AN INVESTIGATION INTO THE ROLE OF ADENOMA AND HOST-SPECIFIC FACTORS ON THE INCIDENCE AND RECURRENCE OF COLORECTAL NEOPLASIA

By

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Abstract

Colorectal cancer (CRC) is the fourth most common cancer in the United Kingdom. For males and females combined, it is the second most common cause of cancer death in the UK.

The majority of CRC develops as a result of malignant transformation of adenomas via the adenoma-carcinoma sequence. Firm evidence exists that bowel screening, colonoscopy, and polypectomy results in a reduction of CRC incidence and death. An understanding of the association between both adenoma-specific and host characteristics, on the incidence and recurrence of colorectal neoplasia, is necessary to target finite colonoscopy resources, enhance post-polypectomy surveillance guidelines and reduce CRC incidence. An improved understanding of the host mechanisms underpinning the early and pre-malignant stage of CRC could encourage the development of targeted intervention strategies aimed at reducing the primary incidence, post-polypectomy recurrence, and progression of colorectal adenomas to cancer. Notably, bowel screening is now understandably an integral part of the strategy to reduce CRC incidence and mortality, mainly by intervention at the pre-malignant stage. However, it must be ensured that several inherent risks of screening are considered, especially in the era of CT colonography (CTC), where the entire abdomen is imaged, resulting in the identification of extracolonic findings.

Chapter 1 presents an overview of CRC, including the risk factors, treatment, and determinants of prognosis and outcome. This is followed by an outline of the process, evidence for, risks, benefits, and outcomes of CRC screening in Scotland. Finally, a detailed summary of the potential risk factors, natural history, management, and surveillance strategies relating to colorectal adenomatous polyps is presented.

Chapter 2 presents findings from a systematic review and meta-analysis using pooled, raw data with regards to post-polypectomy colorectal adenoma recurrence. The work found that

age ≥60 years, OR 1.56 [95% CI; 1.13-2.14, p<0.01], male sex, OR 1.58 [95% CI; 1.42-1.76, p<0.001] and BMI ≥25, OR 1.35 [95% CI; 1.14-1.58, p<0.001] were associated with post-polypectomy adenoma recurrence. The work concluded that these host factors could be considered for inclusion in post-polypectomy surveillance guidelines.

Chapter 3 presents original data from the Scottish Bowel Screening Programme (SBoSP). An examination was undertaken of the association between adenoma-specific and host characteristics, on subsequent adenoma recurrence post-polypectomy in intermediate and high-risk bowel screening patients. The work reported that in high-risk groups, 50% of patients were found to have adenoma recurrence at follow-up, and a third of these patients harbour advanced adenomas. The work also demonstrates that although host characteristics, other than male sex, were not associated with adenoma recurrence, a higher baseline adenoma number was associated with the finding of subsequent adenomas at follow-up (OR 2.23 [95% CI; 1.53-3.25, p<0.001] and 4.19 [9% CI; 2.53-6.97, p<0.001], for 3–4 and ≥5 vs. 1–2 adenomas at baseline respectively). While elevated adenoma number at baseline did not increase the risk of subsequent advanced adenomas at follow-up, the presence of advanced adenomas at baseline was itself a risk for subsequent advanced adenomas, OR 2.34 [95% CI; 1.18-4.61, p<0.05]. This chapter concluded that adenoma-specific factors are superior to host characteristics in predicting future risk for bowel screening patients. On that basis, additional work is required to explore the adenoma further at a genetic level, while additional adenoma-specific factors, other than solely size, should be considered for inclusion in post-polypectomy surveillance guidelines.

Chapter 4 presents original, prospectively collected data, from patients attending for colonoscopy as part of the SBoSP. In contrast to **Chapter 2** and **Chapter 3**, which focussed on secondary prevention (post-polypectomy) of colorectal adenomas, **Chapter 4** focussed on primary prevention. The association between host characteristics, systemic inflammation, and colorectal neoplasia incidence at bowel screening was examined. The work reported

that obesity, adjusted OR 2.72 [95% CI; 1.35–5.49, p<0.01], smoking, OR 2.26 [95% CI; 1.33-3.84, p<0.01] and aspirin use, OR 2.59 [95% CI; 1.15-5.86, p<0.05] were associated with a systemic inflammatory response. Despite this, none of the host factors were associated with an increased risk of incident colorectal neoplasia, while aspirin was associated with reduced risk, OR 0.51 [95% CI; 0.29–0.89, p<0.05] when adjusting for age, sex and smoking. The work concluded that while several host factors are associated with systemic inflammation, a direct link between these host factors, systemic inflammation and incident colorectal neoplasia remains unclear. It also concluded that BMI might be an inferior measure with which to study the effects of adiposity on colorectal neoplasia incidence, and suggested more precise measures of body composition could be used to explore the relationship further.

Chapter 5 presents original data collected from patients undergoing CTC as part of the SBoSP. The association between CT derived body composition and colorectal neoplasia incidence was examined. The work concludes that; similar to **Chapter 4,** BMI was not useful in predicting the risk of colorectal neoplasia, but the presence of visceral obesity was strongly associated with neoplasia incidence, adjusted OR 2.79 [95% CI; 1.48-5.25, p<0.01]. In addition, no association was found between the presence of sarcopenia and early, largely pre-malignant disease. The chapter concluded that targeted interventions specifically for visceral obesity, and further investigation into the mechanism for its association with neoplastic findings should be sought. Moreover, a further examination into the role of sarcopenia and its development between the pre-malignant and malignant stage of CRC is required.

Chapter 6 presents original data collected from patients undergoing CTC as part of the SBoSP with a focus on the risks of bowel screening, where CTC is increasingly being utilised. Original data are reported on the incidence, risk factors for, cost and implications of both colorectal (CRF) and incidental extracolonic findings (ECF) at CTC conducted as

part of the SBoSP. The work reported that ECFs were very common in the bowel screening cohort (62% of patients) and that the subsequent additional yield of useful CRF (11%) from completion CTCs was lower than the incidence of important ECFs (15%). The majority of ECFs that required further investigation were subsequently benign (63%), and as a result of the investigation process, there was an additional estimated cost of £45 per CTC. The work concluded that while CTC remains a useful adjunct for screening programmes, it should be utilised with caution. Both the clinician and patient must have an awareness of the additional risk, cost and implications of a test designed to investigate the colon and rectum, which may have a higher yield of ECFs than important CRFs.

Chapter 7 summarises the main findings presented in the thesis, provides a relevant update on newly published work during the thesis preparation period and suggests some recommendations for future study.

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Authors Declaration

The work presented in this thesis was undertaken between 2015 and 2017 in the Academic Unit of Colorectal Surgery at Glasgow Royal Infirmary. I declare that the work presented herein was undertaken by myself, except where indicated below:

Assistance with data collection was provided by:

- Mr Christopher Morton (Chapter 3, Chapter 5)

- Ms Fiona Ross (Chapter 4)

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Presentations

The work presented in this thesis has resulted in the following presentations:

- **The influence of age, sex, and BMI on colorectal polyp recurrence: A review of the literature and meta-analysis**

  Association of Surgeons of Great Britain & Ireland Annual Conference, Glasgow (May 2017)- *poster presentation*

- **The Influence of adenoma and host factors on colorectal adenoma recurrence within a screening population**

  Association of Surgeons of Great Britain & Ireland Annual Conference, Glasgow (May 2017)- *poster presentation*

- **The incidence, implications, and risk factors for extracolonic findings at CT colonography in a bowel screening population**

  Association of Surgeons of Great Britain & Ireland Annual Conference, Glasgow (June 2020)- *oral presentation (accepted for oral presentation, temporarily postponed due to COVID-19)*

- **The relationship between colorectal neoplasia and body composition in a bowel screening population**

  Association of Surgeons of Great Britain & Ireland Annual Conference, Glasgow (June 2020)- *oral presentation (accepted for oral presentation, temporarily postponed due to COVID-19)*

Definitions and Abbreviations

- ACE — Angiotensin-Converting Enzyme
- ACPGBI — Association of Coloproctology of Great Britain and Ireland
- AJCC — American Joint Committee on Cancer
- *APC* — Adenomatous Polyposis Coli gene
- APR — Abdominoperineal Resection
- ASR — Age-Standardised Rate (European)
- ASAMET: — Aspirin and Metformin (randomised controlled trial)
- BMI — Body Mass Index
- BSG — British Society of Gastroenterology
- CEA — Carcinoembryonic Antigen
- COX — Cyclooxygenase
- CRC — Colorectal Cancer
- CRF — Colorectal Finding
- CRM — Circumferential Resection Margin
- CRP — C-reactive Protein
- CRT — Long-Course Chemoradiotherapy
- CT — Computed Tomography
- CTC — Computed Tomography Colonoscopy
- DEXA — Dual Energy X-ray Absorptiometry
- DICOM — Digital Imaging and Communications in Medicine
- ECF — Extracolonic Finding (refers to incidental ECF)
- EMBASE — Excerpta Medica database
- EPIC — European Prospective Investigation into Cancer and Nutrition
- EU — European Union
- FAP — Familial Adenomatous Polyposis
- FBC — Full Blood Count
- ^{18}FDG — ^{18}Fluoro-Deoxy-Glucose
- FIT — Faecal Immunochemical Test
- FOB — Faecal Occult Blood
- gFOB — Guaic Faecal Occult Blood test
- FOLFOX — Folinic Acid, 5-Fluorouracil and Oxaliplatin
- GP — General Practitioner
- Gy — Gray (unit of radiothorium dose)
- GGC — Greater Glasgow and Clyde
- GPS — Glasgow Prognostic Score
- *H.pylori* — *Helicobacter pylori*
- HGD — High-Grade Dysplasia
- HMG-CoA — Hydroxymethylglutaryl Coenzyme A
- HNPCC — Hereditary Non-Polyposis Colorectal Cancer
- HPV — Human Papilloma Virus
- HR — Hazard Ratio
- HRT — Hormone Replacement Therapy
- HU — Hounsfield units
- IBD — Inflammatory Bowel Disease
- IGF-1 — Insulin-like Growth Factor-1
- IL-6 — Interleukin-6
- INCISE — Integrated Technologies for Improved Polyp Surveillance Project

- IQ Interquartile (range)
- JPEG Joint Photographic Experts Group
- KPI Key Performance Indicator
- LFT Liver Function Tests
- LMR Lymphocyte: Monocyte Ratio
- LNR Lymph Node Ratio
- MACE Major Cardiovascular Events
- MALT Mucosa-Associated Lymphoid Tissue
- MDT Multi-Disciplinary Team
- mGPS Modified Glasgow Prognostic Score
- MMR Mismatch Repair Genes
- MRI Magnetic Resonance Imaging
- MSI Microsatellite Instability
- NBI Narrow Band Imaging
- NF-κβ Nuclear Factor Kappa Beta
- NHS National Health Service (UK)
- NLR Neutrophil: Lymphocyte Ratio
- NNCP Non-Neoplastic Colorectal Pathology
- NSAID Nonsteroidal Anti-Inflammatory Drug
- OR Odds Ratio
- PACS Picture Archiving and Communication System
- PET-CT Positron Emission Tomography CT Scan
- PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses
- PLR Platelet: Lymphocyte Ratio
- RCT Randomised Controlled Trial
- RR Relative Risk
- SAT Subcutaneous Adipose Tissue
- SBoSP Scottish Bowel Screening Programme
- SCPRT Short-Course Preoperative Radiotherapy
- SFI Subcutaneous Fat Index
- SIMD Scottish Index of Multiple Deprivation
- SIR Systemic Inflammatory Response
- SMI Skeletal Muscle Index
- U+E Urea and Electrolytes
- UC Ulcerative Colitis
- US Ultrasound (refers to scan)
- USA United States of America
- USPSTF United States Preventative Services Task Force
- TAT Total Adipose Tissue
- TNM Tumour, Node, Metastases (staging system)
- TNF-α Tumour Necrosis Factor-Alpha
- VAT Visceral Adipose Tissue
- VEGF Vascular Endothelial Growth Factor
- WC Waist Circumference
- WCRF World Cancer Research Fund
- WHO World Health Organisation
- WHR Waist: Hip Ratio

Dedication

To my parents and sisters who have always stood by me and supported me in everything I have done. It means the world.

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1 INTRODUCTION

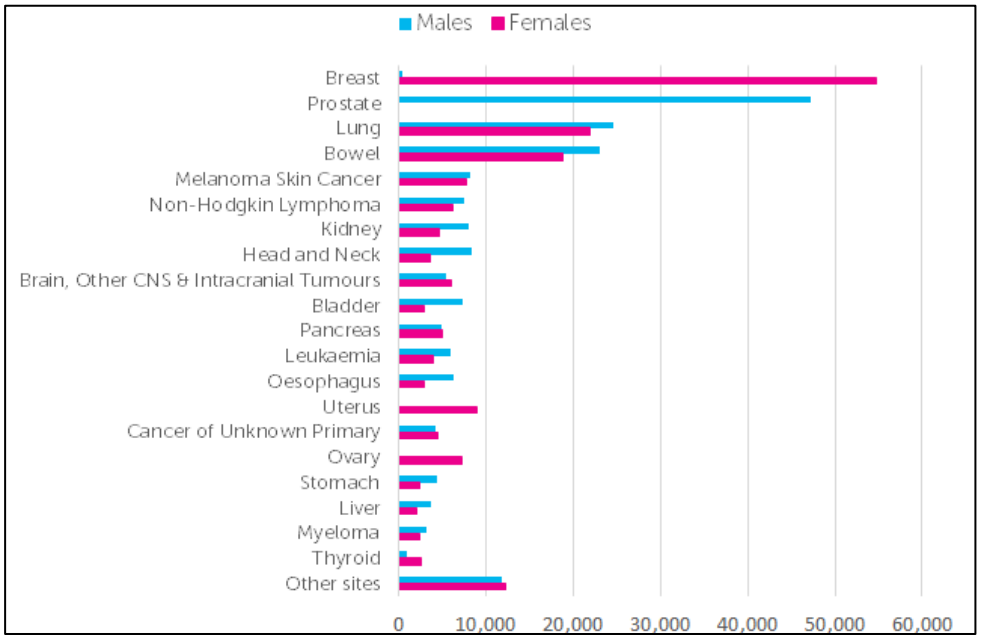
1.1 Colorectal cancer

1.1.1 Epidemiology

Cancer is common, with 17 million new cases and 9.6 million deaths worldwide per year (1). Over 1.8 million new colorectal cancer (CRC) cases are estimated to occur each year, with 880,000 deaths (2). CRC is most common in the developed world with the highest incidence in Europe, North America, New Zealand and Australia (3).

CRC is the fourth most common cancer in the United Kingdom (UK), with around 20,000 new cases each year**[Figure 1.1]** (1). It accounts for 12% of all UK cancer cases (1). It is the third most common cancer in males after prostate and lung and similarly in females after breast and lung cancer (1).

Figure 1.1: The 20 most common cancers in the UK



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CRC is predominantly a disease of older age with a steep rise in incidence from around 50–54 years, the highest rates being in those aged 85–89 years (1).

The overall Incidence of CRC in the UK is 70 per 100,000 people (1), it is more common in males than females, with an incidence of 85 and 57 cases per 100,000, respectively (1). Over the last decade, CRC incidence rates combined for males and females, have stabilised and are projected to fall in the UK by 11% from 2014–2035, with a steeper fall in males **[Figure 1.2]**. A similar pattern has been observed in other developed countries such as the United States of America (USA), Australia, New Zealand, and some Western European countries. Although the reason for this trend is not entirely apparent, it likely multifactorial while reflecting a move towards early and pre-malignant diagnosis through screening, colonoscopy and polypectomy (4).

In a similar manner to incidence, CRC mortality for males and females combined has fallen by 14% over the last decade with a more significant decline in males than females (17% and 12% respectively) **[Figure 1.3]** (1).

Figure 1.2: Observed and projected age-standardised rate (ASR) for colorectal cancer incidence by sex in the UK from 1979-2035

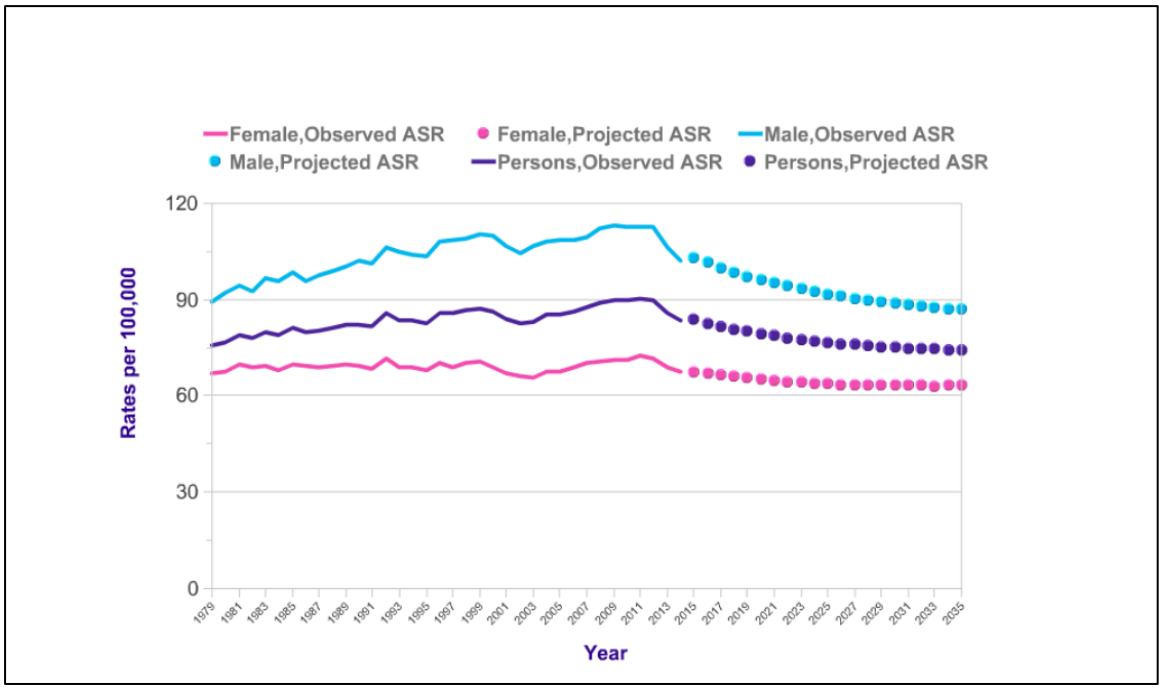

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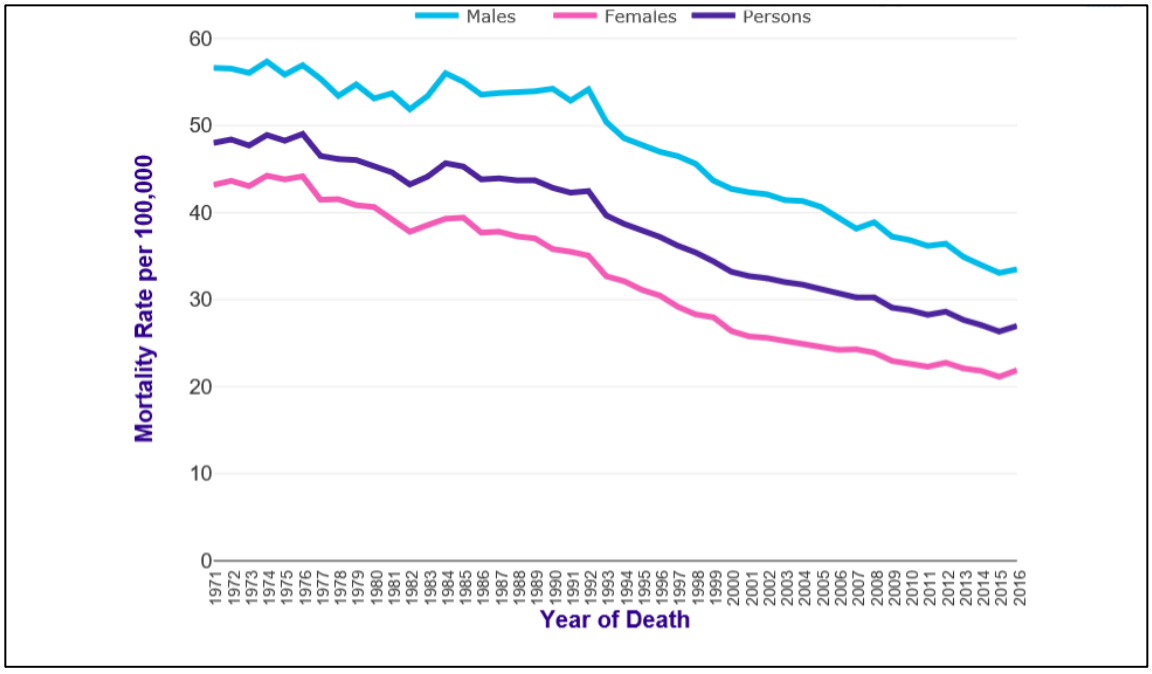
Figure 1.3: Mortality rate per 100,000 population in the UK from 1971-2016



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1.1.2 Risk factors

CRC develops through genetic mutations that accumulate over a prolonged period of time. The majority of CRCs arise sporadically and develop through a complex interaction of genetic, host and environmental factors. In contrast to other cancers, such as lung cancer, no single risk factor accounts for the majority of cases. Nevertheless, a number of modifiable and non-modifiable risk factors have been identified through epidemiological studies. Each is associated with a varying degree of risk. Risk factors can be grouped into four main categories:

1. Socioeconomic and sociodemographic factors
2. Medical factors
3. Lifestyle factors
4. Dietary factors

As a general rule, sociodemographic factors are non-modifiable, such as age and sex. However, lifestyle, dietary, and some medical factors can be modified to minimise cancer incidence.

1.1.2.1 Socioeconomic and sociodemographic factors

Advancing age

As outlined in **Section 1.1.1**, CRC is a disease predominantly of older age with the steepest rise in those aged between 50–54 years and peaking at 85–89 years (1).

Male sex

As mentioned in **Section 1.1.1**, CRC has a male preponderance, although the incidence is falling at a higher rate than in females (1). Both advancing age and male sex are risk factors that cannot be modified, yet the mechanism by which these factors increase CRC

incidence, if identified, could be modifiable. Thus it is plausible that non-modifiable risk factors, in effect, could become modifiable.

Socioeconomic deprivation

Several definitions of socioeconomic deprivation exist. In short, deprivation is present when a population lacks the type of clothing, housing, diet, educational, and working conditions that are customary or could be expected in a reasonable society (5). Recent evidence has shown that deprivation is associated with increased CRC risk. Interestingly, this trend may be more pronounced in males. A study in the West of Scotland reported that males who were least deprived had a 20% lower incidence of CRC than males classed in the most deprived categories (6).

The explanation for this is not entirely clear and again, likely to be multifactorial. It is plausible that deprivation may increase greater exposure to some modifiable risk factors such as cigarette smoking, higher alcohol intake and poor diet (6).

1.1.2.2 Medical conditions, drugs and inflammation

Family history

It is generally accepted that CRC is associated with a family history in around a quarter of cases, indicating a likely heritable component (7). The distinction between heritable and hereditary or inherited is important. Heritability refers to the magnitude with which a person's genetic makeup affects their risk of CRC (8). Twin studies are often used to quantify the heritable effect, where identical and non-identical twins who may or may not be exposed to the same environmental factors can be compared. Using this concept, a study in the New England Journal of Medicine in 2000 concluded that the development of CRC has a significant heritable component of approximately 35% (8).

Hereditary refers to CRC that is associated with specific inherited genetic abnormalities leading to syndromes such as familial adenomatous polyposis (FAP) and Hereditary Non Polyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome. It is believed that up to 5% of CRC cases are related to hereditary syndromes (9). These syndromes are discussed further in **Section 1.1.3.**

Furthermore, having a first degree relative with CRC (sibling, child, parent), for whatever reason, more than doubles the risk of a person being diagnosed subsequently with CRC (10). The risk is elevated further if a person with a first degree relative with the disease has more than one affected relative or a relative who was diagnosed at a younger age (11).

Inflammatory bowel disease

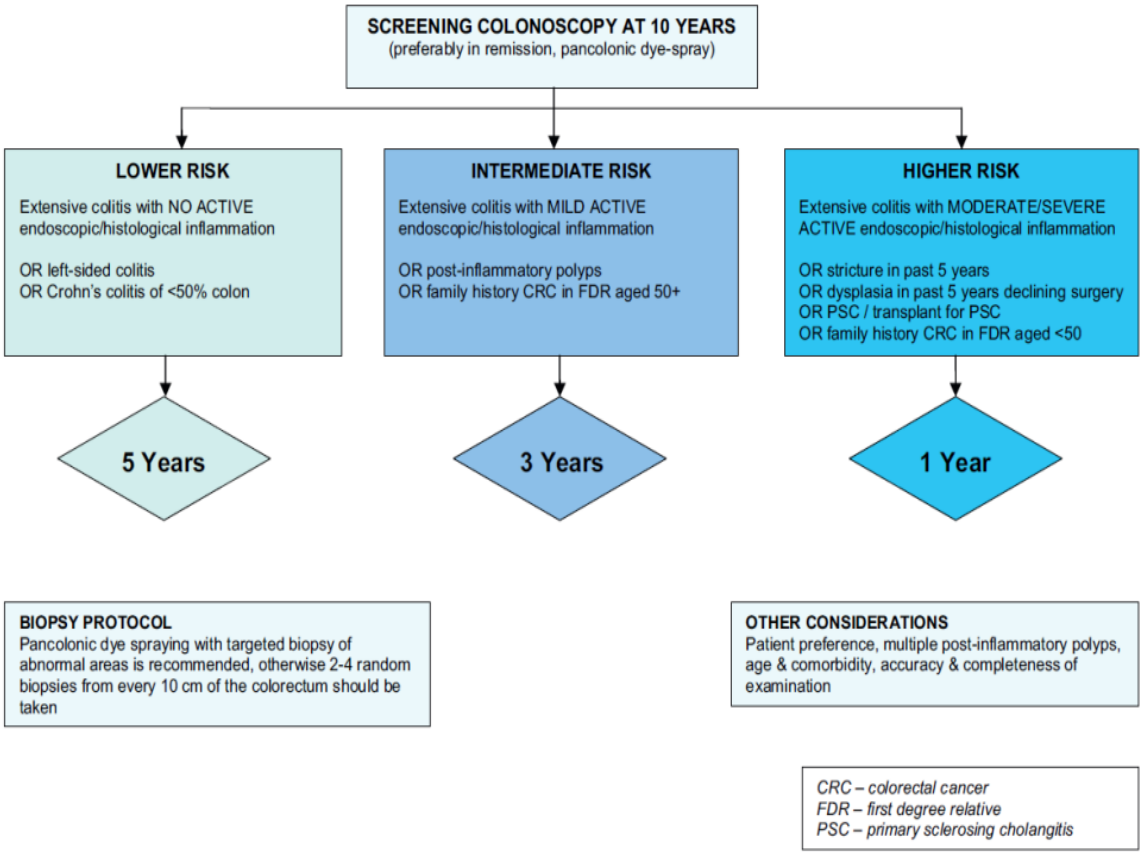
Inflammatory bowel disease (IBD) refers mainly to ulcerative colitis (UC) and Crohn's disease. Only 1% of all cases of CRC are diagnosed in patients with UC. Thus, although UC does not contribute excessively to CRC incidence, it is a significant sequela of the disease and accounts for one-sixth of all deaths in UC patients (12). In comparison to age-matched controls, UC is associated with a five to ten-fold increase in CRC (13). The risk appears to be cumulative with the duration of disease, higher in patients extensive colitis, and in those with co-existing primary sclerosing cholangitis (13, 14). For a patient with UC, the risk of CRC is around 2% after 10 years, 8% after 20 years, and 18% after 30 years from diagnosis (12). The risk is similar in patients with Crohn's colitis (15).

The association between CRC and IBD is likely related to chronic inflammation. IBD-related and sporadic CRCs are similar in that both have a dysplasia-cancer progression that requires multiple mutations to progress to invasive malignancy (14). However, in IBD, the genetic and molecular mutations required in this sequence occur at a faster rate. It is likely that colitis-associated inflammation results in a cascade of abnormal epithelial proliferation with

early mutation of the *p53* gene, whereas this is a later event in sporadic CRC **(Section 1.1.3.1)** (14).

The British Society of Gastroenterology (BSG) initially published guidelines in 2002, which have been updated in 2010, for CRC screening and surveillance for those in moderate to high-risk groups such as IBD (15). The BSG recommended that all patients with UC or Crohn's colitis should undergo a screening colonoscopy approximately 10 years after the onset of colitis symptoms. Thereafter, screening colonoscopies are recommended at one, three, or five-yearly intervals, depending on endoscopic findings and other associated risk factors (15). Patients with IBD who also have active extensive colitis, primary sclerosing cholangitis, or a family history of CRC, are higher risk and should undergo colonoscopy at shorter intervals **[Figure 1.4]** (15).

Figure 1.4: Surveillance guidelines for follow-up bowel screening in patients with inflammatory bowel disease-associated colitis



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Diabetes mellitus

Epidemiological studies suggest that diabetes mellitus, especially type 2, is associated with an increased risk of several cancers, including CRC. A recent umbrella review of meta-analyses determined that CRC, along with breast and endometrial cancer, were associated with type 2 diabetes (16).

Infective risk factors

Common bacterial and viral infections have been investigated as risk factors for CRC.

Helicobacter pylori infection

The bacterial pathogen *Helicobacter pylori* (*H. pylori*) is passed from human to human and colonises the gastric mucosa. The bacterium induces chronic inflammation that can lead to chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma (17). For this reason, studies on the oncogenicity of *H. pylori* have been conducted to examine its role in the development of other gastrointestinal cancers.

At present, studies have found only a statistical association between *H. pylori* infection and colorectal neoplasia, including CRC (18, 19). The risk appears to be modest, and the reports above note that bias cannot be excluded. At present, definitive proof of causality is not established; however, it is plausible from experimental data, that *H. pylori* could be responsible for the induction and perpetuation of inflammatory responses, the result of which may contribute to tumour formation (19, 20).

Viral infection

Studies have assessed the association between CRC and common viruses such as human papillomavirus (HPV), and human herpesvirus, including a recent systematic review, conducted to assess the strength of the evidence (21).

The majority of studies included in the review focussed on HPV, where samples of colorectal tumours, adjacent tissue, adenomas, and healthy controls were examined for the presence of HPV. With the exception of one study, the prevalence of HPV was significantly higher in tumour samples than adjacent non-cancerous tissue. Odds ratios (OR) in the studies ranged from 1.7 [95% CI; 0.9–3.3] to 12.8 [95% CI; 3.7–43.7] (21).

The above systematic review concluded that although a role for viral infection in the aetiology of CRC is biologically plausible, the evidence is limited (21). Nonetheless, this possible association should remain under consideration given the rollout of an HPV vaccine as prophylaxis against cervical cancer.

Medications

Chemoprevention strategies for CRC have been of interest, and research is ongoing. Several of the most common strategies are outlined below.

Hormone replacement therapy

Colorectal adenomas and tumours are more prevalent in males than females. This observation, combined with some pre-clinical and clinical studies, has led to speculation that female hormones, in particular oestrogen, acting at oestrogen receptor β, could provide a protective benefit with respect to CRC (22). Consequently, several extensive epidemiological studies examining the association between female hormone replacement therapy (HRT) and CRC incidence have been conducted. A 2012 meta-analysis showed that current use of oestrogen therapy, and current or previous use of combined oestrogen and progesterone therapy, decreased CRC risk by 20–30% (23). In addition, a recent study in Denmark, recruiting one million women reported that the use of HRT was associated with a 15% reduction in CRC risk (24). Nevertheless, additional extensive studies have not supported these findings (25). The associated risks of long-term HRT in relation to

gynaecological cancers, and venous thrombosis, may limit its application as a primary prevention medication for CRC in any case.

Aspirin use

Aspirin use has been proposed as a chemo protective agent for both colorectal adenomas and CRC. It is plausible that the effect is mediated by aspirin's inhibitory action on the enzyme, cyclooxygenase-2 (COX-2). Two COX isoforms exist. COX-1 is an enzyme expressed in most mammalian tissues, and COX-2 is an enzyme that acts as a catalyst in the reaction that produces prostaglandins from arachidonic acid (26). COX-2 is induced by growth factors, oncogenes, tumour promoters, and inflammatory cytokines (27), while it displays up-regulation in human colonic adenocarcinoma (28). It is plausible that inhibition of this pro-inflammatory, pro-tumour state by the action of aspirin, on the function of COX-2, reduces neoplasia formation. In addition to localised actions in the tumour microenvironment and colorectal epithelium, the effects of aspirin are believed to elicit a tumour inhibitory effect on a systemic level (27).

A significant volume of observational and clinical trial data have reported that regular aspirin ingestion reduces CRC risk (27, 29); however, there is no uniform agreement, and some studies have reported that there is no effect of aspirin on CRC incidence (30, 31). In some cases, randomised controlled trial (RCT) data have been extracted from trials that were primarily designed to examine cardiovascular disease prevention, and they may lack the optimal design with which to investigate CRC incidence (27). At present, there is not a consensus on an optimal duration or dose of aspirin as a chemo protective agent. Large studies concluded that at least 300 mg daily was required for a duration of around 5 years to reduce CRC risk with a latency of 10 years (29). Furthermore, this is a significantly larger dose than that used in cardiovascular disease prevention and may put patients at a higher risk of aspirin-associated complications.

In 2007 the United States Preventative Services Task Force (USPSTF) recommended against the routine use of aspirin for the prevention of CRC. However, this guidance was updated in 2016 (32). The USPSTF now recommends low-dose aspirin for the prevention of cardiovascular disease and CRC, but only in adults fitting the following criteria.

1. Aged 50–59 years
2. A 10% or higher, 10-year cardiovascular disease risk (Framingham score) (33)
3. Are not at increased risk of bleeding
4. Have a life expectancy of at least 10 years
5. Are willing to take low dose aspirin for at least 10 years

The USPSTF recommendations reflect recent studies with longer follow-up, which report a more consistent effect of aspirin on CRC (34). Crucially the USPSTF does not endorse aspirin use for the sole purpose of CRC prevention; however, they do suggest the "additional" benefit of aspirin use for CRC prevention may be favourable in those at higher risk of cardiovascular disease.

In any case, the routine use of aspirin for chemoprevention in patients aged <50 years in the USA and the general population in the UK is not recommended. However, an exception could be made for patients at risk of hereditary CRC related to conditions such as FAP and HNPCC. Robust RCT evidence suggests there is a chemoprophylaxis benefit of aspirin in reducing polyp load in patients with FAP (35) and cancer incidence in HNPCC (35).

Aspirin chemoprevention remains a topic of interest, and ongoing research, specifically, the ASAMET (Aspirin and Metformin) trial is yet to conclude. The ASAMET trial is a randomised, double-blind, placebo-controlled study examining the use of aspirin and

metformin, and their effect on recurrence, prognosis and second primary cancer incidence of patients post-CRC surgery (36).

