluded any patients not in the 48 middle year PCTs and those performed outside of the middle year. I also excluded those who had colonoscopies during an in-patient hospital stay, as this was not a reflection of elective services. I retained only the first colonoscopy performed for any individual patient in the cohort. This produced a total of 454,560 day case procedures occurring across England in the 48 PCTs over the middle year.

The procedure involved four key steps:

1. The first day case colonoscopy for all patients occurring in the 2 years of data (n=454,560) was identified.
2. Colonoscopies for patients not in the 48 middle-year start up PCTs were removed (n=122,248).
3. Procedures not within 6 months either side of the PCTs LSUD were removed. This left 62,152 day case colonoscopies in a new file was called 'FINALColonoscopy'.
4. I split cases into those colonoscopies occurring before the LSUD (n=30,347) and those after the LSUD (n=31,805). I called these files 'FINALPreLSUD' and 'FINALPostLSUD' respectively.

5.2.4 Estimation of crude colonoscopy rates per capita of local population

For each of the 48 PCTs ('Middle Year' group), I calculated the number of patients undergoing their first daycase colonoscopy during the six months before and after the LSUD and divided this by the total adult population in the PCT. The adult PCT population (16 years and over) was taken from ONS data for 2007/07 (2). This yielded a crude rate of daycase colonoscopy per 1,000 population per year.

The procedure involved four key steps:

1. I matched the number of colonoscopies in each PCT to a file containing each PCT's population and age and gender distribution.
2. Then for each PCT, I calculated;
    a. the crude adult rate of colonoscopies/1,000 adult population
    b. the age-specific rate for pre-screening age (<60 years)/1,000 adult population
    c. the age-specific rate for screening age/1,000 adult population
3. I then appended data on the number of emergency CRCs and total CRCs in the 6 months either side of the LSUD for the 48 middle year PCTs.

5.3. Results

5.3.1. Grouping of PCTs into 'Early', 'Middle' and 'Late' adopters according to start-up date of local BCSP

Of the 152 PCTs in the original study reported in *Chapter 4*, just over half were ***late adopters*** (n=77), with screening beginning in their area after September 2007, *Table 5.1*. These PCTs accounted for 52.9% of patients, none of whom would have been living in an area with an active screening programme at the time of their clinical presentation. 10.8% of patients were from the 17 ***early adopting*** PCTs, in which screening began before October 2006. All of these patients would have been living in an area with an active local screening program at the time of presentation. The remaining 22.3% of the original cohort of CRC patients were living in the 48 PCTs that started screening within the middle year (October 2006 – September 2007). Within this group some of the patients would have been diagnosed before the local program went live, others afterwards. Finally, 10 PCTs accounting for 14.0% of cases were excluded because of uncertainty over when local screening began. This was because these PCTs referred patients to two or more screening centres with different start times.

Table 5.2 illustrates the "exposure status" of patients according to their PCT of residence at the time of their clinical presentation – showing the proportion of cases living in the area when there was no active programme, the proportion diagnosed at a time when the local programme had been active for 0-6 months, and the proportion diagnosed at a time when the local programme had been active for 6-12 months. The crude emergency presentation rates were almost identical between the early adopters (36.7%), middle year adopters (36.6%) and late adopters (36.5%), *Tables 5.1* to *5.3*. Likewise, the CRC patient characteristics (age, gender and co-morbidity) were comparable across the three types of PCT, *Table 5.3*. The only significant difference was that the early adopter group contained a higher proportion of deprived patients than the late adopter group (23.2% vs. 15.6% in the most deprived quintile, $p<0.001$), *Table 5.3*.

Both univariate and multivariate analysis failed to show *any* significant difference in the odds of an emergency presentation based on sub-group of PCT that each case was drawn from. Compared with the early adopter group, the OR for an emergency presentation was 1.04 (0.95-1.14, p=0.405) for the middle year adopter group and 1.05 (0.97-1.14, p=0.256) for the late adopter group, *Table 5.4*. These data provide evidence against the 'better services hypothesis' and add weight to the associations reported in *Chapter 4*. Membership of these PCT sub-groups was ***not*** a predictor of risk of emergency admission.

Table 5.1 Registered adult population, CRC cases and crude rates of emergency presentation for PCTs in England: PCTs are divided into three groups (Early adopters, Middle year or Later adopters) according to whether the local start-up date for BCSP fell within the middle year of the data period (Oct 2006 – Sept 2007).

Primary Care Trust Group	**PCTs**, N	**Registered adult population**, N	**CRC cases,** N (%)	**Emergency presentation,** N (%)
Early adopters (screening began before Oct 2006)	17	4,205,043	3,486 (10.8)	1,208 (36.7)
Middle year adopters (Oct 2006 – Sept 2007)	48	10,850,134	7,197 (22.3)	2,637 (36.6)
Later adopters (screening began after Sept 2007)	77	23,501,536	17,080 (52.9)	6,228 (36.5)
Excluded PCTs	10	5,474,162	4,536 (14.0)	1,506 (33.2)
Total	152	44,030,875	32,299 (100.0)	11,579 (35.8)

Table 5.2 Exposure status of CRC cases according to three PCT groupings (Early adopter, Middle year and Later adopter). By definition, all patients in the early adopter group had some screening programme exposure, while in the middle group around half of patients were "exposed". None of the late adopter group were "exposed" at presentation.

	Patients in Early adopter PCTs (screening began before Oct 2006)	**Patients in PCTs starting screening in Middle year (Oct '2006 – Sept 2007)**	**Patients in Later adopter PCTs (screening began after Sept 2007)**	**Patients excluded**
Number of cases	3,486	7,197	17,080	4,536
BCSP Exposure				
None	0	3,249 (45.1)	17,080 (100)	0
BCSP <6 months	1,240 (35.6)	2,990 (41.5)	0	0
BCSP ≥6 months	2,246 (64.4)	958 (13.3)	0	0
Excluded				
No PCT recorded	0	0	0	204 (4.5)
>1 screening start time in PCT	0	0	0	4,332 (95.5)

Table 5.3 Patient characteristics and emergency presentation rates for the three PCT groupings (Early adopter, Middle year and Later adopter)

	Early adopters (screening began before Oct 2006), N (%)	**Started screening in Middle year (Oct 2006 – Sept 2007),** N (%)	**Later adopters (screening began after Sept 2007),** N (%)	**Excluded PCTs,** N (%)
Number of cases	3,486	7,197	17,080	4,536
Age, mean (sd)	70.9 (11.5)	70.6 (12.2)	71.1 (12.3)	71.1 (12.0)
Age group (years)				
<60 years	544 (15.6)	1,242 (17.3)	2,831 (16.6)	730 (16.1)
60-69 years	916 (26.3)	1,820 (25.3)	4,013 (23.5)	1,119 (24.7)
70-79 years	1,184 (34.0)	2,360 (32.8)	5,622 (32.9)	1,485 (32.7)
>79 years	842 (24.2)	1,775 (24.7)	4,614 (27.0)	1,202 (26.5)
Gender				
Male	2,025 (58.1)	4,084 (56.7)	9,398 (55.0)	2,474 (54.5)
Female	1,461 (41.9)	3,113 (43.3)	7,682 (45.0)	2,062 (45.5)
Co-morbidity groups				
No co-morbidity	2,254 (64.7)	4,914 (68.3)	11,660 (68.3)	3,019 (66.6)
1 co-morbidity	279 (8.0)	560 (7.8)	1,237 (7.2)	307 (6.8)
≥ 2 co-morbidity	953 (27.3)	1,723 (23.9)	4,183 (24.5)	1,210 (26.7)
Deprivation				
Missing	9 (0.3)	25 (0.3)	89 (0.5)	199 (4.4)
1 most deprived	810 (23.2)	1,722 (23.9)	2,665 (15.6)	319 (7.0)
2	669 (19.2)	1,653 (23.0)	3,002 (17.6)	720 (15.9)
3	756 (21.7)	1,439 (20.0)	3,599 (21.1)	1,050 (23.1)
4	697 (20.0)	1,357 (18.9)	3,843 (22.5)	1,083 (23.9)
5 least deprived	545 (15.6)	1,001 (13.9)	3,882 (22.7)	1,165 (25.7)
Emergency presentation	1,208 (36.7)	2,637 (36.6)	6,228 (36.5)	1,506 (33.2)

Table 5.4 Factors associated with emergency presentation for CRC patients diagnosed in England during the study period (Oct 2006 – Sept 2007). Each patient was allocated a variable to indicate whether they were living in an early adopter, middle year or late adopter PCT. Binary logistic regression established there was no significant difference in the OR for an emergency presentation based on the time PCTs adopted the screening programme.

Variable*	Emergency presentations / total cases (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	p value	OR	CI	p value
Age group (years)							
<60 years	1,440/4,583 (31.4)	1	-	-	1	-	-
60-69 years	1,975/6,719 (29.4)	0.91	0.84-0.99	0.021	0.90	0.83-0.98	0.016
70-79 years	3,087/9,134 (33.8)	1.11	1.03-1.20	0.005	1.08	1.00-1.17	0.068
>79 years	3,585/7,204 (49.8)	2.16	2.00-2.34	<0.001	2.09	1.93-2.27	<0.001
Gender							
Male	5,320/15,437 (34.5)	1	-	-	1	-	-
Female	4,767/12,203 (39.1)	1.22	1.16-1.28	<0.001	1.18	1.12-1.24	<0.001
Co-morbidity groups							
No co-morbidity	5,085/18,760 (27.1)	1	-	-	1	-	-
1 co-morbidity	914/2,067 (44.2)	2.13	1.94-2.34	<0.001	2.02	1.84-2.22	<0.001
≥ 2 co-morbidity	4,088/6,813 (60.0)	4.03	3.81-4.28	<0.001	4.06	3.83-4.31	<0.001
Deprivation							
1 (most deprived)	2,194/5,197 (42.2)	1	-	-	1	-	-
2	2,013/5,324 (37.8)	0.83	0.77-0.90	<0.001	0.80	0.74-0.87	<0.001
3	2,122/5,794 (36.6)	0.79	0.73-0.85	<0.001	0.76	0.70-0.84	<0.001
4	2,012/5,897 (34.1)	0.71	0.66-0.77	<0.001	0.68	0.62-0.73	<0.001
5 (least deprived)	1,746/5,428 (32.2)	0.65	0.60-0.70	<0.001	0.65	0.59-0.70	<0.001
Time screening adopted by PCT							
Early adopter	1,275/3,477 (36.7)	1	-	-	1	-	-
Middle adopter	2,625/7,172 (36.6)	1.00	0.92-1.08	0.945	1.04	0.95-1.14	0.405
Late adopter	6,187/16,991 (36.4)	0.99	0.92-1.07	0.775	1.05	0.97-1.14	0.256

*after removing patients with excluded PCTs and deprivation codes, there were 27,640 patients

5.3.2. Longitudinal studies focusing on the 'middle year' PCTs only

Although in the last section I found no association between 'adopter' status (early, middle or later) and risk of emergency presentation for patients from all the original PCTs, I wanted to explore alternative

ways to reduce the risks of confounding when testing my overall hypothesis. Hence, I undertook a selective analysis for the 7,920 patients living in the 48 PCTs that started screening during the 'middle year' study period (October 2006 – September 2007). This removed patients from the 'early' and 'later' adopter PCTs entirely, thereby focusing on a group of PCTs that began their local programs within a similar time period (i.e. over the course of one year). However, the exact start date for each PCT was spread widely throughout the study year, hence the proportion of the original middle year cohort of patients 'exposed' to screening would vary substantially from one PCT to the next if I applied the same cross-sectional approach to the data as employed in *Chapter 4*. Hence, I conceived a longitudinal study design, whereby I extracted all CRC patients that presented six months before and six months after the LSUD for each PCT (See METHODS, *Figure 5.1*). This allowed comparison of the impact of screening exposure between a "non-exposed" group (six months before LSUD) and an "exposed" group (six months after LSUD) with closely matched populations for each PCT. By limiting the exposure period to only six months after start up, this design would further explore the ***early***, ***'indirect'*** effects of screening on the wider population.

There was no significant difference in patient characteristics between the six month before- versus the six month after-LSUD groups with respect to age, gender, co-morbidity or deprivation (*Table 5.5*). The proportion of CRC patients falling within the screening age group (60-69 yrs) was slightly higher in the 'after' group but this did not reach significance (26.0% [1,056/4,067] vs. 24.1% [928/3,853], p=0.055). Overall, the crude rates of emergency presentation were 37.3% and 35.6%, respectively, representing a 1.7% absolute reduction in rate. Hence, the unadjusted OR for emergency presentation was 0.92 for those diagnosed in the six months after local start-up (0.82 – 1.00, p=0.054). This result is on the borderline of statistical significance (*Figure 5.3*). In *Chapter 4*, the crude rates of emergency admission for cases 'exposed' for ≤6 months versus 'non-exposed' cohorts of cases across all PCTs were 36.4% and 37.1%, respectively (0.7% reduction, p=0.170). Hence, the absolute 'effect' size appears greater in the present study (in which I focus on a more restricted group of PCTs) compared to the original analysis – again, making it less likely that the original association is confounded by differences in baseline quality of services (i.e. 'better care' hypothesis for early adopter PCTs).

Multivariable binary logistic regression analysis yields similar findings to the results in *Chapter 4* in terms of the association between emergency presentation and the basic patient characteristics. Hence, increased OR for emergency presentation was associated with older patients (apart from in the 60-69 year group), females, those with co-morbidity and patients with increasing deprivation. Membership of the 60-69 year group was associated with the lowest OR of 0.82 (0.71-0.96, p<0.05) relative to the comparator group of under 60 year olds, in line with my chapter 4 findings, *Table 5.6*. The adjusted OR for emergency presentation for patients diagnosed in the six months after local start up was 0.92, again just on the borderline of statistical significance (p=0.054). This is similar to the unadjusted odds ratio,

reflecting the fact that the populations of CRC cases in the 'before' versus 'after' cohorts were closely matched in terms of their other characteristics.

5.3.3. Variability in emergency presentation rates across the '48 middle year' PCTs

The funnel plots in *Figures 5.4* and *5.5* show that the number of PCTs at or beyond the curve representing two standard deviations from the mean were very few in number and there were no extreme outliers to skew the overall data. This analysis was undertaken using crude (unadjusted) data, so there is no adjustment for case-mix and hence this funnel plot is not intended for benchmarking purposes but simply to screen for extreme data points. Interestingly, there were fewer PCT outliers with 'high' rates of emergency admission (beyond 2 sd) in the six month period after launch of the local BCSP, compared to the period prior to launch (three versus six PCTs).

Table 5.5 The patient characteristics in the "Before" and "After" LUSD groups (no significant differences).

Patient characteristics	**Total,** N (%)	**"Before" LUSD,** N (%)	**"After" LUSD,** N (%)
Number of cases	7,920	3,853	4,067
Age, mean (sd)	70.5 (12.3)	70.2 (12.4)	70.8 (12.2)
Age groups			
< 60	1,386 (17.5)	727 (18.9)	659 (16.2)
60-69 years	1,984 (25.1)	928 (24.1)	1,056 (26.0)
70 to 79	2,630 (33.2)	1,295 (33.6)	1,335 (32.8)
>79	1,920 (24.2)	903 (23.4)	1,017 (25.9)
Gender			
Male	4,487 (56.7)	2,173 (56.4)	2,314 (56.9)
Female	3,433 (43.3)	1,680 (43.6)	1,753 (43.1)
Co-morbidity groups			
1 (No co-morbidity)	5,361 (67.7)	2,608 (67.7)	2,753 (67.7)
2 (1 co-morbidity)	652 (8.2)	311 (8.1)	341 (8.4)
3 (2 or more co-morbidity)	1,907 (24.1)	934 (24.2)	973 (23.9)
Patient deprivation			
IMD missing	26 (0.3)	14 (0.4)	12 (0.3)
1 (Most deprived)*	1,853 (23.4)	906 (23.5)	947 (23.3)
2	1,849 (23.3)	911 (23.6)	938 (23.1)
3	1,585 (20.0)	766 (19.9)	819 (20.1)
4	1,519 (19.2)	743 (19.3)	776 (19.1)
5 (Least deprived)	1,088 (13.7)	513 (13.3)	575 (14.1)
Emergency presentation	2,884 (36.4)	1,438 (37.3)	1,446 (35.6)*

*P=0.054

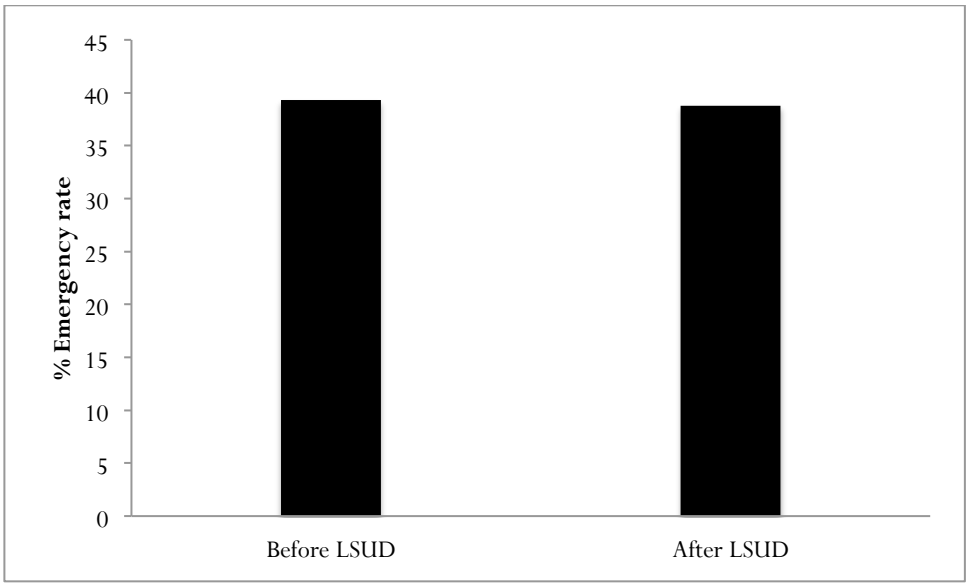


Figure 5.3 Comparison of percentage emergency presentation rates before and after LSUD. There was a 1.7% reduction in the emergency presentation rate between patients presenting before and after the LSUD of screening (this was on the borderline of statistical significance, at p=0.054).

Table 5.6 Binary logistic regression analysis of the patient characteristics associated with emergency presentation in the 48 PCTs starting screening in the middle year. Increasing age, female gender, co-morbidity and deprivation continued to be associated with emergency presentation as was presenting before the LUSD of screening (the latter has p value 0.054).

Variable	Emergency presentations / Total (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	P value	OR	CI	P value
Age group (years)							
<60 years	445/1,377 (32.3)	1	-	-	1	-	-
60-69 years	565/1,975 (28.6)	0.84	0.72-0.97	0.021	0.82	0.71-0.96	0.015
70-79 years	902/2,626 (34.3)	1.10	0.95-1.26	0.196	1.05	0.91-1.22	0.496
>79 years	957/1,915 (50.0)	2.09	1.81-2.42	<0.001	1.95	1.68-2.27	<0.001
Gender							
Male	1,545/4,473 (34.5)	1	-	-	1	-	-
Female	1,324/3,421 (38.7)	1.20	1.09-1.31	<0.001	1.19	1.08-1.32	0.001
Co-morbidity groups							
No co-morbidity	1,426/5,344 (26.7)	1	-	-	1	-	-
1 co-morbidity	319/652 (48.9)	2.63	2.23-3.10	<0.001	2.51	2.12-2.97	<0.001
≥ 2 co-morbidity	1,124/1,898 (59.2)	3.99	3.58-4.45	<0.001	3.97	3.55-4.44	<0.001
Deprivation*							
1 most deprived	751/1,853 (40.5)	1	-	-	1	-	-
2	721/1,849 (39.0)	0.94	0.82-1.07	0.340	0.94	0.81-1.08	0.349
3	588/1,585 (37.1)	0.87	0.75-0.99	0.040	0.88	0.76-1.02	0.096
4	484/1,519 (31.9)	0.69	0.60-0.79	<0.001	0.69	0.60-0.81	<0.001
5 least deprived	325/1,088 (29.9)	0.63	0.53-0.73	<0.001	0.63	0.54-0.75	<0.001
BCSP Exposure							
Before LSUD	1,433/3,839 (37.3)	1	-	-	1	-	-
After LSUD	1,436/4,055 (35.4)	0.92	0.84-1.01	0.077	0.92	0.82-1.00	0.054

*26 patients with missing deprivations scores were excluded

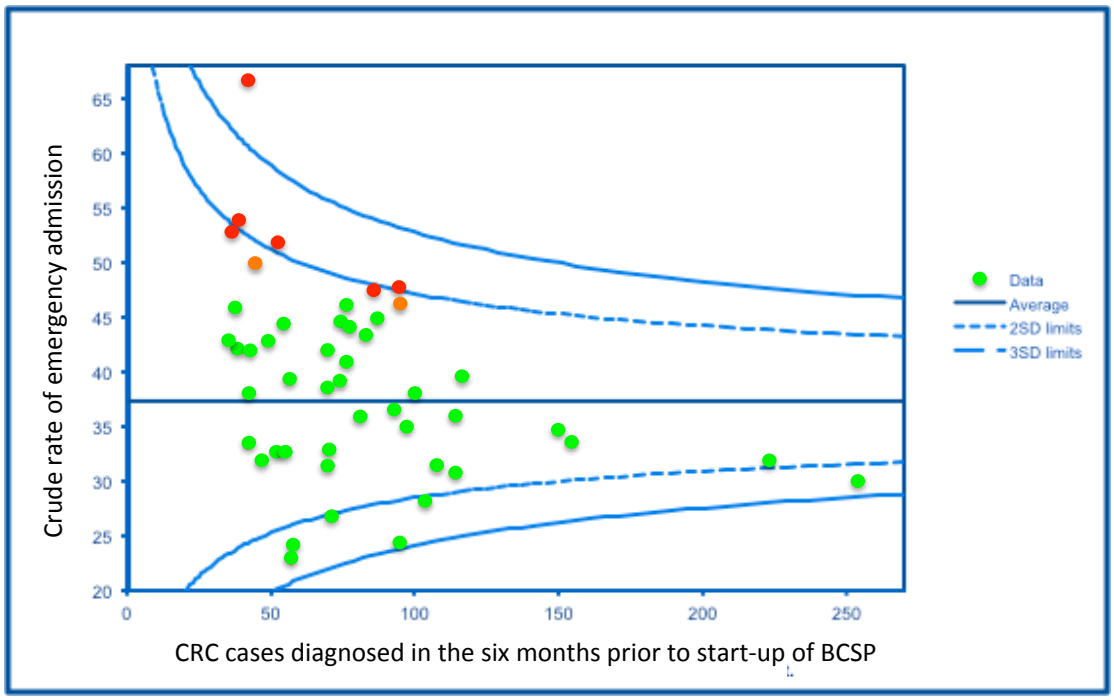


Figure 5.4 Funnel plot of the crude rate of emergency presentations for each of the 48 PCTs that started screening in the middle year: Data for the six-month period before the LSUD of screening.