Nonsteroidal anti-inflammatory drugs

A large systematic review, including 44 studies, investigating the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on colorectal neoplasia risk was published in 2010 (37). The study was concerned with patients at high risk for CRC, such as those with a strong family history, FAP, or HNPCC. The work concluded that NSAID use could reduce the polyp burden, such as size and number, in patients with FAP (37). In individuals with a history of previous adenomas, the meta-analysis concluded that there was a 34% reduction in adenoma recurrence, relative risk (RR), 0.66 [95% CI; 0.60–0.72] and a 55% reduction in advanced adenoma incidence, RR 0.45 [95% CI; 0.35–0.58]. Nonetheless, there is insufficient evidence to recommend the use of NSAIDs for CRC or adenoma prevention in the general, average-risk population (37). It is noteworthy that a majority studies in the above review focussed on the use of the COX-2 inhibitors due to their perceived lower risk of gastrointestinal toxicity. Nevertheless, these are no longer in routine clinical use due to concerns regarding cardiovascular toxicity.

Statins

Statins are a class of lipid-lowering medications known as hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors. HMG-CoA reductase is an enzyme which aids in the synthesis of mevalonate, which is included in a chain of molecules that end in the production of cholesterol. Interest in statins for chemoprevention is based on reports that they may promote apoptosis while inhibiting angiogenesis and cell proliferation (38). Clinical studies have explored the effect of statins on CRC risk and reached disparate conclusions prompting a meta-analysis (39). Approximately two million pooled patients from observational studies and RCTs, primarily undertaken to investigate cardiovascular risk reduction, were included in the above study. The summary results supported a very modest reduction in CRC risk of

around 9% with statin use, RR 0.91 [95% CI; 0.87–0.96, p<0.001]. On this basis, there is insufficient evidence to recommend the use of statins for CRC chemoprevention, yet it may be a welcome, albeit modest, benefit for those already on long-term therapy.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are a class of anti-hypertensive drugs that inhibit the conversion of angiotensin-1 to angiotensin-2. Angiotensin-2 is an active mediator controlling the release of aldosterone from the adrenal cortex while raising arterial blood pressure by vasoconstriction. In addition to its cardiovascular effects, experimental studies have shown that angiotensin-2 also acts as a growth factor and stimulates both neovascularisation and cell replication (40). Furthermore, it has been demonstrated that ACE is differentially expressed in CRC tumour cells, whereas surrounding non-neoplastic tissue rarely expresses it (41). It has also been demonstrated that colorectal adenomas, as precursors of CRC, exhibit a similar expression of ACE to CRC tumour cells (41). The above observations would suggest that ACE may play a role in tumour formation, and its inhibition may provide a chemoprevention effect against CRC.

A large observational study of 5,200 patients attending a West of Scotland blood pressure clinic for 15 years was conducted where the researchers examined all cancer incidence during the follow-up period and found both the incidence and cancer-specific death rates, to be 28% [RR 0.72, 95% CI; 0.55–0.92] and 35% [RR 0.65, 95% CI; 0.44–0.93] lower respectively, for those taking ACE inhibitors compared with controls (40). Nevertheless, other large studies (n=18,000) have failed to replicate these results (42), including a meta-analysis (43).

These studies were concerned with all cancer incidence. In considering CRC specifically, studies using bowel screening patients have reported a reduction in advanced neoplasia incidence for those taking ACE inhibitors (44). In one study, the use of ACE inhibitors

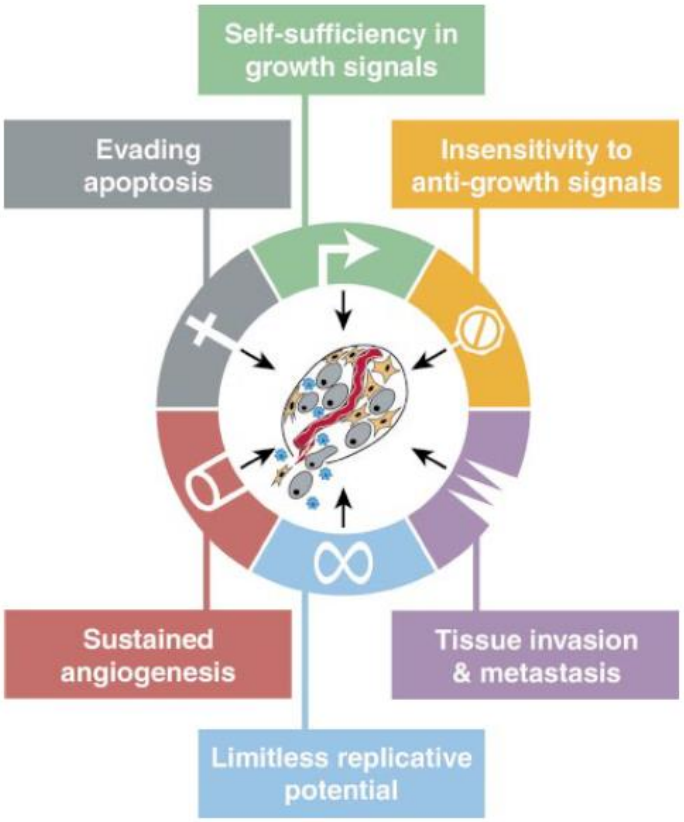
reduced the incidence of advanced adenoma by 41% over a 3–5 year period, but direct evidence of an effect specifically on CRC has yet to be established (45).

Inflammation and cancer

Links between cancer and inflammation were first proposed in the 19th century, arising from the observation that tumour samples were often found to harbour inflammatory cells within the tumour microenvironment. Researchers also noted that many tumours arose at sites of chronic inflammation (46). There is now a general acceptance that inflammation and cancer are linked.

Hanahan and Weinberg proposed the six hallmarks and acquired capabilities of cancer **[Figure 1.5]** in their paper outlining the multistep processes of tumorigenesis (47). It has since been proposed that cancer-related inflammation is the seventh hallmark of cancer; however, the mechanisms that link inflammation and cancer are multiple and complex (48). It is believed that inflammation mediates the progression of healthy cells to malignancy through pro-inflammatory cytokine and free radical pathways (49). In addition, activation of signalling pathways common to both inflammation and carcinogenesis, such as the nuclear factor kappa-beta (NF-κβ) are likely to play a role. NF-κβ controls DNA transcription and regulates the cellular immune response to infection, and incorrect regulation is linked to carcinogenesis.

Figure 1.5: The six hallmarks and acquired capabilities of cancer



Reproduced (with permission) from Hanahan and Weinberg 2000 (47)

Although it is accepted that the tumour microenvironment harbours an inflammatory component, often described as an ongoing "smouldering" inflammation (46), there is a recognition that a general systemic inflammatory response could play a regulatory role in cancer development and progression. C-reactive protein (CRP), is an acute-phase protein and marker of systemic inflammation produced in the liver in response to interleukin-6 (IL-6) secretion by inflammatory cells, namely macrophages and T-cells (50). It is elevated in response to infection, trauma, surgery, immune-mediated inflammatory conditions, and cancer, amongst other conditions (50).

In some cases, a prolonged inflammatory response can be raised as a reaction to specific agents or conditions, the effect of which is a state of chronic, low-grade, systemic inflammation, that may encourage the progression to, and progression of, malignant processes (51).

This hypothesis is supported by epidemiological studies whereby elevated CRP, as a marker of systemic inflammation, in otherwise healthy individuals, is associated with an increased risk of cancer (51). Allin and colleagues (2009) investigated a large cohort of 10,000 individuals from a Danish population with a baseline CRP measurement (51). The researchers observed the cohort for up to 16 years and found that individuals with baseline CRP in the 5th quintile were 30% more likely to develop cancer of any type, than those in the 1st quintile. Crucially, when CRC was explicitly examined in another epidemiology study (52), and a recent meta-analysis (53), the above associations with CRP remained. Certainly, unravelling the links between cancer and inflammation is desirable with a view that cancer related inflammation may be an intervention target (46).

1.1.2.3 Lifestyle factors

The World Cancer Research Fund (WCRF) publishes a continuous update on cancer prevention and survival in relation to diet, nutrition, and physical activity, from all over the world. Worldwide scientific research is continually added to the database, where it is systematically reviewed by a team at Imperial College London (54). It is now clear that a variety of dietary and lifestyle factors can affect an individual's risk of CRC (54).

Tobacco smoking

Tobacco smoking is associated with a modestly increased CRC risk. Meta-analyses and cohort studies have shown that current smokers vs. never smokers have an approximately 20% increased risk, with the association stronger in males than females (55, 56). The risk is thought to increase with the number of cigarettes smoked per day (10% increase per ten cigarettes) (55).

Excessive alcohol consumption

There is convincing evidence that high alcohol consumption is associated with an increased risk of CRC (54). While meta-analysis data concluded that there was no significant risk from

low intake levels of up to 20g per day, consumption above 20g per day was found to increase CRC risk per additional 10g consumed per day (54). In real terms, one standard drink (one can of beer, 100ml wine, or one measure of spirits) contains 10g of ethanol.

The mechanism of potential carcinogenesis is not well understood, however it is believed that ethanol can initiate oxidative stress on tissues, which in turn may elicit a carcinogenic effect (57). Furthermore, it has been suggested that ethanol carcinogenesis could be mediated by its direct breakdown product, acetaldehyde (58). Acetaldehyde is a known carcinogen and is thought to interfere with DNA synthesis and repair (58). It is produced by oxidation of ethanol in the liver and by bacterial activity in the colonic mucosa. Significant concentrations of acetaldehyde have been measured in saliva and colonic contents following moderate alcohol consumption, thus essentially bathing of the colonic mucosa in this compound could be carcinogenic (58).

Obesity and metabolic syndrome

There is robust evidence that obesity, or being overweight, increases the risk of a number of cancers, including CRC. A study of 5.24 million adults in the UK published in The Lancet in 2014, concluded that elevated body mass index (BMI, kg/m^2) was associated with 17 of the 22 most common cancers in the UK (59). The researchers reported that colonic cancer risk increased by approximately 10% per 5 unit increase in BMI, with a hazard ratio (HR) of 1.10 [95% CI; 1.07–1.13, $p<0.001$], and rectal cancer by approximately 5%, HR 1.04 [95% CI; 1.00–1.08, $p<0.05$] (59).

The mechanisms linking obesity and CRC are not fully understood and likely multifactorial. Obesity, particularly visceral obesity, is associated with metabolic syndrome which is a group of interconnected clinical, metabolic, and physiological factors linked to an increased risk of cardiovascular disease, type 2 diabetes, and mortality (60). It results in elevated concentrations of circulating insulin, which promotes cell growth, proliferation, and limits

cellular apoptosis (61). In addition, body "fatness" has been associated with a pro-inflammatory response, mediated by adipokines, particularly insulin and leptin, which have been linked to CRC development (53, 62).

1.1.2.4 Dietary factors

High consumption of red and processed meat

The World Health Organisation's (WHO) specialist group on cancer: The International Agency for Research on Cancer, recently classified red meat as "probably carcinogenic to humans". In addition, they classed processed meat (preserved by salting, curing, smoking, or the addition of chemical preservatives) as "carcinogenic to humans" (63). This classification is based on large population studies that suggest red and processed meat consumption can increase CRC risk by approximately 20% when comparing the highest and the lowest intake groups (64). This relationship may also be dose-dependent, with an observed 15% increase in CRC risk per 100g of daily consumption (64).

Nonetheless, more recent studies have downplayed the potential relationship between red meat and CRC risk, notably a meta-analysis including 27 studies which reported only a weakly elevated summary RR for CRC attributable red meat consumption, RR 1.11 [95% CI; 1.03–1.09] (65). The researchers suggested that current epidemiological data concerning red meat consumption and CRC risk displays significant heterogeneity and is limited by the confounding effects of other dietary and lifestyle factors. Thus, the relationship might be best described as a mild to moderate association (65). In summary, it would seem sensible to recommend limiting the intake of red and certainly processed meat, but disproportionate to recommend total elimination of these.

Fruit and vegetables

Eating a modest to moderate volume of fresh fruit and vegetables might lead to a reduction in CRC risk. Meta-analysis results have suggested the risk reduction may be 8% for fruit and vegetables combined, RR 0.92 [95% CI; 0.86–0.99] (66). It is thought that vitamins and antioxidants found in fruit and vegetables may offer a protective effect against carcinogenesis.

Dietary fibre

A high intake of dietary fibre is believed to induce a protective effect on colorectal carcinogenesis. In a large European study, (EPIC: European Prospective Investigation into Cancer and Nutrition) over 500,000 participants from 10 countries participated in a multi-centre prospective study aiming to investigate the relationship between diet lifestyle, and the incidence of several cancers amongst additional outcomes (67). Dietary intake over the preceding 12 months was assessed by country-specific questionnaires. The results demonstrated an approximate 20% reduction in the risk of CRC for those with the highest fibre intake (mean 35g/day) vs. the lowest intake (mean 15g/day) when adjusting for folate (67). More recently, a meta-analysis of prospective observational studies performed by the WCRF reported a 10% dose-dependent reduction of CRC risk per 10g of daily dietary fibre (54).

The protective effect of fibre might result from faster faecal transit, and it is plausible that this would reduce the time for potential faecal based carcinogens to act on colonic mucosa. In addition, the breakdown of fibre results in the production of short-chain fatty acids, particularly butyrate, which has an anti-proliferative effect.

Fish intake

Limited evidence exists that the consumption of fish reduces the risk of CRC. The EPIC study of 500,000 Europeans mentioned previously reported a 31% decrease in CRC risk

when in excess of 80g/day of fish was consumed, independent of the levels of red and processed meat consumed (67). However, competing studies have reported non-significant or inconsistent results (54). It is postulated that long-chain fatty acids found in fish may provide a chemoprotective effect.

Calcium and vitamin D

Anti-tumorigenic effects of calcium and vitamin D have been demonstrated in experimental studies to limit cellular proliferation, inducing apoptosis, and stimulating cellular differentiation (68). Epidemiological studies report an approximate 20–30% risk reduction in CRC and adenomatous polyps when comparing high and low-intake groups (68). Unfortunately, both calcium and vitamin D are inextricably linked; therefore, it is difficult to ascertain their independent effects. Furthermore, there is a lack of consistency or consensus between studies regarding the optimal dosage as a dietary supplement (68).

A more recent systematic review and meta-analysis data would support calcium, and to a lesser extent, vitamin D supplementation for chemoprevention in those who wish to self-treat (54). As of yet, there is insufficient evidence to recommend supplementation as a population-based chemoprevention strategy.

1.1.2.5 Risk factor summary

In the UK, approximately 50% of CRCs may be attributable to modifiable risk factors. The risk and preventative factors outlined above, and the relative strength of associations are summarised in **Table 1.1.**

Table 1.1: Summary of factors associated with increased or decreased risk of colorectal cancer

Risk Factor	Risk of CRC	Modifiable
Sociodemographic factors		
Advancing age	↑↑↑	No
Male sex	↑↑	No
Socioeconomic deprivation	↑	Yes
Medical factors		
Family history	↑↑	No
Inflammatory bowel disease	↑↑	Potentially with colectomy
Diabetes mellitus	↑	No- Type-1, Yes type-2
Helicobacter pylori	(↑)	Yes
Viral infections	(↑)	Yes
Hormone replacement therapy	↓	Females only
Aspirin	↓	Yes
Statins	(↓)	Yes
Systemic inflammation	↑	Yes
Lifestyle factors		
Smoking	↑	Yes
Excessive alcohol consumption	↑	Yes
Obesity	↑	Yes
Physical activity	↓	Yes
Dietary factors		
Red and processed meat	↑↑	Yes
Dietary fibre	↓	Yes
Fish	(↓)	Yes
Calcium and vitamin D intake	↓	Yes

Adapted from Brenner et al. 2014 (7)

↑↑↑ *Very strong risk increase*
↑↑ *Strong risk increase*
↑ *Moderate risk increase*
↓ *Moderate risk reduction*
( ) ( ) probable association

1.1.3 Aetiology

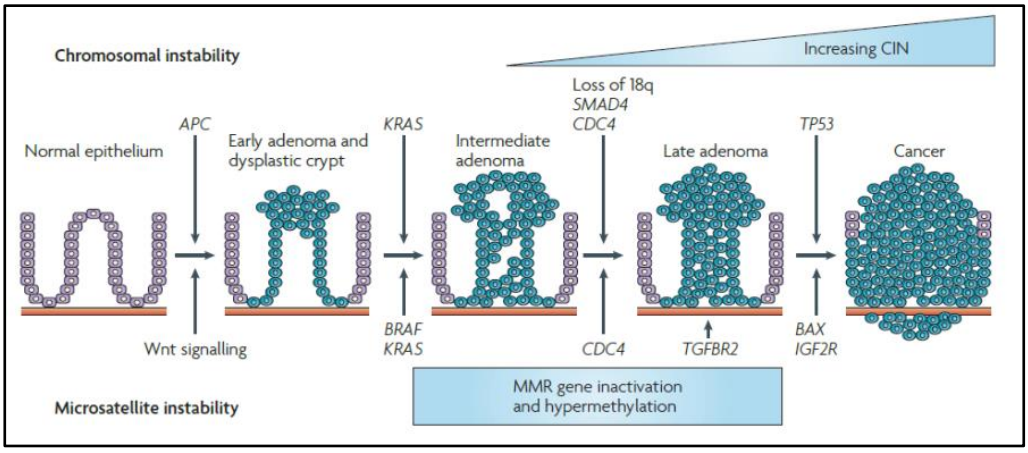
1.1.3.1 The molecular basis of colorectal carcinogenesis

Chromosomal instability

The vast majority (>90%) of invasive colorectal carcinomas develop from a pre-malignant precursor in the form of an adenomatous polyp (69). This process is known as the adenoma-carcinoma sequence and is characterised by the stepwise transition, via genetic mutations, of normal colonic mucosa to adenomatous tissue and eventually adenocarcinoma.

Initially, changes in the tumour suppressor gene, Adenomatous Polyposis Coli (*APC*) results in a loss of its function and is considered a very early step in the process. *APC* changes are identified in approximately 80% of adenomas and carcinomas (69). In a simplified version of events, *APC* mutations are followed by mutations in the *KRAS* gene, resulting in a loss of genetic material on chromosome 18q at *SMAD4*, and deletion of the upper part of chromosome 17 (17p), which houses the critical tumour suppressor gene *TP53*. This sequence of events results in carcinoma formation **[Figure 1.6]** (70, 71)**.**

Figure 1.6: The adenoma-carcinoma sequence model for chromosomal instability in colorectal cancer



Reproduced (with permission) from Walther et al. 2009 (70)

Chromosomal instability is thought of as the traditional pathway to CRC. However, it is acknowledged that this pathway inadequately explains the undoubtedly complex sequences involved in the adenoma-carcinoma sequence and some of these steps may be skipped or occur in a different order (72).

What is clear however, is that progression from adenoma to carcinoma may take several decades, and usefully, this would provide an opportunity for clinicians to intervene with measures such as colonoscopy and polypectomy for the prevention of subsequent CRC (73).

Microsatellite instability

Up to 15% of CRCs are characterised by microsatellite instability (MSI) (74). This pathway is defined by the inactivation of DNA mismatch repair (MMR) genes. The MMR genes play a role in the synthesis of enzymes that identify and correct errors during DNA replication. Mutation of MMR genes lead to inactivity that can result in base pair mismatches during DNA replication. Microsatellites are small stretches of repetitive DNA that due to their repetitive nature, are prone to errors. A defective MMR gene can leave the genome with microsatellites that are either longer or shorter than the parent DNA; this is termed MSI and can result in carcinogenesis (75).

As will be discussed later, MSI is the hallmark of cancers arising in patients with HNPCC and is present in all cases. However, MSI is not limited to hereditary CRC and is identified in sporadic CRCs in approximately 15% of cases. The mechanism that precipitates MSI can vary. For example, in sporadic CRC the cause of MSI is epigenetic silencing (prevention of gene transcription) MMR genes, whereas in hereditary CRC the cause is a germline mutation resulting in defective MMR genes (73).

DNA hypermethylation

Hypermethylation refers to the inappropriate addition of methyl groups to gene promoter regions of DNA (75). As a result of methylation, gene transcription of the affected gene is downregulated (silenced). Hypermethylation of tumour suppressor genes effectively switches them off (72). Up to 20% of CRCs develop via this pathway and are often associated with *BRAF* gene mutations (69). *BRAF* is a human gene that encodes a protein (B-Raf) involved in cell signalling and growth, and mutated versions of it have been identified in several human cancers, including CRC (76).

1.1.3.2 Sporadic Colorectal Cancer

The majority of CRCs are sporadic and arise as a result of progressive genetic alterations or interactions between the host and environmental factors (77). Sporadic CRCs are those which arise from the colon or rectum without a known genetic cause, family history, or diagnosis of IBD. Approximately two-thirds of CRCs fit these criteria. The most common route for the development of sporadic CRC is through the adenoma-carcinoma sequence **(Section 1.1.3.1.)** (77)**.**

1.1.3.3 Hereditary Colorectal Cancer

Less commonly, CRCs arise where the specific cause is apparent. This could be related to a medical or inherited condition that predisposes a patient to CRC.

Hereditary Non-Polyposis Colorectal Cancer

HNPCC, first described in the 1960s by Henry Lynch (78), is an autosomal dominant genetic condition associated with a higher risk of several cancers such as colorectal, endometrial, gastric, small bowel, breast and ovarian (79). HNPCC is the most common of the inherited CRC conditions accounting for approximately 3% of all CRCs (80). These type of CRCs

arise due to an inherited mutation of MMR genes leading to tumours with MSI, as mentioned previously (81).

HNPCC-associated CRCs are often right-sided and characterised by a young age of onset, with a mean age of 45 years, and an elevated risk of synchronous and metachronous cancers (79, 81). Although multiple adenomas may be observed in HNPCC, florid polyposis is not a feature. Despite this, the majority of HNPCC cancers follow the adenoma-carcinoma sequence, which progresses at a faster rate in HNPCC (82). Patients with CRC related to HNPCC tend to have a better prognosis with a 10-year survival of 91% (82).

The disorder can be diagnosed empirically from a detailed family history or by genetic testing (83). However, not all MMR mutated tumours are related to HNPCC which presents a diagnostic challenge if using genetic testing alone. As such, internationally recognised criteria to help identify HNPCC patients, primarily for clinical trials, have been established. Namely the Amsterdam Criteria. These were first described in 1990 as the Amsterdam I Criteria, and have since been updated to the current Amsterdam II Criteria **[Table 1.2]** (81).

Table 1.2: Amsterdam II criteria for the diagnosis of HNPCC

Amsterdam II criteria
1. At least three relatives with HNPCC-associated cancer (CRC, endometrial, small bowel, ureteric, renal pelvis)
2. One should be a first degree relative of the other two
3. At least two successive generations must be affected
4. At least one should be diagnosed before the age of 50 years
5. If the case is a CRC, FAP must be excluded
6. Tumours should be verified by pathological examination

In addition, the Bethesda Guidelines were devised in order to identify CRCs from patients that should undergo additional immunohistochemistry and MSI testing. This is to help

identify patients who are MMR-gene carriers but do not fit the Amsterdam Criteria. The revised Bethesda Guidelines are shown in **Table 1.3** (84)**.**

Table 1.3: Criteria for selection of tumours to be tested for microsatellite instability

Revised Bethesda Guidelines
1. CRC diagnosed in a patient <50 years
2. Presence of synchronous, metachronous colorectal or other HNPCC-associated tumours, regardless of age
3. CRC with MSI diagnosed in a patient <60 years
4. CRC or other HNPCC-associated tumour diagnosed in at least one first degree relative <50 years of age
5. CRC or other HNPCC-associated tumour diagnosed in two first or second-degree relatives at any age

In patients with HNPCC, the lifetime CRC risk is around 80% (15). As such, routine CRC surveillance is warranted. Guidelines published in 2013 recommend patients undergo colonoscopy at 1–2 year intervals (85) since there exists an elevated risk of interval cancers for patients undergoing three-yearly surveillance (85).

Familial Adenomatous Polyposis Syndrome

FAP is an autosomal dominant genetic disorder caused by a mutation and loss of function of the *APC* gene located on chromosome 5q21 (86). The *APC* gene is primarily involved in cellular adhesion but is also a tumour suppressor, and loss of function leads to the clinical presentation of the disease (87). This is characterised by the development of multiple (>100) adenomas within the colon and rectum and the incidence is approximately 1:5,000–1:10,000 with an equal male: female split (88). FAP is a less common cause of CRC than HNPCC, accounting for under 1% of all CRCs (89). For carriers, there is almost a 100% risk of developing CRC by the age of 40 years, so prophylactic colectomy is recommended in the teenage years (90).

1.1.4 Clinical presentation

The mode of presentation in CRC varies. Some patients may present with symptoms relating to the primary tumour, while others may present at a later stage with symptoms related to metastatic disease; but increasingly, asymptomatic patients will be diagnosed as part of a national bowel screening programme.

1.1.4.1 Elective presentation

Elective presentations are related to symptomatic patients visiting their primary care physicians. Symptoms may include one or a combination of three primary symptoms, namely: rectal bleeding, change in bowel habit, and abdominal pain (91). Unfortunately, these symptoms are also common to benign disease, which can reduce their specificity greatly (92). While there is a recognition that many patients with cancer have more than one symptom, in the case of CRC, a palpable abdominal or rectal mass, iron deficiency anaemia, or weight loss are red flags (93). Nonetheless, a degree of clinical judgment must be exercised when deciding on further investigations for suspected CRC.

1.1.4.2 Emergency presentation

Despite screening and efforts to improve referral guidelines in primary care, up to 30% of patients with CRC present to the surgical department as an emergency (94). The presenting condition may be one of large bowel obstruction, perforation or rectal bleeding.

Unfortunately, surgery performed to relieve acute obstruction in the emergency setting results in significantly higher morbidity and mortality (95). Furthermore, the prognosis is poorer in patients who present as an emergency, even if emergency surgery is not required. An early study by McArdle *et al.* in 2004, included over 3,000 patients who underwent surgery for CRC. The researchers reported that those undergoing emergency vs. elective CRC surgery for curative intent had higher postoperative mortality (8.2% vs. 2.8%) and

lower overall and cancer-specific 5-year survival, (39.1% vs. 57.5%) and (52.9% vs. 70.9%) respectively (96).

1.1.4.3 Metastatic disease at presentation

Patients may present with symptoms of metastatic disease; and in the USA, up to 20% of patients are found to have metastatic disease at presentation (97). Symptoms from metastatic disease can vary and are related to the route of disease spread. The most frequent sites of metastatic spread are regional lymph nodes, the liver, the lungs, and the peritoneum. However, spread to bone and brain are not uncommon. Since the majority of venous drainage of the intestinal tract is via the portal system, the liver is often the first site of haematogenous spread. The exception to this is distal rectal tumours that may metastasise to the lungs initially. This occurs since venous drainage via the inferior rectal veins enters the systemic circulation rather than the portal system via the inferior vena cava, thus bypassing the liver. As such, symptoms from metastatic disease can be wide and varied depending on the location and extent of the metastases.

1.1.4.4 Bowel screening presentation

Bowel screening is discussed in **Section 1.2**. As a mode of presentation, screening provides a significant gateway for cancer detection. Mansouri *et al.* in 2016, published data from the Greater Glasgow and Clyde (GGC) Health Board in relation to the Scottish Bowel Screening Programme (SBoSP). During the study period, a total of 1,129 CRCs were diagnosed. Of these, 421 (37%) were screen-detected which indicates the majority of cancers are still diagnosed outside of the screening programme. Although the results may be explained when considering only half (52%) of those eligible for screening accepted the offer (98).

1.1.5 Diagnosis and investigations

The diagnosis of CRC must be confirmed by histological analysis, and in the majority of cases, this occurs prior to any intervention. However, this ideal situation is not always possible. For example, in the emergency setting, if a patient presents with colonic perforation and faecal peritonitis primary surgery would need to be undertaken on an emergency basis. Thereafter, histological confirmation from the resected specimen would follow. In cases where a patient presents with metastatic disease found incidentally on a radiological scan, a search for the primary tumour may be undertaken using a combination of endoscopic investigations, blood sampling for tumour markers, and tissue biopsy using image-guided techniques.

1.1.5.1 Diagnostic tests

Colonoscopy

Colonoscopy is the gold standard for investigating the colon and rectum. It is used both as a diagnostic and a therapeutic tool. This procedure can localise lesions and enable biopsies to be taken. It has high sensitivity and specificity for CRC (99), but there are a number of drawbacks, such as a small but not insignificant risk of perforation, in the order of 1:1,000 (0.1%) (100, 101). This increases with age (101). In addition, the requirement for intravenous sedation is not without risk; formal bowel preparation is unpleasant for 24 hours prior to the colonoscopy, and the procedure can cause discomfort. Other down sides include a failure to complete the investigation. In order to ensure an adequate standard of colonoscopy, practitioners must aim for a minimum 90% caecal intubation rate for all colonoscopies and 95% for a screening colonoscopy (102). Despite this target, incomplete colonoscopy rates can vary from 4–25% (102), which is often related patient discomfort, technical difficulty (e.g. looping of the colon, tight colonic angulation, diverticular disease), or inadequate bowel preparation.

Flexible sigmoidoscopy

Flexible sigmoidoscopy affords direct visualisation of the colon and rectum without the need for intravenous sedation or full bowel preparation. In this regard, it offers an advantage over colonoscopy, especially in frail patients. Flexible sigmoidoscopy would be expected to detect 70% of all cancers since the majority occur distal to the splenic flexure (103). Drawbacks include a failure to examine the colon proximal to the splenic flexure, and variability in the view of this area limited by bowel preparation. In addition, synchronous tumours of the colon are present in up to 5% of cases and thus, diagnosing a tumour via flexible sigmoidoscopy would warrant a full colonoscopy subsequently (104).

Barium enema

A double-contrast barium enema is performed by the insufflation of air into the rectum in combination with radio-opaque barium. The barium and air contrast on subsequent X-rays are used to identify mucosal lesions. The use of this diagnostic test has dwindled with the increasing availability and superiority of colonoscopy and Computed Tomography (CT) scanning.

Computed tomography colonography

Computed tomography colonography (CTC), also referred to as virtual colonoscopy, allows 3D imaging of the colon and rectum. The test was first introduced clinically in 1994 (105). CTC is significantly less invasive than a colonoscopy, and only minimal bowel preparation is required. The procedure is carried out with the patient in the lateral decubitus position, and the colon is distended using room air or carbon dioxide via a small enema tip in the rectum (105). CT scanning is undertaken, and the resulting 2D and 3D images are reviewed by a radiologist using specialised imaging software. Discomfort is minimal and limited to the gaseous distension of the colon, with many patients reporting less discomfort than colonoscopy (105).

Several studies comparing CTC and colonoscopy have been conducted. In general, CTC is regarded as an acceptable alternative to colonoscopy. A 2013 systematic review concluded that CTC is less sensitive than colonoscopy overall, but for larger lesions (e.g. ≥1cm), sensitivity is comparable (91.2% CTC vs. 92.9% colonoscopy) (106).

There are a number of drawbacks of CTC such as the need to visualise directly, biopsy or remove any detected lesions which require a colonoscopy, resulting in a two-stage procedure. In addition, the dose of radiation received in a screening CTC, although lower than standard CT must be considered (107).

A debatable topic, which may be thought of as either a drawback or an advantage, is the detection of extracolonic findings (ECF) at CTC. While ECFs from CTC are common, and the majority are insignificant, one study reported just over a third (37%) are of intermediate or high significance (108). Despite this, only 1% of patients included in the above study required surgical or medical intervention as a result of ECFs. This report implies that there may be a significant degree of work-up and investigation required for what subsequently turns out to be benign disease. This could be viewed negatively by patients in terms of anxiety or discomfort from further invasive investigations, and similarly a health economics standpoint given the cost to a health service of investigating ECFs for minimal health gain. These concerns must be balanced with the potential benefit of diagnosing an important clinical condition such as an aortic aneurysm or solid organ tumour that would otherwise have gone unnoticed.

Blood tests

There are no blood tests that can diagnose CRC; however as previously discussed, the presence of iron deficiency anaemia is an indicator of occult blood loss in the gastrointestinal tract; and as such, it is used as a prompt for endoscopic examination. Carcinoembryonic Antigen (CEA) is a blood test utilised as a tumour marker in patients with CRC. It has a 90%

specificity for CRC, but sensitivity is poor at approximately 40–75% (109) rendering it unhelpful for diagnostic purposes. Its main use is as a prompt for further investigation to detect occult disease recurrence, and it has some value in monitoring the response to chemotherapy (110).

1.1.5.2 Colorectal cancer staging at presentation

The principles of staging

Following histological confirmation of CRC, further investigation is undertaken in order to stage the disease which is useful as a prognostic indicator (**Section 1.1.7**), facilitates management decisions, and aids in clinical research (111). The Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommend three areas are assessed for staging purposes (112).

1. Assessment of local disease relating to the primary tumour
2. Assessment for metastatic disease
3. Assessment for synchronous colonic disease

Modalities used for staging

Local disease is examined by CT scanning of the abdomen and pelvis in order to collect information on the size of the tumour, local spread, or lymph node involvement while assessing for invasion of the abdominal wall or other organs.

For tumours of the rectum (tumour within 15cm of the dentate line during rigid sigmoidoscopy), Magnetic Resonance Imaging (MRI) is used for local staging; and crucially, this modality can estimate the risk of circumferential resection margin (CRM) involvement. A clear CRM is one in which normal tissue is >1mm from malignant tissue. Detailed staging of rectal cancers is essential as it determines the feasibility and timing of potentially curative surgery. An additional modality for rectal tumour staging is endoluminal

ultrasound, whose value is realised in patients where MRI is contraindicated, or where local excision of a small primary tumour is being considered (113).

In addition to the above, CT scanning of the thorax to look for metastatic disease in the lung or pleura is routinely conducted for staging purposes, while suspicious liver lesions can be further assessed by MRI. Positron Emission Tomography CT (PET-CT) scanning can be used to investigate suspicious lesions seen on CT or MRI. However, its real preoperative value lies in the detection of occult disease in patients being considered for surgical management of liver or lung metastases (112). PET-CT is a nuclear imaging modality where patients are injected with radioactive tracers that label molecules such as glucose with positron-emitting radionuclides. The most commonly used being 18-Fluoro-deoxy-glucose (^{18}FDG). Since malignant cells have an elevated glucose uptake, the PET-CT scanner can detect "hot spots" of high metabolic activity, suggesting malignancy (114). Drawbacks of PET-CT include diagnostic uncertainty, where tissue with inherently high physiological activity such as the brain and heart; or the kidneys, where ^{18}FDG is excreted, light up as hot spots. Nonetheless, PET-CT has great value in cases where occult malignancy, such as disease recurrence, are suspected but modalities such as CT fail to pick up convincing abnormalities.

Synchronous cancers occur in up to 5% of patients and must be excluded during the initial diagnostic colonoscopy (104). If synchronous disease has not been excluded (e.g. a diagnosis made with flexible sigmoidoscopy), then a full colonoscopy or CTC should be arranged (112).

Systems and classification of staging

The Tumour, Node, Metastasis (TNM) system is the most commonly used classification and staging system worldwide. It was developed in 1992 by the American Joint Committee on Cancer (AJCC). In this system, CRCs are classified according to the tumour itself (T), the

degree of regional lymph node involvement (N) and the presence or absence of distal organ metastasis (M). The 7th edition of the AJCC TNM staging system for CRC is displayed in **Table 1.4**. This will be superseded for clinical use in 2018 by the 8th edition.

In the preoperative setting, the TNM classification is based on clinical, biopsy and radiological findings and would be allocated a "c" prefix, (e.g. $cT_1N_2M_0$). After surgical resection, re-classification is conducted, and the prefix "p" is given to indicate the updated pathological classification. Pathological staging is superior to clinical as it enables a verified result. The combined TNM classification is subsequently used to stage a patient from I to IV. Stage II and III have subdivisions; however, a simplified outline is presented below.

- **Stage I**: A patient with a T1 or T2 tumour who is lymph node and distant metastases negative
- **Stage II**: A patient with a T3 or T4 tumour who is lymph node and distant metastases negative
- **Stage III**: Varied stage of tumour and lymph node-positive but no distant metastases are present
- **Stage IV**: Metastatic spread

In the UK, an alternative system is still in use called Dukes' staging system, with the Turnbull modification (115). This system allocates stage A–D, and similar to the TNM system, it accounts for local tumour extent, lymph node involvement, and the presence or otherwise of distant metastatic disease **[Table 1.5].**

Table 1.4: TNM staging for CRC: American Joint Committee on Cancer, 7th Edition

Primary tumour (T)	**T Criteria**
T_x	Primary tumour cannot be assessed
T_0	No evidence of primary tumour
T_{is}	Carcinoma *in situ*: intraepithelial tumour or invasion of lamina propria
T_1	Tumour invades the submucosa
T_2	Tumour invades the muscularis propria
T_3	Tumour invades through the muscularis propria into the peri-colorectal tissues
T_{4a}	Tumour penetrates the surface of the visceral peritoneum
T_{4b}	Tumour directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	**N Criteria**
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Metastasis in 1–3 regional lymph nodes
N_{1a}	Metastasis in 1 regional lymph node
N_{1b}	Metastasis in 2–3 regional lymph nodes
N_{1c}	Tumour deposits in the subserosa, mesentery, or non-peritonealised pericolic or perirectal tissues without regional nodal metastasis
N_2	≥4 regional lymph nodes positive
N_{2a}	Metastasis in 4–6 regional lymph nodes
N_{2b}	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	**M Criteria**
M_0	No distant metastasis are seen on imaging
M_1	Metastasis to 1 or more distant sites, organs or peritoneal metastasis
M_{1a}	Metastasis confined to one organ or site only
M_{1b}	Metastasis in more than one organ, site or the peritoneum

The AJCC: Colon and Rectum, Cancer Staging Manual- 7th Edition (116)

Table 1.5: The relationship between Dukes' stage, TNM stage, and 5-year survival in CRC

Dukes' stage	TNM stage	TNM classification	5-year survival (%)
A	I	$T_{1–2}$ N_0 M_0	93
B	II	$T_{3–4}$ N_0 M_0	77
C	III	T_{any} $N_{1–2}$ M_0	48
D	IV	T_{any} N_{any} M_1	6

The National Cancer Intelligence Network UK (117)

1.1.6 Management

1.1.6.1 The multi-disciplinary team

A key component of the investigation and management process for CRC are multi-disciplinary team (MDT) meetings. These constitute a regular meeting of healthcare professionals, namely: surgeons, radiologists, pathologists, oncologists, and nurse specialists all with an interest in CRC (118). Every new cancer case is discussed, the images and pathology results are reviewed, and a management approach is agreed. Cases are re-discussed post-surgery, post-neoadjuvant treatment or if recurrence is suspected. The MDT meetings ensure that high-quality care is delivered in an evidence-based approach. Evidence exists that these meetings result in improved 5-year survival in CRC, and in rectal cancer, a reduction in the rate of CRM involvement (119) (120).

1.1.6.2 Surgical resection

The gold standard of treatment for CRC is surgical resection with curative intent. The majority of patients will have their surgery on an elective basis, but as discussed previously, a proportion of patients will present as an emergency.

Elective surgery

The majority of patients will undergo a planned elective procedure that will, in the vast majority of cases, be conducted by a specialist colorectal surgeon. This approach has been shown to improve long-term survival (121).

The primary goal of surgery is to remove the section of bowel containing the tumour. It is important to ensure the tumour is removed en bloc with a surrounding margin of healthy tissue. It is also critical that the specimen is resected in continuity with its lymphatic drainage pathways to ensure lymph node metastases are excised, and to enable staging.

Rectal cancers are unique in that the surgical decision is made with respect to the preservation or otherwise of the anal sphincter complex. For this reason, preoperative staging, by clinical examination and in particular, MRI is crucial. Above all, it is important to achieve a clear distal resection margin. If a rectal tumour is deemed too low to allow distal margin clearance while maintaining a degree of normal rectal function, then a complete excision of the anus is warranted with the formation of an end colostomy. This operation is called an abdominoperineal resection (APR). Recent thinking has led to a more radical approach for some rectal cancers whereby removal of the levator muscles is conducted with the patient in the prone or jack-knife position. This is called extra-levator, or cylindrical APR and studies have reported good oncological clearance at the CRM (122).

A key aspect during excision of the rectum is to excise the mesorectal fat plane intact, which sits below the peritoneal reflection and envelopes the rectum in a cylindrical fashion. This process is described as a total mesorectal excision (TME), and it has been shown to reduce the risk of subsequent local recurrence (123).

Emergency surgery

Emergency presentation of CRC was discussed in **Section 1.1.4.2**. Despite the modern practice of bowel screening and early referral to secondary care, a substantial proportion of patients still undergo emergency surgery for their oncological resection with the associated downsides which include; a lack of preoperative planning, limited staging, and the absence of an MDT discussion.

1.1.6.3 Neoadjuvant therapy

In simplistic terms, neoadjuvant therapy is designed to shrink tumours and treat involved lymph nodes prior to definitive surgical treatment with curative intent. At present, neoadjuvant therapy, in the form of radiotherapy with or without chemotherapy, is considered in certain rectal cancers but not colonic cancers. As such, distinguishing rectal from colonic cancer is vitally important. MRI can often make this distinction, whereby the rectum is said to begin at the level of the sacral promontory (124). Rectal cancers inherently have a higher risk of local recurrence than colonic cancers due to the absence of serosa and their close proximity to other pelvic structures. These features increase the technical difficulty in obtaining a clear resection margin (125).

In order to reduce the risk of local recurrence, $T_{3–4}$ tumours, those with nodal involvement, or threatened CRM are considered for preoperative neoadjuvant therapy to downstage the tumour (125). The CRM can be accurately assessed preoperatively by MRI and images are then viewed and discussed at the MDT where neoadjuvant therapy is considered (126).

Neoadjuvant therapy can be delivered in one of two regimens: Long-course preoperative chemo radiotherapy (CRT) or short-course preoperative radiotherapy (SCPRT). CRT constitutes radiotherapy over a 5-week interval with a dose of at least 45 Gray (Gy) in 25 fractions with synchronous 5-fluorouracil or oral capecitabine chemotherapy (124). Surgery is then delayed for around 6–10 weeks after completion to allow adequate response time.

The alternative option is SCPRT, which constitutes a dose of 25Gy in five fractions daily for one week, followed by surgery within ten days of completion to minimise the risk of post-radiotherapy complications. This regimen is often used in patients who have a moderate risk of local recurrence but without mesorectal fascia involvement, or in patients with comorbid disease who are less fit for CRT (124).

1.1.6.4 Adjuvant therapy

Adjuvant therapy, in the form of systemic chemotherapy, is considered in patients who are at higher risk of cancer recurrence after attempted curative resection. The justification for this is based on the theory that occult disease left behind during surgery, is most likely responsible for subsequent recurrence. Most centres now offer adjuvant chemotherapy to patients with stage III (node-positive, or Dukes' C) colon cancer and rectal cancer, assuming they are adequately fit and this intervention has led to improved overall and disease-free survival (127). Commonly used chemotherapy agents include 5-fluorouracil, FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin), capecitabine or Xelox (capecitabine and oxaliplatin). The duration of therapy varies but is typically 6–8 months. The decision for adjuvant chemotherapy must be made jointly with the patient and oncologist and include a discussion of the risks and benefits (124). In rectal cancers, salvage radiotherapy can be carried out postoperatively in cases where a positive resection margin has been obtained (124).

1.1.6.5 Palliative management

A substantial proportion of patients present with inoperable disease, metastatic disease or a significant comorbid burden and are not deemed fit for surgical intervention, leaving palliation as the only option. Some patients may choose not to undergo active intervention and are given end of life care, where maintaining quality of life while alleviating suffering is the primary goal. Palliation can be facilitated by good communication between medical

teams including; surgeons, oncologists, nurse specialists, palliative specialists, and other carers such as family and primary care physicians. Some patients can be considered for palliative chemotherapy. Meta-analyses data of RCTs have reported a 3.7-month median survival benefit of palliative chemotherapy when compared with best supportive care (128). In the palliative situation, a colonic or rectal obstruction by the tumour can pose a problem; as such, diversion of the faecal stream by a defunctioning colostomy is considered. An alternative option is the placement of a stent which has rising popularity, although the limitations of stenting include the risk of perforation and technical failure (129).

1.1.7 Postoperative prognosis

Both tumour and host factors contribute to postoperative prognostic stratification, which is important in order to inform patients, and aid decision making for follow-up planning, or adjuvant therapy. **Section 1.1.5** described the most commonly used staging systems in CRC; however, there are a number of other factors to consider when determining prognosis.

1.1.7.1 Tumour specific factors

Additional tumour-related prognostic factors not accounted for in TNM staging are worthy of considering.

Tumour grade

A tumour is graded pathologically depending on the degree of differentiation displayed by its cells. Differentiation is the extent to which a tumour cell resembles the cell type expected in the tissue of origin under normal circumstances. Colorectal tumours may be classed as low-grade (high or moderately differentiated) or high-grade (poorly differentiated), where high-grade is associated with a worse prognosis (130).

Venous invasion

The diagnosis of venous invasion is a pathological one. Venous invasion is evident if tumour cells are observed within an endothelial lined space, with a rim of smooth muscle, in the presence of red blood cells, and is associated with a poorer prognosis (131, 132).

Perineural invasion

The invasion of nerve structures, including nerve sheaths, defines perineural invasion, which is associated with a poorer prognosis (133).

Tumour necrosis

Rapidly growing malignant tumours can outgrow their local blood supply, resulting in self-induced hypoxia and nutrient deprivation. As a result, necrosis occurs in core regions of the tumour (129). In patients undergoing surgery for CRC, tumour necrosis has been associated with reduced cancer-specific survival and is a marker of poor prognosis independent of the pathological stage (134).

Lymph node ratio

The lymph node ratio (LNR) is calculated by dividing the number of positive nodes by the total number of nodes provided in the resection specimen. It has been reported that examining a greater number of lymph nodes increases the likelihood of correct staging. Nevertheless, as a result of surgical technique, variation in the actual number of lymph nodes present, and the efficiency of the pathologist, the number reported can vary. This led to the development of the LNR prognostic indicator. In a large study of over 25,000 patients, an LNR of >0.4 was associated with poorer 5-year survival. The prognostic estimates were comparable to that calculated by the more traditional TNM system (135). At present LNR is not routinely used in clinical practice.

Tumour perforation and peritoneal or margin involvement

A visible defect in the wall of the bowel while analysing the pathological specimen suggests perforation. Both perforation or the presence of visible tumour cells attached to peritoneal surfaces, are associated with a poor prognosis (136). Tumour cells <1mm from the circumferential or longitudinal resection margin is classed as "an involved margin" and is associated with poorer prognosis.

1.1.7.2 Host factors

Other than pathological and tumour specific factors, host characteristics have demonstrated prognostic value. It is difficult to determine whether the host characteristics influence the tumour itself or vice versa, in reality, it is likely there is a complex interplay between the host and the tumour. A sizeable body of work has demonstrated that sociodemographic factors, systemic inflammation, the local inflammatory response, and aspects of body composition have prognostic value.

Sociodemographic and socioeconomic factors

Extensive population studies previously carried out in Scotland have shown that older patients and those who live in areas with a higher level of socioeconomic deprivation suffer poorer overall 5-year survival from CRC when compared to younger and less deprived patients (137). The observed associations remain independent of emergency presentation and cancer stage, which in themselves are determinants of poor prognosis. The explanation for this observation is not clear; however, it may be that those subjected to higher levels of deprivation are less likely to engage with healthcare, and this delays presentation leading to later stage presentation with associated worse outcomes (138). Evidence for this hypothesis was observed in a study by Mansouri *et al.* (139), where the researchers reported that patients exposed to higher levels of deprivation are less likely to engage in population-based screening programmes. Screening is associated with earlier stage disease at diagnosis (in

those without metastases) (140); therefore it is plausible that those exposed to socioeconomic deprivation are more likely to present outside of the screening programme, potentially as an emergency, or with later-stage disease.

The host inflammatory response and prognosis

As discussed in **Section 1.1.2.2**, there is an association between inflammation and cancer. Whether inflammation is a response to the tumour itself or has merely contributed to carcinogenesis is difficult to identify, but in all likelihood, it is a combination of both. In the human body, an inflammatory response is a defence mechanism, but it appears to promote tumour progression as well as destruction. However, what has become clear is that the inflammatory response of the host has prognostic value in CRC.

Systemic inflammatory response

A systemic inflammatory response refers to one which is non-specific and occurs in response to bodily insult or injury. It is a whole-body response and involves a complex cascade of changes in circulating inflammatory cytokines and immune cell activity. As previously discussed, circulating CRP is a sensitive, specific, and routinely measured marker of systemic inflammation (141). As such, it is an optimal marker in which to study the link between systemic inflammation and CRC prognosis. Multiple studies have reported that systemic inflammation, as measured by elevated CRP, and CRP-based scoring systems, are associated with disease progression and poorer long-term survival independent of tumour stage (138, 142, 143).

In addition to CRP, hypoalbuminaemia, as a marker of systemic inflammation is also associated with a poor cancer prognosis (144), and these findings have led to the development of combined albumin and CRP scoring systems, notably the Glasgow Prognostic Score (GPS). The GPS has subsequently been revised, and the modified Glasgow Prognostic Score (mGPS) is now used (143, 145).

The mGPS allocates to a patient, a score of 0,1 or 2, where 2 reflects the most marked systemic inflammatory response. It is scored as follows:

- mGPS = 0 CRP ≤10mg/l AND albumin ≥35g/l
- mGPS = 1 CRP >10mg/l
- mGPS = 2 CRP >10mg/l AND albumin <35g/l

The prognostic power of the mGPS system has been studied extensively in a range of solid organ cancers, particularly CRC. Elevated mGPS, as a marker of systemic inflammation, has repeatedly been associated with poorer outcomes (143); and in CRC, has been shown to predict survival, independent of disease stage (145), emergency presentation (141) and comorbidity (146). In addition, an elevated mGPS has been associated with increased postoperative complications in patients undergoing surgery for potentially curative CRC (147). A recent review paper summarising over 60 studies, including 30,000 patients, concluded that elevated GPS and mGPS scores are independently associated with poorer survival across several cancer types (148).

Additional inflammation-based scoring systems have demonstrated similar prognostic value, and wide-reaching systemic reviews and meta-analyses have been conducted to validate these. They include the neutrophil: lymphocyte ratio (NLR), the platelet: lymphocyte ratio (PLR) and the lymphocyte: monocyte ratio (LMR), yet presently, inflammation-based prognostic scoring systems are mainly used in clinical research (138, 143, 149, 150).

The local inflammatory response

In contrast to the poor prognosis associated with systemic inflammation, a local inflammatory cell reaction in the tumour microenvironment is associated with improved prognosis, as reported by Roxburgh and McMillan in 2012 (151). The authors noted that in order to enhance its clinical relevance, a standardised assessment of the local inflammatory

infiltrate within the tumour microenvironment was needed. A previously validated system, the Klintrup-Makinen criteria was suggested (151). The Klintrup-Makinen criteria is a reproducible grading system where a score of 0–3 is awarded depending on the intensity of the inflammatory cell reaction at the invasive tumour margin. Subsequently, tumours are graded as low-grade (score 0–1) or high-grade (score 2–3), and the authors above previously reported that high-grade tumours were associated with an enhanced 5-year survival when compared to low-grade tumours (87.6% vs. 47%), in Dukes' A and B or lymph node-negative cancers (152).

Body composition and prognosis

In a similar fashion to other solid organ tumours, CRC is associated with progressive nutritional and functional decline. These factors are associated with disease progression and can independently predict poor outcomes (153). In the past, crude measures of nutritional decline such as BMI and weight loss have been utilised for prognostic stratification (154). An advantage of these measures lies in their ease of use, portability and low cost. BMI is an index, and while this enables standardisation of weight for height, it cannot account for the contribution specifically of muscle volume, fat volume and the relative distribution of these tissue types within the body. In addition, sex and race variations introduce difficulty in predicting overall body adiposity from crude measures such as waist circumference or BMI (155). As a result, recent interest of the association between CT derived body composition and cancer prognosis has evolved. CT scanning makes use of the principle that different tissues have a higher or lower radiodensity. Radiodensity is measured by Hounsfield units, and thresholds for fat and skeletal muscle can be set such that the area of each tissue type can be accurately measured. The measured areas can be standardised for height to develop indices such as the subcutaneous fat index, skeletal muscle index, sarcopenia and visceral obesity (154, 156).

Recent interest has specifically surrounded sarcopenia, which has been described as a marker of patient frailty (157) and has been defined as follows:

"A syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" (158).

Thresholds for skeletal muscle index, such as those developed by Dolan *et al.,* (154) for a given BMI, can be used to define patients with radiologically proven sarcopenia. Dolan *et al.* went on to examine a cohort of 650 patients with primary operable CRC and reported that sarcopenia was associated with poor cancer-specific and overall survival (154). What is not entirely clear however, is the role of body composition in early cancer development or adenoma formation and how this may evolve over time.

1.2 Screening for colorectal cancer in Scotland

Principles for mass population screening were first outlined by Wilson and Jungner in 1968 (159). In general, for a condition to be considered for screening, it must be an important health problem, the disease should have a detectable pre-clinical phase, and a better prognosis if treated at an earlier stage. In addition, the test used for screening requires adequate sensitivity and specificity while remaining acceptable, safe and cost-effective. CRC incorporates most of these criteria and is considered a good target for screening (160).

1.2.1 Evidence underpinning bowel screening

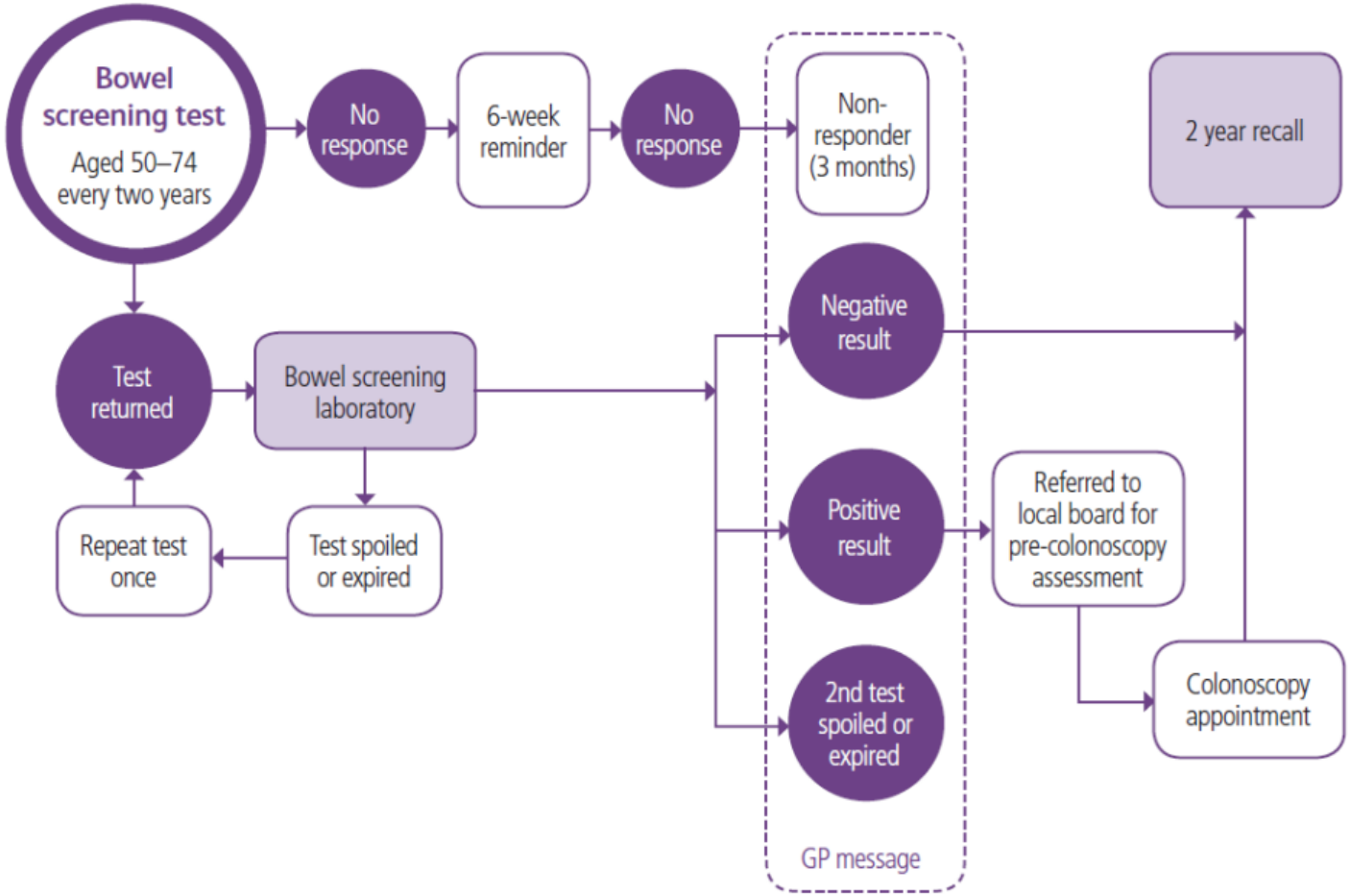
In Scotland, bowel screening was fully rolled out in 2009. The basic principles are that the laboratory detection of occult blood, as a sign of potential CRC, would prompt endoscopic visualisation of the colon. Three key trials ensured bowel screening was supported by data. In the Minnesota Colon Cancer Study, the researchers randomly assigned 46,000 Americans aged 50–80 years to either annual screening for faecal occult blood (FOB), biennial screening, or a control group and patients were followed for 13 years. The researchers reported that annual FOB screening reduced CRC mortality by 33% compared to control groups (161). Similar trials in Nottingham and the Funen trial in Denmark, reported a reduction in CRC mortality of 15% and 18% respectively, when participants were randomised to biennial FOB testing compared to controls (162) (163).

1.2.2 The current pathway for the Scottish Bowel Screening Programme

In Scotland, males and females aged 50–74 years, or those who wish to self-refer at or above 75 years are invited to take part in biennial screening. An illustration of the current pathway for bowel screening in Scotland is represented in **Figure 1.7.** The Faecal Immunochemical Test (FIT) is used for the SBoSP (164). This laboratory test uses antibodies specific to human haemoglobin, specifically the globin component, to test for occult blood in the stool. For this reason, it does not suffer the disadvantages of its predecessor in Scotland, the guaiac faecal

occult blood (gFOB) test. The gFOB test detected the peroxidase activity of haematin in faeces. As such, there was a risk that animal blood products, found in raw meat, peroxidase rich fruit, and vegetables such as broccoli and cauliflower could illicit false-positive results. Since the FIT method detects the globin portion of haemoglobin, which degrades as it traverses the gastrointestinal tract, there is a lower chance of detecting occult blood from the upper gastrointestinal tract. The FIT screening method measures micrograms of human haemoglobin per gram of faeces (µgHb/g). A cut-off of ≥80µgHb/g is accepted as a positive test for screening purposes. The test requires only one sample; thus, it is more straightforward and user friendly than its predecessor, which required two samples on three separate occasions. It is hoped this will improve uptake by those invited to screening.

Figure 1.7: The Scottish Bowel Screening Pathway



The National Health Service (NHS) Scotland: The new Scottish bowel screening test (164)

1.2.3 Uptake and results in Scotland

Statistics related to uptake and results of the SBoSP are periodically published by the Scottish Government, Information Services Division, as Key Performance Indicator (KPI) reports. The KPI report is used to monitor and evaluate the effectiveness of the SBoSP and is published at the end of each bowel screening (biennial) round.

The following information is taken from the latest available report at the time of writing in August 2016. This reports data from 2013 to the end of 2015 (165). The KPI report indicates that uptake of screening overall was 58%, with males less likely than females to partake (54% vs. 61%). There was a significant disparity in uptake depending on the degree of socioeconomic deprivation patients were exposed to. Considering Scotland as a whole, in the most deprived areas, uptake was 45% compared to 67% in the most affluent areas. These results were mirrored when males and females were considered separately. 2% of those who took up the invitation had a positive screening test, and 76% went on to have a colonoscopy with a 96% completion rate. Females were slightly less likely to have successful completion of colonoscopy when compared to males (95% vs. 98%). The KPI reported that 0.5% of patients required admission to hospital as a direct result of colonoscopy complications. Of those who had a screening test and went on to have a colonoscopy, 7% had CRC detected, with a higher incidence in males than females (7% vs. 6%). In those who had a screening test result but were negative for cancer, 39% were found to have at least one adenoma, again with a higher incidence in males than (45% vs. 30%).

These results indicate that the SBoSP detects a significant volume of pathology, although there is room for improvement in the uptake of invitations. The results of this KPI are related to screening rounds where testing was carried out predominantly using the gFOB test. There are hopes that the more practical, single sample, FIT method may improve uptake.

Data previously published from rounds of the SBoSP have already shown a trend towards earlier stage disease, in those without metastases, with the proportion of stage I tumours at diagnosis rising from 17% pre-screening to 28% post-screening ($p<0.001$) (140).

1.2.4 Screening for high-risk groups.

Patients who do not fall under the traditional criteria for population screening but who are at high risk of CRC as a result of inherited conditions are recommended to undergo screening. The ACPGBI in their most recent guidelines recommend that patients diagnosed with HNPCC should commence colonoscopy screening at age 25 and undergo annual or biennial colonoscopy until age 75 years unless comorbid disease dictates screening should end earlier (104). For patients with FAP, colonoscopy surveillance is recommended from age 13–15 years until 30 years, then 3–5 yearly until the age of 60 years (104). In reality, the majority of FAP sufferers, as discussed in **Section 1.1.3.3** would undergo subtotal colectomy before their fourth decade.

1.2.5 Risks of bowel screening

There are a number of disadvantages, drawbacks, and risks of bowel screening. The first is cost. The Scottish Government estimated, at the commencement of the SBoSP, that it would cost £9 million per year. This is likely to rise with improved uptake and cost of healthcare in general (166). Given that less than two-thirds of invitees in Scotland take part in screening, despite the estimated £9 million investment, a sizeable proportion of people will not benefit from this.

Although the screening test itself is unlikely to cause any patient complications, the majority of the 2% of those with a positive screening result will undergo colonoscopy. The risk of serious complications at colonoscopy has been discussed earlier **(Section 1.1.5.1),** and there is a perforation rate of around 1:1,000 (0.1%). This, combined with the 0.5% risk of

admission to hospital from screening colonoscopy complications mentioned in **Section 1.2.3**, must be balanced against the 7% chance of making a cancer diagnosis. Nonetheless, with experienced endoscopists, such as those involved in the SBoSP, the complication rate should remain low, since serious complications such as bleeding and perforation are associated with low volume endoscopists (167).

Patient anxiety is another consideration. 600 patients who had undergone gFOB screening as part of a screening feasibility study in Denmark were assessed for anxiety related to the outcome of the test result prior to any further investigation. Patients with positive gFOB results had significantly higher levels of anxiety than those with negative results, and the effect persisted for up to three months even after further investigations were negative. Nonetheless, anxiety levels returned to baseline by 12 months (168).

A risk associated with screening that is developing interest, but whose impact has not yet been assessed within a bowel screening population, is the risk: benefit ratio of CTC as a screening tool. CTC is conducted on screening positive patients who are either deemed unfit for a colonoscopy, or have undergone an incomplete colonoscopy. As discussed in **Section 1.1.5.1,** there is a high prevalence of ECFs at CTC of around 50–60% (169, 170). The majority of which are of no clinical significance. The difficulty lies in whether to investigate patients with borderline ECFs further, as this may result in multiple or invasive tests for what subsequently turns out to be benign disease (170). This situation could lead to patient anxiety during the investigative phase, and there is also an associated monetary and resource cost to the health service.

Furthermore, the problem may be exaggerated depending on the potential yield of positive intracolonic findings at CTC. In a situation where the yield of colonic findings is low, but the burden of ECFs is high or similar, the implications of ECFs and their possible investigation would need to be discussed with the patient. In a previously reported series,

the yield of important colonic findings was reported as 14% while indeterminate ECFs requiring possible investigation was slightly lower at 11% (171). In situations where patients are symptomatic, or the referring physician has a higher suspicion of cancer, the potential downsides of detecting ECFs may be justified. However, in a publicly funded health system with population screening programmes of asymptomatic patients such as the UK, the risk: benefit ratio of CTC as a second-line screening tool requires further investigation.

1.3 Colorectal polyps

1.3.1 Classification of polyps

A polyp of the colon or rectum is a protuberance that extends into the gut lumen beyond the surrounding mucosa. Adenomatous polyps are of considerable interest and are discussed at length in **Section 1.4**. However, there are a number of non-adenomatous colorectal polyps that require consideration. Generally, polyps of the colon or rectum are classified as either neoplastic or non-neoplastic types. A neoplasm is a new growth of tissue, whose growth continues, despite the absence of conditions for normal cell growth (172), and when a neoplastic growth invades adjacent tissues, it is defined as malignant.

1.3.1.1 Non-neoplastic polyps

Inflammatory polyps

These are non-neoplastic projections of the mucosa, which are densely packed with inflammatory cells. Morphologically they present as pedunculated (on a stalk) or sessile (largely flat). Inflammatory polyps often occur as a result of trauma or surrounding inflammatory conditions. Inflammatory pseudopolyps are in fact islands of normal mucosa surrounded by ulceration and commonly associated with IBD. Inflammatory polyps themselves do not undergo malignant transformation, although, where they are present as part of IBD, there is an increased risk of CRC overall for the patient.

Hamartomatous polyps

Hamartomatous polyps are formed from cell types that are typically present in the gastrointestinal tract, but whose organisation and architecture differ from that normally seen in the tissue (173). Examples of hamartomatous polyps in the colon or rectum include juvenile polyps, which despite their name, can arise at any age although more common in childhood. Juvenile polyps are usually solitary and harbour inflammatory cells, but their malignant potential is negligible.

There exist several rare and heterogeneous disorders termed “hamartomatous polyposis syndromes”. This group of disorders are inherited in an autosomal dominant pattern and are characterised by the development of hamartomatous polyps within the gastrointestinal tract (173). It is also common for patients to display associated extra-intestinal features. Conditions include juvenile polyposis syndrome and Peutz-Jeghers syndrome, amongst others. The hamartomatous polyposis syndromes are associated with a significantly increased risk of colon cancer as well as other solid organ tumours (174).

Sessile serrated lesions

These are a rather heterogeneous classification of polyps which includes hyperplastic polyps, serrated adenomas, and serrated adenomas (often synonymous with sessile serrated polyps). The classification of serrated lesions is still somewhat debated and evolving (175). Hyperplastic polyps are the most common of the non-neoplastic type. They are a type of serrated polyp with a characteristic saw-tooth pattern on histological analysis and harbour typical cellular components with an absence of dysplasia. Hyperplastic polyps are commonly, but not exclusively, small (<5mm) and most readily found in the rectosigmoid area (176). A hyperplastic polyp in itself is not believed to have malignant potential. Nonetheless, some studies have reported that the presence of hyperplastic polyps in the distal colon or rectum are associated with the presence of proximal neoplasia, and in around 5% of cases, advanced proximal neoplasia (177). In most circumstances, hyperplastic polyps are excised during colonoscopy since it is not always possible to distinguish them from adenomatous polyps with certainty. Serrated adenomas differ from hyperplastic polyps in that they are usually more prevalent in the proximal colon, likely to be sessile, may have a mucous cap, and frequently show signs of dysplasia (178). Sessile serrated polyps are thought of as likely precursor lesions to sporadic colon cancer caused by the MSI pathway **(Section 1.1.3.1)** (179). All sessile serrated adenomas should be excised since there is some evidence to suggest they result in rapid progression to cancer (180). Whether this is as a

result of these lesions being missed previously, due to their sessile nature, or previous inadequate removal is unclear.

1.3.1.2 Neoplastic polyps

The most common, well known, and widely studied neoplastic polyps of the colon and rectum are adenomatous polyps. They are discussed at detail in **Section 1.4**, but the histological characteristics and classification are outlined below. An adenoma is a benign tumour, formed from glandular structures in the epithelial lining of organs. Around two-thirds of colorectal polyps are adenomas, and they are frequently found in the presence of synchronous lesions (181, 182). Adenomatous polyps can present as pedunculated, giving them a mushroom type appearance, or they can be sessile. Due to their flat nature, sessile polyps are frequently harder to identify and excise fully. The official classification for polyp morphology is the Paris Classification, which divides adenomas into polypoid and non-polypoid morphologies (183).

From a histological perspective, three subclasses of colorectal adenomas are described. Each is found with varying frequency in the colon and rectum, and each has a different malignant potential. Subtypes include tubular, tubulovillous and villous adenomas **[Table 1.6].** Data from the National Polyp Study, which examined 3,371 adenomas from 1,867 patients in the USA reported some of the earliest data with respect to malignant potential. The researchers reported that larger adenoma size and villous architecture were associated with high-grade dysplasia (HGD) ($p<0.0001$), and by inference, harboured a greater malignant potential (182). The findings of the National Polyp Study were similar to those presented from a 10,000 patient database by Nusko *et al.* **[Table 1.7]** (184). Nonetheless, the majority of adenomas are small at the time of removal and thus have lower malignant potential. Around 75% of excised adenomas measure less than 1cm in diameter (182). Adenomatous polyps

are commonly but not exclusively found distally with approximately two-thirds located in the distal colon and rectum (182).