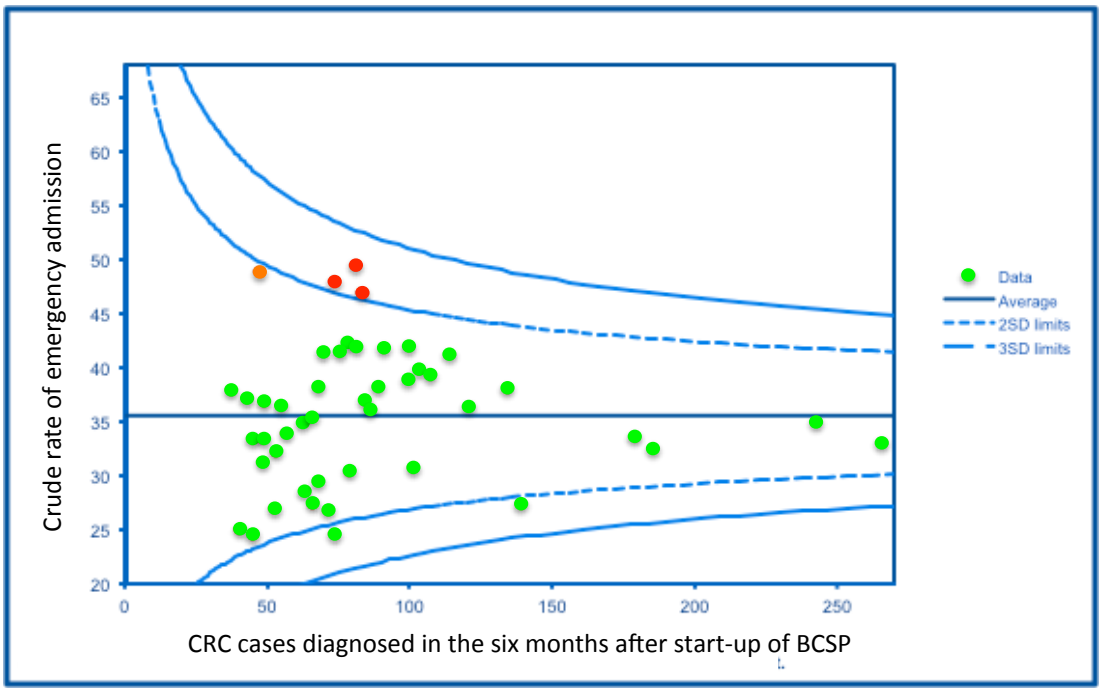


Figure 5.5 Funnel plot of the crude rate of emergency presentations for each of the 48 PCTs that started screening in the middle year: Data for the six month period after the LSUD of screening.

5.3.4. Stratification of data from the 48 'Middle Year' PCTs according to screening age and non-screening age groups

Restricting the analysis to the screening age group (60-69 year olds) showed a significantly lower rate of emergency presentations among patients that presented in the six months after the LSUD (26.4% vs. 31.0%, p=0.025), *Figure 5.6*. Given the two years it takes to roll-out of screening to this age group, this early reduction may reflect an indirect benefit rather than any direct effect of screening. In the non-screening age group, the emergency rate was numerically lower in the group of patients presenting after the LSUD but this difference was not significant (39.3% vs. 38.8%, p=0.670), *Figure 5.7*. These results were comparable to those in *chapter 4*.

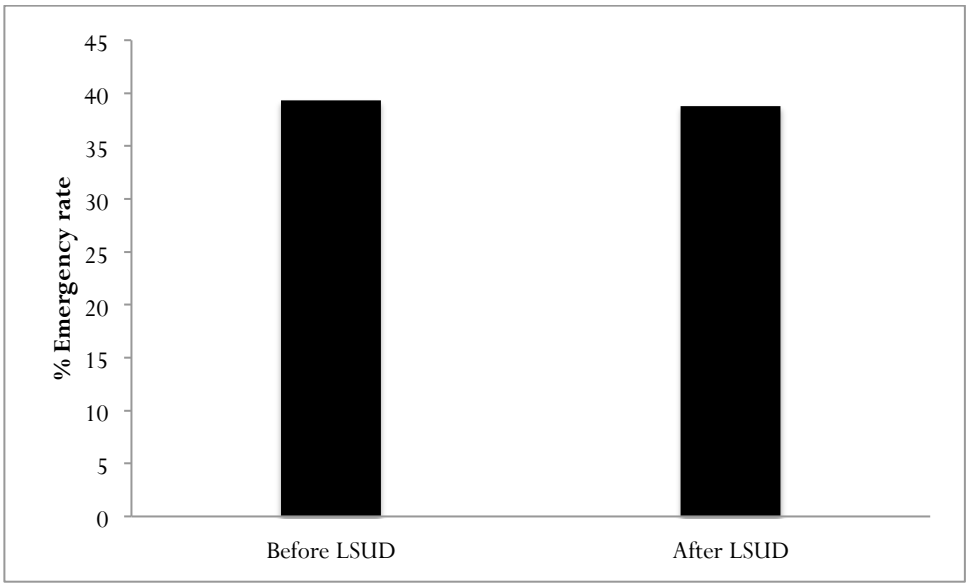


Figure 5.6 Among the 48 PCTs that began screening in the middle year; emergency presentation rate before and after the LSUD among screening age patients (60-69 year olds). Patients presenting within six months of screening starting had a significantly lower emergency presentation rate (p=0.025).

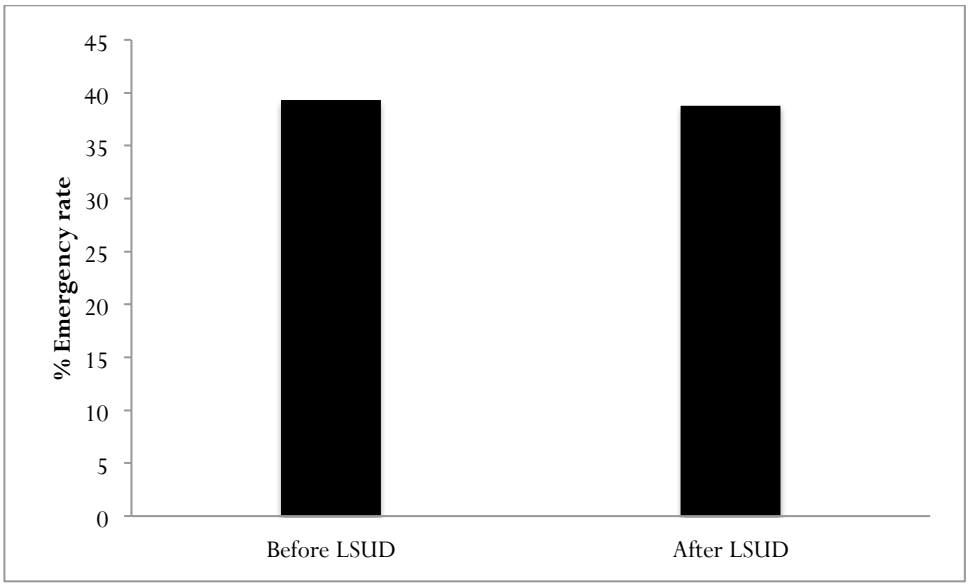


Figure 5.7 Among the 48 PCTs that began screening in the middle year; emergency presentation rate before and after the LSUD among non-screening age patients. Patients presenting within six months of screening starting, had a numerically lower emergency presentation rate but this did not reach significance.

5.3.5. Longitudinal study focusing on the 39 PCTs that started screening in the first six months of the middle year

As a further variation on the study design and inclusion criteria, I examined data for the 39 PCTs that began screening in the first six months of the middle year period. This was to ensure I could include patients diagnosed up to one year after the LSUD. My study of 48 PCTs (above) found a signal to suggest a reduction in rates was apparent within just six months of start-up but at borderline significance ($p=0.054$) and the main effect seen in the screening age population of 60-69 year olds (where p value was significant). The short time scale of observation makes it likely that any 'effects' are early and indirect benefits, rather than resulting from direct impact of screen-detected cancers. However, by extending the observation to 12 months after local launch, I hoped to improve the chance of demonstrating a benefit across the whole population. It was vital to seek evidence to show that people outside the target age group for the BCSP were experiencing a reduction in rate of emergency admission – this would support the notion of a wider population benefit arising from enhanced patient and professional awareness of colon cancer in the immediate wake of a local launch of a screening programme for this condition.

Table 5.7 summarizes the basic patient characteristics of the 'before' and 'after' groups (0-6 months, 6-12 months and combined 0-12 months). The crude rate of emergency presentations was significantly lower in the 6-12 month group, compared with the 'before' (34.1 vs. 38.9%, $p<0.001$), *Table 5.8, Figure 5.8*. Binary logistic regression showed that the adjusted OR for an emergency presentation was

0.86 (CI: 0.76-0.96, p=0.007) for CRC cases diagnosed 6-12 months after their local programme was launched.

In conclusion, this analysis of people living in PCTs that began their screening programs at a very similar time-point shows that risk of emergency presentation among people with CRC is reduced within 6-12 months of local launch. These findings are consistent with the results shown for the full cohort in *Chapter 4*.

Table 5.7 Patient characteristics and rate of emergency presentation for patients living in the 39 PCTs that began screening in the first six months of the middle-year period.

Patient characteristics	**Study cohort, N (%)**	**Before-LSUD, N (%)**	**After (0-6 months), N (%)**	**After (6-12 months), N (%)**	**After (0-12months), N (%)**
Number of cases	8,740	3,117	2,751	2,872	5,623
Age, mean (sd)	70.5 (12.1)	70.1 (12.3)	70.8 (12.1)	70.5 (11.9)	70.7 (12.0)
Age groups					
< 60	1,533 (17.5)	588 (18.9)	460 (16.7)	485 (16.9)	945 (16.8)
60 to 69	2,232 (25.5)	752 (24.1)	716 (26.0)	764 (26.6)	1,480 (26.3)
70 to 79	2,856 (32.7)	1,041 (33.4)	887 (32.2)	928 (32.3)	1,815 (32.3)
>79	2,119 (24.2)	736 (23.6)	688 (25.0)	695 (24.2)	1,383 (24.6)
Gender					
Male	4,919 (56.3)	1,746 (56.0)	1,574 (57.2)	1,599 (55.7)	3,173 (56.4)
Female	3,821 (43.7)	1,371 (44.0)	1,177 (42.8)	1,273 (44.3)	2,450 (43.6)
Co-morbidity groups					
1 (No co-morbidity)	5,967 (68.3)	2,065 (66.2)	1,864 (67.8)	2,038 (71.0)	3,902 (69.4)
2 (1 co-morbidity)	694 (7.9)	251 (8.1)	223 (8.1)	220 (7.7)	443 (7.9)
3 (2 or more co-morbidity)	2,079 (23.8)	801 (25.7)	664 (24.1)	614 (21.4)	1,278 (22.7)
Patient deprivation					
1 (Most deprived)*	2,054 (23.5)	755 (24.2)	645 (23.4)	654 (22.8)	1,299 (23.0)
2	2,035 (23.3)	730 (23.4)	641 (23.3)	664 (23.1)	1,305 (23.1)
3	1,779 (20.4)	627 (20.1)	566 (20.6)	586 (20.4)	1,152 (20.4)
4	1,684 (19.3)	589 (18.9)	523 (19.0)	572 (19.9)	1,095 (19.4)
5 (Least deprived)	1,188 (13.6)	416 (13.3)	376 (13.7)	396 (13.8)	772 (13.7)
Emergency presentation	3,220 (36.8)	1,213 (38.9)	1,029 (37.4)	978 (34.1)	2,007 (35.7)

Table 5.8 A binary logistic regression analysis of the 39 PCTs that began screening in the first six months of the middle-year period. Living in an area where the BCSP had been active for 6-12 months was associated with a significantly reduced odds ratio for emergency presentation.

Variable	Emergency presentations/ total cases (%)	Unadjusted (univariate)			Adjusted (multivariate)		
		OR	CI	P value	OR	CI	P value
Age group (years)							
<60 years	512/1,533 (33.4)	1	-	-	1	-	-
60-69 years	614/2,232 (27.5)	0.76	0.66-0.87	<0.001	0.75	0.64-0.87	<0.001
70-79 years	1,004/2,856 (35.2)	1.08	0.95-1.23	0.244	1.02	0.89-1.18	0.746
>79 years	1,090/2,119 (51.4)	2.11	1.84-2.42	<0.001	1.98	1.71-2.29	<0.001
Gender							
Male	1,724/4,919 (35.0)	1	-	-	1	-	-
Female	1,496/3,821 (39.1)	1.19	1.09-1.30	<0.001	1.16	1.06-1.28	0.002
Co-morbidity groups							
No co-morbidity	1,562/5,967 (26.2)	1	-	-	1	-	-
1 co-morbidity	337/694 (48.6)	2.66	2.27-3.12	<0.001	2.49	2.11-2.93	<0.001
≥ 2 co-morbidity	1,321/2,079 (63.5)	4.92	4.42-5.47	<0.001	4.85	4.35-5.41	<0.001
Deprivation							
1 (most deprived)	703/1,700 (41.4)	1	-	-	1	-	-
2	746/1,896 (39.3)	0.87	0.77-0.98	0.027	0.88	0.76-1.00	0.053
3	652/1,740 (37.5)	0.84	0.74-0.96	0.008	0.91	0.79-1.04	0.167
4	614/1,797 (34.2)	0.67	0.58-0.77	<0.001	0.69	0.60-0.80	<0.001
5 (least deprived)	505/1,605 (31.5)	0.66	0.57-0.77	<0.001	0.69	0.59-0.81	<0.001
BCSP Exposure							
Before-LSUD	1,213/3,117 (38.9)	1	-	-	1	-	-
After (0-6 months)	1,029/2,751 (37.4)	0.94	0.84-1.04	0.235	0.95	0.85-1.07	0.393
After (6-12 months)	978/2,872 (34.1)	0.81	0.73-0.90	<0.001	**0.86**	0.76-0.96	**0.007**

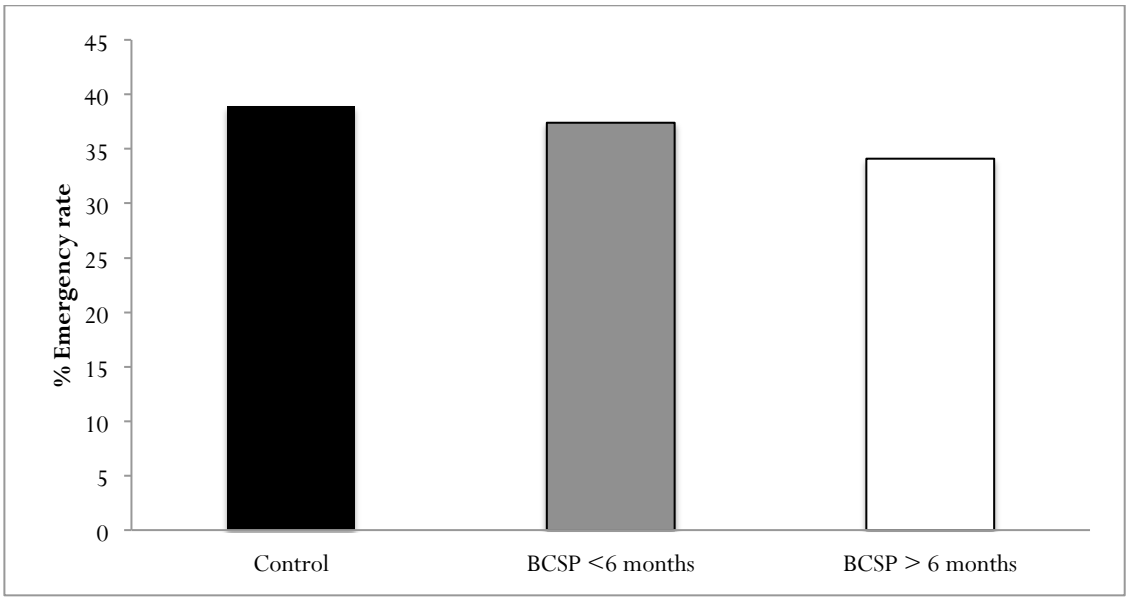


Figure 5.8 In the 39 PCTs that began screening in the first six months of the middle-year period, longer exposure to the BCSP, was associated with an incremental reduction in the emergency rate.

Compared to the six month period before the local start-up of screening, the proportion of total CRC cases that were of screening age (60-69 years) during the year after was greater (24.1% [752/2,365] vs. 26.3% [1,480/4,143], p=0.024). These findings were comparable to the results in *Chapter 4*. Given the PCT populations are matched within the longitudinal study design, this finding suggests a small rise in the age-specific incidence rate of CRC for people of screening age. Some of this increase could reflect additional cases due to screen-detected symptomless cancers in the population. However, it might also reflect the fact that this age group would be more likely to seek early medical attention for symptomatic cancers since they were targeted for information about screening.

5.3.6. Stratification of data from the 39 PCTs according to screening age and non-screening age groups

Among screening age patients (60-69 years), the emergency rate was 31.3% in the 'before' LSUD group, 28.5% in the 0-6 month 'after' group and 23.0% in the 6-12 month 'after' group, *Figure 5.9*. The cumulative risk reduction was 8.3%. In the non-screening age group the emergency rate was 41.4% in the 'before' LSUD group, 40.8% in the 0-6 month 'after' group and 38.2% in the 6-12 month 'after' group. The cumulative risk reduction was 3.2%. Amongst screening age patients, there was a significant difference in the emergency rates between the before LSUD group and the 6-12 month group (p<0.001), in the non-screening age group there was also a significant difference (p=0.030). In order to support my hypothesis of an 'early, indirect' benefit to the general population, I required evidence to suggest that the launch of the screening programme resulted in a risk reduction following only a short period of exposure (i.e. "early effect") and from patients not exposed directly to screening by virtue of age group (i.e. "indirect effect").

There was no overall risk reduction for people living in an area where a programme had been active for 0-6 months (OR 0.95, p=0.393). Given that it takes 2 years to roll-out the BCSP, this time period is certainly too short to see any direct effect from screening and it may be too soon to have detected indirect benefits across the whole population. There may have been an effect within this very short time period but my study may have been underpowered to detect it. It seems reasonable for the 6-12 month period following start-up of BCSP to be regarded as 'early' in the course of a local program, since only half of eligible 60-69 year olds in the area would have been targeted directly by the programme at the end of year one. Overall, patients diagnosed during this period did exhibit a reduction in risk of emergency presentation, with an OR of 0.86 (p=0.007), *Table 5.8*. This provides evidence of an "early effect".

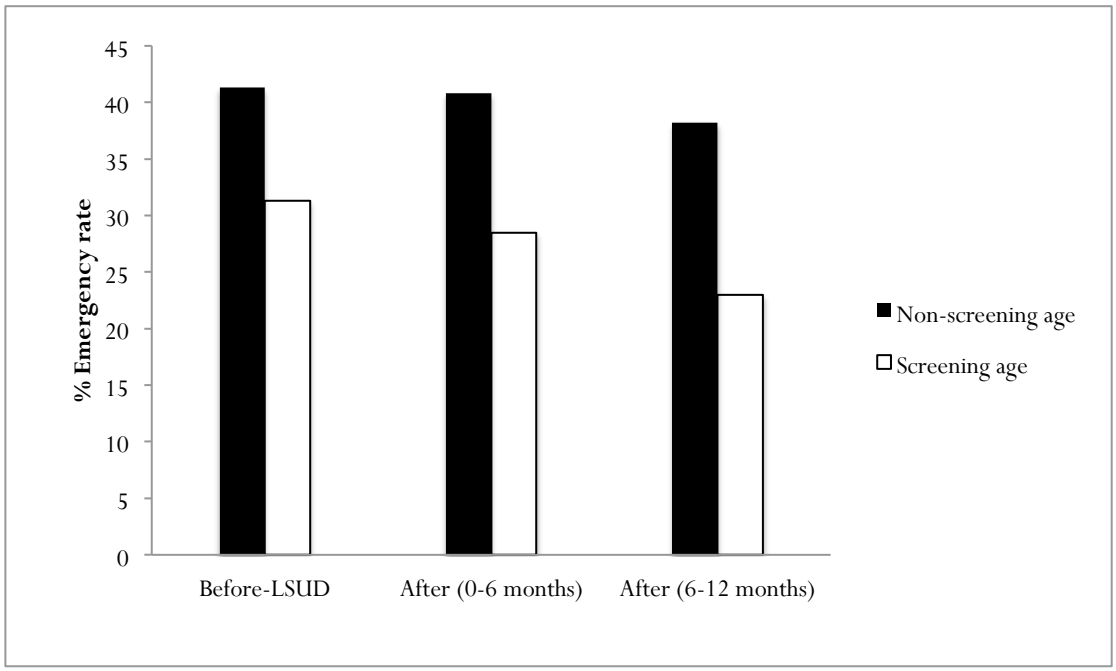


Figure 5.9 Patients belonging to the 39 PCTs that began screening in the first six months of the middle year screening. More than six months exposure was associated with a significant reduction in the risk of emergency presentation for screening age (p<0.001) and non-screening age patients (p=0.030).

5.3.7. Study of trends in colonoscopy volume and rate

This section presents data on the overall volume of colonoscopy in the period when the screening programme was introduced, examining the 48 PCTs that began screening in the middle year. By focusing on colonoscopy activity in the six month periods either side of local start-up for each individual PCT, the populations from which the patients are drawn are assumed to be identical. Hence the pooled results can be expressed as total numbers or crude rates without the need to standardize for potential differences in sociodemographics.

5.3.7.1. Changes in colonoscopy volume in the six months either side of the introduction of screening

I was interested to determine whether there was any change in colonoscopy activity between the six month period before and the six months immediately after the start up of local screening. Within the 48 PCTs that began screening in the middle year, there were 11,128,234 residents aged over 16 years. Of these 49.8% (n=5,542,805) were male and 50.2% (n=5,585,429) were female. The age distribution of the population is shown in *Figure 5.10*. In the period spanning six months either side of each of the 48 PCTs local start up date, a total of 62,152 colonoscopies were performed. The mean age of patients having a colonoscopy was 58.4 years, with almost half (47.5%) performed on patients under 60 years. A total of 53.8% of colonoscopies were performed on females. The most deprived quintile of the population had the lowest share of colonoscopies at 12.8% and this did not change between the before and after LSUD groups, *Table 5.9*.

The total number of day case colonoscopies performed in this population during the six month period before local start-up of the screening programme was 30,347, rising to 31,805 for the six months after (an overall increase of 1,458 procedures, or 4.8%, from baseline). This represents an increase in the overall crude rate of colonoscopy from 5.4 to 5.8 per 1,000 population over the year. The sociodemographic structure of the population is assumed to be stable over a one year period, hence crude rates suffice for studying overall trends. As shown in *Table 5.9*, there was an increase in total day case colonoscopy numbers for all age groups except 70-79 year olds. Although the greatest percentage rise was seen among the 60-69 year old population (8.8%), there was an increase for those under 60 years of 5%. The latter suggests that there was an early rise in elective investigations for lower GI problems among the wider population following start-up of screening – perhaps as a result of increased referrals and consistent with some indirect benefits for the non-screened, symptomatic population.