Table 1.6: Histological classification of colorectal adenomas and the risk of malignant potential

Adenoma subtype	Histopathological appearance	Presence of HGD
Tubular	The majority of the tissue shows a tubular appearance with ≤25% displaying villous architecture	Very low (<2%)
Tubulovillous	26–75% of the tissue displays villous architecture	Moderate (15%)
Villous	>75% of the tissue has a villous appearance	High (30–50%)

Data from the National Polyp Study, USA (182)

Table 1.7: Adenoma size and the percentage containing invasive carcinoma

Adenoma size (mm)	Percentage of polyps (%)	Percentage with carcinoma (%)
<5	44.9	0
6-15	31.5	2.2
16–25	9.4	18.7
26–35	4.6	42.7
>35	9.6	75.8

Data reported by Nusko et al. (184)

1.4 Colorectal adenomatous polyps

1.4.1 Epidemiology

Colorectal adenomas are common. The reported incidence varies between countries, yet in asymptomatic individuals undergoing colonoscopy for varied reasons, an incidence of around 25% is reported (185). Amongst bowel screening patients, the incidence is higher. A 2013 study investigating the early outcomes of the SBoSP reported an adenoma detection rate is as high as 47% in those undergoing colonoscopy for a positive screening (139). The SboSP reports an adenoma incidence of 0.9% for men and 0.4% for women in those who undertook a screening test, regardless of the result (186), which provides an insight into the overall prevalence of adenomas in a screening age population. More recent data from the SboSP (2013–2015) shows that 39% of patients with a positive screening test who underwent colonoscopy, were diagnosed with an adenoma, and 7% with CRC (165). The incidence of adenomatous polyps is thus more than five times that of CRC in a screening population.

1.4.2 Risk factors

A definite aetiology for primary incident colorectal adenomas has not been identified. Potential risk factors are discussed below.

1.4.2.1 Non-modifiable risk factors

Demographic factors

Many of the suggested risk factors for colorectal adenomas bear a resemblance to those for CRC. In particular, advancing age and male sex have consistently been associated with colorectal adenoma incidence (187, 188).

Pre-existing medical conditions

Diabetes has been reported as a risk factor, and a recent study of 375 patients undergoing index colonoscopy in 2014 reported that the risk of colorectal adenomas in younger patients aged 40–49 years, with diabetes, was higher than non-diabetics of the same age, OR 3.1 [95% CI; 1.5–6.4, p<0.01] (189). Although UC is a risk factor for the development of CRC, studies have reported a lower incidence of dysplastic polyps in these patients compared to controls (190, 191). The reason for this is not clear. FAP, as discussed in **Section 1.1.3.3,** is an autosomal dominant genetic disorder caused by a mutation in the *APC* gene located on chromosome five, which results in the formation of hundreds of adenomatous polyps, and equates to a 100% lifetime risk of progression to CRC in those left untreated.

1.4.2.2 Modifiable risk factors

Lifestyle factors

Obesity

Obesity is a growing epidemic, particularly the industrialised world. As discussed in **Section 1.1.2**, obesity has been linked to solid organ cancers, including CRC, and several studies have linked obesity with colorectal adenoma incidence, albeit with some inconsistent results.

Three meta-analyses were recently carried out to examine this possible link. The first investigated the association between elevated BMI and colorectal adenoma incidence reporting that an elevated BMI was associated with a higher risk of incident adenomas, RR 1.19 [95% CI; 1.13–1.26, p<0.001] per five unit increase, although a high level of heterogeneity was displayed between studies (I^2=76.8%) (192). The second meta-analysis was generally in agreement and concluded that overall, those with BMI ≥25 had a significantly increased incidence of colorectal adenomas than those with BMI <25, OR 1.24 [95% CI; 1.16–1.33, p<0.01], there was moderate heterogeneity between studies (I^2=58.9%) (193). The third meta-analysis was concerned with abdominal obesity, as measured by waist circumference and waist: hip ratio. For colorectal adenoma incidence, the researchers

reported a RR of 1.39 [95% CI; 1.13–1.26], when comparing the highest and lowest waist circumference, and a RR of 1.22 [95% CI; 1.10–1.35] for the highest vs. the lowest waist: hip ratio (194).

Tobacco smoking

A recent large study was conducted recruiting 25,000 patients over a 4-year period who underwent health screening, including a colonoscopy. The researchers concluded that active smoking was an independent risk factor for colorectal adenoma incidence. In women specifically, the risk was higher and associated with advanced adenomas (188).

Alcohol intake

There is weak evidence that increasing alcohol intake is associated with the incidence of advanced adenomas. The aforementioned study of 25,000 participants reported that those with higher alcohol use scores were slightly more at risk of colorectal adenomas, OR 1.09 [95% CI; 1.01–1.18] (188).

Dietary habits

Like CRC, red and processed meat has been associated with colorectal adenoma incidence, and a recent meta-analysis of 21 studies was conducted (195). The researchers reported a summary RR of colorectal adenomas for those with the highest vs. the lowest red meat intake of 1.24 [95% CI; 1.12–1.36]. In relation to processed meat, the summary RR was 1.17 [95% CI; 1.08–1.26] when comparing the highest vs. the lowest intake; thus it would seem likely that higher dietary intake of red or processed meat is associated with a significantly increased risk of colorectal adenomas.

The association between dietary fibre intake and the risk of colorectal adenomas has been of interest such that a meta-analysis of case-control and cohort studies was presented in 2014. The researchers included 20 studies totalling 10,948 subjects with colorectal adenomas and

reported a summary RR for colorectal adenoma incidence of 0.72 [95% CI; 0.63–0.83] when comparing high vs. low dietary fibre intake groups (196).

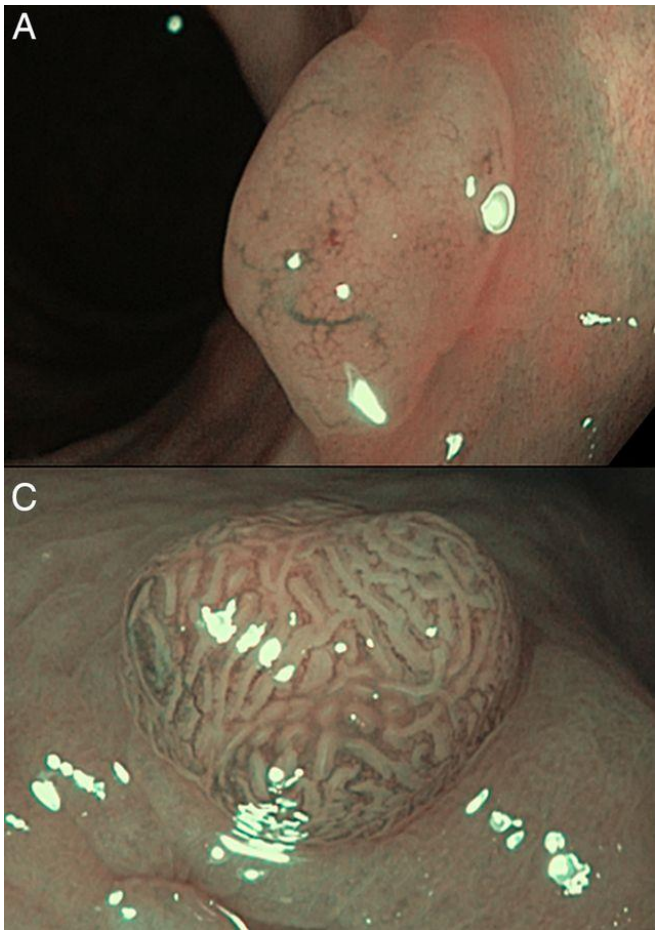
Despite this perceived benefit in reducing the primary incidence, dietary fibre has not been effective in reducing colorectal adenoma recurrence after polypectomy. The Polyp Prevention Trial was a multicentre RCT which recruited 2,079 men in North America. Participants were included if they had a histologically confirmed colorectal adenoma excised within six months of the trial start date. The participants were randomised to either a control group or a dietary intervention group, who were assigned to a high fibre, high fruit, low-fat diet. The study was unable to demonstrate a significant difference in the adenoma recurrence rate between the two groups during a 4-year follow-up (197). When the study period was extended for a further 4 years, the results were similar (198).

1.4.3 Diagnosis and detection

Colorectal polyps can be diagnosed by radiological imaging such as double-contrast barium enema, which has mostly been superseded by CTC. Nevertheless, by far the most common method of diagnosis is under direct vision during endoscopic procedures. The majority of colorectal polyps are detected incidentally as part of bowel screening or when an endoscopic investigation is being undertaken on symptomatic individuals. Confirmation of the polyp subtype and whether it is adenomatous can only definitively be made on histological examination. However, more recently, interest has centred on the use of narrow-band imaging (NBI) during colonoscopy. This technique was first described by Gono *et al.* in 2004 (199). It is a technique whereby red light is removed from the endoscopy source by an electronic filter and narrowed bandwidths of blue and green light are used preferentially in isolation (200). NBI allows enhanced visualisation of the mucosal surface vasculature and epithelial pit pattern (201). This affords an advantage over conventional white light as a method to enhance the detection of adenomatous polyps and distinguish between neoplastic

and non-neoplastic lesions (201). NBI is particularly useful in detecting small flat polyps which are notoriously harder to visualise (199). RCTs have reported that trained endoscopists, when using NBI, can accurately distinguish small (<5mm) adenomas from non-adenomatous polyps (202) under direct vision **[Figure 1.8].** Potentially, this would allow small lesions that are likely benign and hyperplastic to be left *in situ*, thus reducing the risk of excision and any laboratory processing costs.

Figure 1.8: Hyperplastic vs. adenomatous polyp on narrow-band imaging



A: *Hyperplastic polyp in near focus narrow-band endoscopic imaging*
B: *An adenomatous polyp in near focus narrow-band imaging at endoscopy*

Figure cropped and reproduced (with permission) from Kaltenbach et al. 2015 (202)

1.4.4 The natural history of adenomatous polyps

As discussed previously, the majority of CRCs arise as a result of the adenoma-carcinoma sequence via the chromosomal instability pathway **(Section1.1.3.1)**. This is an essential aspect to consider regarding the natural history of adenomatous polyps. Since most adenomas are excised endoscopically when found, recent large trials examining their natural history is limited; however, historical studies which observed adenomas left *in situ* over time have previously reported on their natural history and provided evidence for the adenoma-carcinoma sequence.

A key historical study in 1987 by Stryker *et al*. reported some of the first and most important data on the natural history of colorectal polyps. This retrospective study was conducted in the pre-colonoscopy era in the Mayo Clinic, Minnesota, USA (203). The researchers identified 226 patients with radiographically diagnosed polyps ≥1cm in size. The single largest polyp per patient was labelled as the "index polyp" and where possible was left *in situ* for at least 12 months. The follow-up period included at least two surveillance barium enema studies. During follow-up, 83 (37%) polyps increased significantly in size, and ultimately 107 (47%) polyps were excised, either surgically or endoscopically, mainly due to concerns over continued growth. All excised polyps were adenomatous, and 21 invasive carcinomas were detected at the site of the index polyp on histological examination. In addition, invasive cancer was detected at a site separate from the index polyp in 11 patients during the same follow-up period. The researchers calculated the risk of cancer at the index polyp site, if left *in situ*, was 2.5% at 5 years, 8% at 10 years and rose to 24% at 20 years. This report by Stryker *et al.* was one of the first to suggest that a significant proportion of adenomas may progress to CRC if left *in situ*. These early studies that support the adenoma-carcinoma sequence have since been corroborated by clinical, epidemiological, molecular, and post-mortem data.

As discussed previously in **Section 1.3.1.2**, larger adenoma size and villous histology are important determinants of malignant potential (204). Thus, given that larger polyps are more likely to progress to adenocarcinoma, these are almost never left *in situ*. More recent interest has surrounded the progression and growth rate over time of smaller polyps, which would aid decision making at colonoscopy and help to avoid potentially unnecessary and risky excision of small polyps. A historical study published in 1997 by Bersentes *et al.* monitored the growth rate of small polyps (3–9mm) left *in situ* for a 2-year observation period with bi-annual colonoscopy and reported that no polyps completely regressed, although hyperplastic polyps could reduce in size (205).

A more recent study conducted in the USA in 2013 observed volumetric growth rates of small (6–9mm) colorectal polyps left *in situ,* using CTC. Median follow-up was 2 years, and the researchers reported that 50% of these small polyps remained static in size, while around 25% regressed and 25% progressed (206). Histological evaluation of the polyps was undertaken, which demonstrated that adenomas with at least one advanced feature (size ≥1cm, villous architecture or HGD) underwent more rapid growth, while no polyps progressed to adenocarcinoma in this study.

In summary, it would appear that the majority of adenomas do not progress to invasive cancer, yet the risk increases the longer a polyp remains *in situ*, especially if that polyp is large. Most adenomas will remain the same size, and some will advance in size. Larger polyps, and those that progress in size, harbour the highest malignant potential while smaller polyps (<1cm) are unlikely to progress to malignancy in under 5 years (207). This timeline partly underpins the colonoscopy surveillance intervals outlined later in **Section 1.4.7.**

1.4.5 Management of colorectal polyps and colorectal adenomas

1.4.5.1 Simple polypectomy

Evidence exists that colorectal polypectomy reduces subsequent CRC incidence and mortality (208). For this reason, the principle management of these lesions is excision, where it is safe to do so, and if it is in the best interests of the patient. A number of manoeuvres can be employed for a polypectomy, including a cold biopsy or cold snare technique, which can be used on small polyps less than 4mm in size. For stalked lesions, a snare and diathermy technique can be used. The polyp should be snared and resected approximately halfway up the stalk to facilitate further endoscopic treatment should post-polypectomy bleeding occur. An effort should be made to retrieve the polyp for histological examination.

1.4.5.2 Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is a technique for resection of larger sessile or flat polyps. It requires the injection of fluid into the submucosa to elevate the polyp mucosa away from the muscularis layer of the bowel wall, which minimises thermal injury during the diathermy assisted snare (209). If a polyp does not lift easily, it should raise concern with the endoscopist that the lesion might have undergone malignant invasion of the submucosa. In these cases, the polyp should be marked with dye, biopsied, and referred to the local MDT meeting for discussion.

1.4.5.3 Risk factor modification

Although risk factor modification is not the mainstay of primary adenoma management, it should be emphasised to a patient. A teachable moment exists following polypectomy when patient education to minimise the risk of polyp recurrence should be undertaken.

1.4.5.4 Chemoprevention

Several studies have examined the merit of agents for chemoprevention to reduce the incidence of colorectal adenomas and subsequent post-polypectomy recurrence. Aspirin is probably the best publicised of these agents. The use of aspirin as a chemopreventive agent for CRC was discussed in **Section 1.1.2.2.** In addition to aspirin, other agents such as vitamin D, calcium and fibre supplementation have been investigated.

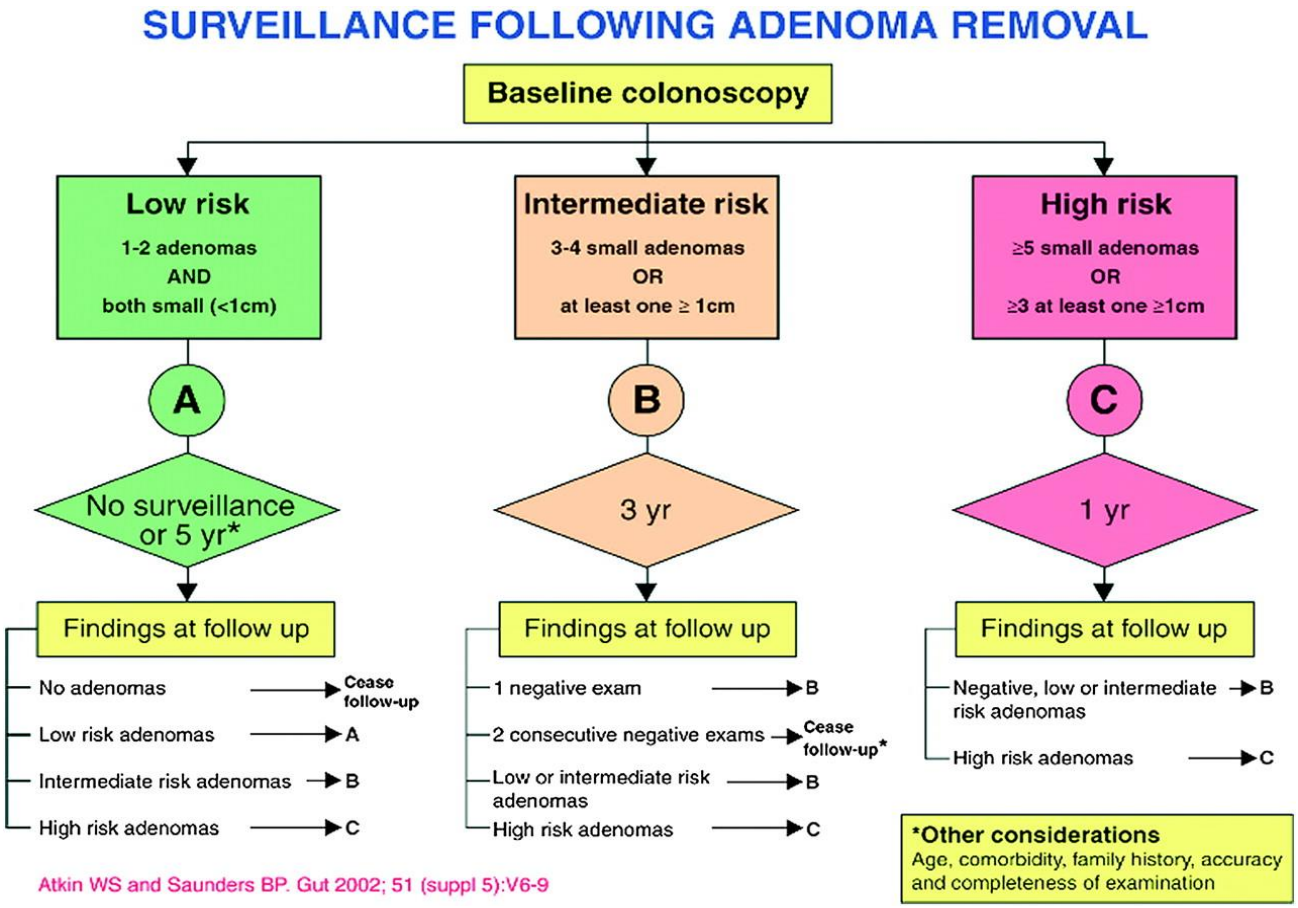
A recent well-designed, multi-centre, RCT, which was triple blinded and placebo-controlled was conducted in Europe, Russia and the USA. It aimed to compare the chemopreventive effects of aspirin, vitamin D and calcium vs. placebo on colorectal adenoma recurrence. The study concluded at three years and reported no effect on adenoma recurrence (210). These findings are in contrast to a recent meta-analysis which included nine studies with 8,521 participants and examined the effect of NSAIDs on the risk of adenoma recurrence (211). The researchers concluded that, although NSAID use reduced adenoma recurrence, the effect was not maintained after three years. The narrative is similar when considering aspirin. A recent Cochrane controlled trial, the APACC (Association pour la Prévention par l'Aspirine du Cancer Colorectal Study Group) trial, published their 4-year follow-up results (212). The researchers found that although daily low dose aspirin reduced adenoma recurrence significantly at 1 year, the effect was diminished by 4 years (212). As a result of the above, and the potential side effect profile of aspirin and NSAIDs, there has not been a widespread recommendation for their use as chemo protective agents.

1.4.6 Adenoma recurrence and post-polypectomy surveillance

Follow-up studies have demonstrated a significant number of patients develop recurrent adenomas after polypectomy, and reports suggest that recurrence is detected in up to two-thirds of patients. Since a significant proportion of patients are diagnosed with recurrent adenomas at follow-up, post-polypectomy surveillance guidelines have been developed, which differ slightly between the European Union (EU), USA and the UK.

In the UK, the most recent guidelines, were published in 2010 by the BSG (15). The guidelines were developed using the best available evidence at the time that suggested the future risk of developing CRC, and any advanced adenomas were related to the size and multiplicity of the baseline adenomas. Based on this, post-polypectomy patients are classed as either low, intermediate or high-risk, and post-polypectomy surveillance varies for each group. The BSG guidelines recommend that for those with 1–2 small (<1cm) adenomas (low-risk), a repeat colonoscopy at 5 years can be offered, but it is optional. For patients with 3–4 small adenomas or at least one adenoma ≥1cm (intermediate risk), a follow-up colonoscopy at 3 years is recommended, and for patients with ≥5 small adenomas or ≥3 adenomas where at least one is ≥1cm (high risk), a colonoscopy is recommended at 1 year from the index examination **[Figure 1.9]**. Although the guidelines call for surveillance, it is meant only as a guide, and the clinician can use their discretion as to how closely it should be followed while considering the patient wishes, age and comorbid status.

Figure 1.9: BSG guidelines for post-polypectomy surveillance



Cairns et al. (2010) (15), initially published by Atkin et al. (2002) (213)

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1.4.7 Polyp cancer

Polyp cancers, also known as malignant polyps, are those with a benign appearance on macroscopic examination, but on histological scrutiny, display a focus of invasive carcinoma that has breached the muscularis mucosae and invaded the submucosa (214). Up to 5% of all excised polyps may be polyp cancers (215).

The management of a patient with a malignant polyp is troublesome because it can be challenging to determine whether malignant cells remain within the bowel wall or are present in regional lymph nodes after polypectomy. Currently, the evidence base underpinning the management of these lesions is poor. Clinicians can employ one of two strategies. The first is surgical resection of the affected bowel, with the risk of morbidity from surgical resection, but the advantage of full pathological staging. However, a significant proportion of patients undergoing resection as a result of polyp cancers turn out to be negative for residual disease and lymph node involvement. In essence, these patients have undergone an unnecessary operation, with the benefit of hindsight (216).

The second option is surveillance only, with repeat biopsies and regular interval colonoscopy. In this approach, the challenge is to provide patients with a reasonable prognostic estimation, and some prognostic information can be yielded from the histopathological examination of the malignant polyp specimen. Two validated prognostic systems include the Haggitt criteria and the Kikuchi level. The Haggitt criteria are utilised mainly for pedunculated polyps and assess the degree of invasion based on the level of the stalk involved. Haggitt described four levels, with level 1, 2 or 3 less likely to be associated with lymphatic spread than level 4, which is classed as invasion below the stalk (217).

When considering sessile malignant polyps, the absence of a stalk would automatically classify these lesions as a Haggitt level 4. In these instances, the Kikuchi level is more appropriate. The Kikuchi system divides the level of tumour invasion of the submucosa into

three (sm1, sm2, and sm3) (218). Sm1 and sm2 refer to the uppermost two-thirds of the submucosa and are associated with an approximate 10% risk of lymphatic involvement, whereas sm3 (lower third of the submucosa) equates to a 25% risk. The main drawback of this system relates to the requirement of muscularis propria in the biopsy, without which the level of submucosal involvement cannot be assessed. However, this depth of excision is not routinely conducted endoscopically, and similarly, piecemeal excision renders the sample challenging to orientate and process correctly.

The ACPGBI in their position statement in 2013 followed a risk stratification model using a scoring system to predict the risk of residual disease after malignant polyp excision (214). They indicated that an endoscopic resection margin <1mm, Haggitt level 4, or Kikuchi level 3 are associated with a >20% risk of residual disease. If any of these criteria are met, the ACPGBI recommends full surgical resection assuming patient fitness allows. Other risk factors such as poor cell differentiation, mucinous tumours, tumour budding and lymphovascular invasion were included in the model but were allocated less weighting (214). In any case all polyp cancers should be discussed at the MDT to decide on appropriate management.

1.5 Summary and aims

1.5.1 Summary

Important topic

CRC is the fourth most common cancer in the UK. For males and females combined, it is the second most common cause of cancer death in the UK (1). A number of risk factors have been studied in relation to CRC development, with advancing age, male sex, lifestyle factors, IBD, obesity and genetic predisposition the most influential. Cancer prevention strategies could involve both risk factor modification and active intervention such as polypectomy as part of a bowel screening programme. A significant number of variables can be considered when staging colorectal cancer and deciding upon further treatment. Outside traditional methods such as tumour factors and lymph node status; systemic inflammation based scoring systems and body composition indices are increasingly linked with long term outcomes and prognosis.

Polypectomy is effective

The majority of CRCs arise as a result of malignant transformation of colorectal adenomas via the adenoma-carcinoma sequence. Data from medium and long-term follow-up trials, notably the long-running UK flexible sigmoidoscopy trial have consistently shown that lower gastrointestinal endoscopy reduces both the incidence (26% reduction) and mortality (30% reduction) from CRC (219). This is most likely as a result of endoscopic polypectomy and post-polypectomy surveillance. The SboSP has been successfully rolled out across Scotland and has resulted in earlier stage presentation (in those without metastasis) (140). Furthermore, the SboSP is detecting and removing a sizable number of colorectal adenomas, and over the long term, it is likely this will reduce CRC incidence.

Risk factor identification to enhance post-polypectomy surveillance guidelines and streamline services

With the above in mind, ensuring a colon clear of adenomatous polyps is highly desirable. Currently, UK guidelines for post-polypectomy surveillance are based solely on the number and size of excised adenomas. Nevertheless, increasingly, across all disciplines of medicine, a move towards patient-centred, personalised and host focussed treatment is underway. It is now accepted that a tumour cannot be considered separately from its host as complex interplay exists between the two. As such, the influence of host factors such as age, sex, and BMI require further examination, particularly within the context of a bowel screening programme to determine if they warrant inclusion into screening or post-polypectomy surveillance guidelines. In addition, a better understanding of adenoma-specific risk factors may lead to the identification of additional adenoma features that can predict future risk and influence modification of surveillance guidelines. This may help to streamline services and enhance cost effectiveness for the health service while minimising the frequency of investigation for patients.

Inflammation as a link between the host and neoplastic formation and proliferation

A significant body of evidence now exists linking inflammation with cancer and inflammation has been described as the 7th hallmark of cancer. While systemic inflammation is associated with poorer outcomes in CRC, the local inflammatory response is associated with improved outcomes. Ultimately this demonstrates there exists a complex interplay between local and systemic inflammation and its varying effect on early cancer development, proliferation and ultimately prognosis. What is not clear is the role systemic inflammation plays in the pre-malignant stage of CRC, and what influence it may have on initial adenoma formation and the progression to invasive carcinoma. There are a small number of population studies mainly retrospective that have investigated this, but there remains a paucity of evidence in the literature. Since there is some evidence that aspirin, likely due to its anti-inflammatory properties, is a chemoprotective agent for CRC, it is likely that inflammatory

pathways may be involved in neoplastic initiation and proliferation. Exploring whether inflammation and in particular systemic inflammation is linked with early or pre-malignant stages of CRC might allow this to be targeted for intervention. It perhaps would allow modification of traditionally non-modifiable, but strong, CRC risk factors such as age and male sex if inflammation could be exposed as a link between the two.

The role of obesity and body composition in pre-malignant and early disease

Elevated BMI and obesity are modifiable lifestyle factors and implicated in several neoplastic and non-neoplastic diseases. Although moderate links between obesity and CRC specifically have been described, there remains a body of conflicting evidence. This is particularly evident with regards to adenomas and warrants further study, particularly within a West of Scotland population which has differing socioeconomic and demographic variables in comparison to populations in some previous reports.

In terms of CRC, recent interest has centred on body composition, particularly with regards to visceral obesity and sarcopenia and its association with prognosis and outcomes. Certainly, growing evidence exists that body composition, in particular sarcopenia, is associated with poorer outcomes in established cancer. Nevertheless, the role of body composition with regards early and pre-malignant disease is not fully understood, and there is a paucity of studies examining this. A greater understanding of the interplay between body composition and its role in pre-malignant disease, the better to target timely intervention, is warranted.

Screening risk and benefits

As previously mentioned, good evidence exists indicating that bowel screening leads to an earlier presentation of CRC, while colonoscopy and polypectomy reduce the incidence of CRC. However, there are risks and drawbacks of screening. Namely the cost, the >50% negative colonoscopy rate, the possible discomfort, and any complications associated with this intervention. Furthermore, boundaries are being pushed ever more for bowel screening resulting in a significant number of CTC scans conducted as a direct result of the SBoSP. Consequently, a significant number of incidental ECFs are identified. In some instances, these findings can have a positive impact on patient health by identifying serious pathology such as aneurysmal disease or occult malignancy. However, in a proportion of cases these findings can result in potentially distressing, expensive and sometimes invasive further investigation for what subsequently is benign disease. To date; in the UK, there are no previous reports examining the cost, risks, benefits and implications of CTC with regards ECFs as part of bowel screening, and this warrants scrutiny. This is particularly important given that screening is costly to both patients and the health service. Any additional burden on resources requires careful analysis. The goal being to streamline services in primary screening and post polypectomy follow up.

1.5.2 Aims

1. To investigate the impact of advancing age, sex, and BMI on the incidence of post-polypectomy adenoma recurrence by means of a systematic review and meta-analysis of the current literature.

2. To investigate the association between adenoma-specific and host-specific risk factors for colorectal adenoma recurrence in intermediate and high-risk patients from the SBoSP.

3. To examine the association between primary colorectal neoplasia incidence and host characteristics, including obesity and the systemic inflammatory response using prospectively collected data from patients attending for colonoscopy as part of the SBoSP.

4. To examine the association between body composition, particularly visceral obesity and sarcopenia, and primary colorectal neoplasia incidence in patients attending for CTC as part of the SBoSP.

5. To examine the cost, risks, benefits and implications of CTC with regards ECFs and its resulting impact on resources and streamlining of care in the SBoSP.

2 THE INFLUENCE OF AGE, SEX AND BMI ON ADENOMA RECURRENCE, A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

2.1 Introduction

An adenoma is a benign tumorous growth that arises from tissue of glandular origin. It is generally accepted that most CRCs arise in or from pre-existing adenomas (213). Evidence for the adenoma-carcinoma sequence stemmed from an early study carried out in 1987 by Stryker *et al.* that monitored colonic polyps ≥1cm left *in situ* for a minimum of 1 year (203). Invasive cancer was subsequently diagnosed at many of the polyp sites during follow-up. A similar but larger study by Nusko *et al.* (1997), supported the adenoma-carcinoma sequence in CRC (220). The researchers looked at 11,380 colorectal adenomas excised during surgery or colonoscopy and found 11.6% of them had invasive carcinoma. Cho and Vogelstein (1992) described a biological model of tumorigenesis via the adenoma-carcinoma sequence (221). Their model proposed that tumours arise as a result of mutational activation of oncogenes coupled with the inactivation of tumour-suppressor genes. They described evidence showing that a proportion of intermediate and end-stage adenomas display activation of the *RAS* oncogene in a similar manner to carcinomas. As such, there is significant interest in the detection and timely removal of colorectal adenomas prior to malignant transformation.

In the UK, bowel screening programmes have been rolled out in a stepwise manner over the last decade. Their aim is to increase the frequency of "early-stage" CRC diagnoses and reduce long-term cancer incidence as a result of polypectomy (222). Since the introduction of the SBoSP in 2006, there has been a reduction in the rate of emergency cancer presentations and in those with no distal metastases; a notable shift towards the diagnosis of earlier stage colorectal tumours in this population (140). Atkin *et al.* (2010) published data

from the UK flexible sigmoidoscopy trial (223). This RCT reported that a once-off flexible sigmoidoscopy, as a screening tool for CRC, reduced both incidence and mortality from CRC. This reduction in incidence of CRC is most likely as a result of polypectomy at the time of sigmoidoscopy. This gave rise to a vested interest in removing adenomas whenever they are identified.

Crucially, patients found to have newly diagnosed adenomatous polyps on initial colonoscopy are likely to have additional polyps diagnosed at follow-up examination (224). Older studies have reported an adenoma recurrence rate in post-polypectomy patients of 30%–60% (225) (224). Some of these studies are ageing; however, even in the endoscopic era, the reported recurrence rates are similar (226-229).

This recurrence rate is disputed by some observers on the basis that it may be unclear which adenomas are truly recurrent as opposed to synchronous adenomas that were missed at the time of the initial colonoscopy. Various studies have sought to quantify the adenoma miss rate at colonoscopy by conducting a second examination shortly after the initial polypectomy, and documented miss rates vary from 5–28%, with smaller polyps (<5mm) the most commonly missed (230-233).

Adenoma size and number are the two factors that are used to produce the BSG guidelines for post-polypectomy surveillance (15). The guidelines recommend carrying out a follow-up colonoscopy at three years in patients with 3–4 small adenomas or at least 1 adenoma ≥1cm in size. For patients with ≥5 small adenomas or ≥3 adenomas where at least one is ≥1cm, a colonoscopy is carried out at one year from the index procedure.

However, in addition to adenoma-specific factors, it is increasingly recognised that host characteristics may play a role in adenoma recurrence. In particular, the current guidelines do not account for host factors such as age, sex, or BMI.

With this in mind, the aim of the present study was to carry out a systematic review and meta-analysis of the available raw data from the literature to investigate the influence of age, sex, and BMI on colorectal adenoma recurrence. This could potentially help refine the current surveillance guidelines by introducing patient-specific risk factors.

2.2 Materials and methods

Search strategy

The present study was conducted with three main areas of interest. The influence of age ≥60 years, male sex, and BMI on the rate of recurrence of colorectal adenomas post-polypectomy.

A comprehensive keyword literature search was carried out using the following databases: The USA National Library of Medicine (MEDLINE), Excerpta Medica Database **(**EMBASE) and PubMed. Furthermore, the Cochrane Database of Systematic Reviews was searched. A pre-planned comprehensive search strategy was employed and carried out between October 2015 and January 2016. Appropriate Ovid truncation [($) (?)] was used to ensure variations in spelling and word endings did not result in potentially useful papers being missed. Non-English language (unless fully translated), animal, duplicate and abstract-only studies were excluded. Systematic reviews were included in the meta-analysis only if the raw data required for the present study were able to be extracted, and the original papers were unavailable or not already included in the present review. The search strategy is outlined below.

- For the influence of age ≥60 years on the incidence of colorectal adenoma recurrence:
    - (Age) AND (Colorectal OR Colon$ OR Rectal OR Rectum) AND (Polyp? OR Adenoma$) AND (Recur$ OR Metachronous)
- For the influence of male sex on the incidence of colorectal adenoma recurrence:
    - (Sex OR Male OR Female OR Gender) AND (Colorectal OR Colon$ OR Rectal OR Rectum) AND (Polyp? OR Adenoma$) AND (Recur$ OR Metachronous)

- For the influence of BMI on the incidence of colorectal adenoma recurrence:

    - (BMI OR Body Mass Index OR obesity OR weight Or Obese) AND (Colorectal OR Colon$ OR Rectal OR Rectum) AND (Polyp? OR Adenoma$) AND (Recur$ OR Metachronous)

Analysis of manuscripts

The full text of each potentially relevant study was obtained and analysed. Inclusion criteria were decided on by the primary investigator (DD) and senior investigator DM). To be considered for inclusion, studies had to report on endpoint data with respect to age, sex, BMI and the number of patients in each group with a recurrence of adenomas. Adenoma recurrence of any subtype (such as non-advanced or advanced) was included. The most widely accepted definition of advanced adenomas is as follows: the presence of at least one adenoma with at least one of the following features: ≥1cm in size, any villous histology or HGD. Data from intervention trials were included if the tested intervention was shown to make no significant or only a borderline difference compared to the control group. Studies with <250 patients were excluded. Studies were required to include patients that had undergone at least one initial full colonoscopy and polypectomy, with a follow-up colonoscopy a minimum of six months later. Patients diagnosed with HNPCC, FAP, CRC, IBD or those who had undergone previous polypectomy were excluded. Similarly, studies that examined the colon by any method other than colonoscopy (barium enema, CTC, flexible sigmoidoscopy) were excluded. A hand search of bibliographies was initiated to identify additional papers of interest. Paper selection, examination and data extraction were completed by the author (DD) with any uncertainties discussed with a senior author (DM). Flow charts of the study selection process for each variable of interest are shown in **Figure 2.1**, **Figure 2.2** and **Figure 2.3.**

Studies used widely varying data reporting methods such as OR's, RR, HRs, and simple percentages. In order to combine as many studies as possible, raw numerical data pertaining to the total number of participants and the number of these participants who went on to have recurrent adenomas were extracted from the studies for the meta-analysis. These data were analysed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software. OR's were calculated for the influence of age >60 years, male sex and BMI on adenomatous polyp recurrence. A random-effects model was used to account for the degree of variability in study methodology and adenoma detection. Heterogeneity of data was estimated using the I^2 statistic, and two-tailed p-values <0.05 were considered to be statistically significant. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was used as a basis for the methodology of this review.

Figure 2.1: Flow chart of the study selection process. Age ≥ 60yr as a risk factor for adenoma recurrence

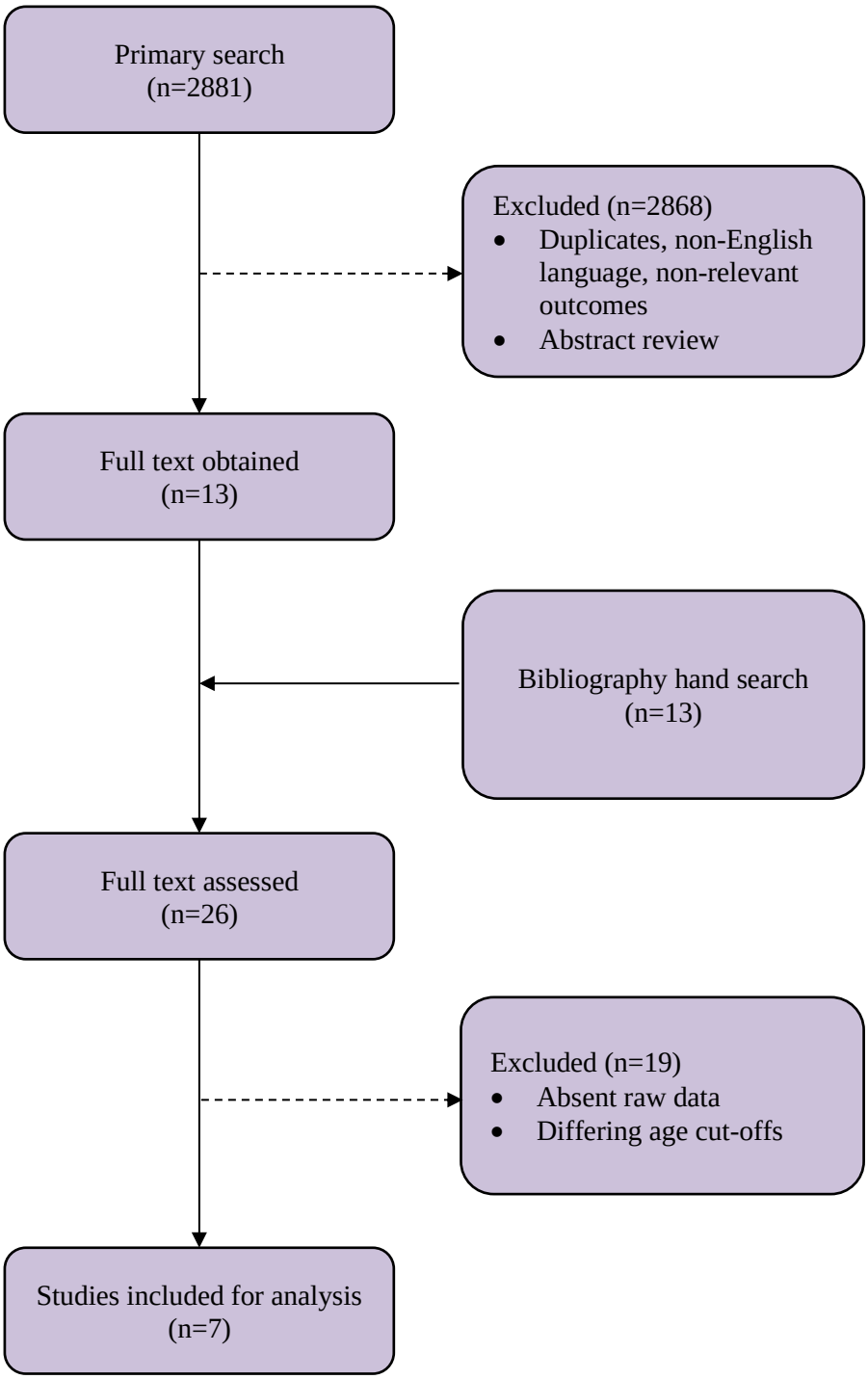


Figure 2.2: Flow chart of the study selection process. Male sex as a risk factor for adenoma recurrence

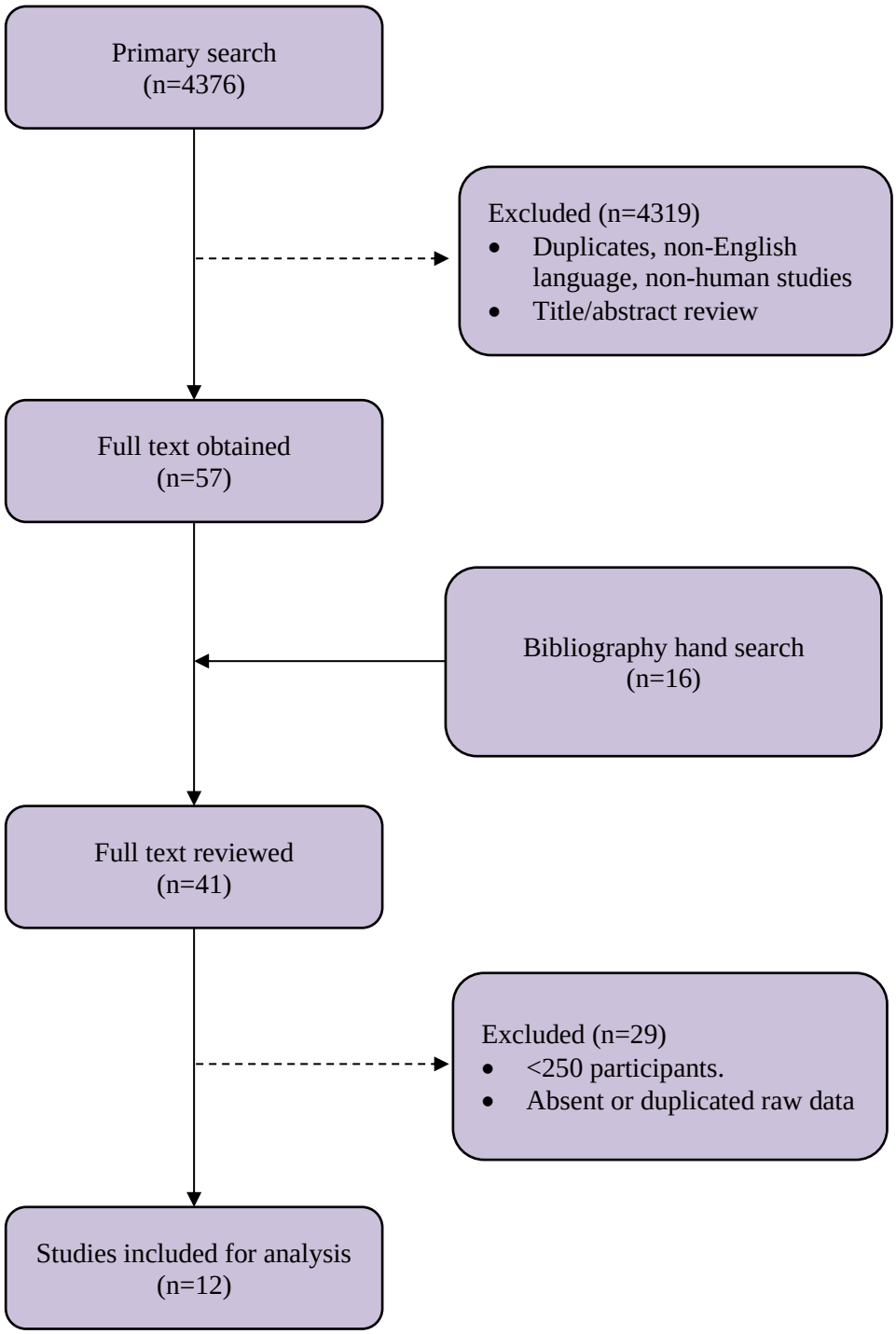
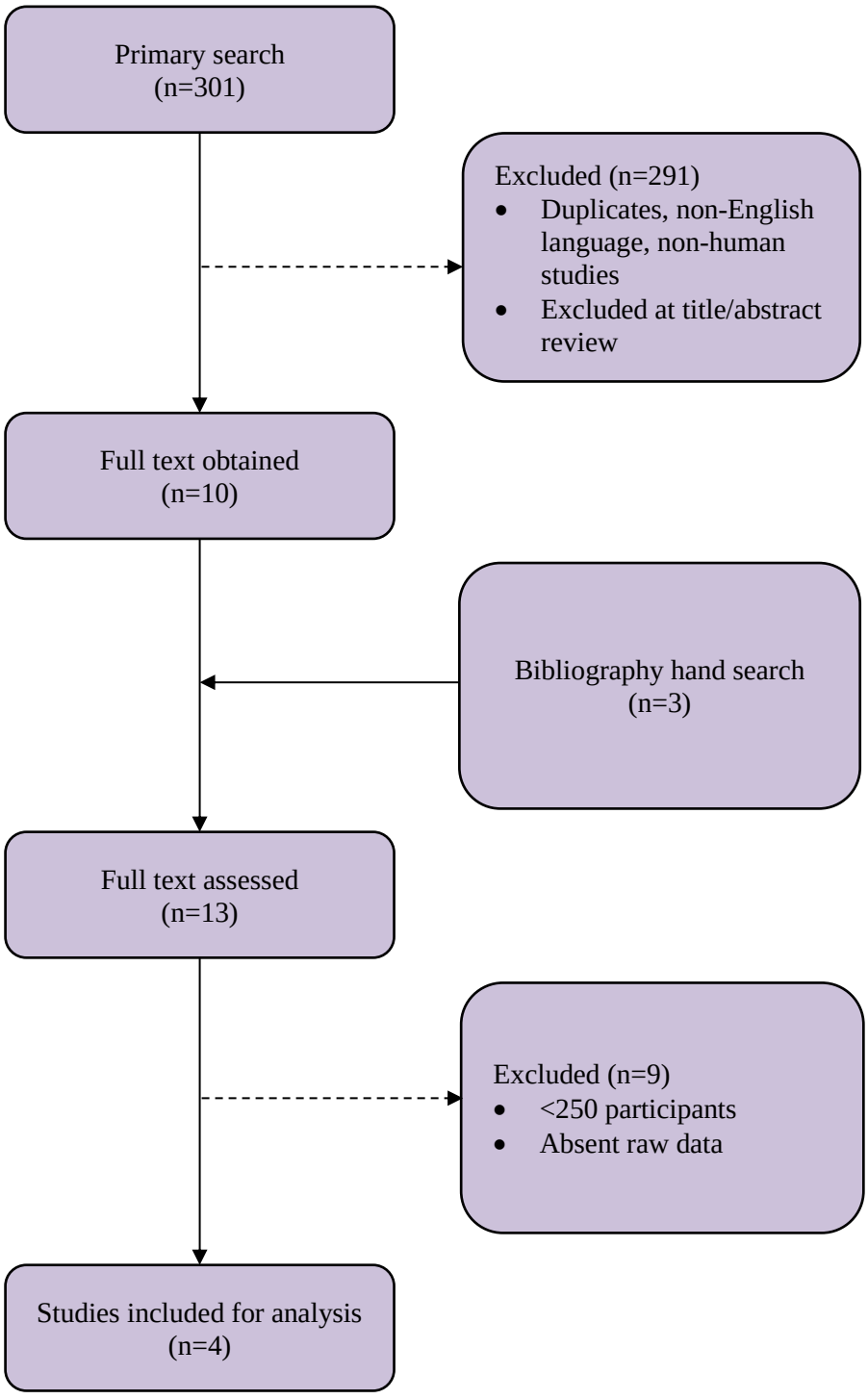


Figure 2.3: Flow chart of the study selection process. BMI ≥ 25 as a risk factor for adenoma recurrence



2.3 Results

The influence of age ≥60 years on colorectal adenoma recurrence

A total of seven studies met the inclusion criteria to investigate age ≥60 years as a risk factor for colorectal adenoma recurrence including one RCT (224), 5 retrospective cohort studies, and 1 study which pooled data from non-effect RCTs **[Table 2.1]** (234-239)**.** Two studies carried out a second colonoscopy within the first year of the baseline colonoscopy, to remove any missed polyps before re-assessing for recurrent adenomas >1 year after the clearing colonoscopy (236, 237). Six studies reported an OR pertaining to an increased risk of recurrence in those aged ≥60 years (224, 235-239); however, it did not reach statistical significance (239). A meta-analysis of the seven selected studies comparing the incidence of colorectal polyp recurrence included 22,547 patients, of which 7,087 (31%) had at least one recurrent adenoma at follow-up. 9,413 (42%) patients were aged ≥60 years. Among these patients, 3,319 (35%) had recurrent adenomas at surveillance compared to 3,768 (29%) in those aged <60 years. The summary OR for adenoma recurrence if aged ≥60 years compared to <60 years was 1.56 [95% CI; 1.13–2.14, p<0.01] **[Figure 2.4].**

Assessment of heterogeneity and publication bias

The I^2 statistic was 95%, indicating a considerable degree of heterogeneity. The funnel plot **[Figure 2.5]** suggests minimal publication bias with smaller studies showing a greater spread of results.

Figure 2.4: Forrest plot. The impact of age ≥ 60 years on the incidence of colorectal adenoma recurrence

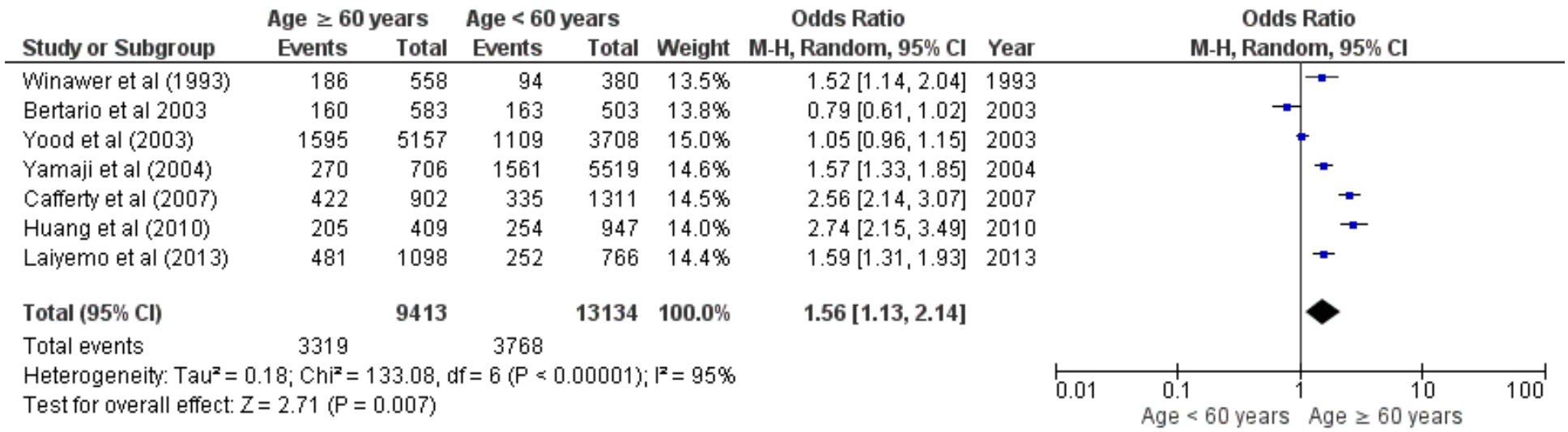
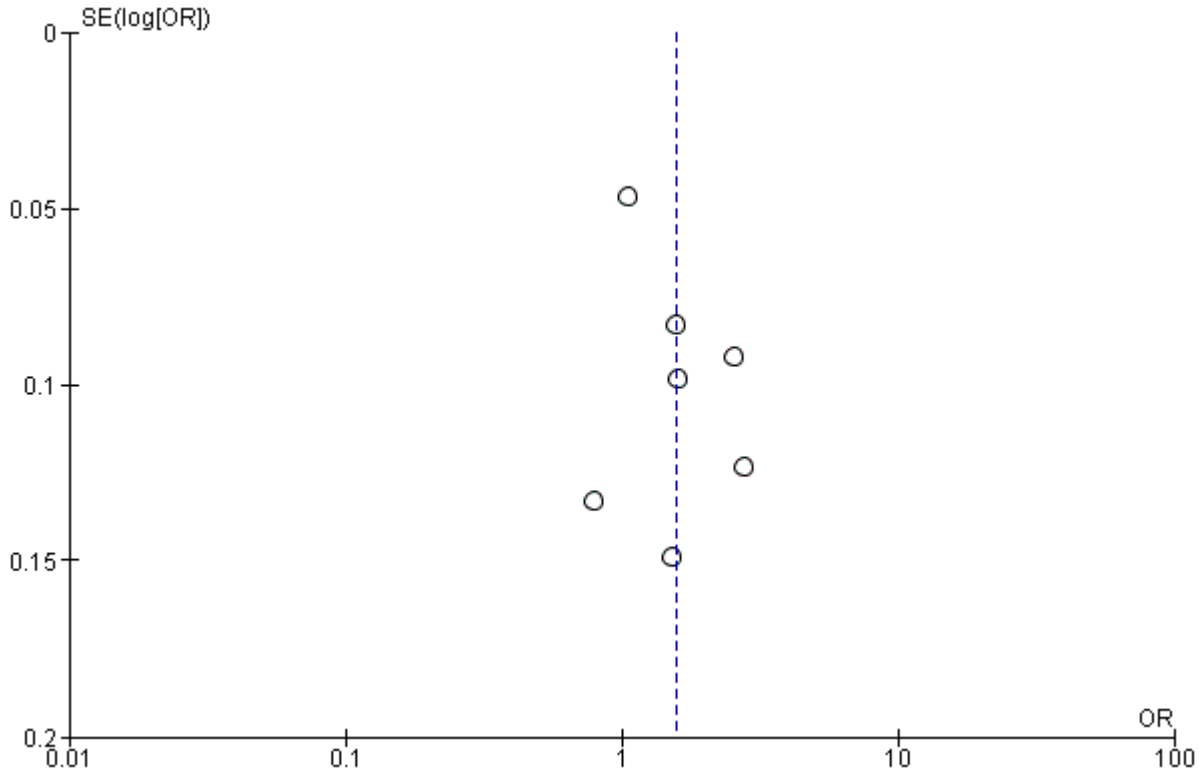


Figure 2.5: Funnel plot. Studies reporting the impact of age ≥ 60 years and the incidence of colorectal adenoma recurrence



The influence of male sex on colorectal adenoma recurrence

Twelve studies met the present study meta-analysis inclusion criteria **[Table 2.2]** (234-236, 239-247). Eight were retrospective cohort studies (234-236, 239, 242, 245-247), two were retrospective analyses of pooled data (240, 241) and two studies were conducted using data from non-effect RCTs (243, 244). A meta-analysis of the twelve studies included 31,277 patients. 12,353 (39%) had a recurrent adenoma at follow-up. 20,215 (65%) were male. 8,787 (43%) of males and 3,566 (32%) of females developed a recurrent adenoma during post-polypectomy surveillance. ORs calculated from all twelve studies individually indicated a positive association between male sex and adenoma recurrence. However, three studies only achieved borderline significance. The summary OR for the influence of male sex on adenoma recurrence at post-polypectomy surveillance was 1.58 [95% CI; 1.42–1.76, $p<0.001$] **[Figure 2.6].**

Assessment of heterogeneity and publication bias

The I^2 statistic was 71%, indicating a moderate degree of heterogeneity as indicated on the funnel plot **[Figure 2.7]**.

Figure 2.6: Forrest plot. The impact of male sex on colorectal adenoma recurrence

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Yood et al (2003)	1726	5295	978	3570	12.3%	1.28 [1.17, 1.41]	2003
Bertario et al 2003	208	599	115	487	7.2%	1.72 [1.32, 2.25]	2003
Jacobs et al (2007)	816	1663	318	802	10.0%	1.47 [1.24, 1.74]	2007
Cafferty et al (2007)	511	1343	263	944	9.7%	1.59 [1.33, 1.90]	2007
Jacobs et al (2009)	3000	5842	947	2371	12.2%	1.59 [1.44, 1.75]	2009
Gao et al (2010)	562	858	215	350	7.5%	1.19 [0.92, 1.54]	2010
Huang et al (2010)	349	863	110	493	7.6%	2.36 [1.84, 3.04]	2010
Laiyemo et al (2012)	522	1180	201	646	9.0%	1.76 [1.43, 2.15]	2012
Kitihara et al (2013)	526	1064	226	612	9.0%	1.67 [1.36, 2.05]	2013
Lin et al (2014)	76	262	18	94	2.7%	1.73 [0.97, 3.08]	2014
Taniguchi et al (2014)	370	846	101	265	6.9%	1.26 [0.95, 1.67]	2014
XU et al (2015)	121	400	74	428	5.8%	2.07 [1.49, 2.88]	2015
Total (95% CI)		**20215**		**11062**	**100.0%**	**1.58 [1.42, 1.76]**	
Total events	8787		3566				

Heterogeneity: Tau² = 0.02; Chi² = 38.04, df = 11 (P < 0.0001); I² = 71%

Test for overall effect: Z = 8.55 (P < 0.00001)

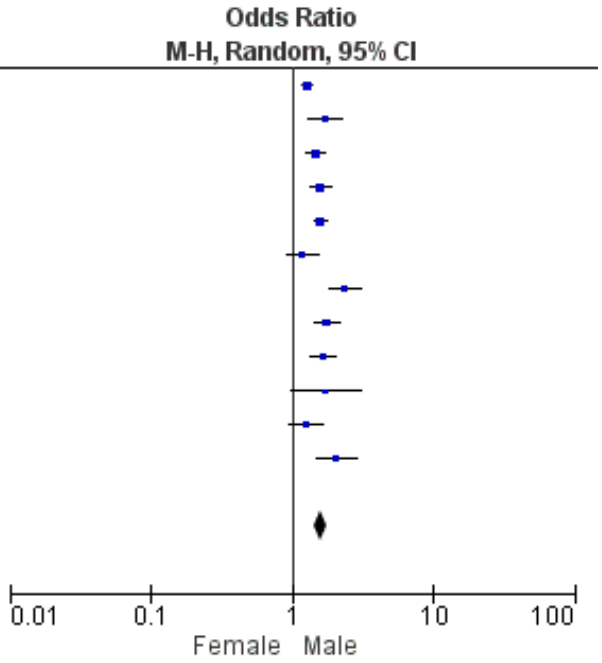
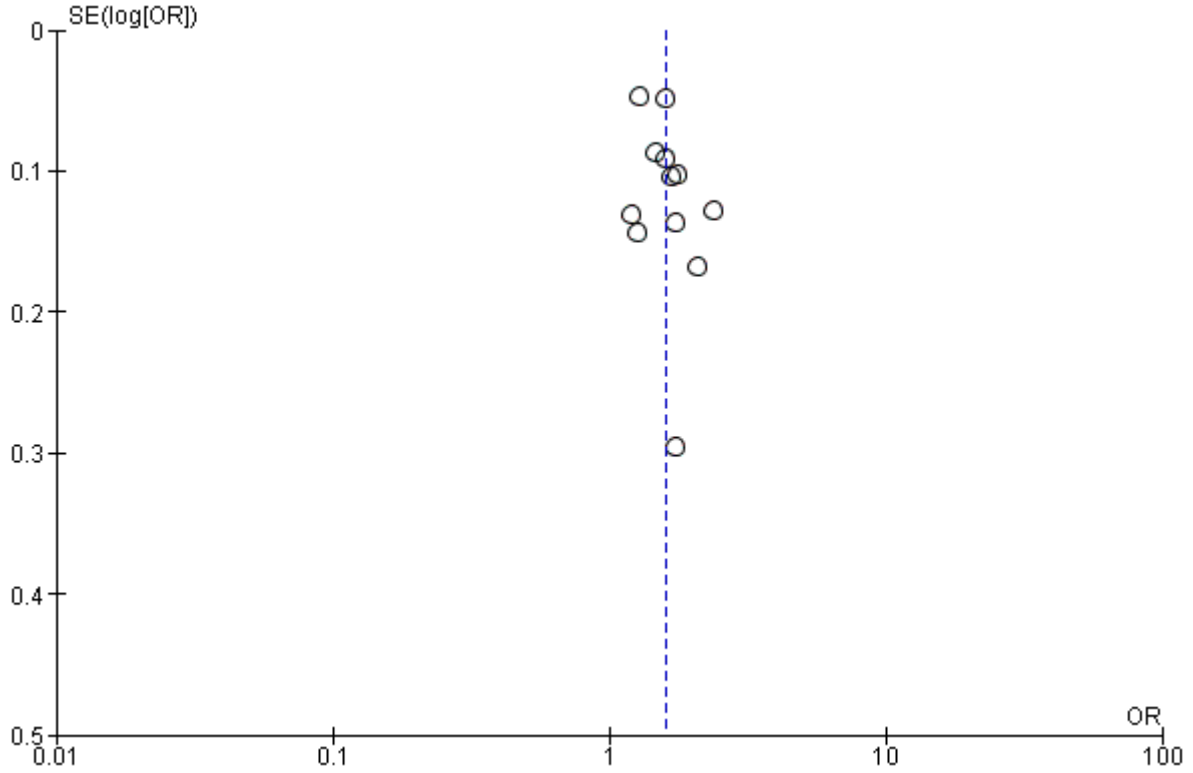


Figure 2.7: Funnel plot. Studies reporting the impact of male sex on colorectal adenoma recurrence



The influence of BMI on colorectal adenoma recurrence

Four studies met the inclusion criteria, there was one retrospective cohort study, one pooled analysis, and two studies used data from non-effect RCTs **[Table 2.3]** (240, 241, 243, 246) and reported on both BMI and colorectal adenoma recurrence while citing raw data that could be used in the present meta-analysis. Three studies split participants into three groups as follows: BMI <25 (normal weight), 25 ≤ BMI <30 (overweight), and BMI ≥30 (obese) (240, 241, 243). One study split participants into two groups (BMI <25 and BMI ≥25) (246). The meta-analysis included 13,606 patients of which 6,275 (46%) developed at least one adenoma during follow-up. 9,224 (68%) patients had a BMI ≥25. 4,431 (48%) of those with a BMI ≥25 were found to have a recurrent adenoma, compared to 1,844 (42%) of those with BMI <25. The summary OR for developing recurrent adenomas in those with a BMI ≥25 was 1.35 [95% CI; 1.14–1.58, p<0.001] **[Figure 2.8].**

Assessment of heterogeneity and publication bias

The I^2 statistic was 69%, indicating a moderate degree of heterogeneity. The funnel plot is limited by the low number of studies included, but a trend towards publication bias is evident with a small positive skew of the lowest precision study **[Figure 2.9].**

Figure 2.8: Forrest plot. The impact of BMI ≥ 25 on colorectal adenoma recurrence

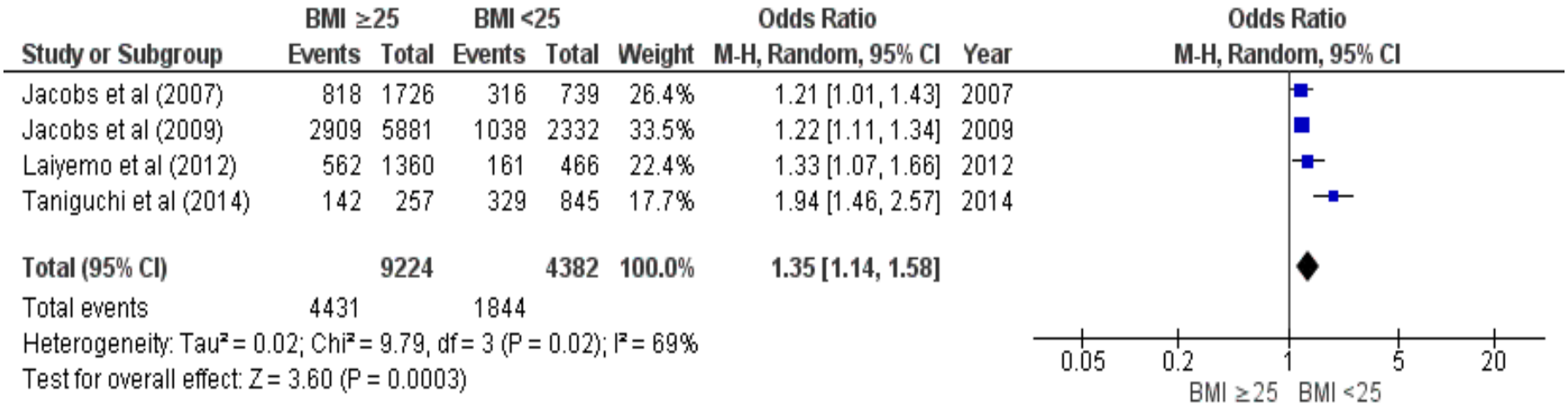
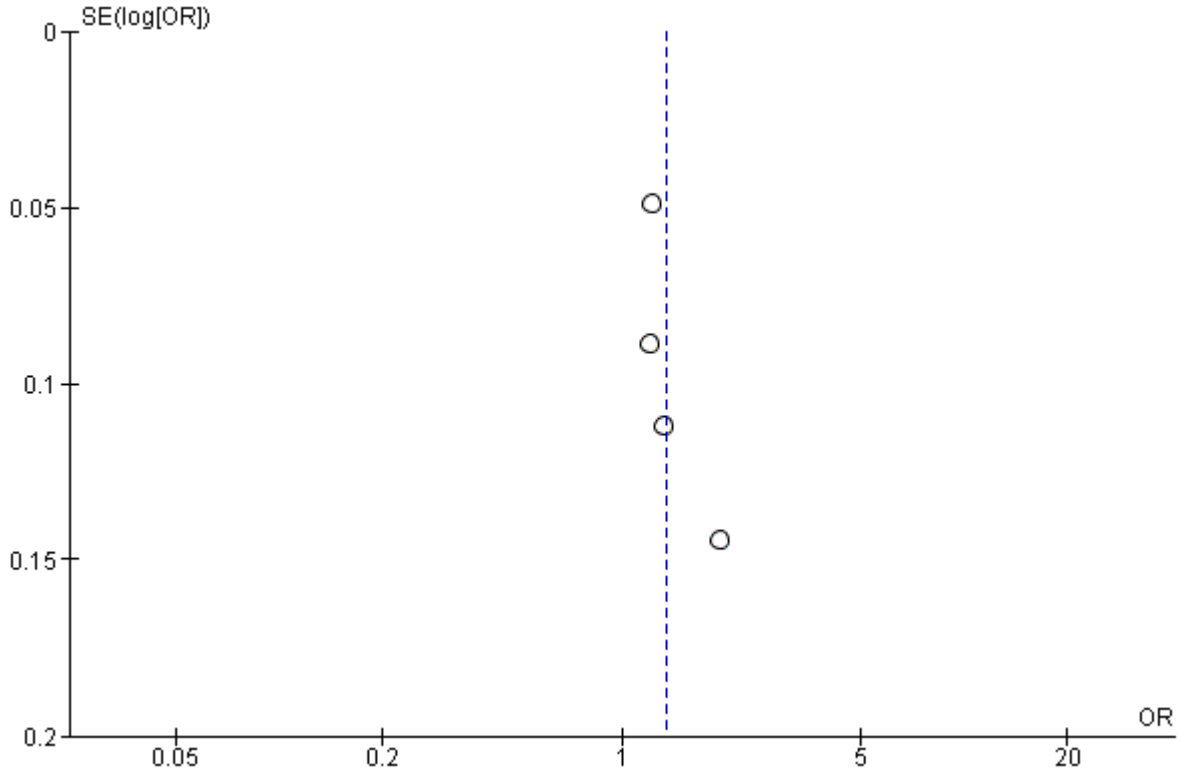


Figure 2.9: Funnel Plot. Studies reporting on the impact of BMI ≥ 25 on colorectal adenoma recurrence



2.4 Discussion

The results of the present meta-analysis suggest that advancing age and male sex are risk factors for the development of recurrent colorectal adenomas after polypectomy. Furthermore, the analysis supports the hypothesis that higher BMI was associated with an increased rate of colorectal adenoma recurrence compared to a lower BMI. Therefore, it is clear that host factors are likely to play a role in the development of recurrent colorectal adenomas, highlighting a potential benefit of including them in follow-up surveillance programmes.

Regarding advancing age, the results of the present meta-analysis showed that age ≥60 years was associated with colorectal adenoma recurrence when compared to those <60 years. These results highlight older age as a risk factor for recurrence, but the magnitude of its effect varied between studies which likely accounted for the heterogeneity observed. The results of the present meta-analysis are consistent with two previously published meta-analyses. Martinez and co-workers conducted a pooled analysis (n=9,167) of post-polypectomy outcomes from eight North American interventional studies aimed at the prevention of colorectal adenoma recurrence (248). The researchers reported an association between advanced age and non-advanced adenoma recurrence, adjusted OR 1.10 [95% CI; 0.98–1.24], OR 1.21 [95% CI; 1.05–1.38] and OR 1.24 [95% CI; 0.69–2.25] for ages 60–69, 70–79 and 80+ years, respectively. However, only the trend was significant ($p<0.001$), making it difficult to accurately quantify the risk for each age group. In the same meta-analysis, a significant association was reported between advancing age and the development of advanced adenomas (≥1cm size, villous features, or HGD). The researchers reported adjusted OR 1.39 [95% CI; 1.16–1.68], OR 1.72 [95% CI; 1.40–2.11] and OR 2.70 [95% CI; 1.31–5.57] in those aged 60–69, 70–79 and 80+ years respectively. In 2011, a further meta-analysis of 27 studies was conducted by De Jonge and colleagues, which included all

relevant studies where participants underwent a baseline colonoscopy and surveillance (249). They examined the association between adenoma and host factors and the recurrence of any adenoma, but they did not distinguish between non-advanced and advanced adenomas. Intervention trials aiming to reduce the rate of polyp recurrence were eligible for inclusion if no statistically significant difference had been found between the groups in the trial. In contrast to the present study, no minimum participant numbers were set, and follow-up was not required to be endoscopic. Post-polypectomy surveillance carried out by barium enema, or CTC was included by the researchers. The researchers reported a summary RR of 1.65 [95% CI; 1.38–1.93] for age ≥60 years vs. age <60 years.