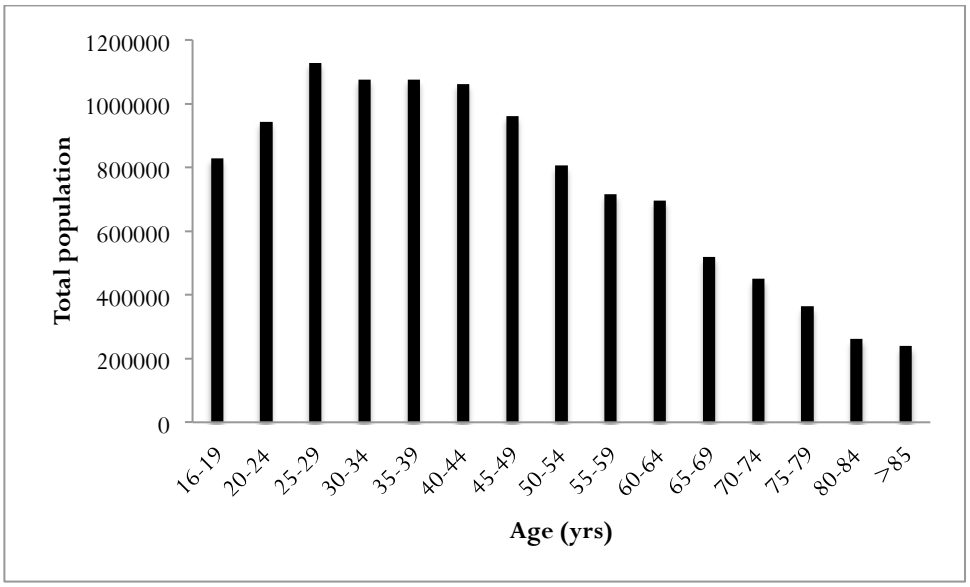


Figure 5.10 The age distribution of the resident population of the 48 middle year PCTs.

Table 5.9 The characteristics of the 62,152 patients having a colonoscopy in the 6 months before and after the LSUD of screening in the 48 PCTs in the middle year group.

Patient characteristics	**Total,** N (%)	**Before LSUD** N (%)	**After LSUD** N (%)
Number of cases	62,152	30,037	31,805
Age, mean (sd)	58.4 (15.9)	58.5 (15.9)	58.3 (15.8)
Age groups			
< 60	29,532 (47.5)	14,397 (47.4)	15,135 (47.6)
60-69	15,946 (25.7)	7,636 (25.2)	8,310 (26.1)
70 to 79	12,061 (19.4)	6,038 (19.9)	6,023 (18.9)
>79	4,613 (7.4)	2,276 (7.5)	2,337 (7.3)
Gender			
Male	28,735 (46.2)	13,946 (46.0)	14,789 (46.5)
Female	33,417 (53.8)	16,401 (54.0)	17,016 (53.5)
Patient deprivation			
Missing IMD	110 (0.2)	48 (0.2)	62 (0.2)
1 (Most deprived)*	15,379 (24.7)	7,614 (25.1)	7,765 (24.4)
2	14,583 (23.5)	7,147 (23.6)	7,436 (23.4)
3	12,508 (20.1)	6,058 (20.0)	6,450 (20.3)
4	11,600 (18.7)	5,592 (18.4)	6,008 (18.9)
5 (Least deprived)	7,972 (12.8)	3,888 (12.8)	4,084 (12.8)

5.4. Discussion

5.4.1. Overview

Chapter 5 has presented evidence to support the key findings of *Chapter 4*, namely that the introduction of the BCSP programme was associated with early, population-wide benefit. These supplementary studies were designed to exclude potential sources of bias or confounding in the original work reported in *Chapter 4*. I have shown that the proportion of CRC cases presenting as an emergency was reduced within 6-12 months of local launch, both for people of screening age and (crucially for my hypothesis) for people outside the target age group for the BCSP. These findings were unlikely to have resulted from confounding due to major differences in the availability or quality of services between PCTs that rolled out screening at different times (I found no evidence to support the 'better care hypothesis'), nor from data quality issues (I found no extreme outliers among PCTs included in the study).

The mechanism for this reduction cannot be determined in my studies, although I have shown a short term increase in elective day case colonoscopy activity across most age groups – suggesting a rise in the number of people being referred for elective investigation. This 4.8% increase (in particular in the non-screening age) could be caused by:

(a) An increase in the number people presenting to their doctor for investigation [indirect benefit of screening – enhanced public awareness]

(b) A lower threshold for referring people for colonoscopy [indirect benefit of screening – enhanced professional awareness]

(c) A period of increased capacity and reduced waiting times, so that people already waiting for colonoscopies are getting them done more quickly [indirect benefit of screening programme – expanded colonoscopy services]

Whichever factor is dominant there is a real increase in numbers of colonoscopies per unit time, which could imply extra capacity or extra referrals. Either of these is a positive way that the launch of the programme led to benefits.

Heightened public and professional awareness of CRC should increase the likelihood of symptomatic patients consulting their GP for medical advice and being referred promptly for investigation. The observation that patients in the screening age group had the greatest reduction in risk of emergency presentation is predictable, since some of the elective diagnoses will have been screen-detected cancers. It is not possible within HES data to identify CRC cases diagnosed in symptomless individuals as a direct consequence of the screening programme. However, within the first year of the BCSP, only half of all 60-69 years old would be invited for screening, 57% will have responded and only 2% of these will test positive on FOBT. Of those invited for a colonoscopy, 88% attend, and of these 9% will be diagnosed with CRC. In total, for the 1,215,911 screening age subjects in the 48 PCTs, an estimated 608 CRCs would be identified. Instead people in the 60-69 year old age group are likely to have benefitted both from the direct effect of screening and from indirect effects of raised awareness. It has been reported that many supposedly asymptomatic patients undergoing screening in fact report that they had experienced large bowel symptoms before enrollment (339) – we do not know whether some people of screening age opted to consult their GP rather than participate in screening.

My work has suggested that the introduction of the NHS BSCP resulted in indirect benefits to the whole population at risk of CRC – a phenomenon not previously described. The evidence for this relates to demonstrating early reductions in risk of emergency admission (before a major direct impact of screening might be expected) and by showing benefits extending to people outside of screening age. Ideally, future work would identify which cases were, and were not, diagnosed through the screening programme(73) and to thereby identify the relative contributions of the direct and indirect effect of screening. This could then lead to further work to identify ways of improving both of these effects by: a) finding ways of improving the direct effect of screening, such as ways of increasing screening uptake (i.e. reaching populations which have a low uptake rate such as the deprived and those living in London) and b) to look at ways to improve the existing FOBt screening test (for a further explanation of this see chapter 6) and other changes to the screening programme such as Flexi-scope trial (a one-off flexible sigmoidoscopy offered to patients at or around their 55th birthday) and also extending access to

screening up to the age of 75 years. There is also a need to introduce new and improved stool based tests such as the Faecal Immunochemical Test (FIT) and, in the future, DNA tests, c) conducting research to build up our understanding of how the indirect effect of screening can be best utilised to increase awareness and reduce barriers to patient presentation to health care professionals. This needs to include looking at how to improve health-related behaviour in hard to reach populations. Further, it will be important to ensure that professionals rapidly refer patients for the best diagnostic test (in the majority of cases, a colonoscopy). This is more difficult research and to date what work that has been done has been largely qualitative with short term follow-up(340). However, the results from my thesis strongly point to the importance of the BCSP as a way of reducing later-presenting CRC that is also, potentially, very cost-effective. Work such as the 'Be clear on cancer' campaigns have already been shown that CRC awareness can be increased within a population, the problem being that the impact appeared to be short lived (341,342), Therefore, while individual advertising campaigns may affect public awareness only in the short-term, one potential advantage of the BCSP is that, because patients are continually invited to screening, then awareness is continually reinforced in communities containing patients of the screening age. My results showing that the crude rate of colonoscopy increased very quickly after screening began. This suggests more work is required to identify whether populations with higher rates of colonoscopy (more opportunistic screening) have better outcomes.

As with any screening programme the proof of success lies in a reduction in 'all cause mortality' (as well as CRC-specific mortality) and a positive effect on screened and non-screened patients. It is also essential to identify interventions to reduce inequalities based on deprivation and ways to increase CRC awareness in these areas.

5.4.2. Conclusion

In summary, in this thesis I have described methodological work to enhance the value and improve the clinical validity of metrics of cancer care based on HES data. I applied clinical logic to overcome limitations of this administrative data source – for example, the lack of a date of diagnosis and the failure to record a cancer code at the time of initial clinical presentation. This has allowed a real world ecological level study to be conducted. In exploring the application of my metric of care (emergency admission during the diagnostic pathway), I have been able to suggest for the first time in a national study that there is an early and population-wide benefit arising from the introduction of the BCSP. That the BCSP affects not only individuals targeted for screening, but also the whole population by virtue of heightened public and professional awareness, suggests that the overall benefits of the programme may exceed those predicted from data relating to expected numbers of screen-detected cancers (i.e. benefits from earlier cancer diagnosis in symptomless people) and polyps (i.e. benefits from reducing future cancer risk in screened individuals without cancer). Further longer term work would be needed to establish the time course for any indirect benefits, although I expect most of the impact on the general

population would be during the first 1-2 years of the programme. Finding ways to sustain or improve upon the wider benefits of screening programmes could be a focus of future research.

In the next chapter, I report a parallel research project in which I explored potential ways to maximize the direct benefits of the screening programme through optimizing the interpretation of the faecal occult blood screening test employed in the UK BCSP.

Chapter 6 - Optimising faecal occult blood screening – retrospective analysis of NHS Bowel Cancer Screening data to improve the screening algorithm

6.1. Abstract

Background: Colorectal neoplasia causes bleeding, enabling detection using Faecal Occult Blood tests (FOBt). The NHS Bowel Cancer Screening Programme (BCSP) guaiac-based FOBt (gFOBt) kits contain 6 sample windows (or 'spots') and each kit returns either a positive, unclear or negative result. Test kits with 5 or 6 positive windows are termed "abnormal" and the subject is referred for further investigation, usually colonoscopy. If 1-4 windows are positive, the result is initially "unclear" and up to two further kits are submitted; further positivity leads to colonoscopy ("weak positive"). If no further blood is detected, the test is deemed "normal" and subjects are tested again in two years' time. I studied the association between Spot Positivity % (SP%) and neoplasia.

Methods: Subjects in the Southern Hub completing the first of two consecutive episodes between April 2009 and March 2011 were studied. Each episode included up to three kits and a maximum of 18 windows (spots). For each positivity combination, the percentage of positive spots out of the total number of spots completed by an individual in a single screening episode was derived and named 'Spot Positivity %' (SP%). Fifty-five combinations of Spot Positivity can occur if the position of positive/negative spots on the same test card is ignored.

The proportion of individuals for whom neoplasia was identified in Episode 2 was derived for each of the 55 spot combinations. In addition, the Episode 1 spot pattern was analysed for subjects with cancer detected in Episode 2.

Results: During Episode 2, 284,261 subjects completed gFOBT screening and colonoscopies were performed on 3,891 (1.4%) subjects. At colonoscopy, cancer was detected in 7.4% (n=286) and a further 39.8% (n=1,550) had adenomas. Cancer was detected in 21.3% of subjects with an abnormal first kit (5 or 6 positive spots) and in 5.9% of those with a weak positive test result.

The proportion of cancers detected was positively correlated with SP%, with an R^2 correlation (linear) of 0.89. As the SP% increased from 11-100%, so the CRC detection rate increased from 4-25%. At the lower SP%s, from 11-25%, the CRC risk was relatively static at approximately 4%. Above an SP% of 25%, every 10-percentage points increase in the SP%, was associated with an increase in cancer detection of 2.5%.

Conclusion: This study demonstrated a strong correlation between SP% and cancer detection within the NHS BCSP. At the population level, subjects' cancer risk ranged from 4-25% and correlated with the gFOBt spot pattern.

Some subjects with an SP% of 11% proceed to colonoscopy, while others with an SP% of 22% do not. Colonoscopy on patients with four positive spots in kit 1 (SP% 22%) would, I estimate, detect cancer in approximately 4% of cases and increase overall colonoscopy volume by 6%. This study also demonstrated how screening programme data could be used to guide its on going implementation and inform other programmes.

6.2. Introduction

Colorectal cancer (CRC) is the second most common cancer in the United Kingdom, accounting for 41,000 new cases and about 16,000 deaths every year(2,27,143). In the United Kingdom, the 5-year survival for CRC is around 54%, which is significantly lower than countries with comparable wealth. In Australia 66% of cases are alive at five years and in Sweden 63%(2,9,27,183,184). The reason for this relatively poor survival is the late presentation of advanced stage cancer, which reduces the chance of curative treatment(27,143). The principle of bowel cancer screening is to detect cancer at a pre-symptomatic stage, leading to earlier diagnosis and improved clinical outcome(183,184). Screening also enables the detection and excision of adenomas, thereby reducing CRC risk.

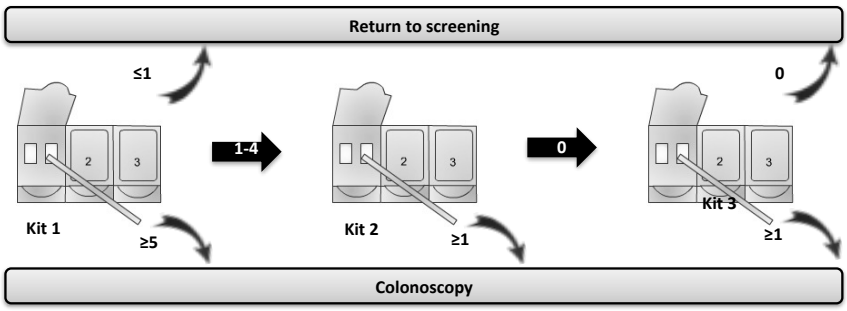
Following a review of all screening options, the National Health Service (NHS) adopted a guaiac-based faecal occult blood test (gFOBt) screening programme. The NHS Bowel Cancer Screening Programme (BCSP) in England began offering biennial gFOBt screening to men and women aged 60–69 years (approximately 10% of the population) in July 2006. The phased roll-out achieved national coverage in January 2010 and from 2008 the screening age range was extended to 74 years. An early analysis of the first 2.1 million subjects invited to screening showed an uptake of 55-60%. Of all subjects tested, 2% were gFOBt positive and 8% had cancer(2,185). From its inception to the end of May 2014, the BCSP had diagnosed 19,045 cancers (personal communication BCSP National Office), with a higher proportion of Dukes' A cancers compared with non-screened patients (35% vs. 13%)(2,9,27,73,185). Currently 3% of patients with CRC are diagnosed through the NHS BCSP (2,73) and is comparable to that reported for countries with similar health systems(2,9,27,74,143).

The BCSP uses the gFOBt (hema-screen; Immunostics, New Jersey, USA), which is designed to identify subjects at risk of colonic neoplasia by detecting intraluminal bleeding from vascularised CRCs and adenomas. The degree of blood loss is related to the size, stage and site of the neoplasia(27,143,186). Subjects perform the test at home by placing in turn two faecal samples from each of three separate stool sample onto a card with a total of six windows. The gFOBt test uses the pseudoperoxidase activity of

haem (from haemoglobin) to release oxygen from hydrogen peroxide and convert colourless guaiac, impregnated in the test card, to a blue colour(183,184,187).

The BCSP in England is co-ordinated by five regional Hubs; screening kits are returned to an accredited Hub laboratory where stool samples applied to all six windows are analysed by a manual qualitative process. A kit is reported as 'normal' if none of the six windows (spots) is positive. A kit with five or six positive spots is designated 'abnormal' and further investigation, usually colonoscopy, is recommended. A kit with between one and four positive spots is considered 'unclear' and a second kit is sent out to the subject. If the second kit result is normal, a third kit is sent out. If either the second or third kits contain one or more positive spots then the outcome is described as 'weak positive' and colonoscopy is recommended. Following an unclear result in kit one, if both kits are normal then patients are returned to the screening programme for repeat testing in two years' time, *Figure 6.1*.

Subjects with abnormal and weak positive test results are referred for colonoscopy. If this is normal the subject is returned to the screening programme for a repeat gFOBt in two years' time. Subjects diagnosed with CRC are referred to their local CRC multidisciplinary team (MDT). If polyps or adenomas are found then surveillance follows the British Society of Gastroenterology (BSG) guidelines(2,27,143,185,188).



This sequence gives 55 possible combinations:

Number of combinations				
	1	4	48	2
Description	• Normal	• Kit 1 unclear • Kit 2/3 –ve	• Kit 1 unclear • Kit 2/3 +ve	• Abnormal
SP%	0%	6-22%	11-83%	83-100%
Outcome	Screening	Screening	Colonoscopy	Colonoscopy

Figure 6.1 This flowchart demonstrates how the different positivity patterns generated by the three kits create 55 positivity combinations. The BCSP algorithm deals with these combinations differently depending on the spot pattern and SP%. There were subjects with an unclear kit one and normal results in kits two and three that are returned to the screening programme with a higher SP% than some weak positive combinations leading to colonoscopy. These weak positive combinations derive from an unclear result in kit one followed by some positive spots in either kit two or three.

6.3. Aims

- To determine the risk of a CRC or adenoma from the gFOBt positivity patterns, using a novel method based on spot positivity % (SP%).
- To determine if the current spot positivity algorithm can be improved to enable more effective use of a limited colonoscopy resource.

6.4. Methods

The Bowel Cancer Screening System (BCSS) database was used to identify all individuals from the BCSP Southern Hub with two consecutive episodes of 'adequate screening'. ('Adequate screening' is defined as a definitive normal or abnormal screening test result). Episode 1 occurred between April 2009 and March 2011 and is referred to as the 'prevalent' round or first screen, Episode 2 refers to the next round or first 'incident' round of screening.

Each test kit was coded with six-digit combinations of N (for negative test spot) or P (for a positive test spot). During the course of an 'adequately screened' episode up to three kits may be returned, each with six spots, providing a maximum of 18 spot results per episode. Overall there were 55 individual spot combinations that map all the potential negative or positive results in the kits. For all combinations in episode 2 that refer participants for colonoscopy, I recorded both CRC and adenoma detection rates. The Programme currently records gFOBt outcomes as abnormal, weak positive or normal. In this study we used a new method of describing the gFOBt spot positivity variable called the 'Spot Positivity percentage' (SP%). The SP% was calculated for each of the 55 combinations by dividing the number of positive spots by the total number of spots returned during a single screening episode. For example, currently a participant with a normal result has 0/6 positive spots or an SP% of 0%. A participant with an abnormal result from having 5/6 positive spots has an SP% of 83%, while a weak positive result of 4/6, 0/6 and 1/6 has a total of 5 positive spots out of a total of 18 or therefore has an SP% of 28%.

For this study individuals with designated abnormal (SP% range from 83-100%) or weak positive (SP% range from 11-83%) results were referred to colonoscopy. Subjects with an unclear kit and one result followed by a normal kit two and three, had SP%s of 6-22% and were returned to the screening programme, *Figure 6.1*. To investigate the possibility that neoplasia in individuals not currently referred for colonoscopy in Episode 1 could be missed, spot positivity patterns at Episode 1 were analysed for individuals with cancer diagnosed at Episode 2.

The statistical analysis was conducted on anonymised data provided by the BCSP Southern Hub. No ethical approval was necessary. Patients scheduled for colonoscopy were consented following NHS guidelines.

SPSS (version 20.0; SPSS Inc., Chicago, Illinois, USA) was used for descriptive, chi-squared, linear and LOESS (Locally weighted scatterpoint smoothing) non-linear regression analysis.

6.5. Results

I studied 284,261 individuals with a mean age at episode 1 of 63.8 years (sd 2.9); female subjects accounted for 54.2% (n=154,085) of the total, *Table 6.1*. Men (1.7% [2,193 /130,176]) were more likely to have a gFOBt spot positivity pattern leading to a colonoscopy than females (1.1% [1,698/154,085]).

In episode 2, 3,891 (1.4%) individuals had a colonoscopy; 286 (7.4%) were diagnosed with CRC, 7.5% had high-risk, 13.1% intermediate-risk and 19.2% low-risk adenomas, *Table 6.2.* Overall, 47.2% of episode 2 colonoscopies identified neoplasia.

Table 6.1 Demographic variables; including gender and age groups and the immediate outcomes following screening for Episode 2. In total, 1.4% of subjects underwent colonoscopy.

Variable	Episode 2, No. (%)
Number	284,261
Gender	
Male	130,176 (45.8)
Female	154,085 (54.2)
Age group	
< 60yrs	0
60-61yrs	16 (0.0)
62-63yrs	50,801 (17.9)
64-65yrs	62,946 (22.1)
66-67yrs	60,104 (21.1)
68-69yrs	55,225 (19.4)
≥ 70yrs	55,169 (19.4)
Screening outcome	
Colonoscopy	3,891 (1.4)
Not screened*	1,272 (0.4)
Other diagnostic test	122 (0)
Returned to screening	278,976 (98.1)

*This corresponds to the lost to follow up.

6.5.1. Colonoscopy findings based on the gFOBt result; abnormal vs. weak positive

In episode 2, 90.6% (3,525/3,891) of colonoscopies were performed following a 'weak positive' result, the remaining 9.4% (366/3,891) followed 'abnormal' results. CRC was detected more frequently in colonoscopies performed following an abnormal gFOBt result (21.3% vs. 5.9%, $p<0.001$). There was no significant difference in the detection rate for all neoplasia (CRC and adenomas) between 'abnormal' and 'weak positive' gFOBt results (51.9% vs. 46.7%, $p=0.06$), which reflected the similar detection rates for adenomas between abnormal and weak positive gFOBt results, *Table 6.2*.

Table 6.2 The number of CRC and adenomas detected following colonoscopy in Episode 2 and split depending on whether the gFOBt result was Abnormal or Weak positive.

Episode 2		Total (n=3,891), No (%)	Abnormal (n=366), No (%)	Weak positive (n=3,525), No (%)	p value
Cancer		286 (7.4)	78 (21.3)	208 (5.9)	<0.001
Adenomas	High Risk	290 (7.5)	20 (5.5)	270 (7.7)	p=0.13
	Intermediate risk	511 (13.1)	33 (9.0)	478 (13.6)	p=0.01
	Low risk	749 (19.2)	59 (16.1)	690 (19.6)	p=0.10
All neoplasia		1,836 (47.2)	190 (51.9)	1,646 (46.7)	p=0.06
Normal		2,055 (52.8)	176 (48.1)	1,879 (53.3)	

6.5.2. CRC risk based on the Spot Positivity percentages (SP%)

There were 16 separate SP%s which ranged from 11-100% and led to a colonoscopy referral. The SP% of 17% was the most common, accounting for 21.8% of colonoscopies. Consistent with the finding that most colonoscopies are performed after weak positive gFOBts, SP%s of ≤25% accounted for 53.1% of all colonoscopies performed, *Table 6.3*.

Increasing SP% was associated with an increase in the CRC detection rate. In episode 2, at an SP% of 11%, the CRC detection rate was 4.2%. At an SP% of 100%, CRC detection had increased to 24.5%, *Figure 6.2*. Between the two extremes, the CRC detection rate broadly increased linearly with an R^2 correlation (linear) of 0.89.