These results indicate that advancing age, particularly ≥60 years, is likely to be a risk factor for recurrent colorectal adenomas. The rate of recurrence may increase in a linear fashion with advancing age, and older patients may be more likely to develop advanced adenomas after polypectomy compared with their younger counterparts.

Concerning sex, the results of the present meta-analysis suggest that male sex is a significant risk factor for the development of recurrent adenomas, consistent with the findings of the previous two meta-analyses described above. In the meta-analysis by Martinez and colleagues, the summary-adjusted OR of a male developing either a non-advanced or advanced, recurrent adenoma irrespective of age was 1.45 [95% CI; 1.30–1.62] and 1.40 [95% CI; 1.19–1.62], respectively. In the meta-analysis by De Jonge and colleagues, male sex was associated with a RR of 1.22 [95% CI; 1.12–1.32] for recurrent adenomas of any type.

Regarding BMI, the results of the present meta-analysis imply there is a significant association between higher BMI and recurrent colorectal adenomas when compared to those with a lower BMI. Taniguchi and colleagues in 2014 reported an OR of 1.97 [95% CI; 1.49–

2.61, p<0.001] for any adenoma recurrence in subjects with higher BMI (≥25) compared to lower BMI (<25) (246). In the meta-analysis by Martinez and colleagues discussed previously, an OR of 1.23 [95% CI; 1.08–1.41, p<0.05] is reported for non-advanced adenoma recurrence, in those with a BMI ≥30, compared to those with a BMI <25.

Considering advanced adenoma recurrence specifically, the same researchers report an OR of 1.00 [95% CI; 0.84–1.19] for those with a BMI of 25–29.9 and an OR of 1.13 [95% CI; 0.93–1.38] for those with BMI ≥30, (p-trend=0.23) (248). Therefore, higher BMI would appear to be a risk factor for recurrence of non-advanced adenomas; however, it is unclear if the same can be said for advanced adenoma recurrence.

Moreover, it remains unclear if risk increases with ever-increasing BMI in a linear fashion. None of the studies included in the present meta-analysis examined morbid obesity (BMI ≥35). It is also unclear whether a higher BMI is associated with the development of advanced adenomas. Furthermore, the health risks associated with increasing BMI have been shown to occur at a lower BMI in Asian populations when compared to western populations (250). Although the WHO classification remains unchanged at present, it is likely the classification of obesity should be lower in Asian populations. This makes comparisons of the effect of BMI and the label of "obesity" on adenoma recurrence between studies in Asian and western populations difficult.

The underlying mechanism for the observed association between advancing age, male sex, and increasing BMI on colorectal adenoma recurrence is not fully understood. A greater understanding of these mechanisms would help clinicians refine post-polypectomy surveillance guidelines. Finding and removing a colorectal adenoma may act as a "teachable moment" for a patient, where there can be a clinical intervention, such as dietary changes, weight loss or administration of a chemoprotective agent in order to reduce the chance of

adenoma recurrence. Unlike higher BMI, age and sex are non-modifiable risk factors; however, the mechanism by which age and sex mediate polyp recurrence may be modifiable.

A plausible mechanism by which age and BMI play a role in adenoma formation is through a chronic inflammatory response. Clinical studies have previously suggested an association between colorectal adenoma prevalence and higher concentrations of circulating pro-inflammatory cytokines IL-6 and tumour necrosis factor-α (TNF-α) (251). It has been suggested that advancing age is associated with chronic systemic inflammation (252), sometimes termed "inflammaging" and that this is associated with the morbidity and mortality seen in elderly people. In 2013, Delongui *et al*. reported that increasing age was associated with higher circulating CRP in otherwise apparently healthy individuals (253). Therefore, the presence of an age-associated chronic systemic inflammatory response may be a contributory factor for the higher polyp recurrence in older subjects.

A higher BMI has been linked with CRC. A meta-analysis by Renehan *et al.* (2008) demonstrated the relationship between increasing BMI and the incidence of colonic as well as a number of additional adult cancers (254). Studies by Visser and colleagues in 1999 and Aronson in 2004 indicate that elevated levels of CRP were found in overweight and obese patients when compared to a population of non-obese patients (255) (256). In addition, Renehan and colleagues in 2006 commented that obesity is thought to induce a low-level systemic inflammatory response (257). Taken together, these studies suggest a correlation between obesity and colonic cancer which may be mediated through obesity-induced inflammation. It follows that these same inflammatory pathways may be driving the higher rate of colorectal adenoma formation, as the precursors of CRC in obese individuals. The link between colorectal polyp recurrence and inflammation may be further evidenced by the fact that aspirin has been shown to be more effective in preventing colorectal adenomas in those with a higher BMI, who may be systemically inflamed (258).

With the implication of systemic inflammation as a potential contributing factor in recurrent adenomas, interventions to prevent recurrence could be aimed at lowering obesity and age-related systemic inflammation.

Weight loss, following bariatric surgery, has been associated with a reduced CRP when compared to the preoperative levels in a study by Tedesco and colleagues in 2016 (259). Despite these results, Laiyemo and colleagues in 2012, did not find a significant reduction in the rate of adenoma recurrence with either weight loss or gain (243). It may be that the damage from long-term obesity and chronic inflammation has limited reversibility once already developed. Chronic obesity-related systemic inflammation could lead to adenoma formation through DNA damage or altered signalling pathways, but the true mechanism remains unclear.

A large volume of work has been carried out examining the link between CRC, inflammation, and the use of aspirin as a chemoprotective agent **(Section 1.1.2.2)** and similarly with colorectal adenomas **(Section 1.4.5.4)**. A Cochrane systematic review in 2014 concluded that aspirin significantly reduces the recurrence of adenomatous polyps after 1–3 years and that the drug may support regression of these polyps in patients with FAP (260). The mechanism by which aspirin achieves this effect may be as a result of its anti-inflammatory properties, which supports the systemic inflammation theory of adenoma formation and recurrence.

As discussed previously, NSAIDs have not been widely used for CRC **(Section 1.1.2.2)** or adenoma prophylaxis **(Section 1.4.5.4)**. This is partly due to their toxicity in terms of GI bleeding risk and, in the case of COX-2 Inhibitors, their risk of serious cardiovascular events. Nonetheless, if a selected cohort of patients at increased risk can be identified, such as those

discussed in the present study (males, aged ≥60 years old, with an elevated BMI), then it may be that the protective benefits to these higher-risk patients will outweigh the risks (261).

Strengths and limitations

A significant strength of the present study is the large numbers of participants that were included in the meta-analysis (n=22,547, 31,277 and 13,606 for the influence of age ≥60 years, male sex and elevated BMI, respectively). Studies were only included if there was full endoscopic surveillance of participants which ensured the contemporary relevance of the data analysed. In addition, the present study is unique in that it utilised the raw data provided by studies allowing it to be directly entered into the Review Manager software for summary and OR.

A limitation of the present meta-analysis was the number of studies excluded. Only studies that provided raw data for the number of participants and the number of adenoma recurrences could be used. Several studies did not publish these data, or published OR, RR, HR or percentages, which precluded the inclusion of these studies. This resulted in the loss of some studies that would otherwise have been eligible for inclusion. Heterogeneity within the present meta-analysis may be explained by the varied designs of the included studies, patient demographics, endoscopic techniques and the retrospective collection of data used. Statistical tests of heterogeneity should be considered with caution, especially since the present meta-analysis included a relatively small number of studies in some outcomes such as the influence of BMI. Another limitation with regards to male sex as a risk factor was that approximately two-thirds of our data were from male patients (n=20,215) (65%) compared to females. This was a similar picture in the meta-analysis by De Jong *et al.* in 2011, where 70% of the participants were male (249). This may have skewed the data, and it would be important for future analyses to be carried out with a more balanced ratio of males to females, such as a bowel screening population. An inherent weakness with any study examining

adenoma recurrence is the possibility that adenomas found at follow-up are actually those that were missed at the first examination. The impact of this was minimised in a number of the studies that were included in the present meta-analysis. In these cases, the researchers carried out a second colonoscopy within a year to clear any missed polyps before the final colonoscopy at the end of the study period (236, 237, 243). The generalisability of the results of the present meta-analysis may be somewhat limited, especially to the UK and in particular the West of Scotland population. The majority of studies included in the literature review are carried out in the USA and Southeast Asia where BMI thresholds, lifestyle, and diets can be quite different and where the indication for colonoscopy was wide and varied.

Final conclusions and further work required

Results from the present review indicate that host factors such as age ≥60 years, male sex and BMI ≥25 are associated with a higher risk of developing recurrent adenomas. The strength of the association was moderate (56% increased risk if ≥60 years, 58% for male sex, 35% for BMI ≥25), yet adenoma number and size are the sole risk factors used in the BSG guidelines for colorectal polyp surveillance (15). The magnitude of effect for these adenoma-specific factors appears larger than for host factors which likely validates the guidelines. In the National Polyp Study in the USA, the OR for adenoma recurrence at first follow-up colonoscopy after polypectomy was 2.4 [95% CI; 1.7–3.5, $p<0.01$] for those with three or more polyps at baseline. Similarly, for those with medium and large adenomas, the OR for recurrence at first follow-up was 1.6 [95% CI; 1.1–2.5; $p<0.05$] (224).

Although the influence of host factors appears to be less than that of adenoma-specific factors, the present study supports the inclusion of host factors into current guidelines. This could be used to identify an increasingly patient-centred “high-risk” and “low-risk” population. The present meta-analysis cannot determine whether age >60 years, male sex and BMI ≥25 elicit a cumulative effect. It is also unable to determine whether these host

factors, in combination with the above adenoma factors, produce an ever-greater additive effect on predicting colorectal polyp recurrence. If this was the case, it could prove to be an important and powerful prognostic tool. Nevertheless, further studies are required to examine such a proposal. A closer investigation of the effect of both host and adenoma-specific factors on adenoma recurrence within a bowel screening population would be useful. Finally, studies scrutinising the interaction between patient factors, the systemic inflammatory response and colorectal adenoma formation are warranted.

Table 2.1: Studies included in the meta-analysis: The impact of age ≥ 60 years on the incidence of colorectal adenoma recurrence

Author	Year	Design	Country	Purpose of the study	n	Inclusion / exclusion criteria	Corrected for missed adenomas?
Winawer *et al.* (224)	**1993**	RCT	USA	To determine the ideal follow-up period post-polypectomy. 1-year vs. 3-year colonoscopy.	938	All patients referred for colonoscopy for any reason. IBD, FAP, CRC patients excluded.	No
Bertario *et al.* (234)	**2003**	Retrospective cohort	Italy	To determine the risk of colonic neoplasia recurrence based on host and polyp characteristics.	1086	Exclusion of patients with hyperplastic/inflammatory polyps, FAP, HNPCC.	No
Yood *et al.* (239)	**2003**	Retrospective cohort	USA	To determine the natural history (risk of recurrence and timing of recurrence) of colorectal adenomas.	8865	Data from a large integrated health management organisation in the USA. Excluded patients with a history of CRC, Crohn's, or < 1year in the health scheme.	No
Yamaji *et al.* (238)	**2004**	Retrospective cohort	Japan	To determine both the incidence and recurrence rate of colorectal neoplasm in asymptomatic Japanese patients.	6225	Exclusion based on a personal history of CRC or IBD.	No
Cafferty *et al.* (235)	**2007**	Retrospective cohort	Taiwan	To help determine post-polypectomy follow-up guidelines.	2213	All patients undergoing colonoscopy for any reason. Even those with normal baseline scope were given a follow-up colonoscopy. A retrospective review of records.	No
Huang *et al.* (236)	**2010**	Retrospective cohort	China	To determine the true recurrence rate of adenomas.	1356	Prospectively collected database of adenomas excised at colonoscopy from 1976–2007 in a South China population. FAP, IBD, CRC patients excluded.	Yes
Laiyemo *et al.(237)*	**2013**	Data from non-effect RCTs	USA	To analyse patient and demographic factors associated with colorectal adenoma recurrence.	1864	Data from patients who were randomised and enrolled in the Polyp Prevention Trial (dietary intervention trial). Exclusion of patients with IBD, CRC or FAP.	Yes

Table 2.2: Studies included in the meta-analysis: The impact of male sex on the incidence of colorectal adenoma recurrence

Author	Year	Design	Country	Purpose of the study	n	Inclusion / exclusion criteria	Corrected for missed adenomas
Yood *et al.* (239)	**2003**	Retrospective cohort	USA	To determine the natural history (risk of recurrence and timing of recurrence) of colorectal adenomas.	8,865	Data from a large integrated health management organisation in the USA. Excluded patients with a history of CRC, Crohn's, or <1year in the health scheme.	No
Bertario *et al.* (234)	**2003**	Retrospective cohort	Italy	To determine the risk of colonic neoplasia recurrence based on host and polyp characteristics.	1,086	Exclusion of patients with hyperplastic/inflammatory polyps, FAP, HNPCC.	No
Cafferty *et al.* (235)	**2007**	Retrospective cohort	Taiwan	To help determine post-polypectomy follow-up guidelines.	2,213	All patients undergoing colonoscopy for any reason. Even those with normal baseline scope were given a follow-up colonoscopy. Retrospective review of records.	No
Jacobs *et al.* (240)	**2007**	Retrospective pooled analysis	USA	Investigate the effect of obesity on adenoma recurrence.	2,465	All patients who completed the UDCA (ursodeoxycholic acid) and WBF (Wheat Bran Fibre) trial in the USA.	
Jacobs *et al.* (241)	**2009**	Retrospective pooled analysis	USA	To determine the relationship between BMI, sex and the incidence of recurrent colorectal adenomas.	8,213	All studies ≥800 participants, at least one follow-up colonoscopy. Endpoint data had to be available for all adenomas detected. Exclusion of those who had CRC detected at baseline or if <6 months follow-up.	No
Gao *et al.* (242)	**2010**	Retrospective cohort	China	To determine the ideal follow-up/surveillance programme after polypectomy and to analyse the risk factors for colorectal adenoma recurrence.	1,208	Included patients had lower GI symptoms present. (not a screening population). Patient excluded if a clean colon was found on the index scope, IBD, FAP, HNPCC or CRC. Must have had a polypectomy at index scope and at least one follow-up colonoscopy.	No

Huang *et al.* (236)	**2010**	Retrospective cohort	China	To determine the true recurrence rate of adenomas	1,356	Prospectively collected database of adenomas excised at colonoscopy from 1976–2007 in a South China population. FAP, IBD, CRC patients excluded.	Yes
Laiyemo *et al.* (243)	**2012**	Retrospective analysis of data from non-effect RCTs	USA	To analyse patient and demographic factors associated with colorectal adenoma recurrence.	1,826	Data extracted from patients who were randomised and enrolled on the Polyp Prevention Trial (dietary intervention trial). Exclusion of IBD, CRC, previous polyp resection or FAP.	Yes
Kitahara *et al.* (244)	**2013**	Retrospective analysis of subgroup data from RCT	USA	A RCT to evaluate the efficacy of screening methods for cancer. An ancillary study nested within the main trial examined the recurrent colorectal adenoma.	1,676	Baseline colonoscopy and polypectomy required for inclusion. Must have undergone surveillance colonoscopy >6 months to 10 years later. Excluded IBD, polyposis, Gardner's syndrome, previous colorectal polyps, missing results or extremes of BMI .	No
Lin *et al.* (245)	**2014**	Retrospective cohort	Taiwan	To evaluate the predictors of recurrent colorectal adenomas after screening colonoscopy.	356	Asymptomatic patients who underwent two consecutive "health check" colonoscopies with polypectomy at first colonoscopy between 2003–2010. Exclusion of CRC, IBD, non-adenomatous polyps, NSAID use.	No
Taniguchi *et al.* (246)	**2014**	Retrospective cohort	Japan	To investigate the role of metabolic factors on the recurrence of colorectal adenomas.	1,111	Must have undergone complete colonoscopy with polypectomy for screening purposes. Required 3 follow-up colonoscopies. Exclusion if age <50yr, or >85yr, IBD, HNPCC, FAP, CRC, NSAID use, previous colonic or appendicular resection, or life expectancy <2 years.	No
Xu *et al. (247)*	**2015**	Retrospective cohort	China	To determine the incidence of advanced, recurrent adenoma over a 5-year period.	828	Colonoscopy database accessed. Clear colon, non or advanced adenomas included. Excluded IBD, Intestinal TB, coagulopathy, any polyposis syndromes, prior colorectal resection or prior adenomas.	No

Table 2.3: Studies included in the meta-analysis: The impact of BMI ≥ 25 on the incidence of colorectal adenoma recurrence

Author	Year	Design	Country	Purpose of the study	n	Inclusion / exclusion criteria	Corrected for missed adenomas
Jacobs *et al.* (240)	**2007**	Data extracted from two RCTs that showed no difference between the outcomes in each group.	USA	To assess whether obesity and/or waist circumference were associated with colorectal adenoma recurrence.	2465	All patients who had taken part and completed the studies from which the data were pooled: The UDCA (ursodeoxycholic acid) and WBF (Wheat Bran Fibre) trial in the USA.	No
Jacobs *et al.* (241)	**2009**	Retrospective pooled analysis.	USA	To determine the relationship between BMI, sex and the incidence of recurrent colorectal adenomas.	8213	All studies ≥800 participants, at least one follow-up colonoscopy. Endpoint data had to be available for all adenomas detected. Exclusion of those who had CRC detected at baseline or if <6 months follow-up.	No
Laiyemo *et al.* (243)	**2012**	Retrospective analysis of data from non-effect RCT.	USA	To analyse patient and demographic factors associated with colorectal adenoma recurrence.	1826	Data extracted from the polyp prevention trial (dietary intervention trial). Exclusion of IBD, CRC, previous polyp resection or FAP.	Yes
Taniguchi *et al.* (246)	**2014**	Retrospective cohort.	Japan	To investigate the role of metabolic factors on the recurrence of colorectal adenomas.	1111	Must have undergone complete colonoscopy with polypectomy for screening purposes. Required 3 follow-up colonoscopies. Excluded if age <50years, or >85years, IBD, HNPCC, FAP, CRC, NSAID use, previous colonic or appendicular resection, or life expectancy <2 years.	No

3 THE DETERMINANTS OF ADENOMA RECURRENCE WITHIN A BOWEL SCREENING POPULATION

3.1 Introduction

CRC is the fourth most common cancer by incidence, and the second most common cause of cancer death in the UK (1). The majority of cancers originate from colorectal adenomas through the adenoma-carcinoma sequence (203, 204, 262, 263). Identification and excision of adenomas prior to malignant transformation is recommended to reduce CRC incidence. The UK flexible sigmoidoscopy trial showed that a once-only flexible sigmoidoscopy reduced the incidence of CRC, most likely as a result of prophylactic polypectomy (223). Other large well-designed studies such as the Minnesota Colon Cancer Control Study, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the National Polyp Study drew similar conclusions (264) (265) (208).

In the UK, EU and the USA, recommendations for post-polypectomy surveillance follow a risk stratification model. Certain adenoma characteristics are thought to confer a higher risk of malignant transformation and lead to a predisposition towards advanced neoplasia (CRC or advanced adenomas). Adenomas with at least one of the following characteristics are classed as advanced adenomas: large size (≥1cm), villous architecture or the presence of HGD (266). Currently, in the UK, patients with one or more adenomas at colonoscopy are classified into low, intermediate or high-risk groups with patients then offered post-polypectomy surveillance at varying intervals based on the perceived level of risk. The BSG published guidelines in 2002 (updated in 2010) to direct clinicians on optimal post-polypectomy surveillance (15). For those classed as low-risk (1–2 small adenomas <1cm), they recommend a 5-year re-examination by colonoscopy or no further examination at all. Patients classed as intermediate (3–4 small adenomas or at least one ≥1cm), or high-risk (≥5

small adenomas or ≥3 adenomas with at least one ≥1cm) should be offered a three or 1-year endoscopic re-examination, respectively.

Surveillance is a costly component of bowel screening meaning it is vital to weigh the perceived benefits against the burden on resources, patient discomfort and the risk of complications (267). As such, surveillance colonoscopy is best utilised in selected groups of individuals most at risk of developing recurrent adenomas, advanced adenomas or cancer.

As mentioned in **Chapter 2**, current UK surveillance guidelines are based on baseline adenoma-specific characteristics of size and number. They do not account for adenoma histology or host characteristics despite evidence that host characteristics may play a role in adenoma recurrence **(Chapter 2)**. Questions remain as to the applicability of the above evidence (of which a significant volume is from Southeast Asia), to a bowel screening population, particularly in Scotland. Further examination is warranted. In particular, scrutiny of the case for host factors to be included in future post-polypectomy surveillance guidelines would be useful.

The present study utilises a UK bowel cancer screening population, with an extended median follow-up of more than six years to examine the association between adenoma-specific and host characteristics on the incidence of adenoma recurrence.

3.2 Materials and methods

Study protocol, inclusion and exclusion criteria

Primary data were obtained from the GGC bowel screening database. In Scotland, patients aged between 50–74 years who tested positive in the SBoSP were invited for colonoscopy. In the present study, all screening patients between March 2009–April 2011 who underwent polypectomy and were classed as intermediate or high-risk according to the BSG guidelines were included in the study (15). The risk classification of these patients meant they were recommended for surveillance colonoscopy at least once within the follow-up period. Patients required to have undergone a full baseline colonoscopy complete to the caecum. Only those with colorectal polyps identified, who underwent excision of all visible lesions and at least one follow-up colonoscopy ≥1 year from the baseline examination were included. Cold or hot biopsy of polyps using forceps for polyps <5mm was classed as full excision. For polyps ≥5mm, a formal polypectomy or Endoscopic Mucosal Resection (EMR) was required for acceptable excision.

Patients in whom there was uncertainty regarding the removal of all polyps were excluded from the study. In addition, follow-up by any means other than colonoscopy, the presence of cancer at baseline, or during follow-up (in the absence of synchronous adenomas), or segmental colonic resection during the follow-up period, resulted in exclusion. A number of patients required more than one colonoscopy to remove all baseline polyps. Colonoscopy results for this or any other reason <1 year from the initial colonoscopy were combined and considered as a single baseline colonoscopy. Initial examination findings were recorded from medical notes, pathology reports and the endoscopy reporting system (UNISOFT®). Medical notes covering the period between March 2009 and October 2016 were examined for post-polypectomy surveillance colonoscopy results. Any finding of at least one histologically proven adenoma at any follow-up colonoscopy during the study period was

classed as adenoma recurrence. Those who were found to have CRC at follow-up were included if they had synchronous adenomas.

Data collection and analysis: Adenoma characteristics

Identical polyp and adenoma-specific findings at both baseline and follow-up colonoscopy were sought from the endoscopy report. The total number of polyps visualised, excised, and received in the lab were recorded. From the histological analysis, the number of confirmed hyperplastic polyps, non-advanced and advanced adenomas were recorded. Hyperplastic polyps were excluded. Only patients with a histologically proven adenoma at baseline were included. In those with adenoma recurrence, the presence of advanced adenomas was recorded along with the size of the adenomas and the presence of any advanced histological features. Patients were classed as having advanced adenomas if at least one of the adenomas removed had one or more of the following features: size (from pathology specimen) ≥1cm or villous features and / or HGD.

Data collection: Host factors

Age, sex, BMI, socioeconomic deprivation, smoking status and medication use, were recorded. Age was recorded at the date of baseline colonoscopy. BMI was calculated from the General Practitioner (GP) records of height and weight. Deprivation was assessed using the Scottish Index of Multiple Deprivation (SIMD) 2009. This is an index of relative deprivation combining multiple detailed indicators based on postcodes across seven domains (268). Scores for SIMD were ordered with patients grouped into quintiles. Those in the first quintile (most deprived), are likely to have higher levels of poverty, unemployment, and poorer health than those in the fifth quintile (least deprived). Data on the use of ACE inhibitors, aspirin or statins for enrolled patients were recorded from GP records. Those who had a repeat prescription for these medications valid at the date of baseline colonoscopy were assumed to be actively using the medication.

Study endpoints

The two main endpoints of the study were:

1. Any adenoma recurrence: the presence of at least one adenoma, of any type (advanced or non-advanced) at post-polypectomy follow-up ≥1 year from baseline examination

2. Advanced adenoma recurrence: the presence of at least one advanced adenoma at follow-up ≥1 year from baseline examination

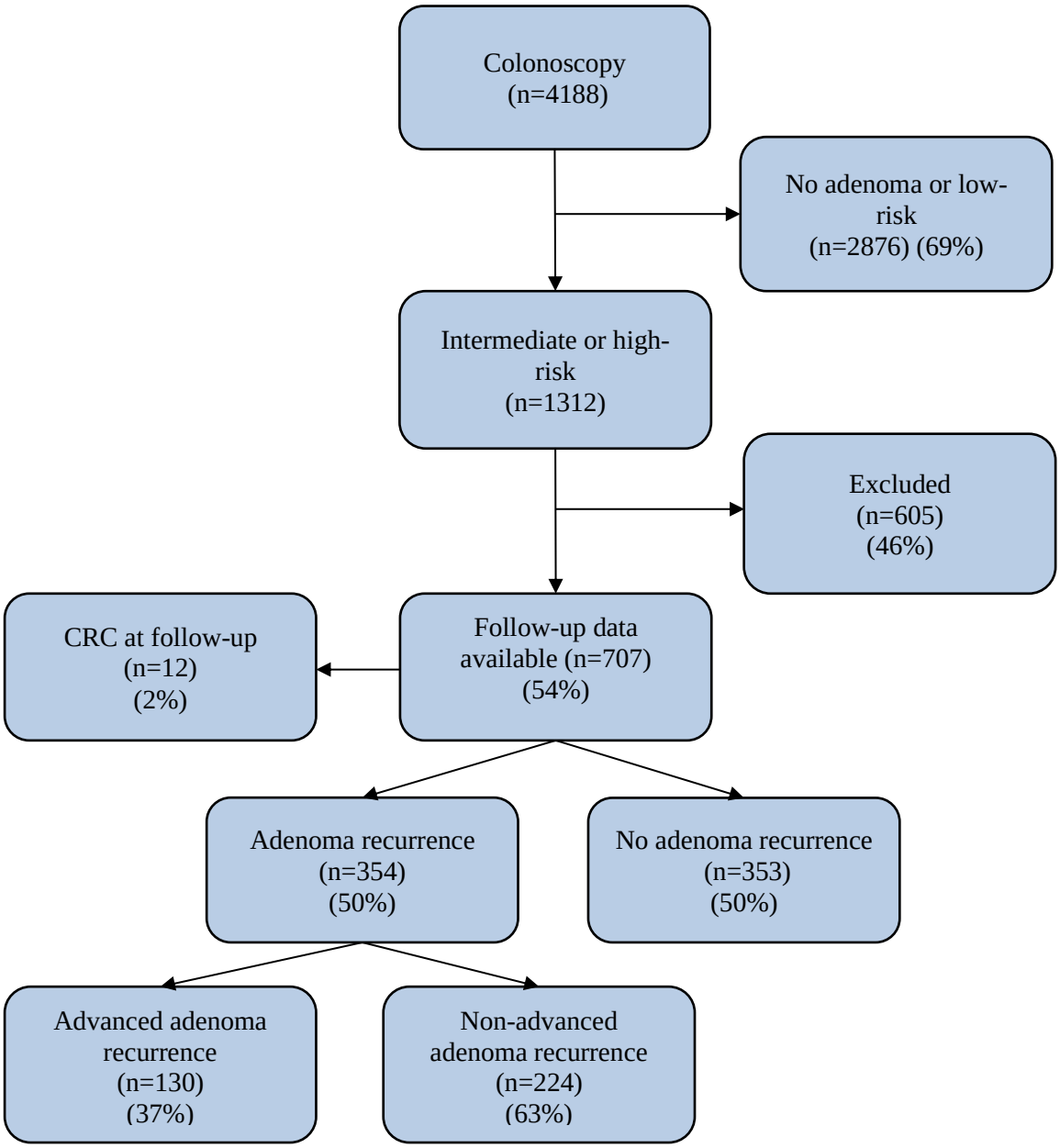
Statistical analyses

Statistical analyses were conducted to assess the relationship between adenoma-specific and host characteristics and adenoma recurrence. Patients were grouped appropriately to prepare categorical variables for analysis. Standard WHO thresholds for BMI were used to categorise patients as underweight, normal weight, overweight or obese (269). Age groups were selected based on established and validated age ranges used to stratify risk in CRC patients. A $\chi 2$ test was used to test for statistical significance. ORs were expressed to estimate risk. Binary logistic regression was used to assess categorical variables with two or more groups against a reference group. Any odds ratios associated with a p-value <0.1 at univariable analysis were included in the multivariable model. In all analyses, a two-tailed p-value of <0.05 was considered statistically significant. All statistical analysis was carried out using IBM® SPSS® Statistics version 22 (SPSS Inc., Chicago, IL, USA).

3.3 Results

Figure 3.1 illustrates the outcome and follow-up from the 4,188 patients undergoing screening-based colonoscopy. 2,876 (69%) patients were classed as low-risk (no adenomas or 1–2 small adenomas <1cm). 1,312 (31%) were classed as intermediate or high-risk (>2 adenomas or at least one ≥1cm) and recommended for repeat colonoscopy in 1–3 years. 605 (46%) patients were excluded or lost to follow-up **[Table 3.1].** Complete follow-up data were available for 707 (54%) patients**.**

Figure 3.1: Flow diagram for those attending colonoscopy and post-polypectomy surveillance



Baseline patient characteristics

Baseline characteristics are displayed in **Table 3.2**. There were 515 (73%) males, and the median age was 65 years [interquartile (IQ) range 59–69]. BMI data were available for 430 (61%) patients. The cohort was predominantly overweight, with a median BMI of 29 kg/m^2 [IQ range 26–32]. The majority of the cohort lived in areas of high socioeconomic deprivation, with 374 (53%) classed in the most deprived SIMD quintiles (1^{st} and 2^{nd}). 446 (63%) were ex or current smokers. Median follow-up was 75 months [IQ range 69–81].

Any adenoma recurrence

354 (50%) patients had adenoma recurrence at the follow-up colonoscopy **[Table 3.2]**. In terms of adenoma-specific characteristics, a greater number of adenomas at baseline were significantly associated with an increased risk of recurrence. Compared to 1–2 adenomas at baseline, the presence of 3–4 or ≥5 adenomas at baseline resulted in an OR of 2.47 [95% CI; 1.72–3.52, p<0.001] and 4.60 [95% CI; 2.81–7.54, p<0.001] for adenoma recurrence respectively. The presence of any adenoma ≥1cm was associated with a reduced risk of adenoma recurrence, OR 0.52 [95% CI; 0.33–0.84, p<0.01]. HGD and the presence of villous features individually were not associated with adenoma recurrence. The presence of any advanced adenoma, which was predominantly driven by the presence of larger adenomas was associated with a lower risk of recurrence, OR 0.45 [95% CI; 0.29–0.70, p<0.001]. However, this did not retain significance on multivariable analysis when adjusting for adenoma number.

Multivariable analysis was carried out to adjust for sex, adenoma number, advanced adenomas and the presence of any adenoma ≥1cm at baseline. Baseline adenoma number remained a statistically significant risk factor for any adenoma recurrence on the multivariable model. Compared to 1–2 adenomas at baseline, the presence of 3–4 or ≥5 adenomas resulted in an OR of 2.23 [95% CI; 1.53–3.25, p<0.001] and 4.19 [95% CI; 2.53–6.97, p<0.001] respectively.

Concerning host characteristics, only male sex, OR 1.46 [95% CI; 1.05–2.04, p<0.05] was associated with adenoma recurrence at follow-up, but statistical significance was not retained on multivariable analysis. Advancing age, elevated BMI, socioeconomic deprivation, the use of aspirin, ACE inhibitors or statins were not associated with adenoma recurrence in this cohort.

Adenoma number at baseline was compared with other baseline characteristics that were significantly associated with adenoma recurrence **[Table 3.3]**. At baseline, higher adenoma numbers were associated with male sex (p<0.001) and those with higher numbers of adenomas were less likely to have large (p<0.001) or advanced adenomas (p<0.001).

Advanced adenoma recurrence

Of the 354 patients with adenoma recurrence, 130 (37%) had advanced adenoma recurrence at follow-up. This equates to 18% of the entire study cohort of 707 **[Table 3.4].**

With respect to adenoma-specific factors, overall adenoma number at baseline did not influence the risk of advanced adenoma at follow-up. However, the presence of advanced adenomas at baseline was associated with advanced adenomas at follow-up, OR 2.34 [95% CI; 1.18–4.61, p<0.05]. There was no similar association found when the features of advanced adenoma (size ≥1cm, villous histology or HGD) were considered separately.

With respect to baseline host characteristics, none were significantly associated with advanced adenomas at follow-up.

3.4 Discussion

This longitudinal cohort study reports on the association between adenoma and host characteristics at baseline colonoscopy and the subsequent risk of recurrent adenomas and advanced adenomas in a bowel screening population. The results suggest that in this population, increasing adenoma number significantly increases the risk of adenoma recurrence. In addition, the presence of an advanced adenoma at baseline colonoscopy is associated with an increased risk of an advanced adenoma at follow-up. These findings were independent of age, sex and BMI.

Approximately 50% of patients were found to have a recurrent adenoma at follow-up. This is in keeping with the literature where recurrence rates range from 22–53% (235, 246, 248, 270-273). Of those who had any adenoma recurrence, 130 (37%) had features of advanced adenomas, equating to 18% of the entire screening cohort. Thus, the present study largely supports the BSG guidelines recommending patients with multiple adenomas and advanced adenomas (larger size) undergo surveillance colonoscopy within 1–3 years (15).

Adenoma-specific factors and adenoma recurrence

This study reports on the relationship between baseline adenoma characteristics and the risk of any and advanced adenoma recurrence. A number of previous studies with similar methodologies have been published over the last 15 years with varying results. These are shown in **Table 3.5.**

Current UK guidelines are based on adenoma-specific factors of size and multiplicity to recommend post-polypectomy surveillance. This is based upon the perceived increased risk of advanced neoplasia in patients at follow-up. Histological subtypes and colonic location are not used. In the USA, recommendations for follow-up are largely similar but, in addition, they consider histological subtypes of adenomas at baseline (274). Increased adenoma number at baseline has been consistently shown to increase the risk of any adenoma

recurrence during surveillance (234, 246-248, 267, 270-272, 275-278). The results of the present study are consistent with these observations. It is possible that patients with higher numbers of adenomas are predisposed, by genetic or environmental factors, to be "polyp formers". In addition, the miss rate at colonoscopy has been reported as between 5 and 28% (230-232); therefore, it may be that those with higher adenoma numbers result in some adenomas being missed during colonoscopy.

Evidence of the relationship between adenoma number at baseline and the risk of advanced adenoma recurrence is less well established. A number of studies report a higher incidence of advanced adenoma recurrence in those with multiple adenomas at baseline (272), yet other studies found no effect of multiplicity (234, 247). The present study did not find an association between baseline adenoma multiplicity and advanced adenoma recurrence.

Villous features or HGD were not associated with any adenoma recurrence when considered individually, although patients with larger adenomas (≥1cm) at baseline were significantly less likely to have any adenoma at follow-up. However, this was not retained on multivariable analysis when correcting for baseline adenoma number. This is likely due to the finding that larger adenomas were associated with fewer adenoma numbers overall.

With respect to advanced adenoma recurrence, villous features, larger size and the presence of HGD at baseline have been associated with advanced neoplasia at follow-up (274). This forms the basis of the USA post-polypectomy guidelines. These class patients with larger adenomas (≥1cm), multiple adenomas (3+), or any adenomas with HGD or villous features as high-risk for advanced, recurrent neoplasia. As such, they recommend a repeat colonoscopy at three years for this patient subgroup (274). The European Society of Gastrointestinal Endoscopy surveillance guidelines are largely similar to those of the USA (279).

Currently, in the UK, the histological subtype is not considered as a predictor of future risk; a decision based on the opinion that histological subtyping is inconsistent, with poor reproducibility. Furthermore, it could be argued that for patients with larger or multiple adenomas, the presence of HGD or villous architecture may be academic only, as these patient cases are already classed as high-risk due to their size and multiplicity. In addition, size is often strongly correlated to histology, and as such, most villous adenomas are encompassed into the high-risk surveillance group based on size criteria (280).

In the present study, villous features, larger adenomas (≥1cm) and HGD did not appear to influence advanced adenoma recurrence in isolation, however, when combined into one variable (the presence of an adenoma with any advanced feature), they were associated with a significantly higher risk of subsequent advanced adenomas at follow-up. This may strengthen the case for the inclusion of advanced histological factors as a combined package into future UK guidelines similar to those from the USA.

Host characteristics and any adenoma recurrence

Older age is strongly associated with CRC (139). In the present study, advancing age was not associated with adenoma recurrence. Contrary to these findings, the majority of published studies, including meta-analyses, have reported that advancing age is associated with adenoma recurrence (223, 224, 235-239, 249). Multiple studies enrol a substantial number of patients aged <50 years (235-238, 272, 273, 277, 281, 282), which is younger than the 50-year minimum age of bowel screening patients. As such, it may account for the conflicting results reported in this study. Moreover, it is plausible that by 50 years, the “age effect” has already induced its influence. In addition, the present study used a cohort of patients who were defined as having higher risk adenomas at baseline and were specifically selected for follow-up based on the BSG criteria; therefore, this population may differ slightly from previous studies.

The role of male sex as a risk factor for adenoma recurrence is plausible, given its association with CRC (139). Previous studies have reported similar results for male sex with respect to adenoma recurrence (195, 234-236, 239-246), including a meta-analysis (272) and a pooled analysis (248). However, in the present study, the effect of male sex was not significant in the multivariable analysis. Since higher adenoma number is a strong predictor of recurrence and also associated with male sex in the present study, it may be that the adenoma multiplicity is acting as a confounder.

Nonetheless, it is biologically plausible for there to be a male preponderance to adenoma formation, especially given the suggestion that oestrogen may provide a chemoprotective action for women (283). In 2008, Kennelly and co-workers suggested that in particular, oestrogen receptor β has a crucial role in colonic cell homeostasis, including modulation of cell proliferation and apoptosis, although the exact mechanisms are yet to be determined (284). In addition, differing patterns of potential confounding factors such as BMI, comorbid disease, smoking and lifestyle may contribute to sex-specific differences in prevalence. More recently, the differences in body composition between males and females and their effect on cancer incidence have been examined. Intersex comparison has shown that in general men have a higher volume of visceral adipose tissue while women tend towards higher volumes of subcutaneous adipose tissue for a given BMI (285). Considering that recent work has linked higher visceral adipose tissue to colorectal adenoma incidence (286, 287), body composition differences between the sexes may play a role in any disparity.

The present study did not find an association between socioeconomic deprivation and any or advanced adenoma recurrence. Previous large population studies have reported on the associations between socioeconomic deprivation and CRC. In particular, a recent large study of 17,000 patients in the UK reports that those from a Black Afro-Caribbean or socially deprived background were more likely to present with late, stage IV disease, than white

British or patients from a more affluent background, OR 1.37 [95% CI; 1.18–1.59, p<0.001] and OR 1.26 [95% CI; 1.13–1.14, P<0.001], respectively (288). In addition, a recent study examining a bowel screening cohort in the same geographical region as the present study was conducted by Mansouri *et al.* (139). It was reported that patients with a high level of socioeconomic deprivation were less likely to attend for screening. However, there are a limited number of studies examining the influence of social deprivation with regards to adenoma incidence and recurrence. Although no significant association was found in the present study, any effect may benefit from further investigation, given that social deprivation is associated with many other health inequalities, particularly in Scotland.

The present study did not find a difference in any or advanced adenoma recurrence rates in those who currently or previously smoked compared to lifelong non-smokers. Smoking has been linked with CRC incidence as well as mortality (289) (290). Two studies reported an association between smoking and adenomatous polyp incidence (291, 292) and in particular, the incidence of advanced neoplasia (292). This agrees with an earlier study in 2005 (293).

The present study did not find an appreciable link between the use of daily aspirin, statins or ACE inhibitors and adenoma recurrence, including advanced adenomas. Many studies have investigated the role of NSAIDs, notably aspirin, in reducing the incidence and recurrence of colorectal adenomas. These include a Cochrane review and two systematic reviews (260) (211, 294). The Cochrane review was published in 2004. It cautiously reported that there was some evidence to support daily aspirin or regular NSAID use as a risk reduction strategy for recurrent colorectal adenoma. However, the reviewers noted that universal agreement regarding timing, dose and duration of use was yet to be gained. Overall the review did not recommend general use of NSAIDs and aspirin for chemoprevention, mainly due to the risk of adverse effects (260). More recently, the first of two systematic reviews was conducted in 2015 and included nine studies with 8,521 subjects (211). The researchers reported that

NSAID use was associated with a reduction in the recurrence of any type of adenoma and specifically advanced adenomas; however, the effect was not retained at three years. The second systematic review and meta-analysis concluded that approximately 10 years of aspirin use was required to achieve a reduction in CRC incidence and mortality (294). The researchers found some evidence that aspirin use reduced adenoma recurrence, but results were inconsistent, especially with regards to dosing, which ranged from 81–325 mg/day. The contrasting results in the present study may be explained by the relatively small numbers of patients taking these medications and an absence of data regarding the duration of treatment.

In the present study, BMI was not associated with overall adenoma recurrence. This is in contrast to some previous reports. Firstly, when considering primary adenoma incidence rather than recurrence, studies have reported that higher BMI is associated with higher adenoma incidence, including advanced adenomas (295). Although as mentioned previously **(Chapter 1, Chapter 2),** the results are not consistent and a linear relationship with BMI is not certain (240, 241, 243, 244, 246, 296, 297). This can make it difficult to draw clear conclusions. A large and recent trial in Korea examined 2,176 patients with respect to any and advanced adenoma recurrence. No significant relationship between baseline BMI and any adenoma recurrence was found in a similar manner to the present study (298). The researchers did, however, find a significant risk of advanced adenoma recurrence in patients with a baseline BMI ≥30, HR 4.66 [95% CI; 1.70–12.7]. A direct comparison between the above and the present study must be considered with caution however since the Korean study used a much younger patient cohort (mean age 41 years) where participants underwent a colonoscopy as part of a routine health check-up. In contrast, the present study had an older population and used patients with intermediate and high-risk baseline risk from a bowel screening population.

An additional three studies reported an increased risk of recurrence of any adenoma type in those with higher BMI (241, 243, 246). One study split participants into two groups (BMI <25 and BMI ≥25) (246), while the others used three groups (<25, 25–29.9, ≥30) (241, 243) rendering comparison more difficult.

Two additional studies found no effect of increasing BMI on any adenoma recurrence when genders were combined (240, 244), but one study found a slight association between any adenoma recurrence and increasing BMI in males alone (240).

It appears however that studies showing the closest relationship between BMI and adenoma recurrence were those from Japan (246) and South Korea (296), suggesting that Southeast Asian populations are potentially more BMI sensitive, an effect that has been shown previously in relation to cardiovascular disease (299). In the present study, the population was predominantly male and overweight (median BMI 29) and had intermediate or high-risk adenomas at baseline. It may be that a younger population encompassing those with low-risk baseline adenomas and a more even gender split would show a greater influence of BMI.

In summary, in terms of baseline host characteristics, the present study suggests host factors do not play a crucial role in predicting adenoma recurrence in a high-risk bowel screening group. Increasing BMI may be associated with adenoma recurrence and potentially in advanced adenoma recurrence at follow-up, but clear conclusions cannot be drawn from the present study.

Strengths and limitations

The present study aimed to investigate adenoma recurrence rates in a bowel screening population in the West of Scotland. Many of the studies used to collate current evidence in this field are based on the USA and Southeast Asian populations. This limits generalisation to our patient population. The West of Scotland has a unique population in that there are significantly high levels of socioeconomic deprivation and comorbidity. As such, findings from the present study may be more valid in this population. In addition, the present study used a relatively long follow-up time, with a median of 72 months.

A number of limitations were identified. Firstly, the large attrition rate. Of the original 1,312 patients that were expected to undergo colonoscopy surveillance, 605 were excluded from the analysis; the majority were due to a lack of follow-up data available in medical records (n=416). The reasons for loss of follow-up data are varied with a combination of patients not attending appointments, changing their geographical base, clinicians not adhering to surveillance guidelines and patients being lost to follow-up as a result of administration pathways. It is not uncommon to see this, with previous studies showing that up to 40% of patients with advanced neoplasia had not undergone surveillance within five years (300). In addition, the 1,312 patients initially eligible for analysis were selected as they had been identified as intermediate or high-risk at baseline, making them potentially more likely to develop subsequent adenoma. A useful control group may have been those with no adenoma or small and non-advanced adenomas only at baseline. These low-risk patients are not routinely re-examined in the UK; hence their inclusion in a real-world analysis such as this was not possible.

In any study examining adenoma recurrence, there are inherent methodological weaknesses. The present study assumed a colon free of polyps at baseline such that any adenoma at follow-up was assumed to be new. It is likely that some adenomas, likely small, could be

missed at the initial colonoscopy and it is those that are found at follow-up. However, index colonoscopy was performed as part of the SBoSP. This is noted as high-quality endoscopy, with all endoscopists being registered with, and meeting the criteria set out by the Joint Advisory Group (JAG) on gastrointestinal endoscopy.

Final conclusions and further work required

The present study concludes that in a bowel screening population higher adenoma number at baseline is associated with adenoma recurrence. The presence of advanced adenomas at baseline is strongly associated with advanced adenomas at follow-up; therefore, those with advanced and multiple adenomas require robust surveillance. The present study supports the current BSG post-polypectomy surveillance guidelines thus cannot recommend incorporation of host factors at present. However, including patients with any features of advanced adenomas at baseline in the high-risk group should be considered in future updates.

The relationship between BMI and adenoma recurrence may warrant further investigation, given the contrasting results in the present study with other reports. It is feasible that BMI may be a less useful measure in this cohort which represents a predominantly overweight population. As such, measures of body composition in place of BMI may provide a more sensitive analysis. This should be explored further. Since both obesity and body composition are modifiable characteristics, further work on the precise relationship between body composition and adenoma incidence and recurrence is warranted.

Table 3.1 Reason for exclusion or attrition in the present study

Reason for exclusion	Explanation	n
All patients		**605**
Follow-up colonoscopy report could not be sourced	-Did not attend follow-up colonoscopy (DNA) -Extensive comorbid disease, further colonoscopy clinically inappropriate -Unclear reason for absence of follow-up	416
Death	-Patient death prior to follow-up colonoscopy	63
Cancer	-Cancer diagnosed at follow-up (including polyp cancer) in the absence of synchronous polyps/adenomas -Cancer diagnosed from baseline colonoscopy findings at a later date (delayed result)	9
Missing or unsatisfactory data	-Missing colonoscopy report -Missing pathology report -Unclear report -Colonoscopy completion failure -No colonoscopy follow-up (barium enema, CT pneumocolon, flexible sigmoidoscopy)	77
Unable to confirm a clear colon	-Colonoscopy and pathological reports did not indicate if all visible polyps were excised.	13
Insufficient follow-up time	-Follow-up colonoscopy <1 year from baseline	5
Cancer at baseline	-Cancer diagnosed at baseline, resulting in non-standard follow-up and / or resection	2
Colonic resection during follow-up	-Patients who underwent any form of colonic resection, for either benign or malignant disease during follow-up, were excluded on the basis that they would have an incomplete colon	15
Incomplete colon at baseline	-Those with an incomplete colon due to previous resection, would likely have less change of developing adenomas due to the smaller length of colon and were therefore excluded	4
Active inflammation	-Severe inflammation limiting the identification of polyps	1

Table 3.2: The influence of adenoma-specific and host characteristics on any adenoma recurrence at follow-up

Baseline characteristics	All patients with follow-up colonoscopy (%)	No adenoma at follow-up (%)	Adenoma at follow-up (%)	OR (univariable) [95% CI]	p-value	OR (multivariable)[1] [95% CI]	p-value
All patients	707 (100)	353 (50)	354 (50)				
Age (years)							
<55	90 (13)	53 (15)	37 (11)	1.0	-	-	-
55–64	252 (36)	124 (35)	128 (36)	1.48 [0.91–2.41]	-	-	-
65–74	322 (45)	151 (43)	171 (48)	1.62 [1.01–2.61]	-	-	-
75+	43 (6)	25 (7)	18 (5)	1.03 [0.49–2.16]	0.31	-	-
Sex							
Female	192 (27)	109 (31)	82 (23)	-	-	-	
Male	515 (73)	244 (69)	272 (77)	1.46 [1.05–2.04]	**0.03**	1.21 [0.85–1.71]	0.29
BMI[2] (kg/m^2)							
20–24.9 (normal weight)	82 (19)	40 (20)	42 (18)	1.0	-	-	-
<20 (underweight)	12 (3)	3 (2)	9 (4)	2.86 [0.72–11.32]	-	-	-
25–29.9 (overweight)	161 (37)	77 (38)	84 (36)	1.04 [0.61–1.77]	-	-	-
30+ (obese)	175 (41)	80 (40)	95 (42)	1.13 [0.67–0.91]	0.82	-	-
Social deprivation quintile							
5 (least deprived)	142 (20)	78 (22)	64 (18)	1.0	-	-	-
4	85 (12)	44 (12)	41 (11)	0.93 [0.61–1.46]	-	-	-
3	106 (15)	53 (15)	53 (15)	1.00 [0.68–1.46]	-	-	-
2	139 (20)	73 (21)	66 (19)	0.90 [0.65–1.26]	-	-	-
1 (most deprived)	235 (33)	105 (30)	130 (37)	1.24 [0.96–1.60]	0.34	-	-
Smoking status							
Never	253 (37)	128 (37)	125 (36)	-	-	-	-
Ex / current	446 (63)	221 (63)	225 (64)	1.04 [0.77–1.42]	0.79	-	-

Aspirin							
No	614 (87)	312 (88)	302 (85)	-	-	-	-
Yes	93 (13)	41 (12)	52 (15)	1.31 [0.85–2.03]	0.23	-	-
Statin							
No	582 (82)	297 (84)	285 (81)	-	-	-	-
Yes	125 (18)	56 (16)	69 (19)	1.28 [0.87–1.89]	0.21	-	-
ACE-inhibitor							
No	635 (90)	322 (91)	313 (88)	-	-	-	-
Yes	72 (10)	31 (9)	41 (12)	1.36 [0.83–2.23]	0.22	-	-
Adenoma number							
1-2	424 (60)	258 (73)	166 (47)	-	-	-	-
3-4	181 (26)	70 (20)	111 (32)	2.47 [1.72–3.52]	-	2.23 [1.53–3.25]	-
≥5	99 (14)	25 (7)	74 (21)	4.60 [2.81–7.54]	<**0.001**	4.19 [2.53–6.97]	<**0.001**
Advanced adenomas[3]							
Absent	86 (12)	31 (9)	55 (15)	-	-	1.0	
Present	621 (88)	322 (91)	299 (85)	0.52 [0.33–0.84]	**0.006**	1.82 [0.63–5.31]	0.27
Villous features							
Absent	339 (48)	162 (46)	177 (50)	-	-	-	-
Present	368 (52)	191 (54)	177 (50)	0.85 [0.64–1.14]	0.27	-	-
Adenoma size ≥1cm							
No	104 (15)	35 (10)	69 (20)	-	-	-	
Yes	603 (85)	318 (90)	285 (80)	0.45 [0.29–0.70]	<**0.001**	0.42 [0.15–1.15]	0.09
HGD							
Absent	605 (86)	301 (85)	304 (86)	1.0	-	-	-
Present	102 (14)	52 (15)	50 (14)	0.95 [0.63–1.45]	0.82	-	-

[1]*After adjustment for sex, adenoma number, advanced adenomas and the presence of large adenomas ≥1cm*
[2]*430 patients with BMI data available*
[3]*The presence of at least 1 adenoma with advanced features (≥1cm, villous features, HGD) at baseline colonoscopy*

Table 3.3: The relationship between baseline adenoma number, sex, adenoma size and advanced adenomas

Baseline characteristics	All patients with follow-up colonoscopy (%)	1–2 adenomas at baseline (%)	3–4 adenomas at baseline (%)	5+ adenomas at baseline (%)	p-value (linear by linear)
All patients	707[1]	424 (60)	181 (26)	99 (14)	
Sex					
Female	192 (27)	139 (33)	43 (24)	10 (10)	-
Male	512 (73)	285 (67)	138 (76)	89 (90)	**<0.001**
Adenoma size ≥1cm					
No	103 (15)	22 (5)	57 (31)	24 (24)	-
Yes	601 (85)	402 (95)	124 (69)	75 (76)	**<0.001**
Advanced adenomas					
Absent	86 (12)	17 (4)	48 (27)	21 (21)	-
Present	618 (88)	407 (96)	133 (73)	78 (79)	**<0.001**

[1]704 included in this analysis. 3 patients excluded as overall baseline adenoma number not clear from endoscopy report

Table 3.4: The influence of adenoma-specific and host characteristics on advanced adenoma recurrence in those with any adenomas at follow-up

Baseline characteristics	All patients with adenoma recurrence (%)	Non-advanced adenomas at follow-up (%)	Advanced adenomas at follow-up (%)	OR (univariate) [95% CI]	p-value
All patients	354 (100)	224 (63)	130 (37)		
Age (years)					
<55	37 (11)	27 (12)	10 (8)	1.0	-
55–64	128 (36)	83 (37)	45 (35)	1.46 [0.65–3.29]	-
65–74	171 (48)	103 (46)	68 (52)	1.78 [0.81–3.92]	-
75+	18 (5)	11 (5)	7 (5)	1.72 [0.52–5.67]	0.16
Sex					
Female	82 (23)	50 (22)	33 (25)	-	-
Male	272 (7)	174 (78)	97 (75)	0.88 [0.51–1.39]	0.51
BMI[1] (kg/m^2)					
20–24.9 (normal weight)	42 (18)	27 (19)	15 (17)	1.0	-
< 20 (underweight)	9 (4)	7 (5)	2 (2)	0.51 [0.09–2.79]	-
25–29.9 (overweight)	84 (37)	54 (39)	30 (33)	1.00 [0.46–2.17]	-
30+ (obese)	95 (41)	52 (37)	43 (48)	1.49 [0.70–3.15]	0.21
Smoking status					
Never	125 (36)	85 (38)	40 (32)	-	-
Ex/current	225 (64)	138 (62)	87 (68)	1.34 [0.84–2.13]	0.21
Social deprivation quintile					
5 (least deprived)	64 (18)	43 (19)	21 (16)	1.0	-
4	41 (11)	24 (10)	17 (13)	1.45 [0.64–3.26]	-
3	53 (15)	35 (16)	18 (14)	1.05 [0.49–2.28]	-
2	66 (19)	37 (17)	29 (22)	1.60 [0.79–3.27]	-
1 (most deprived)	130 (37)	85 (38)	45 (35)	1.08 [0.57–2.06]	0.87

Aspirin					
No	302(85)	192 (86)	110 (85)	-	-
Yes	52 (15)	32 (14)	20 (15)	1.09 [0.59–1.99]	0.78
Statin					
No	285 (80)	182 (81)	103 (79)	-	-
Yes	69 (20)	42 (19)	27 (21)	1.14 [0.66–1.95]	0.64
ACE-inhibitor					
No	313 (88)	197 (88)	116 (89)	-	-
Yes	41 (12)	27 (12)	14 (11)	0.88 [0.44–1.75]	0.72
Adenoma number					
1–2	166 (47)	101 (45)	65 (51)	1.0	-
3–4	111 (32)	73 (33)	38 (30)	0.81 [0.49–1.33]	-
≥5	74 (21)	49 (22)	25 (19)	0.79 [0.45–1.41]	0.36
Advanced adenomas					
Absent	55 (16)	43 (19)	12 (9)	-	-
Present	298 (84)	181 (81)	117 (91)	2.34 [1.18–4.61]	**0.02**
Villous features					
Absent	177 (50)	118 (53)	59 (45)	-	-
Present	177 (50)	106 (47)	71 (55)	1.36 [0.87–2.07]	0.19
Adenoma size ≥1cm					
No	69 (20)	49 (22)	20 (16)		-
Yes	285 (80)	175 (78)	110 (84)	1.54 [0.87–2.73]	0.14
HGD					
Absent	304 (86)	197 (88)	107 (82)		-
Present	50 (14)	27 (12)	23 (18)	1.57 [0.86–2.87]	0.14

[1]230 patients with BMI data available
[2]250 patients with smoking status available
[3]351 patients with adenoma number at baseline data available

Table 3.5: Studies reporting on the relationship between baseline adenoma characteristics and adenoma recurrence

Author	Year	Design	Variable	Any adenoma recurrence[1]	Advanced adenoma recurrence[2]
Kulling *et al.*(276)	2002	Retrospective cohort	↑Adenoma number	↑	↔
			Size ≥1cm	↔	↔
			HGD	↔	↔
			Villous features	↔	↔
Avidan *et al.*(278)	2002	Retrospective Cohort	↑Adenoma number	↑	n/a
			Size ≥1cm	↑	n/a
			Villous features	↔	n/a
Bertario *et al.*(234)	2003	Prospective cohort	↑Adenoma number	↑	↔
			Size ≥1cm	Inconclusive[4]	↔
			HGD	↔	↔
			Villous features	↑	↔
Bonithon-Kopp *et al.*(272)	2004	From a non-effect intervention trial	↑Adenoma number	↑	↑
			Size ≥1cm	↔	↔
			HGD	↔	↔
			Villous features	↔	↔
Lieberman *et al.*(301)	2007	Prospective cohort	↑Adenoma number	n/a	↑
			Size ≥1cm	n/a	↑
			HGD	n/a	↑
			Villous features	n/a	↑
Nusko *et al.*(270)	2009	Prospective cohort	↑Adenoma number	↑	↑
			Size ≥1cm	↑	↑
			HGD	↔	n/a
			Villous features	↔	↑
Martinez *et al.*(248)	2009	Pooled data from prospective trial	↑Adenoma number	↑	↑
			Size ≥1cm	↔	↑
			HGD	↔	↑[3]
			Villous features	↔	↑
Chung *et al.*(277)	2011	Prospective cohort	↑Adenoma umber	↑	↑
			Size ≥1cm	↔	↑
			Villous features	↔	↔
Viel *et al.*(275)	2012	Prospective cohort	↑Adenoma umber	↑	n/a
Van Heijningen *et al.*(267)	2013	Retrospective cohort	↑Adenoma umber	↑	↑
			Size ≥1cm	↔	↑
			HGD	↔	↑[3]
			Villous features	↔	↑
Taniguchi *et al.*(246)	2014	Retrospective cohort	↑Adenoma number	↑	n/a
			Size ≥1cm	↑	n/a
			HGD	↑	n/a
			Villous features	↑[c]	n/a
Van Enckevort *et al.*(271)	2014	Retrospective cohort	↑Adenoma number	↑	n/a
			Size ≥1cm	↔	n/a
			HGD	↑	n/a
			Villous features	↔	n/a

Xu *et al.* (247)	2015	Retrospective review	↑Adenoma number	↑	↔
			Size ≥1cm	↔	↔
			HGD	n/a	n/a
			Villous features	n/a	n/a

↑ *Increased risk of recurrence*
↔ *No significant difference found*
n/a Study did no analyse data for these endpoints
[1]*Any adenoma recurrence of any type or non-advanced adenoma recurrence*
[2]*Advanced adenoma recurrence; the presence of any features of (≥1cm size, villous features, HGD)*
[3]*significance lost on multivariable analysis*
[4]*Study reports hazard ratios for adenomas ≥1cm, 1–2cm and >2cm rather than a simple <1cm ≥ category*

4 THE RELATIONSHIP BETWEEN COLORECTAL NEOPLASIA, SYSTEMIC INFLAMMATION AND HOST CHARACTERISTICS IN A BOWEL SCREENING POPULATION

4.1 Introduction

In many cancers, there exists a pre-malignant stage. Screening reduces the incidence of CRC largely due to endoscopic polypectomy (223). Nonetheless, there remains a high adenoma recurrence rate post-polypectomy of 30–60% (224, 225, 302). It follows that a reduction in the incidence of both primary and recurrent adenomas could lead to a reduction in CRC incidence. In terms of healthcare economics this would minimise screening and treatment costs. Identifying modifiable risk factors for adenoma development would also be a logical next step.

Hanahan and Weinberg (2000) proposed six hallmarks of cancer in their paper discussing the multistep process of tumorogenesis (47). Inflammation has since been described as the 7th hallmark of cancer (48). Large studies have shown that blood biomarkers of the systemic inflammatory response (SIR), such as elevated CRP, are associated with the presence of cancer (303, 304). They have also been associated specifically with CRC risk in long-term follow-up and epidemiological studies (305) (306). However, this association is not unanimous (307). In addition, the SIR has demonstrated a predictive value on disease progression and poorer outcomes in both operable and non-operable disease across a range of cancer types (142) (308). In CRC, the SIR is noted as a predictor of poorer outcomes independent of tumour stage (142). Furthermore, a link between systemic inflammation and cancer is biologically plausible. As part of the SIR, pro-inflammatory cytokines and growth factors are released and may contribute to tumour maintenance and proliferation (309).

To date, despite the links between systemic inflammation and established cancer, the role of the SIR at the pre-cancerous and early neoplastic stage of CRC is less well studied. It is

feasible that the SIR may play a stimulatory role in the formation of colorectal adenomas from otherwise normal colorectal mucosa. Although largely experimental, studies investigating the mechanisms of colitis-associated cancer development have shown that IL-6 is a critical tumour promoter (310). Furthermore, one study used a colitis-inducing mouse model to demonstrate that up-regulation of TNF-α was associated with the development of multiple colonic tumours (311). Moreover, when these mice were treated with a TNF-α blocker, the number and size of tumours in the colon were reduced (311). It is likely that the same inflammatory mechanism could be acting on otherwise normal colonic mucosa inducing a dysplastic change. In addition, case-control studies have shown that patients with adenomas are more likely to have high circulating endotoxin concentrations (312). It is postulated that this is due to dysbiosis between colonic flora, resulting in a higher concentration of Gram-negative bacteria. The result is an increased release of pro-inflammatory cytokines and subsequent bloodstream absorption of endotoxin, which may demonstrate a link between inflammatory cytokines and adenoma formation mediated by gut bacteria (312).

Clinically, CRP can be used as a surrogate marker of the pro-inflammatory cytokines, IL-6 and TNF-α. CRP is released into the circulation by hepatocytes in response to elevations in the above two cytokines. This suggests CRP, which is routinely measured by laboratories, could be used in epidemiologic studies, as a clinically relevant biomarker of inflammation (313). Clinically, establishing a link between systemic inflammation, as measured by CRP, and the pre-malignant stage of CRC, could help in developing early intervention pathways.

Given the aforementioned relationship between the inflammatory process and cancer development, it would be clinically advantageous to determine which, if any, host characteristics are associated with systemic inflammation to allow clinical interventions within an “at-risk” population. Previous studies have suggested links between obesity, as

part of the metabolic syndrome (314) and ageing, often termed “inflammageing” with low-grade systemic inflammation (315).

The present prospective study aimed to examine the relationship between the incidence of colorectal neoplasia, host characteristics and systemic inflammation within a UK bowel screening population.

4.2 Methods

Study design

The present study was a multi-centre prospective cohort study carried out within NHS GGC, Scotland, UK. Research ethics approval was obtained as outlined in the thesis declaration (page 14). Patients were recruited from those attending for a colonoscopy at any of five major Glasgow hospitals as part of the SBoSP from February 2016 to July 2017. All patients who had tested positive as part of the previously described bowel screening programme (140) **(Section 1.2.2)**, were eligible for inclusion. The recruitment and data gathering process are summarised in **Figure 4.1.**

Colonoscopy lists were sourced two weeks in advance. This enabled study invitation packs to be posted to patients prior to their colonoscopy. There were no pre-selection exclusion criteria. On attendance for the colonoscopy, each consenting patient underwent height and weight measurement from which BMI (kg/m^2) was calculated. For patients whose height and weight were not measured on the day, data were obtained from recent primary care medical records. Blood sampling was undertaken on the day of colonoscopy and used to obtain a full blood count (FBC), along with urea and electrolyte (U+E), liver function test (LFT), CRP and bone profile (calcium, phosphate and alkaline phosphatase) measurements. Demographic data including age, sex, medication use, smoking status and socioeconomic deprivation were obtained from medical records. Deprivation was assessed using the SIMD ranking system **(Chapter 3)**. Scores for SIMD were then ordered, and patients grouped into quintiles. The screening colonoscopy reports were reviewed, and pathology results from excised polyps were recorded. Non-neoplastic polyps were excluded. Non-advanced neoplasia was defined as; the presence of an adenoma without advanced features and the absence of cancer. Advanced neoplasia was the presence of an advanced adenoma (≥1cm size, villous histology, HGD) or adenocarcinoma. Active colonic inflammation was noted either macroscopically during colonoscopy or microscopically based on pathology results.

Post-participation exclusion criteria were: any previous colonic resection, or an incomplete colonoscopy, when these findings became apparent during the data collection process.

Criteria for markers of the SIR

CRP thresholds of ≥5mg/l and ≥10mg/l have been validated as markers of the SIR in patients with established cancer (308). Several previous studies have grouped CRP into quartiles and used the 1st quartile as a reference group when examining the risk of colorectal neoplasia. The present study set the threshold for systemic inflammation as CRP ≥3 mg/l. It is accepted that this threshold for the SIR allows stratification of patients into a high risk group future cardiac events (316). Furthermore using this threshold provides a clinically relevant cut-off point.

Study endpoints

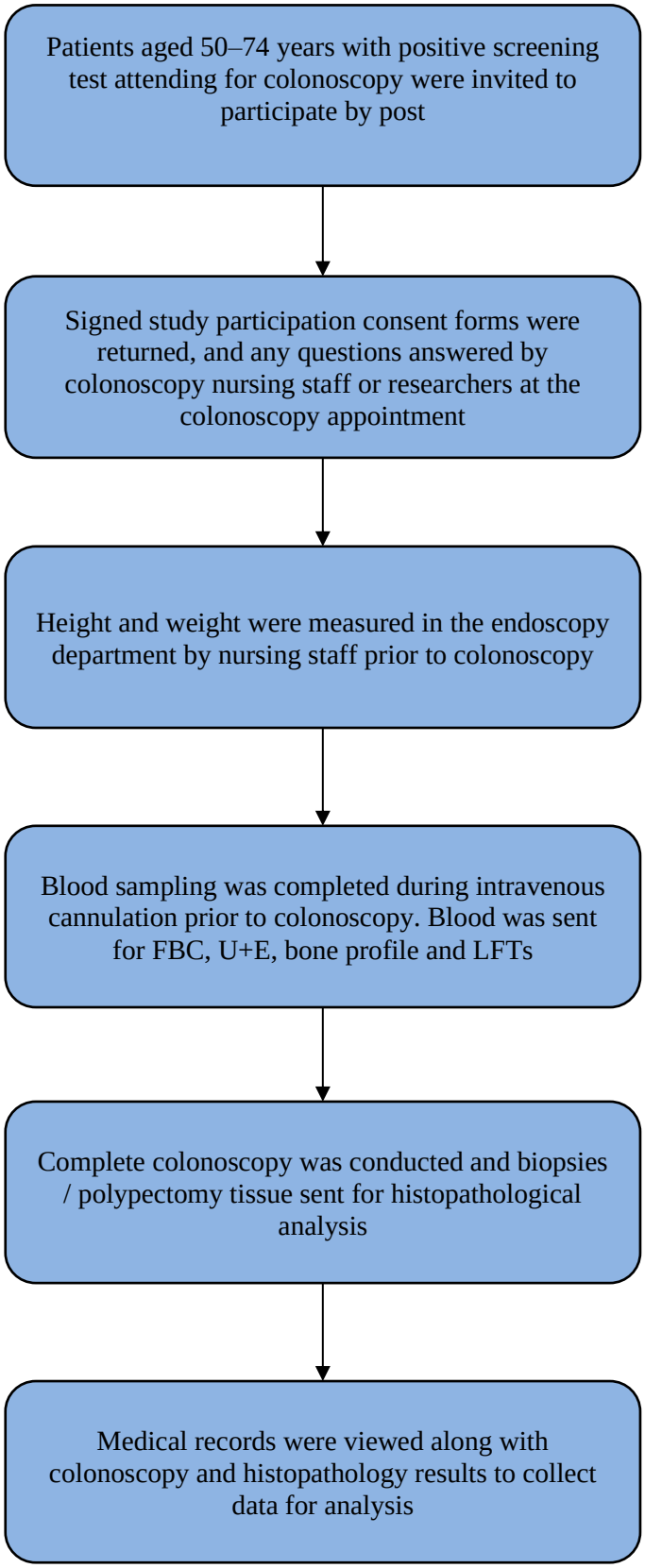
The study had a number of endpoints. Firstly, the association between host factors and the SIR as measured by elevated CRP (≥3mg/l) was examined. The study further sought to determine the association between host factors, including the SIR and the incidence of abnormal findings at colonoscopy. Abnormal findings at colonoscopy were defined as any colorectal pathology, both neoplastic or non-neoplastic (haemorrhoids, diverticulosis, anal fissure, proctitis, angiodysplasia, colitis). Considering only patients with an abnormal colonoscopy, the relationship between host factors and advancing severity of pathology (non-neoplastic colorectal pathology, [NNCP], adenoma only, or adenocarcinoma) was examined. The relationship between host factors and the presence of any neoplasia or advanced neoplasia was examined.