Table 6.3 The frequency of colonoscopies performed for the different Spot Positivity percentages (SP%). The cumulative column showed that SP%s less than or equal to 25% accounted for 53.1% of all colonoscopies.

SP% (Episode 2)	No (%)	Cumulative, No (%)
11%	286 (7.4)	286 (7.4)
17%	847 (21.8)	1,133 (29.1)
22%	241 (6.2)	1,374 (35.3)
25%	693 (17.8)	2,067 (53.1)
28%	106 (2.7)	2,173 (55.8)
33%	564 (14.5)	2,737 (70.3)
39%	21 (0.5)	2,758 (70.9)
42%	289 (7.4)	3,047 (78.3)
44%	9 (0.2)	3,056 (78.5)
50%	230 (5.9)	3,286 (84.5)
56%	0 (0)	3,286 (84.5)
58%	121 (3.1)	3,407 (87.6)
67%	68 (1.7)	3,475 (89.3)
75%	32 (0.8)	3,507 (90.1)
83%	176 (4.5)	3,683 (94.7)
100%	208 (5.3)	3,891 (100)

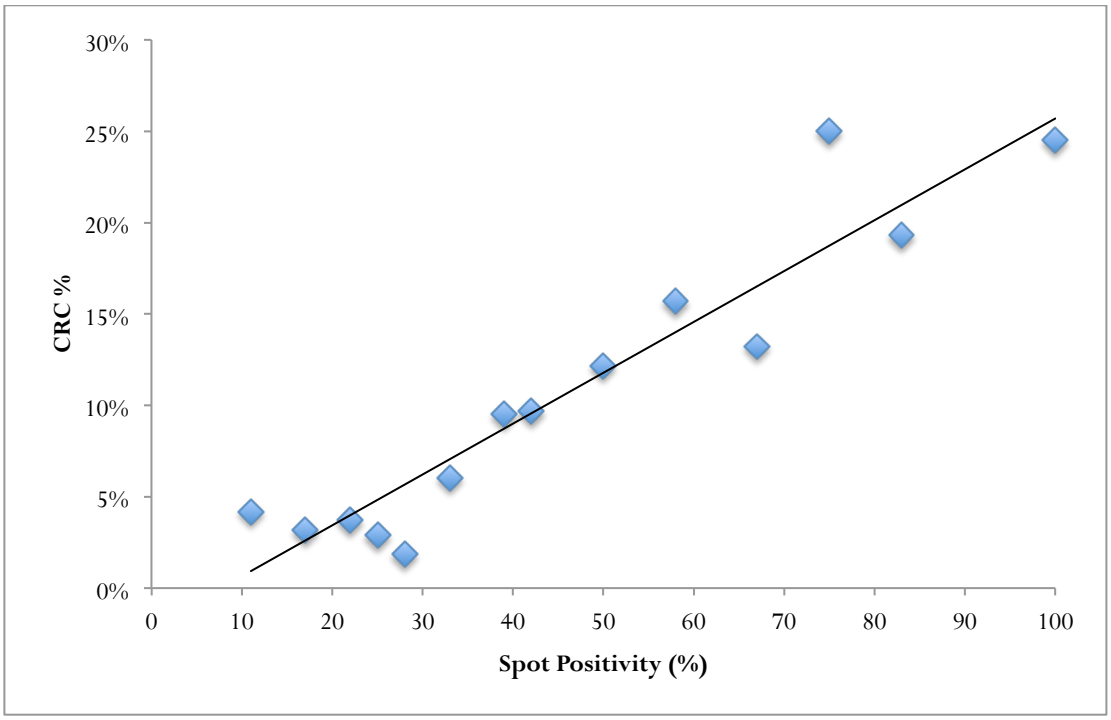


Figure 6.2 Correlation between Spot Positivity (SP%) and CRC detection rate (%) for gFOBT screening (Episode 2 of the BCSP, incident round). There is a linear relationship with $R^2 = 0.89$ ($p<0.01$).

A LOESS (Locally weighted scatterpoint smoothing) curve for non-linear regression modelled the risk of CRC at different SP%s, *Figure 6.3*. At low SP%s, of 11-25%, the CRC risk was approximately 4%. Within this range, lies the spot positivity pattern 4-0-0 (created by 4 positive spots in kit one and normal results for kits two and three), with an SP% of 22%. Subjects with this pattern are currently not referred for colonoscopy. Above an SP% of 25%, the CRC detection began to increase almost linearly; for every 10 percentage points increase in SP%, the CRC detection rate increased by 2.5%, *Figure 6.3*.

The gFOBt positive patterns have 55 combinations and include combinations that have 'unclear' in kit one followed by two normal kits (n=4). These combinations had SP% rates of 6-22% and are all currently returned for screening after two years, while the 48 combinations that are unclear in kit one and then contained one or more positive spots in either kit two or three (weak positives) had SP%s of 11-83% and are all currently offered colonoscopy. There was one combination in the 'unclear then normal group' with an SP% the same or higher than combinations in the unclear then positive group. This combination was 4-0-0 gFOBt and has an SP% of 22%, *Figure 6.3*.

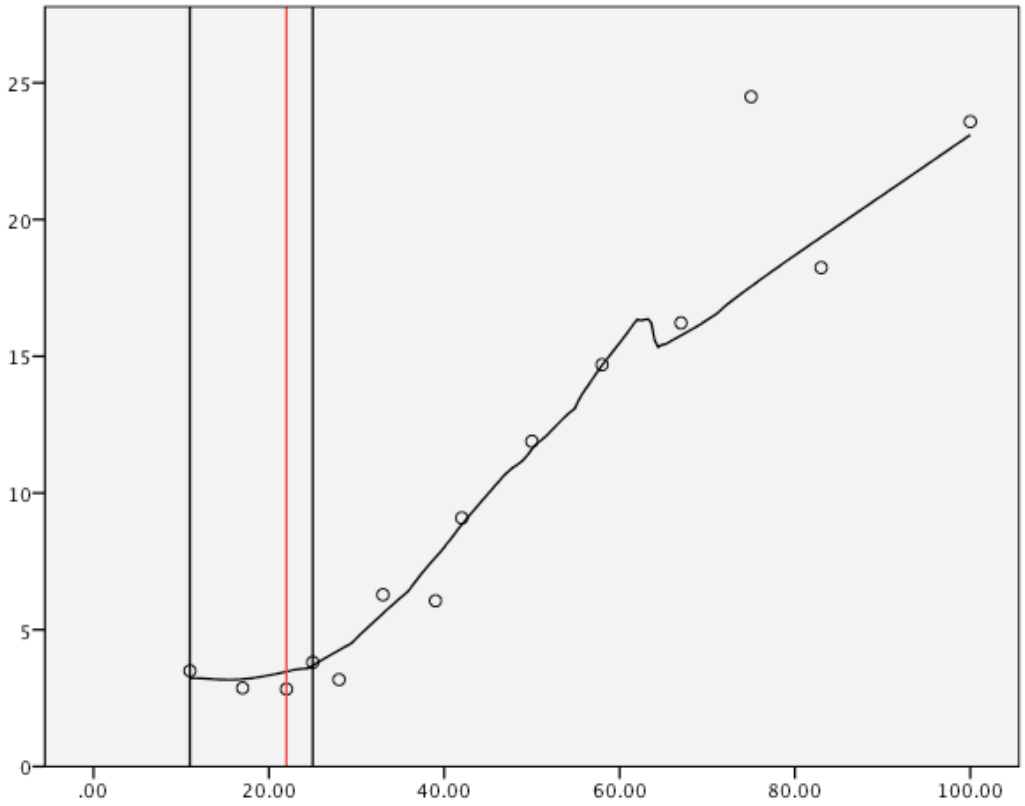


Figure 6.3 LOESS (Locally weighted scatterpoint smoothing) non-linear regression modelling demonstrated that between an SP% of 11-25%, the CRC detection rate remained approximately 4%. Above an SP% of 25%, every 10-percentage points increase was associated with a 2.5% increase in cancer. The vertical line drawn at an SP% of 22%, corresponds to the positivity pattern 4NN (created by 4 positive spots in kit one and normal results for kits two and three) a pattern not currently referred to colonoscopy.

6.5.3. Spot Positivity percentages (SP%) and neoplasia (CRC and adenoma) risk

There was no correlation between SP% and risk of any neoplasia (adenomas or CRC) (R^2=0.09), *Figure 6.4.*

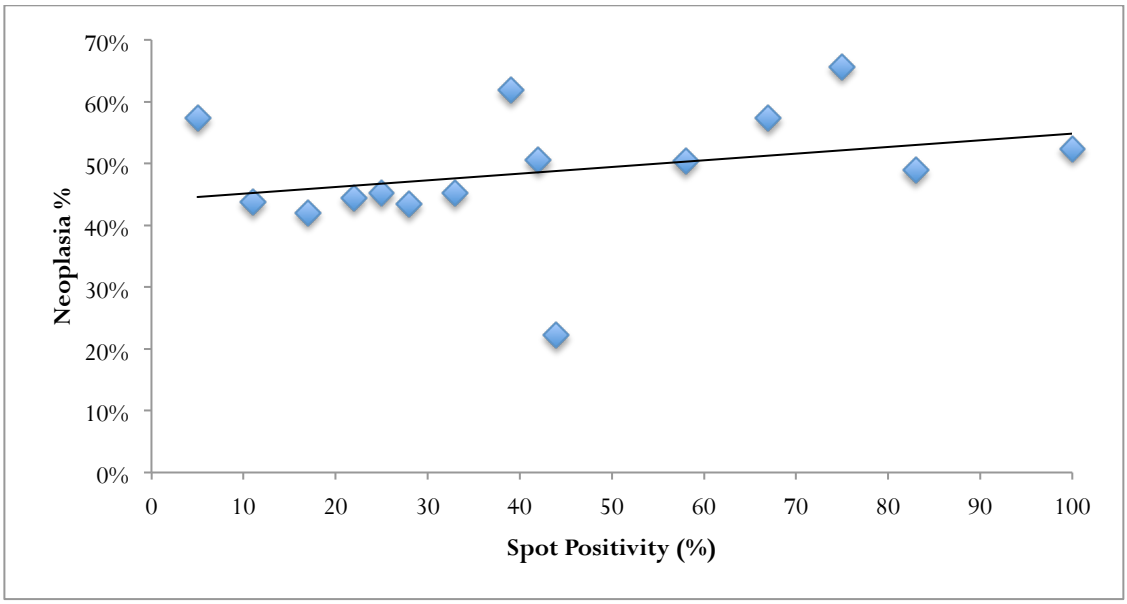


Figure 6.4 Correlation between Spot Positivity (SP%) and overall neoplasia (cancer and adenomas) rate (%) for gFOBT screening (Episode 2 of the BCSP, incident round). There is a poor linear relationship with $R^2 = 0.09$.

6.5.4. The association between SP%, CRC detection and sex

Compared with females, male subjects were more likely to have a gFOBt combination that led to a referral for colonoscopy (1.7% vs. 1.1%) and were more likely to have CRC diagnosed at colonoscopy (8.3% vs. 6.2%). Females had a lower risk of CRC detection at all SP%s, while the linear correlation between SP% and CRC was higher for males (R^2=0.92) than females (R^2=0.66), *Figure 6.5*.

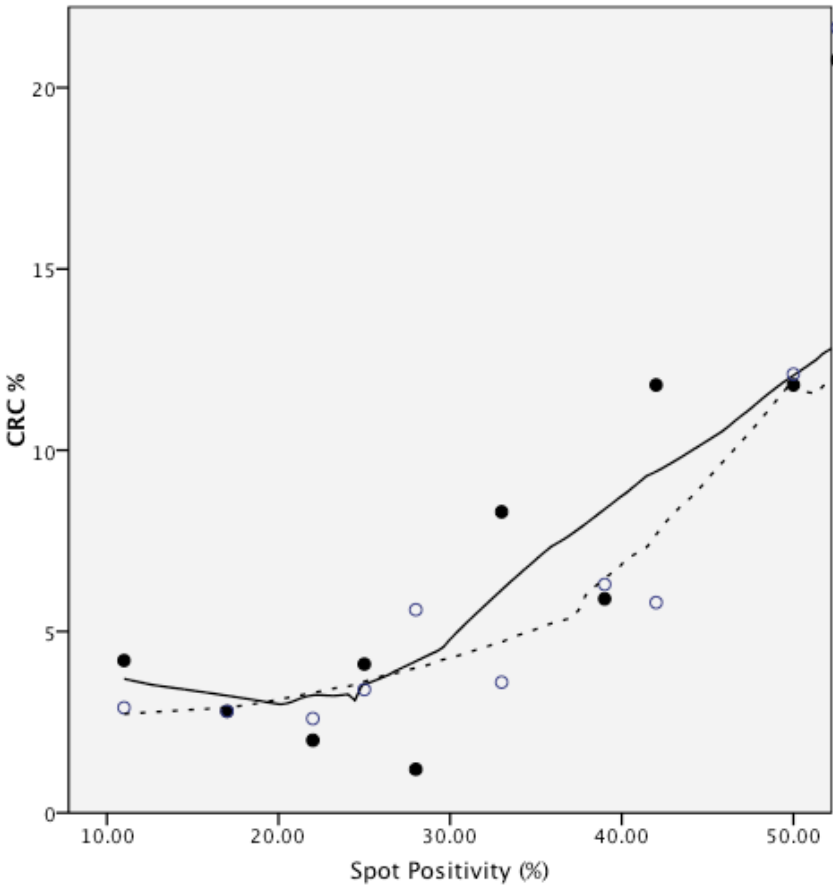


Figure 6.5 A LOESS curve demonstrates the relationship between SP% and CRC detection rate for male (solid line) and female subjects (dotted line). The R^2 linear correlation in males was 0.92. However the CRC% was approximately 4% between an SP% of 11-25% and only above an SP% of 25% did the CRC% increase lineally. In females the R^2 linear correlation was 0.66. The CRC% remained below 5% from an SP% of 11-35% and it is only when the SP% was over 35% that the CRC% increased over 5%.

6.5.5. Episode 1 gFOBt positivity patterns in subjects diagnosed with CRC in Episode 2

In episode 2, there were 286 subjects diagnosed with CRC, of whom 259 (90.6%) had normal gFOBT results (i.e. had six negative spots) at episode 1. The remaining 27 (9.4%) subjects had some positive spots at episode 1 and four had colonoscopy, one patient had a low risk adenoma and three had normal investigations. The remaining 23 CRC participants from episode 2 all had an unclear first kit followed by normal kits 2 and 3 at episode 1, *Figure 6.6*. These subjects had SP%s that ranged from 6% to 22%.

Referral to colonoscopy of all individuals with an 'unclear' result for kit 1 (SP%s 6-22%) would identify all 23 cancers (or advanced adenoma) in episode 1 and would have required an additional 6,115 colonoscopies with a CRC detection rate of only 0.4%. If individuals with four positive spots on kit 1 (an SP% of 22%) had been referred for colonoscopy in episode 1, 229 additional colonoscopies would have been required with, potentially, five more cancers (or advanced adenoma) diagnosed, (detection rate 2.2%). In contrast, other spot combinations with an SP% of 22% had a CRC detection of 4%,

Figure 6.3. The resource implications of offering colonoscopy to all individuals with an SP% of 22% would have required an additional 229 colonoscopies or 6% of the total colonoscopy workload.

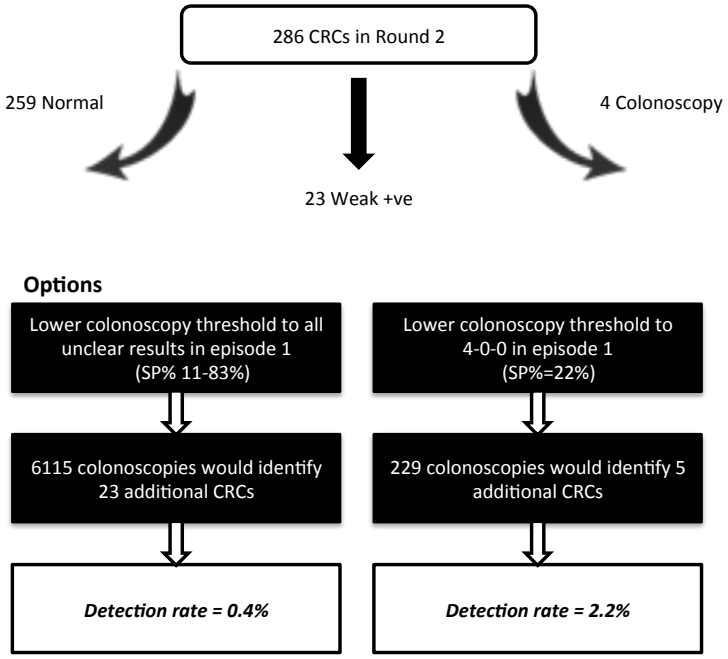


Figure 6.6 A flowchart that describes the gFOBt combinations in Episode 1 for individuals diagnosed with CRC following Episode 2. If all subjects with an unclear test result (n=6,115) received a colonoscopy, the CRC detection rate would be low (0.4%). However if only patients with an SP% of 22% (following 4 positive spots in kit 1) were offered colonoscopy, then detection would be 2.2%.

6.6. Discussion

This study provides a novel approach to evaluating the yield of gFOB testing by looking in detail at the gFOBt spot patterns and reveals the spot patterns of individuals that led to a diagnosis of CRC. Participants referred for colonoscopy on the basis of the current BCSP's algorithm have a CRC risk of 4% - 25%. The increase in risk is broadly consistent with increasing gFOBt Spot Positivity % (SP%).

Most participants with an SP%s of 11-100% are currently offered colonoscopy. At low levels of SP% (11-25%) the risk of CRC appears relatively constant at about 4%. At higher SP%s (>25%) the risk of CRC increases linearly, so that for every 10% increase in the SP%, the risk of CRC increases by 2.5%. A previous study of NHS BCSP data showed the CRC risk was about one in four in the abnormal group, compared with one in eleven in the weak positive group(2,9,27,73,183-185,343). I have demonstrated similar findings, with a CRC rate in the abnormal group (21%) equating to a one in five risk of CRC compared with a one in 17 risk (6%) in the weak positive group. The results of this study show that not

only is there a difference in risk between the two groups (abnormal or weak positive) but that there is a continuum of increasing risk with increasing spot positivity (SP%).

The increase in CRC risk with SP% was not entirely linear. Between 11-25% positivity, the risk remained at a fairly constant 4%. Importantly, this group of subjects accounted for the majority (53.1%) of colonoscopies performed in the study. The consistency of CRC rate at around 4% despite quite considerable change in the proportion of positive results is likely to be a limitation of the gFOBT. A systematic review found that the sensitivity of gFOBt for all neoplasms ranged from 6.2% to 83.3% and specificity from 65.0% to 99.0%(27,143,313). The low specificity is likely to be due to positive tests from non-cancer related GI bleeding and to analytical interference from dietary constituents. The high level of inter-study variability is due to differences in the study populations and test positivity definitions used. A meta-analysis of screening for CRC amongst asymptomatic individuals showed that repeated invitations to gFOBT screening, annually or biennially, reduced deaths from CRC by 16%(183,184). Despite this, gFOBT has a low clinical sensitivity and specificity, which means that many colonoscopies are scheduled for participants without pathology and some CRCs are missed due to false negative results. Our approach could not predict adenoma risk, even in patients with high-risk lesions. This has been shown in previous studies and demonstrates that while current gFOBt programmes can improve CRC survival they have not been shown to reduce CRC incidence through the accurate detection of pre-cancerous lesions. I have also shown that the correlation between SP% and CRC was greater for males than females. The reasons for this correlation are not clear but it is consistent with previous reports of a significantly greater sensitivity of FOBt in men(2,185,344). It may be that this is related to the higher rectal to colon ratio of cancers present in males(345).

This study has estimated the CRC risk for gFOBt positive spot combinations that do not currently lead to colonoscopy. This involved identifying subjects diagnosed with CRC in episode 2 and studying their episode 1 gFOBt combinations. I showed that subjects with four positive spots in kit one and normal results for kits two and three (4-0-0) in episode 1, had a CRC risk of 2.2% at Episode 2. This is much higher than other combinations involving an unclear kit 1, which had an overall CRC risk of 0.4%, while lower than the CRC detection rate for subjects currently offered colonoscopy, which is approximately 4%. This may be an underestimate as this only reflects patients picked up in a further round of screening. The 4-0-0 combination does seem to be more risky than other unclear kit 1 combinations and the CRC rate is likely to be over 2.2% and around 4% as would be predicted from its SP% of 22%. This CRC risk is comparable with that of most subjects undergoing a BCSP colonoscopy. Additional evidence suggesting this group may be at increased risk comes from a study demonstrating that 7.8% of interval CRCs arise from gFOBts with an unclear result in kit one followed by two normal kits(2,9,27,73,185,346).

The effects of adjusting the NHS BCSP to offer colonoscopy to patients with a 4-0-0 combination need consideration because it is likely to produce a 6% increase in colonoscopy activity. In an average size

endoscopy unit, covering a population of half a million, this would mean approximately two more lists a year (based on a 40 week year).(2,73,347) Each colonoscopy (including pathology) currently costs £245. Assuming a 4% detection rate, each additional CRC diagnosis made would cost £6,125, which is well within the willingness-to-pay threshold of £20,000 currently employed by NICE(2,9,27,74,143,348).

This work has shown it may be possible to predict an individual's CRC risk more accurately, based on their gFOBt result. It must be borne in mind, however, that this is a screening programme so whilst these data may be used to advise patients about likely risks and benefits, advice must be set in the context of the wider role of screening and the importance of subsequent rounds. These results raise interesting questions about the information that should be provided to patients regarding their risk of a diagnosis of cancer.

Goyder et al, argue that when screening tests results are discussed with patients, there should be an attempt to not only discuss potential benefits and harms of further investigations but also the statistical chance of such events occurring.(27,143,186,349) Therefore, instead of delivering an abnormal ('positive') or normal ('negative') result, the focus is on a numeric scale, such as 1 in 20 or 1 in 4 chance of CRC. Ideally, in future, this would take account of more than simply the gFOBt result but factors such as age and sex. This idea is not novel, and numeric risk is well established for pregnant women having the 'triple test' for Down's syndrome(183,184,187,350). Information can be delivered to patients in many ways depending on preference. Individual risk can be described to subjects; numerically (the risk is 5%), graphically (for example; one of twenty stick men on a page is differently coloured) or qualitatively (by comparing the risk with risky activities). The choice of tools used will depend on the subject's preferences, knowledge and needs(351). Shared decision-making between health professional and subjects using a personal risk assessment and decision aid appears to increase uptake of CRC screening(352).

Traditionally, screening programmes have not sought to identify new understanding of disease, although they are, in fact, ideal ways of seeing how healthcare affects illness. Furthermore, it is rare for screening programmes to change in the face of new information gleaned from the programme(353). A highly organized programme such as the NHS BCSP provides an ideal dataset for interrogation and analysis to refine and improve its own programme and others.

Limitations of the study included missing data on the site and stage of some of the CRCs, which prevented analysis of how these characteristics might affect the gFOBt result and SP%. I also used an approximation of the CRC risk for gFOBt combinations that did not undergo colonoscopy. The clinical limitations of gFOBt (poor sensitivity and the development of disease in the period between episodes), is likely to have under estimated our risk estimates.

The current BCSP algorithm was based on the understanding that cancers bleed intermittently. This requirement means that in this programme, many subjects who have colonoscopy (except those with an abnormal kit one) need to have demonstrated bleeding in at least two kits some time apart. Our approach based on the SP% is less dependent on recurrent bleeding over time. To test our new methodological approach and in particular whether subjects with a 4-0-0 combination have a similar CRC risk to subjects already offered colonoscopy, would require a change to the BCSP algorithm and prospective evaluation of the CRC detection rate in these patients.

The *European guidelines for quality assurance in CRC screening and diagnosis* concluded in 2010 that Faecal Immunochemical Tests (FIT) offer substantially greater analytical sensitivity and specificity and allow enhanced detection of both cancer and adenomas. Since these guidelines were published all countries commencing population screening have adopted FIT. The countries of the UK are now considering changing to FIT. A pilot study in Scotland has already shown that FIT improves uptake (354) and a pilot using FIT that commenced in England in April 2014 is also demonstrating markedly increased uptake from current gFOBt (BCSP Southern Hub report).

This paper explores the potential of determining risk from a binary test (spot positive or negative); FIT will provide a quantitative haemoglobin concentration that lends itself to the development of a multivariate risk score. The different sex-related sensitivities of blood as a biomarker for CRC and adenomas that have been highlighted in this paper can be exploited with FIT by applying different risk parameters for men and women. Longitudinal data from successive screening episodes that have been examined in this study shows great potential for enhancing risk prediction in any computerised population-based programme. Quantitative FIT will enable age, sex, screening history and even BMI, drinking, smoking and dietary history to be used in a way that is not easily achieved by gFOBt. However it will take several years before FIT is rolled out, while the suggested changes to the screening programme could be adopted quickly and at minimal expense.

6.6.1. Conclusion

In conclusion, it is possible to demonstrate the risk of CRC arising from a particular gFOBt positivity pattern. The spot positivity percentage appears to predict CRC risk. Currently subjects with an SP% of 11-100% are offered colonoscopy with CRC detection between 4 and 25%. In subjects currently referred for colonoscopy, those with an SP% of 11-25% have a CRC risk of approximately 4%. When the SP% is >25%, for every 10% points increase, the CRC rate increases by 2.5%. Consideration should be given to the merit of changing the current BCSP algorithm to address possible inequalities in detection of CRC risk (such as with 4-0-0 result). More detailed study of the risks, benefits and workload including health economics modelling should be undertaken. Additional consideration should

be given to the information conveyed to subjects given the relative cancer risk of particular combinations.

References

1. Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut. 2002 Jan 1;50(6):840–4.

2. Statistics OFN. Office for National Statistics [Internet]. 2010 ed. Available from: http://www.ons.gov.uk/ons/search/index.html?newquery=cancer+registrations. Accessed Nov 2013

3. Sasieni PD, Shelton J, Ormiston-Smith N, Thomson CS, Silcocks PB. What is the lifetime risk of developing cancer?: the effect of adjusting for multiple primaries. Br J Cancer. 2011 Jul;105(3):460–5.

4. Davila RE, Rajan E, Baron TH, Adler DG, Egan JV, Faigel DO, et al. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc. 2006 Apr;63(4):546–57.

5. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004 Oct;96(19):1420–5.

6. National Institute for Clinical Excellence. Improving Outcomes in Colorectal Cancers. National Institute for Clinical Excellence, editor. 2004 ed. Available from: http://www.nice.org.uk/nicemedia/pdf/CSGCCfullguidance.pdf. Accessed Nov 2013

7. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014 Jan;15(1):23–34.

8. Shack LG, Shah A, Lambert PC, Rachet B. Cure by age and stage at diagnosis for colorectal cancer patients in North West England, 1997-2004: a population-based study. Cancer Epidemiol. 2012 Dec;36(6):548–53.

9. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol. 2007 Sep;8(9):773–83.

10. Hanna SJ, Muneer A, Khalil KH. The 2-week wait for suspected cancer: time for a rethink? Int J Clin Pract. 2005 Nov;59(11):1334–9.

11. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993 May;328(19):1365–71.

12. Pollard MF, Thompson-Fawcett MW, Stringer MD. The human ileocaecal junction: anatomical evidence of a sphincter. Surg Radiol Anat. 2012 Jan;34(1):21–9.

13. Sears CL. A dynamic partnership: celebrating our gut flora. Anaerobe. 2005 Oct;11(5):247–51.

14. Suau A, Bonnet R, Sutren M, Godon JJ, Gibson GR, Collins MD, et al. Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut. Appl Environ Microbiol. 1999 Nov;65(11):4799–807.

15. O'Keefe SJD. Nutrition and colonic health: the critical role of the microbiota. Curr Opin Gastroenterol. 2008 Jan;24(1):51–8.

16. Davis CD, Milner JA. Gastrointestinal microflora, food components and colon cancer prevention. J Nutr Biochem. 2009 Oct;20(10):743–52.

17. SR H, B V, Kudo S. Carcinoma of the colon and rectum. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System. Lyon, France: IARC Press; (2000):103–43.

18. Kang H, O'Connell JB, Leonardi MJ, Maggard MA, McGory ML, Ko CY. Rare tumors of the colon and rectum: a national review. Int J Colorectal Dis. 2007 Feb;22(2):183–9.

19. Compton CC. Pathology report in colon cancer: what is prognostically important? Dig Dis. 1999;17(2):67–79.

20. Ilyas M, Straub J, Tomlinson IP, Bodmer WF. Genetic pathways in colorectal and other cancers. Eur J Cancer. 1999 Dec;35(14):1986–2002.

21. Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, et al. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. Nature. 1994 Mar;368(6468):258–61.

22. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990 Jun;61(5):759–67.

23. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, et al. Identification of c-MYC as a target of the APC pathway. Science. 1998 Sep;281(5382):1509–12.

24. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol. 1990 Jun;14(6):524–37.

25. Goldstein NS, Bhanot P, Odish E, Hunter S. Hyperplastic-like colon polyps that preceded microsatellite-unstable adenocarcinomas. Am J Clin Pathol. 2003 Jun;119(6):778–96.

26. Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. J Clin Pathol. 2010 Aug;63(8):681–6.

27. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011 Jan;377(9760):127–38.

28. Bowel cancer incidence statistics [Internet]. Cancer Research UK; [cited 2010 Aug 20]. Accessed Nov 2013

29. Jemal A, Siegel R, Ward E, Murray T. Cancer statistics. 2006. CA-A Cancer J Clin, vol. 56, no. 2, pp. 106-130, 2006

30. Raine R, Wong W, Scholes S, Ashton C, Obichere A, Ambler G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. BMJ. 2010;340:b5479.

31. Cheng X, Chen VW, Steele B, Ruiz B, Fulton J, Liu L, et al. Subsite-specific incidence rate and stage of disease in colorectal cancer by race, gender, and age group in the United States, 1992-1997. Cancer. 2001 Nov;92(10):2547–54.

32. Cancer Care Ontario [Internet]. Available from: https://www.cancercare.on.ca/cancerfacts/. Accessed Nov 2013

33. Abrams JS, Reines HD. Increasing incidence of right-sided lesions in colorectal cancer. Am J Surg. 1979 Apr;137(4):522–6.

34. Rabeneck L, Davila JA, El-Serag HB. Is there a true "shift" to the right colon in the incidence of colorectal cancer? Am J Gastroenterol. 2003 Jun;98(6):1400–9.

35. National Cancer Intelligence Network. http://www.nycris.nhs.uk/colorectal-cancer/publications. Accessed Nov 2013

36. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. N Z Med J. 2011 Jul;124(1338):76–88.

37. Jack RH, Linklater KM, Hofman D, Fitzpatrick J, Moller H. Ethnicity coding in a regional cancer registry and in Hospital Episode Statistics. BMC Public Health. 2006;6:281.

38. Grulich AE, Swerdlow AJ, Head J, Marmot MG. Cancer mortality in African and Caribbean migrants to England and Wales. Br J Cancer. 1992 Nov;66(5):905–11.

39. Hebbar S, Fuggle WJ, Nevill AM, Veitch AM. Colorectal cancer incidence and trend in UK South Asians: a 20-year study. Colorectal Dis. 2012 Jun;14(6):e319–22.

40. Porta M. A dictionary of epidemiology, 5th edition. A call for submissions through an innovative wiki. J Epidemiol Community Health. BMJ Group; 60 (8):653–3.

41. Lynch HT, Rubinstein WS, Locker GY. Cancer in Jews: introduction and overview. Fam Cancer. 2004;3(3-4):177–92.

42. Ziegler RG, Devesa SS, Fraumeni JFJ. Epidemiologic patterns of colorectal cancer. Important Adv Oncol. 1986; 209–32.

43. Center, Melissa M, Jemal A, Ward E. International trends in colorectal cancer incidence rates. Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1688–94.

44. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med. 1995 Mar;122(5):327–34.

45. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med. 1990 Dec;323(24):1664–72.

46. Baron JA, Sandler RS, Haile RW, Mandel JS, Mott LA, Greenberg ER. Folate intake, alcohol consumption, cigarette smoking, and risk of colorectal adenomas. J Natl Cancer Inst. 1998 Jan;90(1):57–62.

47. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001 Apr;48(4):526–35.

48. Lakatos P-L, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. World J Gastroenterol. 2008 Jul;14(25):3937–47.

49. Sachar DB. Cancer in Crohn's disease: dispelling the myths. Gut. 1994 Nov;35(11):1507–8.

50. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol. 2004 Jul;287(1):G7–17.

51. Squillace S, Berggreen P, Jaffe P, Fennerty MB, Hixson L, Garewal H, et al. A normal initial colonoscopy after age 50 does not predict a polyp-free status for life. Am J Gastroenterol. 1994 Aug;89(8):1156–9.

52. Khullar SK, DiSario JA. Colon cancer screening. Sigmoidoscopy or colonoscopy. Gastrointest Endosc Clin N Am. 1997 Jul;7(3):365–86.

53. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut. 1982 Oct;23(10):835–42.

54. van Stolk RU, Beck GJ, Baron JA, Haile R, Summers R. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. The Polyp Prevention Study Group. Gastroenterology. 1998 Jul;115(1):13–8.

55. Noshirwani KC, van Stolk RU, Rybicki LA, Beck GJ. Adenoma size and number are predictive of adenoma recurrence: implications for surveillance colonoscopy. Gastrointest Endosc. 2000 Apr;51(4 Pt 1):433–7.

56. Loeve F, van Ballegooijen M, Boer R, Kuipers EJ, Habbema JDF. Colorectal cancer risk in adenoma patients: a nation-wide study. Int J Cancer. 2004 Aug;111(1):147–51.

57. Yang G, Zheng W, Sun QR, Shu XO, Li WD, Yu H, et al. Pathologic features of initial adenomas as predictors for metachronous adenomas of the rectum. J Natl Cancer Inst. 1998 Nov;90(21):1661–5.

58. Winawer SJ. Colorectal cancer screening comes of age. N Engl J Med. 1993 May 13;328(19):1416–7.

59. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of Colorectal Cancer by Colonoscopic Polypectomy. N Engl J Med. Massachusetts Medical Society; 2012 Jan 6;329(27):1977–81.

60. Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF. Incidence of synchronous and metachronous colorectal carcinoma. Br J Surg. 1984 Dec;71(12):941–3.

61. Pinol V, Andreu M, Castells A, Paya A, Bessa X, Jover R. Synchronous colorectal neoplasms in patients with colorectal cancer: predisposing individual and familial factors. Dis Colon Rectum. 2004 Jul;47(7):1192–200.

62. Bouvier A-M, Latournerie M, Jooste V, Lepage C, Cottet V, Faivre J. The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up. Eur J Cancer. 2008 Mar;44(4):522–7.

63. He J, Stram DO, Kolonel LN, Henderson BE, Le Marchand L, Haiman CA. The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. Br J Cancer. 2010 Jun;103(1):120–6.

64. Renehan AG, O'Connell J, O'Halloran D, Shanahan F, Potten CS, O'Dwyer ST, et al. Acromegaly and colorectal cancer: a comprehensive review of epidemiology, biological mechanisms, and clinical implications. Horm Metab Res. 2003 Nov;35(11-12):712–25.

65. Park HY, Chang BJ, Lim SW, Kim J, Kim JY, Chang DK, et al. Risk of colorectal neoplasia in patients with solid organ transplantation. Clinical Transplantation. Blackwell Publishing Ltd; 2012 Jan 1;26(1):50–6.

66. Shao T, Yang Y-X. Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol. 2005 Aug;100(8):1813–20.

67. Merkel S, Meyer C, Papadopoulos T, Meyer T, Hohenberger W. [Urgent surgery in colon carcinoma]. Zentralbl Chir. 2007 Feb;132(1):16–25.

68. Wong SKC, Jalaludin BB, Morgan MJ, Berthelsen AS, Morgan A, Gatenby AH, et al. Tumor pathology and long-term survival in emergency colorectal cancer. Dis Colon Rectum. 2008 Feb;51(2):223–30.

69. McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg. John Wiley & Sons, Ltd; 2004 Jan 1;91(5):605–9.

70. Bass G, Fleming C, Conneely J, Martin Z, Mealy K. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. Dis Colon Rectum. 2009 Apr;52(4):678–84.

71. Coco C, Verbo A, Manno A, Mattana C, Covino M, Pedretti G, et al. Impact of emergency surgery in the outcome of rectal and left colon carcinoma. World J Surg. 2005 Nov;29(11):1458–64.

72. Scott NA, Jeacock J, Kingston RD. Risk factors in patients presenting as an emergency with colorectal cancer. Br J Surg [Internet]. 1995 Mar;82(3):321–3.

73. Morris EJA, Whitehouse LE, Farrell T, Nickerson C, Thomas JD, Quirke P, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. Br J Cancer. 2012 Aug;107(5):757–64.

74. Lynch BM, Baade P, Fritschi L, Leggett B, Owen N, Pakenham K, et al. Modes of presentation and pathways to diagnosis of colorectal cancer in Queensland. Med J Aust. 2007 Mar;186(6):288–91.

75. Chaplin A, Curless R, Thomson R, Barton R. Prevalence of lower gastrointestinal symptoms and associated consultation behaviour in a British elderly population determined by face-to-face interview. Br J Gen Pract. 2000 Oct;50(459):798–802.

76. Douek M, Wickramasinghe M, Clifton MA. Does isolated rectal bleeding suggest colorectal cancer? Lancet. 1999 Jul;354(9176):393.

77. Toit du J, Hamilton W, Barraclough K. Risk in primary care of colorectal cancer from new onset rectal bleeding: 10 year prospective study. BMJ. 2006 Jul;333(7558):69–70.

78. Fijten GH, Blijham GH, Knottnerus JA. Occurrence and clinical significance of overt blood loss per rectum in the general population and in medical practice. Br J Gen Pract. 1994 Jul;44(384):320–5.

79. Olde Bekkink M, McCowan C, Falk GA, Teljeur C, Van de Laar FA, Fahey T. Diagnostic accuracy systematic review of rectal bleeding in combination with other symptoms, signs and tests in relation to colorectal cancer. Br J Cancer. 2010 Jan;102(1):48–58.

80. Kent AJ, Woolf D, McCue J, Greenfield SM. The use of symptoms to predict colorectal cancer site. Can we reduce the pressure on our endoscopy services? Colorectal Dis. 2010 Feb;12(2):114–8.

81. Logan ECM, Yates JM, Stewart RM, Fielding K, Kendrick D. Investigation and management of iron deficiency anaemia in general practice: a cluster randomised controlled trial of a simple management prompt. Postgrad Med J. 2002 Sep;78(923):533–7.

82. Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. Br J Cancer. 2005 Aug;93(4):399–405.

83. Stapley S, Peters TJ, Sharp D, Hamilton W. The mortality of colorectal cancer in relation to the initial symptom at presentation to primary care and to the duration of symptoms: a cohort study using medical records. Br J Cancer. 2006 Nov;95(10):1321–5.

84. Ellis BG, Thompson MR. Factors identifying higher risk rectal bleeding in general practice. Br J Gen Pract. 2005 Dec;55(521):949–55.

85. Mulcahy HE, O'Donoghue DP. Duration of colorectal cancer symptoms and survival: the effect of confounding clinical and pathological variables. Eur J Cancer. 1997 Aug;33(9):1461–7.

86. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration, and clues to location. Am J Gastroenterol. 1999 Oct;94(10):3039–45.

87. Umpleby HC, Bristol JB, Rainey JB, Williamson RC. Survival of 727 patients with single carcinomas of the large bowel. Dis Colon Rectum. 1984 Dec;27(12):803–10.

88. Scholefield JH, Robinson MH, Mangham CM, Hardcastle JD. Screening for colorectal cancer reduces emergency admissions. Eur J Surg Oncol. 1998 Feb;24(1):47–50.

89. Elliss-Brookes L, McPhail S, Ives A, Greenslade M, Shelton J, Hiom S, et al. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. Br J Cancer. 2012 Oct;107(8):1220–6.

90. Health DO. Referral Guidelines for Suspected Cancer. London: Department of Health. 2010

91. Janssen HA, Borghouts JA, Muris JW, Metsemakers JF, Koes BW, Knottnerus JA. Health status and management of chronic non-specific abdominal complaints in general practice. Br J Gen Pract. 2000 May;50(454):375–9.

92. Hamilton W, Sharp D. Diagnosis of colorectal cancer in primary care: the evidence base for guidelines. Fam Pract. 2004 Feb;21(1):99–106.

93. Clarke A, Blundell N, Forde I, Musila N, Spitzer D, Naqvi S, et al. Can guidelines improve referral to elective surgical specialties for adults? A systematic review. Qual Saf Health Care. 2010 Jun;19(3):187–94.

94. Baughan P, Keatings J, O'Neill B. Urgent suspected cancer referrals from general practice: audit of compliance with guidelines and referral outcomes. Br J Gen Pract. 2011 Nov;61(592):e700–6.

95. McArdle CS, Hole DJ. Outcome following surgery for colorectal cancer. British Medical Bulletin. 2002 Jan 1;64(1):119–25.

96. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996 Nov;348(9040):1472–7.

97. Rabeneck L, Paszat LF, Li C. Risk factors for obstruction, perforation, or emergency admission at presentation in patients with colorectal cancer: a population-based study. Am J Gastroenterol. 2006 May;101(5):1098–103.

98. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996 Nov;348(9040):1467–71.

99. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. BMJ. 2003 Nov 22;327(7425):1196–201.

100. Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology. 1997 Jan;112(1):17–23.

101. Bowles CJA, Leicester R, Romaya C, Swarbrick E, Williams CB, Epstein O. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut. 2004 Jan 1;53(2):277–83.

102. Gavin DR, Valori RM, Anderson JT, Donnelly MT, Williams JG, Swarbrick ET. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. Gut. 2013 Feb;62(2):242–9.

103. Sarkar S, Geraghty J, Moore AR, Lal S, Ramesh J, Bodger K. A multicentre study to determine the incidence, demographics, aetiology and outcomes of 6-day emergency readmission following day-case endoscopy. Eur J Gastroenterol Hepatol. 2012 Dec;24(12):1438–46.

104. Waye JD, Kahn O, Auerbach ME. Complications of colonoscopy and flexible sigmoidoscopy. Gastrointest Endosc Clin N Am. 1996 Apr;6(2):343–77.

105. Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet. 2005 Jan;365(9456):305–11.

106. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology. 2011 May;259(2):393–405.

107. Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, Wagner von C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet. 2013 Feb.

108. Pickhardt PJ, Kim DH, Meiners RJ, Wyatt KS, Hanson ME, Barlow DS, et al. Colorectal and extracolonic cancers detected at screening CT colonography in 10,286 asymptomatic adults. Radiology. 2010 Apr;255(1):83–8.

109. Ng CS, Wei W, Doyle TC, Courtney HM, Dixon AK, Freeman AH. Minimal-preparation abdomino-pelvic CT in frail and elderly patients: prognostic value of colonic and extracolonic findings. Clin Radiol. 2008 Apr;63(4):424–32.

110. Rabeneck L, Lewis JD, Paszat LF, Saskin R, Stukel TA. Risk of proximal and distal colorectal cancer following flexible sigmoidoscopy: a population-based cohort study. Am J Gastroenterol. 2008 Aug;103(8):2075–82.

111. Frenette CT, Strum WB. Relative rates of missed diagnosis for colonoscopy, barium enema, and flexible sigmoidoscopy in 379 patients with colorectal cancer. J Gastrointest Cancer. 2007;38(2-4):148–53.

112. Irvine EJ, O'Connor J, Frost RA, Shorvon P, Somers S, Stevenson GW, et al. Prospective comparison of double contrast barium enema plus flexible sigmoidoscopy v colonoscopy in rectal bleeding: barium enema v colonoscopy in rectal bleeding. Gut. 1988 Sep;29(9):1188–93.

113. Rokkas T, Papaxoinis K, Triantafyllou K, Ladas SD. A meta-analysis evaluating the accuracy of colon capsule endoscopy in detecting colon polyps. Gastrointest Endosc. 2010 Apr;71(4):792–8.

114. Newton KF, Newman W, Hill J. Review of biomarkers in colorectal cancer. Colorectal Dis. 2012 Jan;14(1):3–17.

115. Dukes CE. The classification of cancer of the rectum. J Pathol. John Wiley & Sons, Ltd; 1932 Jan 1;35(3):323–32.

116. ASTLER VB, COLLER FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. Ann Surg. 1954 Jun;139(6):846–52.

117. Leufkens AM, van den Bosch MAAJ, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol. 2011 Jul;46(7-8):887–94.

118. Dighe S, Purkayastha S, Swift I, Tekkis PP, Darzi A, A'Hern R, et al. Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. Clin Radiol. 2010 Sep;65(9):708–19.

119. Muhi A, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K, et al. Diagnosis of colorectal hepatic metastases: Contrast-enhanced ultrasonography versus contrast-enhanced computed tomography versus superparamagnetic iron oxide-enhanced magnetic resonance imaging with diffusion-weighted imaging. J Magn Reson Imaging. 2010 Nov;32(5):1132–40.

120. Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and

MR imaging--a meta-analysis. Radiology. 2004 Sep;232(3):773–83.

121. Lahaye MJ, Engelen SME, Nelemans PJ, Beets GL, van de Velde CJH, van Engelshoven JMA, et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR. 2005 Aug;26(4):259–68.

122. Bipat S, van Leeuwen MS, Comans EFI, Pijl MEJ, Bossuyt PMM, Zwinderman AH, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology. 2005 Oct;237(1):123–31.

123. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009 Aug;27(22):3677–83.

124. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev. 2008;(2):CD003432.

125. National Institute for Health and Clinical Excellence [homepage on the Internet] Laparoscopic Surgery for Colorectal Cancer. Aug, 2006. [Accessed July 1, 2014]. (NICE technology appraisal guidance 105). revised 2009. Available from: http://www.nice.org.uk/guidance/TA105.

126. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 2009 May;11(4):354–64–discussion364–5.

127. West NP, Morris EJA, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol. 2008 Sep;9(9):857–65.

128. Wiig JN, Carlsen E, Soreide O. Mesorectal excision for rectal cancer: a view from Europe. Semin Surg Oncol. 1998 Sep;15(2):78–86.

129. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet. 1994 Sep;344(8924):707–11.

130. Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg. 2005 Jul;242(1):74–82.

131. Huser N, Michalski CW, Erkan M, Schuster T, Rosenberg R, Kleeff J, et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg. 2008 Jul;248(1):52–60.

132. Siddiqui A, Khandelwal N, Anthony T, Huerta S. Colonic stent versus surgery for the management of acute malignant colonic obstruction: a decision analysis. Aliment Pharmacol Ther. 2007 Nov 15;26(10):1379–86.

133. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 55 (Suppl 3):iii1–iii8.

134. Kirchhoff P, Clavien P-A, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. Patient Safety in Surgery. BioMed Central; 2010;4:5–5.

135. Morris EJA, Maughan NJ, Forman D, Quirke P. Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology. Gut. 2007 Oct;56(10):1419–25.

136. Figueredo A, Fine S, Maroun J, Walker-Dilks C, Wong S. Adjuvant therapy for stage III colon cancer after complete resection. Provincial Gastrointestinal Disease Site Group. Cancer Prev Control. 1997 Oct;1(4):304–19.

137. Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. Br J Cancer. 2000 Jun;82(11):1789–94.

138. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JPA. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol. 2007 Oct;8(10):898–911.

139. McCarthy EP, Phillips RS, Zhong Z, Drews RE, Lynn J. Dying with cancer: patients' function, symptoms, and care preferences as death approaches. J Am Geriatr Soc. 2000 May;48(5 Suppl):S110–21.

140. Morris EJA, Sandin F, Lambert PC, Bray F, Klint A, Linklater K, et al. A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. Gut. 2011 Aug;60(8):1087–93.

141. Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008 Aug;9(8):730–56.

142. Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, et al. Cancer survival in England and Wales at the end of the 20th century. Br J Cancer. 2008 Sep;99 Suppl 1:S2–10.

143. Gatta G, Capocaccia R, Sant M, Bell CM, Coebergh JW, Damhuis RA, et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut. 2000 Oct;47(4):533–8.

144. Rachet B, Maringe C, Nur U, Quaresma M, Shah A, Woods LM, et al. Population-based cancer survival trends in England and Wales up to 2007: an assessment of the NHS cancer plan for England. Lancet Oncol. 2009 Apr;10(4):351–69.

145. Tingle J. The Care Quality Commission's end-of-year report. Br J Nurs. 2011 Sep;20(16):1004–5.

146. Mays N. Reducing unwarranted variations in healthcare in the English NHS. BMJ. 2011;342:d1849.

147. Chassin MR. Explaining geographic variations. The enthusiasm hypothesis. Med Care. 1993 May;31(5 Suppl):YS37–44.

148. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. Lancet. 2013 Sep;382(9898):1121–9.

149. Warwick J, Will O, Allgood P, Miller R, Duffy S, Greenberg D. Variation in colorectal cancer treatment and survival: a cohort study covering the East Anglia region. Colorectal Dis. 2013;15(10):1243–52.

150. National Bowel Cancer Audit [Internet]. Report No.: 2007. Available from: http://www.ic.nhs.uk/webfiles/Services/NCASP/Cancer/New%20web%20documents%20(Bowel)/BowelExecSummFinal.pdf. Accessed Nov 2013

151. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. Br J Cancer. 2007 Dec 4;98(1):60–70.

152. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. Br J Cancer. Cancer Research UK; 101(S2):S92–S101.

153. J C, C P, F T, P M, J B. Delay in seeking advice for symptoms that potentially indicate bowel cancer. Am J Health Behav. Cancer Research UK; 2003;27:401–7.

154. Langenbach MR, Schmidt J, Neumann J, Zirngibl H. Delay in treatment of colorectal cancer: multifactorial problem. World J Surg. 2003 Mar;27(3):304–8.

155. Pullyblank AM, Dixon N, Dixon AR. The impact of bowel cancer awareness week. Colorect Dis. 2002 Nov;4(6):483–5.

156. McCaffery K, Wardle J, Waller JO. Knowledge, attitudes, and behavioral intentions in relation to the early detection of colorectal cancer in the United Kingdom. Prev Med. 2003 May;36(5):525–35.

157. Dent OF, Goulston KJ, Tennant CC, Langeluddecke P, Mant A, Chapuis PH, et al. Rectal bleeding. Dis Colon Rectum. 1990 Oct;33(10):851–7.

158. Funch DP. Diagnostic delay in symptomatic colorectal cancer. Cancer. 1985 Oct 15;56(8):2120–4.

159. Young CJ, Sweeney JL, Hunter A. Implications of Delayed Diagnosis in Colorectal Cancer. ANZ J Surg. 2000 Sep 14;70(9):635–8.

160. MacArthur C, Smith A. Factors associated with speed of diagnosis, referral, and treatment in colorectal cancer. J Epidemiol Community Health. 1984 Jun;38(2):122–6.

161. Bain NS. Striking the right balance in colorectal cancer care--a qualitative study of rural and urban patients. Fam Pract. 2002 Aug 1;19(4):369–74.

162. Harris GJ, Simson JN. Causes of late diagnosis in cases of colorectal cancer seen in a district general hospital over a 2-year period. Ann R Coll Surg Engl. 1998 Jul;80(4):246–8.

163. Power E, Simon A, Juszczyk D, Hiom S, Wardle J. Assessing awareness of colorectal cancer symptoms: measure development and results from a population survey in the UK. BMC Cancer. 2011;11:366.

164. Richards MA. The National Awareness and Early Diagnosis Initiative in England: assembling the evidence. Br J Cancer. Nature Publishing Group; 2009 Dec 3;101 (Suppl 2):S1–S4.

165. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration, and clues to location. Am J Gastroenterol. 1999 Oct;94(10):3039–45.

166. Terhaar sive Droste JS, Oort FA, van der Hulst RWM, Coupe VMH, Craanen ME,

Meijer GA, et al. Does delay in diagnosing colorectal cancer in symptomatic patients affect tumor stage and survival? A population-based observational study. BMC Cancer. 2010;10:332.

167. Gonzalez-Hermoso F, Perez-Palma J, Marchena-Gomez J, Lorenzo-Rocha N, Medina-Arana V. Can early diagnosis of symptomatic colorectal cancer improve the prognosis? World J Surg. 2004 Jul;28(7):716–20.

168. Rupassara KS, Ponnusamy S, Withanage N, Milewski PJ. A paradox explained? Patients with delayed diagnosis of symptomatic colorectal cancer have good prognosis. Colorectal Dis. 2006 Jun;8(5):423–9.

169. Kozuka S, Nogaki M, Ozeki T, Masumori S. Premalignancy of the mucosal polyp in the large intestine: II. Estimation of the periods required for malignant transformation of mucosal polyps. Dis Colon Rectum. 1975 Sep;18(6):494–500.

170. Jones R, Rubin G, Hungin P. Is the two week rule for cancer referrals working? BMJ. 2001 Jun;322(7302):1555–6.

171. Logan RFA, Patnick J, Nickerson C, Coleman L, Rutter MD, Wagner von C. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut. 2012 Oct;61(10):1439–46.

172. Greenwald B. Promoting community awareness of the need for colorectal cancer screening: a pilot study. Cancer Nurs. 2006 Mar;29(2):134–41.

173. Lyon D, Knowles J, Slater B, Kennedy R. Improving the early presentation of cancer symptoms in disadvantaged communities: putting local people in control. Br J Cancer. 2009 Dec;101 Suppl 2:S49–54.

174. Khong T, Naik K, Sivakumar R, Shah S. PTH-073 United Kingdom National Bowel Cancer Awareness Programme – More Pain, No Gain? Gut. 2014 Jun 1;63(Suppl 1):A241–2.

175. de Nooijer J, Lechner L, Candel M, de Vries H. Short- and long-term effects of tailored information versus general information on determinants and intentions related to early detection of cancer. Prev Med. 2004 Jun;38(6):694–703.

176. Davies RJ, Ewings P, Welbourn R, Collins C, Kennedy R, Royle C. A prospective study to assess the implementation of a fast-track system to meet the two-week target for colorectal cancer in Somerset. Colorectal Dis. 2002 Jan;4(1):28–30.

177. Flashman K, O'Leary DP, Senapati A, Thompson MR. The Department of Health's 'two week standard' for bowel cancer: is it working? Gut. 2004 Mar;53(3):387–91.

178. C A, H B, Erens B. National Survey of NHS Patients - Cancer: National Overview 1999/2000. 2002nd ed. Department of Health.

179. Logan ECM, Yates JM, Stewart RM, Fielding K, Kendrick D. Investigation and management of iron deficiency anaemia in general practice: a cluster randomised controlled trial of a simple management prompt. Postgrad Med J. 2002 Sep;78(923):533–7.

180. Jacob BJ, Moineddin R, Sutradhar R, Baxter NN, Urbach DR. Effect of colonoscopy on colorectal cancer incidence and mortality: an instrumental variable analysis. Gastrointest Endosc. 2012 Aug;76(2):355–64.e1.

181. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand J Gastroenterol. 1994 May;29(5):468–73.

182. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008 Jun;103(6):1541–9.

183. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007;(1):CD001216.

184. Bernie T, Les I, Paul G, Jan K, David W, Chris S. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. BMJ. 1998;317(7158):559–65.

185. Rees CJ, Bevan R. The National Health Service Bowel Cancer Screening Program: the early years. Expert Rev Gastroenterol Hepatol. 2013 Jul;7(5):421–37.

186. Macrae FA, St John DJ. Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancers or adenomas. Gastroenterology. 1982 May;82(5 Pt 1):891–8.

187. Greegor DH. Occult blood testing for detection of asymptomatic colon cancer. Cancer. 1971 Jul;28(1):131–4.

188. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJW, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010 May;59(5):666–89.

189. Weller DP, Campbell C. Uptake in cancer screening programmes: a priority in cancer control. Br J Cancer. Nature Publishing Group; 2009 Dec 3;101(Suppl 2):S55–9.

190. Baum M. Harms from breast cancer screening outweigh benefits if death caused by treatment is included. BMJ. 2013;346:f385.

191. Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, Walter LC. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. BMJ. 2013;346:e8441.

192. Chassin MR, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. JAMA. 1998 Sep;280(11):1000–5.

193. K L. Committee to Design a Strategy for Quality Review and Assurance. In: Medicare, editor. Medicare: a strategy for quality assurance. Washington, DC: National Academy Press, 1990.

194. Mainz J. Defining and classifying clinical indicators for quality improvement. Int J Qual Health Care. 2003 Dec;15(6):523–30.

195. Mulley AG. Improving productivity in the NHS. BMJ. 2010;341:c3965.

196. McColl A, Roderick P, Wilkinson E, Gabbay J, Smith H, Moore M, et al. Clinical

governance in primary care groups: the feasibility of deriving evidence-based performance indicators. Quality in Health Care. 2000 Jun 1;9(2):90–7.

197. Campbell SM, Roland MO, Buetow SA. Defining quality of care. Soc Sci Med. 2000 Dec;51(11):1611–25.

198. McArdle CS, Hole DJ. Outcome following surgery for colorectal cancer. British Medical Bulletin. 2002 Jan 1;64(1):119–25.

199. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ. 1996 May;312(7040):1215–8.

200. Sinha S, Peach G, Poloniecki JD, Thompson MM, Holt PJ. Studies using English administrative data (Hospital Episode Statistics) to assess health-care outcomes--systematic review and recommendations for reporting. The European Journal of Public Health. 2013 Jan 24;23(1):86–92.

201. Black N, Payne M. Directory of clinical databases: improving and promoting their use. Qual Saf Health Care. 2003 Oct;12(5):348–52.

202. Black N, Barker M, Payne M. Cross sectional survey of multicentre clinical databases in the United Kingdom. BMJ. 2004 Jun;328(7454):1478.

203. Campbell SE, Campbell MK, Grimshaw JM, Walker AE. A systematic review of discharge coding accuracy. J Public Health Med. 2001 Sep;23(3):205–11.

204. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. J Public Health (Oxf). 2012 Mar;34(1):138–48.

205. Westaby S, Archer N, Manning N, Adwani S, Grebenik C, Ormerod O, et al. Comparison of hospital episode statistics and central cardiac audit database in public reporting of congenital heart surgery mortality. BMJ. 2007 Oct;335(7623):759.

206. Steering Group on Health Services Information. Supplement to the 1st and 4th reports to the secretary of state. London: HMSO; 1985.

207. Scott N, Williams G, Parker M. Colorectal surgery performance. HESteria or hype? BMJ. 2011;343:d5947.

208. Goodyear SJ, Stallard N, Gaunt A, Parker R, Williams N, Wong L. Local impact of the English arm of the UK Bowel Cancer Screening Pilot study. Br J Surg. 2008 Sep;95(9):1172–9.

209. Logan RFA. The effects of population-based faecal occult blood test screening upon emergency colorectal cancer admissions in Coventry and north Warwickshire. Gut. 2008 Sep;57(9):1333–authorreply1333–4.

210. Davies RJ, Collins CD, Vickery CJ, Eyre-Brook I, Welbourn R. Reduction in the proportion of patients with colorectal cancer presenting as an emergency following the introduction of fast-track flexible sigmoidoscopy: a three-year prospective observational study. Colorectal Dis. 2004 Jul;6(4):265–7.

211. Garout M, Tilney HS, Tekkis PP, Aylin P. Comparison of administrative data with the Association of Coloproctology of Great Britain and Ireland (ACPGBI) colorectal cancer database. Int J Colorectal Dis. 2008 Feb;23(2):155–63.

212. Burns EM, Bottle A, Aylin P, Darzi A, Nicholls RJ, Faiz O. Variation in reoperation after colorectal surgery in England as an indicator of surgical performance: retrospective analysis of Hospital Episode Statistics. BMJ. 2011;343.

213. Malats N, Belloc J, Gallen M, Porta M. Disagreement between hospital medical records and a structured patient interview on the type and date of the first symptom in cancers of the digestive tract. Rev Epidemiol Sante Publique. 1995 Dec;43(6):533–40.

214. Porta M, Fernandez E, Belloc J, Malats N, Gallen M, Alonso J. Emergency admission for cancer: a matter of survival? Br J Cancer. 1998;77(3):477–84.

215. Aylin P, Bottle A, Elliott P, Jarman B. Surgical mortality: Hospital episode statistics v central cardiac audit database. BMJ. 2007 Oct;335(7625):839–authorreply839–40.

216. Dixon J, Sanderson C, Elliott P, Walls P, Jones J, Petticrew M. Assessment of the reproducibility of clinical coding in routinely collected hospital activity data: a study in two hospitals. J Public Health Med. 1998 Mar;20(1):63–9.

217. Nicholl J. Case-mix adjustment in non-randomised observational evaluations: the constant risk fallacy. J Epidemiol Community Health. 2007 Nov;61(11):1010–3.

218. DeCosse JJ, Ngoi SS, Jacobson JS, Cennerazzo WJ. Gender and colorectal cancer. Eur J Cancer Prev. 1993 Mar;2(2):105–15.

219. Corkum M, Urquhart R, Kendell C, Burge F, Porter G, Johnston G. Impact of comorbidity and healthcare utilization on colorectal cancer stage at diagnosis: literature review. Cancer Causes Control. 2012 Feb;23(2):213–20.

220. Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Loof L, Danielsson A, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol. 2002 Mar;36(3):321–7.

221. Kemppainen M, Raiha I, Rajala T, Sourander L. Delay in diagnosis of colorectal cancer in elderly patients. Age Ageing. 1993 Jul;22(4):260–4.

222. Gonzalez EC, Ferrante JM, Van Durme DJ, Pal N, Roetzheim RG. Comorbid illness and the early detection of cancer. South Med J. 2001 Sep;94(9):913–20.

223. Curless R, French JM, Williams GV, James OF. Colorectal carcinoma: do elderly patients present differently? Age Ageing. 1994 Mar;23(2):102–7.

224. Marshall JR, Funch DP. Gender and illness behavior among colorectal cancer patients. Women Health. 1986;11(3-4):67–82.

225. Gross CP, Andersen MS, Krumholz HM, McAvay GJ, Proctor D, Tinetti ME. Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer. JAMA. 2006 Dec;296(23):2815–22.

226. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. Journal of Chronic Diseases. 1970;23(7):455–68.

227. Jaen CR, Stange KC, Nutting PA. Competing demands of primary care: a model for the delivery of clinical preventive services. J Fam Pract. 1994 Feb;38(2):166–71.

228. Siddiqui AA, Spechler SJ, Huerta S, Dredar S, Little BB, Cryer B. Elevated HbA1c is an independent predictor of aggressive clinical behavior in patients with colorectal cancer: a

case-control study. Dig Dis Sci. 2008 Sep;53(9):2486–94.

229. Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer Detect Prev. 2006;30(5):466–72.

230. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. J Am Geriatr Soc. 2004 Oct;52(10):1681–7.

231. Mitry E, Rachet B. [Prognosis of colorectal cancer and socio-economic inequalities]. Gastroenterol Clin Biol. 2006 Apr;30(4):598–603.

232. Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. Br J Cancer. 2007 Oct;97(7):999–1004.

233. Schrijvers CT, Mackenbach JP. Cancer patient survival by socioeconomic status in seven countries: a review for six common cancer sites [corrected]. J Epidemiol Community Health. 1994 Oct;48(5):441–6.

234. Ionescu MV, Carey F, Tait IS, Steele RJ. Socioeconomic status and stage at presentation of colorectal cancer. Lancet. 1998 Oct;352(9138):1439.

235. Lejeune C, Sassi F, Ellis L, Godward S, Mak V, Day M, et al. Socio-economic disparities in access to treatment and their impact on colorectal cancer survival. Int J Epidemiol. 2010 Jun;39(3):710–7.

236. Korsgaard M, Pedersen L, Sorensen HT, Laurberg S. Reported symptoms, diagnostic delay and stage of colorectal cancer: a population-based study in Denmark. Colorectal Dis. 2006 Oct;8(8):688–95.

237. Neal RD, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: analysis of data from the "National Survey of NHS Patients: Cancer". Br J Cancer. 2005 Jun;92(11):1971–5.

238. Esteva M, Leiva A, Ramos M, Pita-Fernandez S, Gonzalez-Lujan L, Casamitjana M, et al. Factors related with symptom duration until diagnosis and treatment of symptomatic colorectal cancer. BMC Cancer. 2013;13:87.

239. Nur U, Rachet B, Parmar MKB, Sydes MR, Cooper N, Lepage C, et al. No socioeconomic inequalities in colorectal cancer survival within a randomised clinical trial. Br J Cancer. 2008 Dec;99(11):1923–8.

240. van Ryn M, Burke J. The effect of patient race and socio-economic status on physicians' perceptions of patients. Soc Sci Med. 2000 Mar;50(6):813–28.

241. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014 Mar;64(2):104–17.

242. Abraham KA, Thompson EB, Bodger K, Pearson M. Inequalities in outcomes of acute kidney injury in England. QJM. 2012 Jul 20;105(8):729–40.

243. Walker PP, Thompson E, Crone H, Flatt G, Holton K, Hill SL, et al. Use of mortality within 30 days of a COPD hospitalisation as a measure of COPD care in UK hospitals. Thorax. 2013 Jun 20.

244. Shawihdi M, Thompson E, Kapoor N, Powell G, Sturgess RP, Stern N, et al. Variation

in gastroscopy rate in English general practice and outcome for oesophagogastric cancer: retrospective analysis of Hospital Episode Statistics. Gut. 2013 Feb.

245. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40(5):373–83.

246. Office for National Statistics. Cancer Statistics [Internet]. Available from: http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843. Accessed Nov 2013

247. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004 Dec;57(12):1288–94.

248. Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. BMJ. 1998;317(7153):245–52.

249. Bodger K, Bowering K, Sarkar S, Thompson E, Pearson MG. All-cause mortality after first ERCP in England: clinically guided analysis of hospital episode statistics with linkage to registry of death. Gastrointest Endosc. 2011 Oct;74(4):825–33.

250. Iversen LH. Aspects of survival from colorectal cancer in Denmark. Dan Med J. 2012 Apr;59(4):B4428.

251. Moller H, Sandin F, Robinson D, Bray F, Klint S, Linklater KM, et al. Colorectal cancer survival in socioeconomic groups in England: variation is mainly in the short term after diagnosis. Eur J Cancer. 2012 Jan;48(1):46–53.

252. Cancer Mortality in Scotland [Internet]. 2011 ed. Information Services Department. Available from: http://www.isdscotland.org/Health-Topics/Cancer/Publications/2012-10-30/2012-10-30-CancerMortality-Report.pdf

253. Statistics OFN. Cancer survival in England [Internet]. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Cancer. Accessed Nov 2013

254. Gonzalez EC, Roetzheim RG, Ferrante JM, Campbell R. Predictors of proximal vs. distal colorectal cancers. Dis Colon Rectum. 2001 Feb;44(2):251–8.

255. Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. Lancet. 2000 Sep;356(9234):968–74.

256. Tannenbaum SL, Hernandez M, Zheng DD, Sussman DA, Lee DJ. Individual- and neighborhood-level predictors of mortality in Florida colorectal cancer patients. PLoS One. 2014;9(8):e106322.

257. McArdle CS, McMillan DC, Hole DJ. Male gender adversely affects survival following surgery for colorectal cancer. Br J Surg. 2003 Jun;90(6):711–5.

258. Wichmann MW, Muller C, Hornung HM, Lau-Werner U, Schildberg FW. Gender differences in long-term survival of patients with colorectal cancer. Br J Surg. 2001 Aug;88(8):1092–8.

259. Wu X, Cokkinides V, Chen VW, Nadel M, Ren Y, Martin J, et al. Associations of subsite-specific colorectal cancer incidence rates and stage of disease at diagnosis with county-level poverty, by race and sex. Cancer. 2006 Sep;107(5 Suppl):1121–7.

260. Cheng X, Chen VW, Steele B, Ruiz B, Fulton J, Liu L, et al. Subsite-specific incidence rate and stage of disease in colorectal cancer by race, gender, and age group in the United States, 1992-1997. Cancer. 2001 Nov;92(10):2547–54.

261. Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer. 2007 Mar;96(5):828–31.

262. Devesa SS, Chow WH. Variation in colorectal cancer incidence in the United States by subsite of origin. Cancer. 1993 Jun;71(12):3819–26.

263. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. Int J Cancer. 2011 Apr;128(7):1668–75.

264. Gonzalez EC, Roetzheim RG, Ferrante JM, Campbell R. Predictors of proximal vs. distal colorectal cancers. Dis Colon Rectum. 2001 Feb;44(2):251–8.

265. Munro AJ, Bentley AHM. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. Eur J Cancer Care (Engl). 2004 Jul;13(3):254–62.

266. Aylin P, Alves B, Best N, Cook A, Elliott P, Evans SJ, et al. Comparison of UK paediatric cardiac surgical performance by analysis of routinely collected data 1984-96: was Bristol an outlier? Lancet. 2001 Jul;358(9277):181–7.

267. Faiz O, Warusavitarne J, Bottle A, Tekkis PP, Clark SK, Darzi AW, et al. Nonelective excisional colorectal surgery in English National Health Service Trusts: a study of outcomes from Hospital Episode Statistics Data between 1996 and 2007. J Am Coll Surg. 2010 Apr;210(4):390–401.

268. Mays N. Reducing unwarranted variations in healthcare in the English NHS. BMJ. 2011;342:d1849.

269. Williams JG, Mann RY. Hospital episode statistics: time for clinicians to get involved? Clin Med. 2002 Jan;2(1):34–7.

270. Raftery J, Roderick P, Stevens A. Potential use of routine databases in health technology assessment. Health Technol Assess. 2005 May;9(20):1–92–iii–iv.

271. Steele RJC, McClements P, Watling C, Libby G, Weller D, Brewster DH, et al. Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. Gut. 2012 Apr;61(4):576–81.

272. Koo JH, Jalaludin B, Wong SKC, Kneebone A, Connor SJ, Leong RWL. Improved survival in young women with colorectal cancer. Am J Gastroenterol. 2008 Jun;103(6):1488–95.

273. Nelson RL, Dollear T, Freels S, Persky V. The relation of age, race, and gender to the subsite location of colorectal carcinoma. Cancer. 1997 Jul;80(2):193–7.

274. De Marco MF, Janssen-Heijnen ML, van der Heijden LH, Coebergh JW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. Eur J Cancer. 2000 Jan;36(1):95–9.

275. Stower MJ, Hardcastle JD. The results of 1115 patients with colorectal cancer treated over an 8-year period in a single hospital. Eur J Surg Oncol. 1985 Jun;11(2):119–23.

276. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sorensen HT. Age and colorectal cancer with focus on the elderly: trends in relative survival and initial treatment from a Danish population-based study. Dis Colon Rectum. 2005 Sep;48(9):1755–63.

277. Yancik R, Wesley MN, Ries LA, Havlik RJ, Long S, Edwards BK, et al. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer. 1998 Jun;82(11):2123–34.

278. Palser TR, Cromwell DA, Hardwick RH, Riley SA, Greenaway K, van der Meulen JHP. Impact of route to diagnosis on treatment intent and 1-year survival in patients diagnosed with oesophagogastric cancer in England: a prospective cohort study. BMJ Open. 2013;3(2).

279. Chen HS, Sheen-Chen SM. Obstruction and perforation in colorectal adenocarcinoma: an analysis of prognosis and current trends. Surgery. 2000 Apr;127(4):370–6.

280. Chohan DPK, Goodwin K, Wilkinson S, Miller R, Hall NR. How has the "two-week wait" rule affected the presentation of colorectal cancer? Colorectal Dis. 2005 Sep;7(5):450–3.

281. Ratcliffe R, Kiff RS, Kingston RD, Walsh SH, Jeacock J. Early diagnosis in colorectal cancer. Still no benefit? J R Coll Surg Edinb. 1989 Jun;34(3):152–5.

282. Cleary J, Peters TJ, Sharp D, Hamilton W. Clinical features of colorectal cancer before emergency presentation: a population-based case-control study. Fam Pract. 2007 Feb;24(1):3–6.

283. Porta M, Gallen M, Belloc J, Malats N. Predictors of the interval between onset of symptoms and first medical visit in patients with digestive tract cancer. Int J Oncol. 1996 May;8(5):941–9.

284. Mohammed MA, Sidhu KS, Rudge G, Stevens AJ. Weekend admission to hospital has a higher risk of death in the elective setting than in the emergency setting: a retrospective database study of national health service hospitals in England. BMC Health Serv Res. 2012;12:87.

285. Hwang H. Emergency presentation of colorectal cancer at a regional hospital: An alarming trend? BCMJ. 54:83–7.

286. Sjo OH, Larsen S, Lunde OC, Nesbakken A. Short term outcome after emergency and elective surgery for colon cancer. Colorectal Dis. 2009 Sep;11(7):733–9.

287. Fielding LP, Phillips RK, Hittinger R. Factors influencing mortality after curative resection for large bowel cancer in elderly patients. Lancet. 1989 Mar;1(8638):595–7.

288. Waldron RP, Donovan IA, Drumm J, Mottram SN, Tedman S. Emergency presentation and mortality from colorectal cancer in the elderly. Br J Surg. 1986 Mar;73(3):214–6.

289. Faivre-Finn C, Bouvier-Benhamiche A-M, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. Gut. 2002 Jul;51(1):60–4.

290. Edwards RT, Bransom CJ, Crosby DL, Pathy MS. Colorectal carcinoma in the elderly: a geriatric and surgical practice compared. Age Ageing. 1983 Aug;12(3):256–62.

291. Singh H, Daci K, Petersen LA, Collins C, Petersen NJ, Shethia A, et al. Missed

opportunities to initiate endoscopic evaluation for colorectal cancer diagnosis. Am J Gastroenterol. 2009 Oct;104(10):2543–54.

292. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg. 2004 Jun;28(6):558–62.

293. Lin J-T, Wang W-S, Yen C-C, Liu J-H, Yang M-H, Chao T-C, et al. Outcome of colorectal carcinoma in patients under 40 years of age. J Gastroenterol Hepatol. 2005 Jun;20(6):900–5.

294. Chan KK, Dassanayake B, Deen R, Wickramarachchi RE, Kumarage SK, Samita S, et al. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and long-term: analysis of survival and prognostic markers. World J Surg Oncol. 2010;8:82.

295. Mitry E, Benhamiche AM, Jouve JL, Clinard F, Finn-Faivre C, Faivre J. Colorectal adenocarcinoma in patients under 45 years of age: comparison with older patients in a well-defined French population. Dis Colon Rectum. 2001 Mar;44(3):380–7.

296. Farraye FA, Wong M, Hurwitz S, Puleo E, Emmons K, Wallace MB, et al. Barriers to endoscopic colorectal cancer screening: are women different from men? Am J Gastroenterol. 2004 Feb;99(2):341–9.

297. Menees SB, Inadomi JM, Korsnes S, Elta GH. Women patients' preference for women physicians is a barrier to colon cancer screening. Gastrointest Endosc. 2005 Aug;62(2):219–23.

298. Kim WH, Cho YJ, Park JY, Min PK, Kang JK, Park IS. Factors affecting insertion time and patient discomfort during colonoscopy. Gastrointest Endosc. 2000 Nov;52(5):600–5.

299. Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. BMJ. 1998;317(7153):245–52.

300. Cowling TE, Cecil EV, Soljak MA, Lee JT, Millett C, Majeed A, et al. Access to primary care and visits to emergency departments in England: a cross-sectional, population-based study. PLoS One. 2013;8(6):e66699.

301. Smothers L, Hynan L, Fleming J, Turnage R, Simmang C, Anthony T. Emergency surgery for colon carcinoma. Dis Colon Rectum. 2003 Jan;46(1):24–30.

302. Anderson JH, Hole D, McArdle CS. Elective versus emergency surgery for patients with colorectal cancer. Br J Surg. 1992 Jul;79(7):706–9.

303. Johal A, Mitchell D, Lees T, Cromwell D, van der Meulen J. Use of Hospital Episode Statistics to investigate abdominal aortic aneurysm surgery. Br J Surg. John Wiley & Sons, Ltd; 2012 Jan 1;99(1):66–72.

304. Biondo S, Marti-Rague J, Kreisler E, Pares D, Martin A, Navarro M, et al. A prospective study of outcomes of emergency and elective surgeries for complicated colonic cancer. Am J Surg. 2005 Apr;189(4):377–83.

305. Wagner von C, Good A, Wright D, Rachet B, Obichere A, Bloom S, et al. Inequalities in colorectal cancer screening participation in the first round of the national screening programme in England. Br J Cancer. 2009 Dec;101 Suppl 2:S60–3.

306. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010 Feb;116(3):544–73.

307. Jemal A, Clegg LX, Ward E, Ries LAG, Wu X, Jamison PM, et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. Cancer. 2004 Jul;101(1):3–27.

308. Group UCCSP. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ. 2004;329(7458):133.

309. McClements PL, Madurasinghe V, Thomson CS, Fraser CG, Carey FA, Steele RJC, et al. Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiol. 2012 Aug;36(4):e232–42.

310. Weller D, Coleman D, Robertson R, Butler P, Melia J, Campbell C, et al. The UK colorectal cancer screening pilot: results of the second round of screening in England. Br J Cancer. Nature Publishing Group; 2007;97(12):1601–5.

311. Moayyedi P, Achkar E. Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. Am J Gastroenterol. 2006 Feb;101(2):380–4.

312. Cancer cure rates improving in Europe JA . Cancer Research UK. http://www.cancerresearchuk.org/about-us/cancer-news/news-report/2009-03-25-cancer-cure-rates-improving-in-europe. Accessed Nov 2013.

313. Burch JA, Soares-Weiser K, St John DJB, Duffy S, Smith S, Kleijnen J, et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. J Med Screen. 2007;14(3):132–7.

314. BCSP Intranet [Internet]. Available from: http://www.bcsp.nhs.uk/pi/statistics_documents. Accessed Nov 2013.

315. UK CR, editor. Charity predicts 20,000 fewer deaths from bowel cancer [Internet]. Available from: http://info.cancerresearchuk.org/news/archive/pressrelease/2007-07-24-charity-predicts-20000-fewer-deaths-from-bowel-cancer. Accessed Nov 2013.

316. Croswell JM, Ransohoff DF, Kramer BS. Principles of Cancer Screening: Lessons from History and Study Design Issues. Seminars in oncology. 2010 Jun 1;37(3):202–15.

317. Day NE. The theoretical basis for cancer screening. Cancer Treat Res. 1996;86:9–24.

318. Etzioni RD, Connor RJ, Porok PC, Self SG. Design and analysis of cancer screening trials. Stat Methods Med Res. 1995 Mar;4(1):3–17.

319. Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ. 2011;342:d1539.

320. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev. 2013;1:CD004720.

321. Mechanic D, Tanner J. Vulnerable people, groups, and populations: societal view. Health Aff (Millwood). 2007 Sep;26(5):1220–30.

322. McCaffery K, Wardle J, Waller J. Knowledge, attitudes, and behavioral intentions in

relation to the early detection of colorectal cancer in the United Kingdom. Prev Med. 2003 May;36(5):525–35.

323. Minopoulos GI, Lyratzopoulos N, Efremidou HI, Romanidis K, Koujoumtzi I, Manolas KJ. Emergency operations for carcinoma of the colon. Tech Coloproctol. 2004 Nov;8 Suppl 1:s235–7.

324. Goodyear SJ, Leung E, Menon A, Pedamallu S, Williams N, Wong LS. The effects of population-based faecal occult blood test screening upon emergency colorectal cancer admissions in Coventry and north Warwickshire. Gut. 2008 Jan 1;57(2):218–22.

325. Bowel Cancer Screening Programme;roll-out [Internet]. Available from: http://www.cancerscreening.nhs.uk/bowel/roll-out.html. Accessed Nov 2013.

326. Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer. 2004 Apr;90(7):1367–73.

327. Sloggett A, Joshi H. Higher mortality in deprived areas: community or personal disadvantage? BMJ. 1994 Dec;309(6967):1470–4.

328. Macleod U, Mitchell E, Black M, Spence G. Comorbidity and socioeconomic deprivation: an observational study of the prevalence of comorbidity in general practice. Eur J Gen Pract. 2004 Mar;10(1):24–6.

329. Dixon A, Le Grand J, Henderson J, Murray R, Poteliakhoff E. Is the British National Health Service equitable? The evidence on socioeconomic differences in utilization. J Health Serv Res Policy. 2007 Apr;12(2):104–9.

330. Gordon-Dseagu V. Cancer and Health Inequalities; an introduction to current evidence

[Internet]. Cancer Research UK. Available from: http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/crukmig_1000ast-3344.pdf. Accessed Nov 2013.

331. Kobayashi LC, Wardle J, Wagner von C. Limited health literacy is a barrier to colorectal cancer screening in England: evidence from the English Longitudinal Study of Ageing. Prev Med. 2014 Apr;61:100–5.

332. Lindau ST, Tomori C, McCarville MA, Bennett CL. Improving rates of cervical cancer screening and Pap smear follow-up for low-income women with limited health literacy. Cancer Invest. 2001;19(3):316–23.

333. Gostick J, Fry T, Evans M, Manku M, Corallo D, Lighting P. Tackling Cancer: Improving the Patient Journey. Department of Health.

334. Protheroe J, Nutbeam D, Rowlands G. Health literacy: a necessity for increasing participation in health care. Br J Gen Pract. 2009 Oct;59(567):721–3.

335. Boulos MNK. British internet-derived patient information on diabetes mellitus: is it readable? Diabetes Technol Ther. 2005 Jun;7(3):528–35.

336. Baker D, Middleton E. Cervical screening and health inequality in England in the 1990s. J Epidemiol Community Health. 2003 Jun;57(6):417–23.

337. Tappenden P, Chilcott J, Eggington S, Sakai H, Karnon J, Patnick J. Option appraisal of

population-based colorectal cancer screening programmes in England. Gut. 2007 May 1;56(5):677–84.

338. Peacock O, Clayton S, Atkinson F, Tierney GM, Lund JN. "Be Clear on Cancer": the impact of the UK National Bowel Cancer Awareness Campaign. Colorectal Dis. 2013 Aug;15(8):963–7.

339. Rajasekhar PT, Ritchie M, Rutter MD, Clifford G, Waddup G, Dempsey N, et al. Lower gastrointestinal symptoms are prevalent among individuals colonoscoped within the Bowel Cancer Screening Programme. Colorectal Dis. 2012 Sep;14(9):e603–7.

340. Pande R, Leung E, McCullough P, Smith S, Harmston C. Impact of the United kingdom national bowel cancer awareness campaign on colorectal services. Dis Colon Rectum. 2014 Jan;57(1):70–5.

341. Bethune R, Marshall MJ, Mitchell SJ, Oppong C, Cartmel MT, Arumugam PJ, et al. Did the "Be Clear on Bowel Cancer" public awareness campaign pilot result in a higher rate of cancer detection? Postgrad Med J. 2013 Jul;89(1053):390–3.

342. Peacock O, Clayton S, Atkinson F, Tierney GM, Lund JN. "Be Clear on Cancer": the impact of the UK National Bowel Cancer Awareness Campaign. Colorectal Dis. 2013 Aug;15(8):963–7.

343. Lee TJW, Clifford GM, Rajasekhar P, Rutter MD, Kometa S, Ritchie MC, et al. High yield of colorectal neoplasia detected by colonoscopy following a positive faecal occult blood test in the NHS Bowel Cancer Screening Programme. J Med Screen. 2011;18(2):82–6.

344. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol. 2010 Nov;105(11):2457–64.

345. Massat NJ, Moss SM, Halloran SP, Duffy SW. Screening and primary prevention of colorectal cancer: a review of sex-specific and site-specific differences. J Med Screen. 2013;20(3):125–48.

346. Gill MD, Bramble MG, Rees CJ, Lee TJW, Bradburn DM, Mills SJ. Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. Br J Cancer. 2012 Jul;107(3):417–21.

347. Nnoaham KE, Lines C. Modelling future capacity needs and spending on colonoscopy in the English bowel cancer screening programme. Gut. 2008 Sep;57(9):1238–45.

348. Longworth L, Youn J, Bojke L, Palmer S, Griffin S, Spackman E, et al. When does NICE recommend the use of health technologies within a programme of evidence development? : a systematic review of NICE guidance. Pharmacoeconomics. 2013 Feb;31(2):137–49.

349. Goyder E, Barratt A, Irwig LM. Telling people about screening programmes and screening test results: how can we do it better? J Med Screen. 2000;7(3):123–6.

350. Fletcher J, Hicks NR, Kay JD, Boyd PA. Using decision analysis to compare policies for antenatal screening for Down's syndrome. BMJ. 1995 Aug;311(7001):351–6.

351. Bogardus STJ, Holmboe E, Jekel JF. Perils, pitfalls, and possibilities in talking about medical risk. JAMA. 1999 Mar;281(11):1037–41.

352. Schroy PC3, Emmons KM, Peters E, Glick JT, Robinson PA, Lydotes MA, et al. Aid-assisted decision making and colorectal cancer screening: a randomized controlled trial. Am J Prev Med. 2012 Dec;43(6):573–83.

353. Bretthauer M, Hoff G. Comparative effectiveness research in cancer screening programmes. BMJ. 2012;344:e2864.

354. Steele RJ, McDonald PJ, Digby J, Brownlee L, Strachan JA, Libby G, et al. Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity. United European Gastroenterol J. 2013 Jun;1(3):198–205.

Appendices

Appendix 1.
Appendix 1.1. A list of red flag codes searched in positions 1 to 7

HES code	ICD-10 diagnosis
K625	Haemorrhage of anus and rectum
K566	Other and unspecified intestinal obstruction
R11X	Nausea and vomiting
R104	Other and unspecified abdominal pain
K590	Constipation
R18X	Ascites
R634	Abnormal weight loss
K631	Perforation of intestine (nontraumatic)
K921	Melaena
K650	Acute peritonitis
R103	Pain localized to other parts of lower abdomen
R194	Change in bowel habit
R190	Intra-abdominal and pelvic swelling mass and lump
K922	Gastrointestinal haemorrhage unspecified
K920	Haematemesis
R53X	Malaise and fatigue
N321	Vesicointestinal fistula
K659	Peritonitis unspecified
K632	Fistula of intestine
K259	Unspec as acute or chronic w out haemorrhage or perforation
R630	Anorexia
R14X	Flatulence and related conditions
K269	Unspec as acute or chronic w out haemorrhage or perforation

R15X	Faecal incontinence
N823	Fistula of vagina to large intestine
K624	Stenosis of anus and rectum
K562	Volvulus
A09X	Diarrhoea and gastroenteritis of presumed infectious origin
K623	Rectal prolapse
K593	Megacolon not elsewhere classified
K561	Intussusception
R100	Acute abdomen

Appendix 1.2 . A list of anaemia codes searched in positions 1 to 7

HES code	**ICD Diagnosis**
D649	Anaemia unspecified
D509	Iron deficiency anaemia unspecified
D508	Other iron deficiency anaemias
D630	Anaemia in neoplastic disease
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D638	Anaemia in other chronic diseases classified elsewhere

Appendix 1.3. A list of gastrointestinal type diagnostic codes searched in positions 1 to 7

HES code	**ICD-10 diagnosis**
A09X	Diarrhoea and gastroenteritis of presumed infectious origin
A047	Enterocolitis due to Clostridium difficile
A084	Viral intestinal infection unspecified
C169	Malignant neoplasm of stomach unspecified
C211	Malignant neoplasm of anal canal
D120	Malignant neoplasm of anal canal
D122	Benign neoplasm of ascending colon
D123	Benign neoplasm of transverse colon
D124	Benign neoplasm of descending colon
D125	Benign neoplasm of sigmoid colon
D126	Benign neoplasm of colon unspecified
D127	Benign neoplasm of rectosigmoid junction
D128	Benign neoplasm of rectum
D131	Benign neoplasm of stomach
D135	Benign neoplasm of extrahepatic bile ducts
D376	Neo uncert / unkn behav liver gallbladder and bile ducts
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D508	Other iron deficiency anaemias
D509	Iron deficiency anaemia unspecified
D62X	Acute posthaemorrhagic anaemia
D630	Anaemia in neoplastic disease
D638	Anaemia in other chronic diseases classified elsewhere
D649	Anaemia unspecified

I846	Residual haemorrhoidal skin tags
I848	Unspecified haemorrhoids with other complications
I849	Unspecified haemorrhoids without complication
I859	Oesophageal varices without bleeding
K20X	Oesophagitis
K210	Gastro-oesophageal reflux disease with oesophagitis
K219	Gastro-oesophageal reflux disease without oesophagitis
K221	Ulcer of oesophagus
K222	Oesophageal obstruction
K228	Other specified diseases of oesophagus
K257	Gastric ulcer chronic without haemorrhage or perforation
K259	Unspec as acute or chronic w out haemorrhage or perforation
K264	Duodenal ulcer chronic or unspecified with haemorrhage
K269	Unspec as acute or chronic w out haemorrhage or perforation
K291	Other acute gastritis
K294	Chronic atrophic gastritis
K295	Chronic gastritis unspecified
K296	Other gastritis
K297	Gastritis unspecified
K298	Duodenitis
K299	Gastroduodenitis unspecified
K315	Obstruction of duodenum
K317	Polyp of stomach and Duodenum
K319	Disease of stomach and duodenum unspecified
K350	Acute appendicitis with generalized peritonitis
K359	Acute appendicitis unspecified
K409	Unilat or unspec inguin hernia without obstruct or gangrene
K501	Crohn s disease of large intestine
K509	Crohn s disease unspecified
K519	Ulcerative colitis unspecified
K521	Toxic gastroenteritis and colitis
K529	Noninfective gastroenteritis and colitis unspecified
K552	Angiodysplasia of colon
K560	Paralytic ileus
K561	Intussusception
K562	Volvulus
K565	Intestinal adhesions [bands] with obstruction
K566	Other and unspecified intestinal obstruction
K567	Ileus unspecified
K571	Diverticular dis of small intestine without perf or abscess
K572	Diverticular dis of large intestine with perf and abscess
K573	Diverticular dis of large intestine without perf or abscess
K578	Diverticular dis of intest part unspec with perf and absces
K579	Divertic dis of intest part unspec without perf or abscess
K589	Irritable bowel syndrome without diarrhoea
K590	Constipation
K593	Megacolon not elsewhere classified
K603	Anal fistula

K610	Anal abscess
K611	Rectal abscess
K620	Anal polyp
K621	Rectal polyp
K623	Rectal prolapse
K624	Stenosis of anus and rectum
K625	Haemorrhage of anus and rectum
K625	Haemorrhage of anus and rectum
K626	Ulcer of anus and rectum
K627	Radiation proctitis
K628	Other specified diseases of anus and rectum
K631	Perforation of intestine (nontraumatic)
K632	Fistula of intestine
K633	Ulcer of intestine
K635	Polyp of colon
K638	Other specified diseases of intestine
K650	Acute peritonitis
K658	Other peritonitis
K659	Peritonitis unspecified
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage unspecified
L299	Pruritus unspecified
N321	Vesicointestinal fistula
N823	Fistula of vagina to large intestine
N823	Fistula of vagina to large intestine
Q430	Meckel s diverticulum
R100	Acute abdomen
R101	Pain localized to upper abdomen
R103	Pain localized to other parts of lower abdomen
R104	Other and unspecified abdominal pain
R11X	Nausea and vomiting
R13X	Dysphagia
R14X	Flatulence and related conditions
R15X	Faecal incontinence
R18X	Ascites
R190	Intra-abdominal and pelvic swelling mass and lump
R194	Change in bowel habit
R53X	Malaise and fatigue
R630	Anorexia
R634	Abnormal weight loss
R634	Abnormal weight loss
R932	Abn findings diagnostic imaging of liver and biliary tract
R933	Abn finds diagnostic imaging of oth parts of digestive trac
Z931	Gastrostomy status
Z934	Other artificial openings of gastrointestinal tract status

Appendix 2.

Appendix 2.1. A list of codes for lower gastrointestinal endoscopy searched in positions 1 to 14

HES code	OPCS-4 description of procedure
H221	Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon
H251	Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fibreoptic sigmoidoscope
H281	Diagnostic endoscopic examination of sigmoid colon and biopsy of lesion of sigmoid colon using rigid sigmoidoscope
H681	Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using colonoscope
H682	Diagnostic endoscopic examination of colonic pouch using colonoscope nec
H683	Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using colonoscope
H684	Diagnostic endoscopic examination of ileoanal pouch using colonoscope nec
H691	Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using fibreoptic sigmoidoscope
H692	Diagnostic endoscopic examination of colonic pouch using fibreoptic sigmoidoscope nec
H693	Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using fibreoptic sigmoidoscope
H694	Diagnostic endoscopic examination of ileoanal pouch using fibreoptic sigmoidoscope nec
H701	Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using rigid sigmoidoscope
H702	Diagnostic endoscopic examination of colonic pouch using rigid sigmoidoscope nec
H703	Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using rigid sigmoidoscope
H704	Diagnostic endoscopic examination of ileoanal pouch using rigid sigmoidoscope nec

Appendix 2.2. A list of gastrointestinal type procedure codes searched in positions 1 to 7

HES code	OPCS-4 description of procedure
G451	Fibreoptic endoscopic examination of upper gastrointestinal tract and biopsy of lesion of upper gastrointestinal tract
G459	Unspecified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract
T462	Drainage of ascites NEC
T461	Paracentesis abdominis for ascites
U082	Ultrasound of abdomen
U081	Computed tomography of abdomen NEC
U091	Computed tomography of pelvis
Y981	Radiology of one body area (or < 20 minutes)
Y982	Radiology of two body areas
X339	Unspecified other blood transfusion
U175	Computed tomography of colon
Y972	Radiology with pre contrast
U011	Computed tomography of whole body
U211	Magnetic resonance imaging NEC
U174	Barium enema

U091	Computed tomography of pelvis

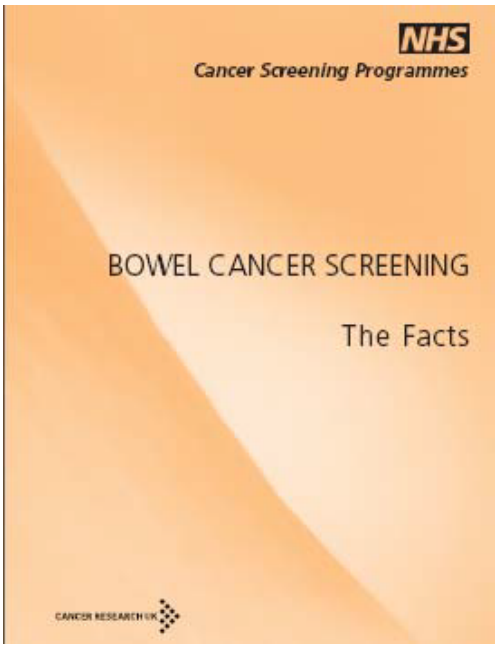
Appendix 3.

Appendix 3.1. A list of codes for colorectal resections and diversion operations searched in positions 1 to 14

HES code	OPCS-4 description of procedure
H333	Ant resection
H334	Ant resection
H335	AP resection
H331	AP resection
H336	AP resection and col
H072	Rt hemi
H073	Rt hemi
H071	Rt hemi
H078	Rt hemi
G722	Rt hemi
H064	Rt hemi and ileostomy
H074	Rt hemi and ileostomy
H061	Extended rt hemi and anas
H063	Extended rt hemi and anas
H069	Extended rt hemi and anas
H068	Extended rt hemi and anas
H151	Loop colostomy
H152	End colostomy
G742	Defunctioning ileostomy
G743	Defunctioning ileostomy
H101	Sigmoid colectomy + anas
H102	Sigmoid colectomy + anas
H102	Sigmoid colectomy + anas
H105	Sigmoid colectomy + anas and colostomy
H104	Sigmoid colectomy + anas and ilestomy
H091	Left hemi and anas
H092	Left hemi and anas
H093	Left hemi and anas
H098	Left hemi and anas
H099	Left hemi and anas
H095	Left hemi and anas and colostomy
H094	Left hemi and anas and ileostomy
G741	Creation continemt ileostomy
H298	Subtotal colostomy
H114	Colectomy and ilesotomy
H053	Colectomy and ilesotomy

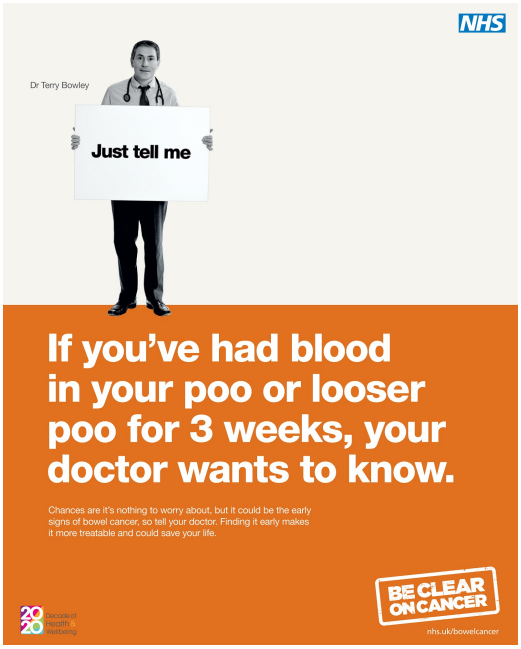
H131	Colectomy and anas
G723	Colectomy and anas
H112	Colectomy and anas
H051	Colectomy and anas
H111	Colectomy and anas
H113	Colectomy and anas
H108	Unspec Sigmoid colectomy
H109	Unspec Sigmoid colectomy
H081	Transverse colectomy and Anas
H082	Transverse colectomy and Anas
H083	Transverse colectomy and Anas
H133	Transverse colectomy and Anas
H089	Transverse colectomy and Anas
H118	Unspec colectomy
H119	Unspec colectomy
H059	Unspec colectomy
H338	Rectal excision
H339	same as ant resection
H341	same as ant resection
H332	Proctolcolectomy and anas to Anus
G725	Colectomy and pouch
H042	Colectomy and pouch
H293	Colectomy and pouch
H291	Colectomy and pouch
H292	Colectomy and pouch
H294	Colectomy and pouch
H084	Total colectomy and anastomosis
H085	Total colectomy and anastomosis
G724	ileal to rectal anas
H041	Panproctocolectomy and ileostomy
H299	Unspec subtotal colectomy
H159	Unspec exteriorsation
H115	colectomy and exterior
H079	rt colon exteriorised
H158	other bowel exteriorisation

Appendix 4. The front-page of a booklet sent in the post to all participants offered screening.



Appendix 5. A poster designed to be displayed in the primary care setting as well as local community centres.

Appendix 6. A poster used to accompany a television and print media advertising campaign.

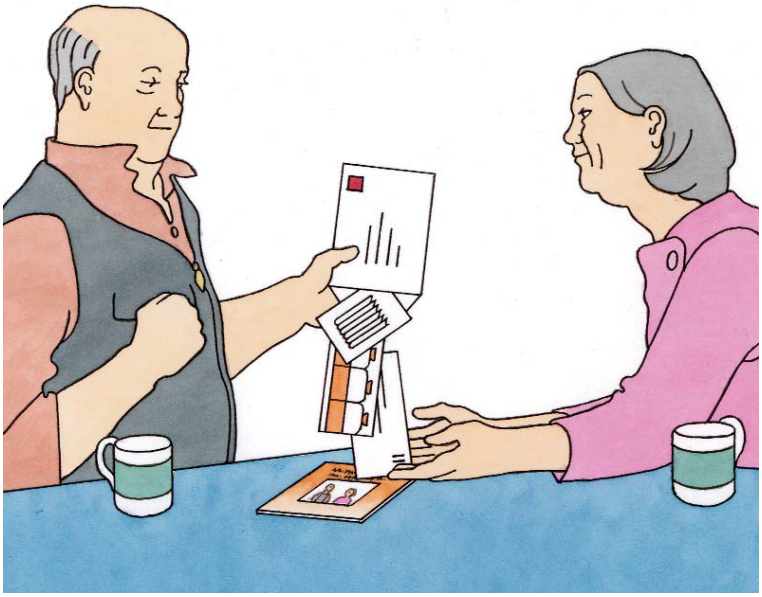


Appendix 7. A poster designed to encourage men to join in the screening programme, using a sports theme to encourage participation.

Appendix 8. A poster designed to encourage men's spouses to encourage their participation.

Appendix 9. A page from the pictorial booklet 'Easy Guide to Bowel Cancer Screening' that is aimed

at people with learning difficulties.



Appendix 10. A list of the screening centres that serve each of the 152 PCTs, along with the start date of screening. Note that some PCTs are served by more than one screening centre.

Screening Centre	PCT Name	PCT Code	Screening start date
Wolverhampton	WOLVERHAMPTON CITY PCT	5MV	01.07.2006
Wolverhampton	WALSALL TEACHING PCT	5M3	01.07.2006
Wolverhampton	DUDLEY PCT	5PE	01.07.2006
Wolverhampton	SOUTH STAFFORDSHIRE PCT (1)	5PK	01.07.2006
Wolverhampton	SHROPSHIRE COUNTY PCT	5M2	01.07.2006
Wolverhampton	TELFORD AND WREKIN PCT	5MK	01.07.2006
Cheshire & Merseyside	LIVERPOOL PCT	5NL	01.09.2006
Cheshire & Merseyside	SEFTON PCT	5NJ	01.09.2006
Cheshire & Merseyside	WIRRAL PCT	5NK	01.09.2006
Cheshire & Merseyside	CENTRAL AND EASTERN CHESHIRE PCT	5NP	01.09.2006
Cheshire & Merseyside	WESTERN CHESHIRE PCT	5NN	01.09.2006
Cheshire & Merseyside	WARRINGTON PCT	5J2	01.09.2006
Cheshire & Merseyside	HALTON AND ST HELENS PCT	5NM	01.09.2006
Cheshire & Merseyside	KNOWSLEY PCT	5J4	01.09.2006
Bolton	ASHTON, LEIGH AND WIGAN PCT	5HG	01.02.2007
Bolton	BOLTON PCT	5HQ	01.02.2007
Bolton	SALFORD PCT	5F5	01.02.2007
Heart of England	SOUTH STAFFORDSHIRE PCT (1)	5PK	01.04.2007
Heart of England	SOLIHULL CARE TRUST	TAM	01.04.2007
Heart of England	BIRMINGHAM EAST AND NORTH PCT	5PG	01.04.2007
Coventry and Warwickshire	COVENTRY TEACHING PCT	5MD	01.07.2007

Coventry and Warwickshire	WARWICKSHIRE PCT	5PM	01.07.2007
Sandwell & W Birmingham	SANDWELL PCT	5PF	01.03.2008
Sandwell & W Birmingham	HEART OF BIRMINGHAM TEACHING PCT	5MX	01.03.2008
Sandwell & W Birmingham	SOUTH BIRMINGHAM PCT	5M1	01.03.2008
Cumbria and Westmorland	CUMBRIA PCT	5NE	01.03.2008
Pennine	BURY PCT	5JX	01.04.2008
Pennine	HEYWOOD, MIDDLETON & ROCHDALE PCT	5NQ	01.04.2008
Pennine	OLDHAM PCT	5J5	01.04.2008
Pennine	MANCHESTER PCT	5NT	01.04.2008
Lancashire	NORTH LANCASHIRE PCT	5NF	01.04.2008
Lancashire	BLACKPOOL PCT	5HP	01.04.2008
Lancashire	CENTRAL LANCASHIRE PCT	5NG	01.04.2008
Lancashire	EAST LANCASHIRE PCT	5NH	01.04.2008
Lancashire	BLACKBURN WITH DARWEN PCT	5NP	01.04.2008
North Staffordshire	STOKE ON TRENT PCT	5PJ	01.09.2008
North Staffordshire	NORTH STAFFORDSHIRE PCT	5PH	01.09.2008
North Staffordshire	SOUTH STAFFORDSHIRE PCT	5PK	01.09.2008
Withington	STOCKPORT PCT	5F7	01.12.2009
Withington	TRAFFORD PCT	5NR	01.12.2009
Withington	TAMESIDE AND GLOSSOP PCT	5LH	01.12.2009
Hereford and Worcestershire	HEREFORDSHIRE PCT	5CN	01.09.2009
Hereford and Worcestershire	WORCESTERSHIRE PCT	5PL	01.09.2009
South Devon	DEVON PCT (13)	5QQ	01.09.2006
South Devon	TORBAY CARE TRUST	5CW	01.09.2006
South Devon	PLYMOUTH TEACHING PCT	5F1	01.09.2006
Gloucestershire	GLOUCESTERSHIRE PCT	5QH	01.01.2007
Solent and West Sussex	PORTSMOUTH CITY PRIMARY CARE TRUST	5FE	01.03.2007
Solent and West Sussex	HAMPSHIRE PCT (2)	5QC	01.03.2007
Solent and West Sussex	WEST SUSSEX PCT (3)	5P6	01.03.2007
Solent and West Sussex	ISLE OF WIGHT NHS PCT	5QT	01.03.2007
Dorset	DORSET PCT	5QM	01.03.2008
Dorset	BOURNEMOUTH & POOLE PCT	5QN	01.03.2008
Dorset	HAMPSHIRE PCT (2)	5QC	01.03.2008
Hampshire	HAMPSHIRE PCT (2)	5QC	01.03.2008
Hampshire	SOUTHAMPTON CITY PCT	5Q1	01.03.2008
Somerset	SOMERSET PCT	5QL	01.03.2008
Berkshire	BERKSHIRE WEST PCT	5QF	01.05.2008
Berkshire	BERKSHIRE EAST PCT	5QG	01.05.2008
Surrey	SURREY PCT	5P5	01.09.2008
Surrey	WEST SUSSEX PCT	5P6	01.09.2008
Surrey	HAMPSHIRE PCT (2)	5QC	01.09.2008
Sussex	BRIGHTON AND HOVE CITY PCT	5LQ	01.11.2008
Sussex	EAST SUSSEX DOWNS & WEALD	5P7	01.11.2008

	PCT (4)		
Sussex	WEST SUSSEX PCT (3)	5P6	01.11.2008
Sussex	HASTINGS & ROTHER PCT	5P8	01.11.2008
Cornwall	CORNWALL & ISLES OF SCILLY PCT	5QP	01.10.2009
Exeter and North Devon	DEVON PCT (13)	5QQ	01.06.2009
Bath, Swindon and Wiltshire	BATH AND NORTH EAST SOMERSET PCT	5FL	01.02.2009
Bath, Swindon and Wiltshire	SWINDON PCT	5K3	01.02.2009
Bath, Swindon and Wiltshire	WILTSHIRE PCT	5QK	01.02.2009
East Kent	EASTERN & COASTAL KENT PCT (5)	5QA	01.04.2009
Oxford	OXFORDSHIRE PCT	5QE	01.01.2010
Buckinghamshire	BUCKINGHAMSHIRE PCT	5QD	01.10.2009
Buckinghamshire	MILTON KEYNES PCT	5CQ	01.10.2009
West Kent and Medway	WEST KENT PCT	5P9	01.07.2009
West Kent and Medway	MEDWAY PCT	5L3	01.07.2009
West Kent and Medway	EASTERN & COASTAL KENT PCT (5)	5QA	01.07.2009
West Kent and Medway	EAST SUSSEX DOWNS & WEALD PCT (4)	5P7	01.07.2009
Bristol and Weston	BRISTOL PCT	5QJ	01.12.2008
Bristol and Weston	SOUTH GLOUCESTERSHIRE PCT	5A3	01.12.2008
Bristol and Weston	NORTH SOMERSET PCT	5M8	01.12.2008
St Marks	BRENT TEACHING PCT	5K5	01.10.2006
St Marks	HARROW PCT	5K6	01.10.2006
St Marks	HILLINGDON PCT	5AT	01.10.2006
St Marks	EALING PCT (6)	5HX	01.10.2006
St Georges	WANDSWORTH PCT	5LG	01.11.2006
St Georges	RICHMOND AND TWICKENHAM PCT	5M6	01.11.2006
St Georges	SUTTON AND MERTON PCT	5M7	01.11.2006
St Georges	KINGSTON PCT	5A5	01.11.2006
St Georges	CROYDON PCT	5K9	01.11.2006
North East London	TOWER HAMLETS PCT	5C4	01.03.2007
North East London	NEWHAM PCT	5C5	01.03.2007
North East London	CITY AND HACKNEY TEACHING PCT	5C3	01.03.2007
North East London	WALTHAM FOREST PCT	5NC	01.03.2007
North East London	REDBRIDGE PCT	5NA	01.03.2007
North East London	BARKING AND DAGENHAM PCT	5C2	01.03.2007
North East London	HAVERING PCT	5A4	01.03.2007
North East London	WEST ESSEX PCT (7)	5PV	01.03.2007
University College London	CAMDEN PCT	5K7	01.03.2007
University College London	ISLINGTON PCT	5K8	01.03.2007
University College	HARINGEY TEACHING PCT	5C9	01.03.2007

London			
University College London	ENFIELD PCT	5C1	01.03.2007
University College London	BARNET PCT	5A9	01.03.2007
West London	HAMMERSMITH AND FULHAM PCT	5H1	01.09.2007
West London	KENSINGTON AND CHELSEA PCT	5LA	01.09.2007
West London	WESTMINSTER PCT	5LC	01.09.2007
West London	EALING PCT (6)	5HX	01.09.2007
West London	HOUNSLOW PCT	5HY	01.09.2007
South East London	LEWISHAM PCT	5LF	01.01.2008
South East London	GREENWICH TEACHING PCT	5A8	01.01.2008
South East London	SOUTHWARK PCT	5LE	01.01.2008
South East London	LAMBETH PCT	5LD	01.01.2008
South East London	BROMLEY PCT	5A7	01.01.2008
South East London	BEXLEY CARE TRUST	TAK	01.01.2008
Tees	HARTLEPOOL PCT	5D9	01.02.2007
Tees	NORTH TEES PCT	5E1	01.02.2007
Tees	MIDDLESBROUGH PCT	5KM	01.02.2007
Tees	NORTH YORKSHIRE AND YORK PCT	5NV	01.02.2007
Tees	COUNTY DURHAM PCT (8)	5ND	01.02.2007
Tees	REDCAR AND CLEVELAND PCT	5QR	01.02.2007
South of Tyne	COUNTY DURHAM PCT (8)	5ND	01.02.2007
South of Tyne	GATESHEAD PCT	5KF	01.02.2007
South of Tyne	SOUTH TYNESIDE PCT	5KG	01.02.2007
South of Tyne	SUNDERLAND TEACHING PCT	5KL	01.02.2007
Hull	HULL PCT	5NX	01.02.2007
Hull	EAST RIDING OF YORKSHIRE PCT	5NW	01.02.2007
Hull	NORTH EAST LINCOLNSHIRE CARE TRUST PLUS	5AN	01.02.2007
Hull	NORTH LINCOLNSHIRE PCT	5EF	01.02.2007
Hull	NORTH YORKSHIRE AND YORK PCT (9)	5NV	01.02.2007
Bradford & Airedale	BRADFORD AND AIREDALE TEACHING PCT	5NY	01.09.2007
Bradford & Airedale	NORTH YORKSHIRE AND YORK PCT (9)	5NV	01.09.2007
County Durham & Darlington	COUNTY DURHAM PCT (8)	5ND	01.11.2007
County Durham & Darlington	DARLINGTON PCT	5J9	01.11.2007
North of Tyne	NEWCASTLE PCT	5D7	01.02.2008
North of Tyne	NORTH TYNESIDE PCT	5D8	01.02.2008
North of Tyne	NORTHUMBERLAND CARE TRUST	TAC	01.02.2008
South Yorkshire	BARNSLEY PCT	5JE	01.02.2008
South Yorkshire	DONCASTER PCT	5N5	01.02.2008
South Yorkshire	ROTHERHAM PCT	5H8	01.02.2008
South Yorkshire	SHEFFIELD PCT	5N4	01.02.2008

South Yorkshire	BASSETLAW PCT	5ET	01.02.2008
Harrogate, Leeds and York	LEEDS PCT	5N1	01.06.2009
Harrogate, Leeds and York	NORTH YORKSHIRE AND YORK PCT (9)	5NV	01/06/09
Calderdale, Kirklees and Wakefield	CALDERDALE PCT	5J6	01.04.2009
Calderdale, Kirklees and Wakefield	KIRKLEES PCT	5N2	01.04.2009
Calderdale, Kirklees and Wakefield	WAKEFIELD DISTRICT PCT	5N3	01.04.2009
Norwich	NORFOLK PCT	5PQ	01.07.2006
Norwich	GREAT YARMOUTH AND WAVENEY PCT	5PR	01.07.2006
Derbyshire	DERBYSHIRE COUNTY PCT	5N6	01.03.2007
Derbyshire	DERBY CITY PCT	5N7	01.03.2007
Cambridge	CAMBRIDGESHIRE PCT (10)	5PP	01.10.2007
Cambridge	SUFFOLK PCT (11)	5PT	01.10.2007
Cambridge	WEST ESSEX PCT (7)	5PV	01.10.2007
Leicestershire, Northampton & Rutland	NORTHAMPTONSHIRE PCT	5PD	01.12.2007
Leicestershire, Northampton & Rutland	LEICESTERSHIRE COUNTY & RUTLAND PCT	5PA	01.12.2007
Leicestershire, Northampton & Rutland	LEICESTER CITY PCT	5PC	01.12.2007
West Herts	WEST HERTFORDSHIRE PCT	5P4	01.03.2008
Nottinghamshire	NOTTINGHAMSHIRE COUNTY TEACHING PCT	5N8	01.03.2008
Nottinghamshire	NOTTINGHAM CITY PCT	5EM	01.03.2008
East & North Hertfordshire	EAST & NORTH HERTFORDSHIRE PCT	5P3	01.03.2008
South Essex	SOUTH WEST ESSEX PCT	5PY	01.09.2008
South Essex	SOUTH EAST ESSEX PCT	5P1	01.09.2008
North Essex	NORTH EAST ESSEX PCT	5PW	01.02.2009
North Essex	MID ESSEX PCT	5PX	01.02.2009
North Essex	SUFFOLK PCT (11)	5PT	01.02.2009
Bedford	LUTON PCT	5GC	01.03.2009
Bedford	BEDFORDSHIRE PCT	5P2	01.03.2009
Peterborough and Huntingdon	PETERBOROUGH PCT	5PN	01.07.2009
Peterborough and Huntingdon	LINCOLNSHIRE PCT (12)	5N9	01.07.2009
Peterborough and Huntingdon	CAMBRIDGESHIRE PCT (10)	5PP	01.07.2009
Lincoln	LINCOLNSHIRE PCT (12)	5N9	01.12.2009

Appendix 11. A list of the HES codes used to record a colonoscopy procedure.

Colonoscopy codes; H221, H201, H202, H203, H205