Statistical analyses

Statistical analyses were carried out using IBM® SPSS® Statistics version 22 (SPSS Inc., Chicago, IL, USA). Associations between categorical variables with two groups were examined using a χ^2 test. For categorical variables with more than two groups, a binary

logistic regression was carried out comparing each variable to the reference group. Any known or likely associated variables or those with a $p<0.1$ were included in the multivariable analysis. Ors were calculated for risk, and a value of $p<0.05$ was considered statistically significant.

Figure 4.1: Recruitment and data gathering process for consenting patients



4.3 Results

1,867 invitation packs were sent to patients between February 2016 and June 2017. 456 (24%) patients consented and were eligible for inclusion with 12 patients subsequently excluded due to previous colorectal resections (n=5), or incomplete investigations (n=7). This left 444 patients for the final analysis **[Figure 4.2]**. Baseline characteristics are shown in **Table 4.1**. 209 (47%) participants were male. The median age was 63 years (IQ range 56–67). The cohort were predominantly overweight: 303 (75%) had a BMI of ≥25. There was a high level of socioeconomic deprivation among the included participants: 206 (47%) were classed in the two most deprived quintiles (1st and 2nd) using the SIMD scoring system.

The relationship between host factors and any abnormal findings at colonoscopy

Figure 4.3 shows the outcomes of colonoscopy. Of the 444 participants, 308 (69%) had an abnormal finding at colonoscopy. Of these patients, 107 (35%) had NNCP, 182 (59%) had an adenoma. 19 (6%) had an adenocarcinoma. Among those with an adenoma, 87 (48%) had a non-advanced adenoma, and 95 (52%) had at least one advanced adenoma. When examining this entire bowel screening cohort, the incidence of adenoma and adenocarcinomas were 41 % and 4%, respectively. In considering the group as a whole, 201 (45%) patients had neoplastic findings at colonoscopy.

Figure 4.2: Flow chart of recruitment and exclusion process

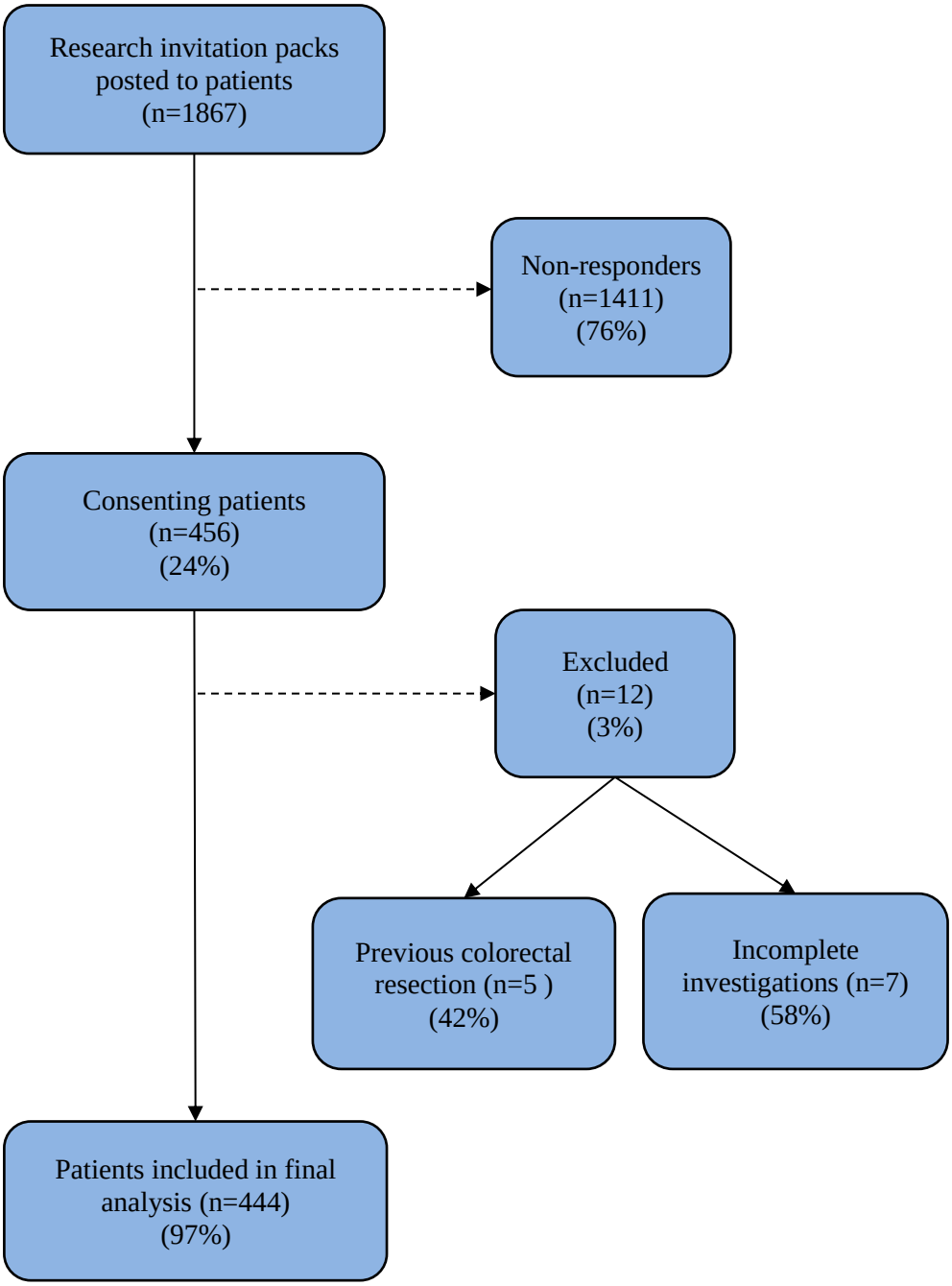


Table 4.2 shows the relationship between host factors and abnormal findings at colonoscopy. Advancing age was associated with abnormal colonoscopy ($p<0.001$). Patients aged 65–74 years had an OR of 3.81 [95% CI; 2.19–6.61] when compared to those <55 years. This observation remained consistent on multivariable analysis when adjusting for sex and smoking, OR 3.65 [95% CI; 2.05–6.48] ($p<0.001$). When compared to females, males were less likely to have abnormal colonoscopy findings overall, OR 0.63 [95% CI; 0.42–0.94, $p<0.05$]. This observation remained significant on the multivariable analysis when adjusting for age and smoking status, OR 0.63 [95% CI; 0.41–0.97, $p<0.05$]. Patients with a history of smoking were significantly more likely to have abnormalities detected at colonoscopy on univariable analysis, OR 1.86 [95% CI; 1.22–2.83, $p<0.01$]. This observation remained significant on multivariable analysis when adjusting for age and sex, OR 1.59 [95% CI; 1.03–2.47, $p<0.05$]. Social deprivation, BMI, CRP and medication use were not associated with abnormal colonoscopy findings in this cohort.

The relationship between host factors and severity of abnormality at colonoscopy

Of the 308 patients with an abnormality at colonoscopy, 107 (35%) had the least severe abnormal finding (NNCP), 182 (59%) had moderate pathology (adenoma), and 19 (6%) had the most severe abnormality (CRC) **[Figure 4.3]**. The relationship between host factors and the increasing severity of abnormalities found at colonoscopy is displayed in **[Table 4.3]**. There was no significant association between host factors, including the SIR and the severity of abnormalities detected at colonoscopy.

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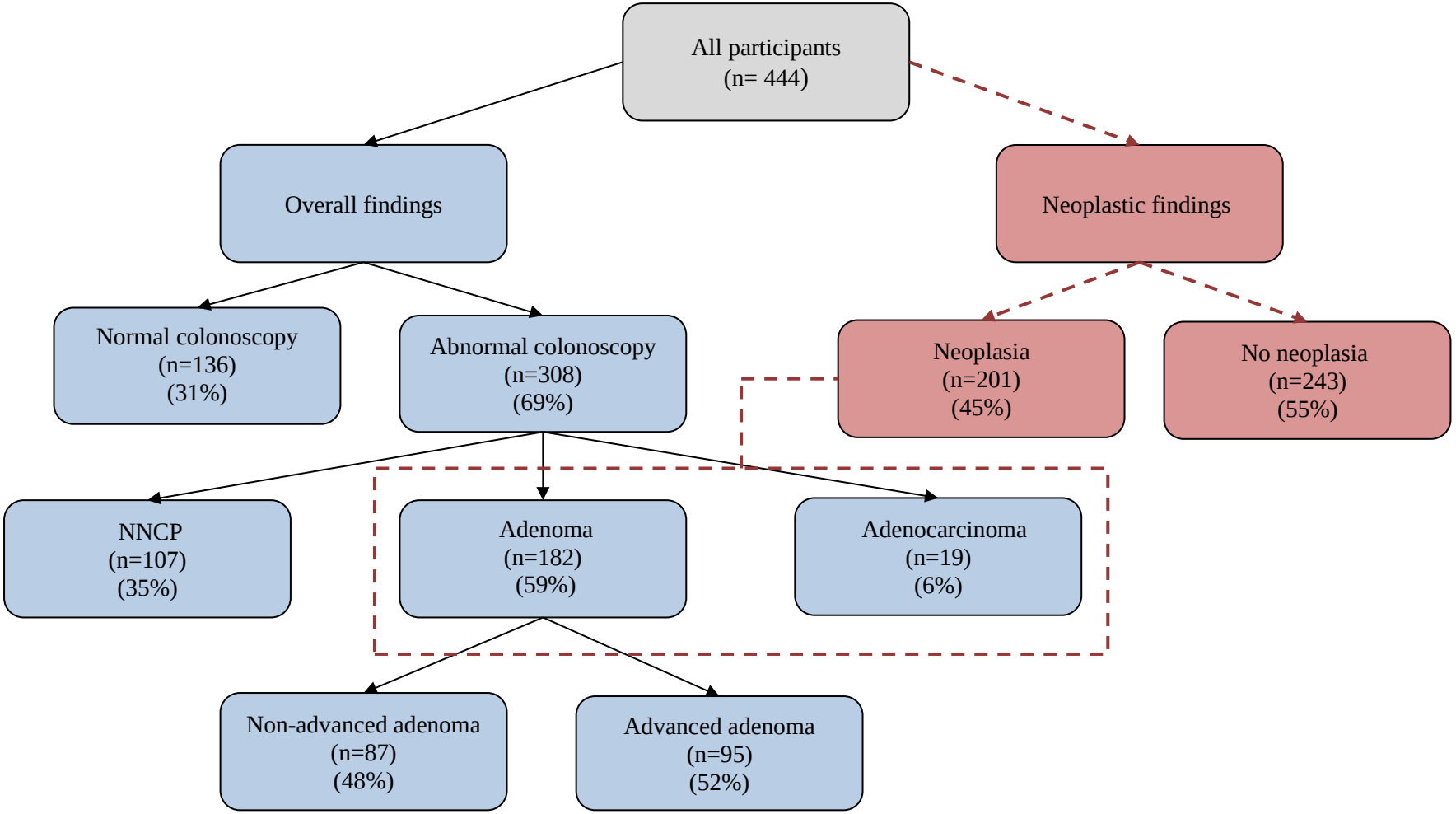
Figure 4.3: Prospectively recorded outcomes from screening colonoscopy



The relationship between host factors and the incidence of any colorectal neoplasia

Table 4.4 shows the relationship between host factors and the incidence of neoplasia. Only advancing age was associated with the presence of neoplasia, OR 2.49 [95% CI; 1.48–4.22] for those aged 65–74 years when compared to those aged <55 years, ($p<0.01$). This observation remained significant on multivariable analysis when adjusting for age, sex, smoking status and aspirin use, OR 2.84 [95% CI; 1.62–4.99] ($p<0.01$). There was no association between any other host characteristics, including the SIR, as measured by CRP ≥3mg/l, and neoplasia in the present study.

Table 4.5 shows the relationship between host characteristics and the incidence of advanced and non-advanced neoplasia in those with any neoplastic findings. Statin users were less likely to have advanced adenomas at colonoscopy OR, 0.49 [95% CI; 0.28–0.87, $p<0.05$]. There was no significant relationship between host characteristics, including the SIR as measured by CRP ≥3mg/l, and the incidence of advanced neoplasia. In the absence of any significant findings upon univariable analysis, a multivariable analysis was not carried out.

The relationship between host factors and markers of the SIR

Table 4.6 shows the relationship between host factors and the SIR, as measured by CRP ≥ 3 mg/l. Social deprivation was associated with the SIR on univariable analysis, OR 2.69 [95% CI; 1.28–5.65, $p<0.01$] and OR 2.36 [95% CI; 1.27–4.39, $p<0.01$] for those in the two most deprived quintiles (1^{st} and 2^{nd}) compared with the least deprived quintile (5^{th}) respectively. This observation did not retain statistical significance on the multivariable model when correcting for BMI, smoking and aspirin use. Obesity (BMI ≥30), was associated with the SIR, OR 2.54 [95% CI; 1.33–4.87, $p<0.01$] and this relationship remained on multivariable analysis when adjusting for socioeconomic deprivation, smoking and aspirin use, OR 2.72 [95% CI; 1.35–5.49, $p<0.01$]. The SIR was associated with smoking history, OR 2.37 [95% CI; 1.49–3.76, $p<0.0001$] and aspirin use, OR 3.43 [95% CI; 1.63–7.22, $p<0.01$] and both of these variables remained statistically significant on multivariable

analysis, OR 2.26 [95% CI; 1.33–3.84, $p<0.01$] and OR 2.59 [95% CI; 1.15–5.86, $p<0.05$] respectively.

4.4 Discussion

The present prospective study reports on the relationship between the incidence of colorectal neoplasia, the SIR, as measured by elevated CRP, and host characteristics in a UK bowel screening population.

In the present study, age, female sex and smoking increased the likelihood of abnormal colonoscopy findings. None of the host characteristics were associated with more advanced pathology at colonoscopy. Advancing age was associated with an increased risk of incident neoplasia at colonoscopy, while those using aspirin were less likely to have incident neoplasia. No host factors were associated with an increased risk of advanced neoplasia. The SIR, as measured by elevated CRP, was not associated with the presence of colorectal neoplasia but was strongly associated with obesity, smoking, aspirin use and moderately associated with socioeconomic deprivation.

Increasingly, a "host targeted" approach to bowel screening is desirable to reduce costs and the burden on healthcare services. Identification of a higher risk group, which is then targeted for colonoscopy, may be beneficial towards delivering this. As such, the present study aimed to determine whether clinically relevant and modifiable risk factors for colorectal neoplasia could be identified in a bowel screening population. It also aimed to investigate the relationship between the SIR, host characteristics and colorectal neoplasia incidence. This was on the basis that systemic inflammation might be a linking mechanism between host factors such as age, male sex, and elevated BMI previously associated with colorectal neoplasia incidence and recurrence (317, 318) (319) (193). This may allow targeting of the SIR for intervention, which could be particularly useful with respect to the above host characteristics that are either, non-modifiable (e.g. age and sex), or difficult to modify in the short term (e.g. socioeconomic deprivation and obesity)

Host characteristics and systemic inflammation

In the present study, elevated CRP was strongly associated with obesity as measured by BMI ≥30. This supports the theory that obesity induces a pro-inflammatory state within the body. Obesity, as a reflection of high body adiposity, has previously been linked to inflammation (251, 320, 321). This association is plausible given that adipose tissue is recognised as an endocrine organ rather than simply a fat storage site. Furthermore, obesity has been specifically associated with increased circulating levels of CRP and the pro-inflammatory cytokines: TNF-α and IL-6 (251). A recent systematic review and meta-analysis reported on the relationship between BMI, body fat percentage, exercise and systemic inflammation, as measured by CRP (322). The researchers noted that exercise is associated with a reduction in CRP and that this effect is largely driven by a decrease in BMI and body fat percentage. These findings support the results of the present study.

In the present study, aspirin use was associated with the SIR, as measured by elevated CRP. This would seem counterintuitive given the anti-inflammatory properties of aspirin. In this study, it is likely that patients using aspirin for clinical reasons (mainly cardiovascular risk modification) are subject to an increased burden of comorbid disease compared to the general population. This could induce a low-level SIR in aspirin users, such that the elevated CRP in these patients is reflective of their comorbid state rather than their aspirin use. Similar conclusions were drawn in a study in 2008 (251), which investigated the relationship between pro-inflammatory cytokines and colorectal adenoma incidence and reported higher levels of pro-inflammatory cytokines in who regularly used NSAIDs. Overall, the relationship between inflammatory markers and aspirin use has been inconsistent, with some studies finding aspirin was associated with a reduction in CRP (323) and other studies finding no change in CRP concentration with aspirin use (324).

Smoking was also associated with an elevated SIR in the present study. Smoking is linked to a number of medical conditions; thus, it is plausible that the elevated SIR is likely to

reflect this link. In addition, smoking itself may well induce a low-level inflammatory response.

The present study did not detect a strong link between advancing age and systemic inflammation. Previous researchers have suggested that ageing results in a global reduction in the body's ability to deal with a variety of physical stressors. This results in a pro-inflammatory state (325). It is likely that a low-level inflammatory response associated with ageing remains largely subclinical and difficult to detect with more routine blood sampling such as CRP.

Host characteristics and abnormal colonoscopy findings

With respect to host characteristics and the likelihood of an abnormal finding at colonoscopy, older patients and those who smoked were more likely to have abnormalities at colonoscopy, either neoplastic or NNCP. Advancing age and smoking are both associated with worsening general health, so this result is unsurprising. However, female sex was significantly associated with an abnormal colonoscopy. When isolating only those with NNCP and then considering neoplastic pathology, 54% and 58%, respectively, were female. This suggests that the increased rate of abnormal findings at colonoscopy in females is driven by both neoplastic and non-neoplastic pathology. The mechanism for this effect is not clear, especially given that CRC incidence in the UK is higher in males (1). However, the difference between sexes is marginal, and the use of large studies may allow clarification or attenuation of this observation. Besides this, the present study sought to determine whether specific host characteristics were associated with more advanced pathology at colonoscopy, such as adenocarcinoma vs. adenoma vs. non-neoplastic pathology **[Table 4.3].** The present study found no association in this regard but was not designed for the analysis of CRC incidence.

The relationship between host factors and incident colorectal neoplasia

This study found that increasing age was associated with an increased incidence of colorectal neoplasia at the screening. This observation was maintained when adjusting for sex, smoking and aspirin use. This is perhaps unsurprising, given that age is an accepted risk factor for colorectal adenomas (326). Neither sex nor smoking were associated with neoplasia incidence in the present study. This is in contrast to a population-based study in the USA using data from phase I and II of the national colonoscopy study. The study suggested that male sex and smoking were risk factors for adenoma incidence ($p<0.001$) (326). Most notably, the researchers used data obtained from a younger cohort with a large number of patients under 55 years collected from the general population. This is in contrast to the present study that reports on an older, bowel-screened population. Furthermore, the present study population had previously tested positive at bowel screening and therefore, were more likely to harbour pathology at the outset. These differences in study populations may explain the contrasting results.

The present study found no appreciable association between BMI, in particular, obesity, and colorectal neoplasia incidence. This is in contrast to a meta-analysis carried out in 2012. It concluded that higher BMI (per 5-unit increase) was associated with higher colorectal adenoma incidence (192). However, there was significant heterogeneity between the included studies in this meta-analysis as reflected by the forest plot and I^2 statistic of 76.8%. The overall effect was small, with a pooled RR of 1.19 [95% CI; 1.13–1.26]. Another recent meta-analysis reached similar conclusions to the above study (297). Similarly, the conclusions were based on a pooled OR, and many of the included studies reported non-significant results. Neither of these studies reported a linear relationship between BMI and colorectal adenoma incidence. Inherently when assessing increasing BMI and neoplasia incidence, there are a considerable number of confounding variables, particularly in

retrospective observational studies. In reality, it seems the relationship between BMI and early colorectal neoplasia (e.g. adenomas) remains inconclusive and small.

The present study noted that when adjusting for age, sex and smoking, aspirin use was associated with a 50% reduction in colorectal neoplasia incidence. This is perhaps unsurprising as aspirin has been associated with a reduction in CRC and colorectal adenoma incidence. This association was discussed at length in **Chapter 1 (Section 1.1.2.2** and **Section 1.4.4.4)** and **Chapter 2**.

Systemic inflammation and colorectal neoplasia

It was hypothesised that systemic inflammation might play a role in the formation and pre-malignant stage of CRC and thus may provide a target for intervention at an early stage of the disease. In the present study, the SIR, as measured by elevated CRP, was not associated with the presence of either non-advanced or advanced colorectal neoplasia. Additional analysis produced the same result when considering adenoma and adenocarcinoma individually. A recent meta-analysis of observational studies investigating the effect of systemic inflammation on colorectal adenoma incidence was published in 2017, and similar to the present study, the authors were unable to determine a definite relationship between circulating IL-6, TNF-α and CRP, and adenoma incidence (327). However, in contrast to the present study, the researchers found a weak association between elevated CRP and advanced adenoma incidence with a pooled OR of 1.59 [95% CI; 1.09-2.32].

The results of the present study are in contrast to a study carried out in 2008, investigating the relationship between colorectal adenoma incidence and the circulating inflammatory cytokines, TNF-α, IL-6 and CRP (251). The study concluded that only patients in the highest tertile groups of circulating TNF-α and IL-6 were associated with the presence of colorectal adenomas (OR 1.85 and 1.66, respectively). The researchers also concluded that those in the highest tertile group for CRP were more likely to have colorectal adenomas, OR 1.47 [95%

CI; 0.96–2.25], compared to the lowest tertile. However, the confidence interval crosses 1.0, and therefore, statistical significance is questionable. There were 873 participants in the above study; however, there were significantly more males ($p<0.04$), and patients as young as 30 years were included. In addition, eligible patients included those with abdominal pain and PR bleeding, as well as asymptomatic screened patients. These significant differences between the cohort used in the above study and the present study could explain our contrasting findings.

Systemic inflammation and established colorectal cancer

The present study was not powered to investigate the relationship between the SIR and incident CRC. Nonetheless, previous work investigating this is worth mentioning. Based on the results of the present study, it would seem reasonable to conclude that the association between circulating CRP, colorectal adenomas and early neoplasia remains unproven. In terms of established CRC, there appears to be a stronger association with systemic inflammation. A recent study by Park *et al*. published in 2016 examined data from 1,000 consecutive patients undergoing potentially curative CRC resection from the same geographical region as the present study. They found that 37% of patients had elevated CRP (>10mg/l). These results conflict with those from the present study, which showed that only 13% of individuals with pre-cancerous colorectal adenomas had CRP > 10mg/l. Thus, it would seem plausible that the progression from pre-malignant disease to malignant disease explains the higher inflammatory response in cancer patients.

A meta-analysis published in 2014 concluded that increasing pre-diagnosis CRP was weakly associated with CRC risk, OR 1.12 [95% CI; 1.05–1.21] (53). However, when looking at colon and rectal cancer separately, the association was lost for rectal cancer. In addition, the researchers found that when analysing the sexes separately, the relationship was only present in men, making it difficult to draw any firm conclusions. Furthermore, a recent study published in the British Journal of Cancer, investigating 4,764 patients diagnosed with CRC

did not find any association between baseline CRP many years prior and subsequent to the development of CRC. However, the researchers did find a weak association between CRC risk and circulating leukocytes and haptoglobins (307). A number of weaknesses were inherent in the above study; for example, the blood markers were collected between 1986 and 1999 (a time when high sensitivity CRP testing was not available) meaning measurements <10mg/l could not be detected. The one-off blood measurements were carried out many years prior to the eventual diagnosis of CRC, with a mean follow-up of 18 years. This is in contrast to the present study which evaluated the SIR at diagnosis. These differences in methodology are understandable given that the present study aimed to determine if CRP, as a marker of current, active, systemic inflammation, could be used as a potential marker of early neoplasia.

In summary, the relationship between CRP and early CRC development or diagnosis is as yet, inconclusive.

Strengths and limitations

To our knowledge, this is the first study within a UK bowel screening cohort to investigate the relationship between systemic inflammation, host factors and colorectal neoplasia at the time of diagnosis. Data were collected prospectively in order to minimise bias. Bowel screening patients have a high incidence of colorectal neoplasia (45% in the present study), and neoplastic findings are overwhelmingly pre-malignant adenomas. As such, this group are an optimal cohort with which to study the impact of potentially modifiable risk factors on early and pre-malignant disease. This makes the present study clinically relevant.

There are, however, a number of weaknesses in the present study. It was not possible to draw firm conclusions with respect to CRC given that there were only 19 cases from the 444 patients. Furthermore, cross-sectional measurement of host factors such as CRP or BMI at the time of colonoscopy is useful to determine whether these host factors can be used to form

a “high-risk” patient profile for colonoscopy. The disadvantage of this method is that it only reflects the status at the time of diagnosis, meaning that without knowledge of the long-term trend of a patient’s BMI, CRP, and other host factors over time, it is more difficult to draw firm conclusions as to whether certain host factors could have contributed to the diagnosis.

Final conclusions and further work required

The present study has found that elevated BMI, smoking and aspirin use is associated with a systemic inflammatory response. Advancing age is associated with an increased risk of colorectal neoplasia. Active aspirin use may reduce this risk. Systemic inflammation was neither associated with non-advanced nor advanced neoplasia. As such, the present study was unable to link the SIR associated with the host factors above, to colorectal neoplasia incidence. Thus, the present study is unable to determine the clinical usefulness of CRP or other host factors in predicting those at risk of colorectal neoplasia in bowel screened patients.

With specific reference to BMI, although it was not associated with colorectal neoplasia in the present study, it is a modifiable risk factor, and other studies have found a link between the two. Thus, future work in bowel screening patients could focus on different measures of adiposity and “body fatness” other than BMI, which has several limitations as a specific marker of adiposity. Recent focus has been on body fat distribution rather than overall weight or fat load. In addition, future studies might wish to follow-up cohorts of screening patients over time, perhaps with serial measurements of CRP and BMI to study the role of longer-term chronic systemic inflammation and obesity on CRC development. Screening patients who undergo polypectomy in the UK are routinely followed-up by means of subsequent colonoscopy and as such, are an ideal population to be used in investigating the long-term effect of systemic inflammation and host factors.

Table 4.1: Baseline characteristics of the study cohort

Baseline characteristics	Number (%)
All	444 (100)
Age (years)	
<55	92 (21)
55–64	156 (35)
65–74	187 (42)
75+	9 (2)
Sex	
Female	235 (53)
Male	209 (47)
Social deprivation quintile	
5 (least deprived)	95 (21)
4	72 (16)
3	71 (16)
2	74 (17)
1 (most deprived)	132 (30)
BMI[1] (kg/m^2) groups	
20–24.9 (normal weight)	92 (23)
<20 (underweight)	8 (2)
25–29.9 (overweight)	150 (37)
30+ (obese)	153 (38)
Smoking status[2]	
Never smoked	204 (48)
Ever smoked	219 (52)
CRP (mg/l)[3]	
<3	120 (33)
≥3	248 (67)
Aspirin	
No	369 (83)
Yes	74 (17)
Statin	
No	268 (60)
Yes	175 (40)
ACE-inhibitor	
No	354 (80)
Yes	89 (20)

[1]Data available for 403 patients
[2]Data available for 423 patients
[3]Data available for 368 patients

Table 4.2: The relationship between host factors and abnormal findings at colonoscopy

Baseline characteristics	All patients (%)	Normal colonoscopy (%)	Abnormal colonoscopy (%)	OR (univariable)	p-value	OR (multivariable)[1]	p-value
All patients	444 (100)	136 (31)	308 (69)				
Age (years)							
<55	92 (21)	43 (32)	49 (16)	1.0	-	1.0	-
55–64	156 (35)	56 (41)	100 (33)	1.57 [0.93–2.65]	-	1.59 [0.92–2.75]	-
65–74	187 (42)	35 (26)	152 (49)	3.81 [2.19–6.61]	-	3.65 [2.05–6.48]	-
75+	9 (2)	2 (1)	7 (2)	3.07 [0.61–15.58]	**<0.001**	6.15 [0.70–52.2]	**<0.001**
Sex							
Female	235 (53)	61 (45)	174 (56)	-	-	1.0	-
Male	209 (47)	75 (55)	134 (44)	0.63 [0.42–0.94]	**0.02**	0.63 [0.41–0.97]	**0.04**
Social deprivation quintile							
5 (least deprived)	95 (21)	25 (18)	70 (23)	1.0	-	-	-
4	72 (16)	21 (15)	51 (17)	0.87 [0.44–1.72]	-	-	-
3	71 (16)	21 (15)	50 (16)	0.85 [0.43–1.69]	-	-	-
2	74 (17)	22 (16)	52 (16)	0.84 [0.43–1.66]	-	-	-
1 (most deprived)	132 (30)	47 (36)	85 (28)	0.65 [0.36–1.15]	0.15	-	-
BMI (kg/m^2) groups							
20–24.9 (normal weight)	92 (23)	31 (25)	61 (22)	1.0	-	-	-
<20 (underweight)	8 (2)	1 (1)	7 (2)	0.36 [0.42–30.2]	-	-	-
25–29.9 (overweight)	150 (37)	41 (34)	109 (39)	1.35 [0.77–2.37]	-	-	-
30+ (obese)	153 (38)	49 (40)	104 (37)	1.08 [0.62–1.87]	0.84	-	-
Smoking status							
Never smoked	204 (48)	76 (59)	128 (44)	-	-	1.0	-
Ever smoked	219 (52)	53 (41)	166 (56)	1.86 [1.22–2.83]	**0.004**	1.59 [1.03–2.47]	**0.04**

CRP (mg/l)							
<3	120 (33)	34 (32)	86 (33)	-	-	-	-
≥3	248 (67)	72 (68)	176 (67)	1.035 [0.645–1.68]	0.89	-	-
Aspirin							
No	370 (83)	111 (82)	259 (84)	-	-	-	-
Yes	74 (17)	25 (18)	49(16)	0.84 [0.49–1.43]	0.52	-	-
Statin							
No	268 (60)	86 (63)	182 (59)	-	-	-	-
Yes	176 (40)	50 (37)	126 (41)	1.19 [0.79–1.81]	0.41	-	-
ACE-inhibitor							
No	355 (80)	110 (81)	245 (80)	-	-	-	-
Yes	89 (20)	26 (19)	63 (20)	1.09 [0.65–1.81]	0.75	-	-

[1]*Adjusted for age, sex and smoking status*

Table 4.3: The relationship between host factors and severity of abnormality found at colonoscopy in those with an abnormal colonoscopy

Baseline characteristics	Patients with any abnormality at colonoscopy[1] (%)	NNCP (%)	Adenoma (%)	Adenocarcinoma (%)	p-value (linear by linear)
All patients	308 (100)	107 (35)	182 (59)	19 (6)	
Age (years)					
<55	49 (16)	20 (19)	28 (15)	1 (5)	-
55–64	100 (33)	32 (30)	63 (35)	5 (27)	-
65–74	152 (49)	52 (48)	88 (48)	12 (63)	-
75+	7 (2)	3 (3)	3 (2)	1 (5)	0.28
Sex					
Female	174 (56)	58 (54)	107(59)	9 (47)	-
Male	134 (44)	49 (46)	75 (41)	10 (53)	0.89
Social deprivation quintile					
5 (least deprived)	70 (23)	20 (19)	46 (25)	4 (21)	-
4	51 (16)	20 (19)	26 (14)	5 (26)	-
3	50 (16)	20 (19)	26 (14)	4 (21)	-
2	52 (17)	15 (14)	34 (19)	3 (16)	-
1 (most deprived)	85 (28)	32 (29)	50 (28)	3 (16)	0.36
BMI[2] Groups(kg/m^2)					
20–24.9 (normal weight)	61 (22)	24 (24)	35 (21)	2 (12)	-
<20 (underweight)	7 (2)	4 (4)	3 (2)	0 (0)	-
25–29.9 (overweight)	109 (39)	32 (32)	69 (42)	8 (50)	-
30+ (obese)	104 (37)	40 (40)	58 (35)	6 (38)	0.54
Smoking Status					
Never smoked	128 (44)	44 (43)	75 (43)	9 (50)	-
Ever smoked	166 (56)	58 (57)	99 (57)	9 (50)	0.85

CRP (mg/l)[3]					
<3	86 (33)	30 (34)	50 (32)	6 (35)	-
≥3	176 (67)	59 (66)	106 (68)	11 (65)	0.93
Aspirin					
No	259 (84)	85 (79)	157 (86)	17 (90)	-
Yes	49 (16)	22 (21)	25 (14)	2 (10)	0.10
Statin					
No	182 (59)	63 (59)	105 (58)	14 (74)	-
Yes	126 (41)	44 (41)	77 (42)	5 (26)	0.52
ACE-inhibitor					
No	245 (80)	81 (76)	147 (81)	17 (90)	-
Yes	63 (20)	26 (24)	35 (19)	2 (10)	0.14

[1]Number of those with any abnormality (excluding haemorrhoids) at colonoscopy were 308 of the entire cohort of 444 (not all patients had blood results available)
[2]Data available for 281 patients
[3]Data available for 262 patients

Table 4.4: The relationship between host factors and incident neoplasia at bowel screening colonoscopy

Baseline characteristics	All patients (%)	No neoplasia (%)	Any neoplasia (%)	OR (univariable)	p-value	OR (multivariable)[1]	p-value
All patients	444	243 (55)	201 (45)				
Age (years)							
<55	92 (21)	63 (26)	29 (14)	1.0	-	1.0	-
55–64	156 (35)	88 (36)	68 (34)	1.68 [0.98–2.89]	-	1.82 [1.04–3.23]	-
65–74	187 (42)	87 (36)	100 (50)	2.49 [1.48–4.22]	-	2.84 [1.62–4.99]	-
75+	9 (2)	5 (2)	4 (2)	1.73 [0.43–6.95]	**0.001**	2.69 [0.59–12.05]	**<0.001**
Sex							
Female	235 (53)	119 (49)	116 (58)	-	-	-	-
Male	209 (47)	124 (51)	85 (42)	0.70 [0.48–1.02]	0.07	0.73 [0.49–1.09]	0.12
Social deprivation quintiles							
5 (least deprived)	95 (21)	45 (19)	50 (25)	1.0	-	-	-
4	72 (16)	41 (17)	31 (15)	0.68 [0.37–1.26]	-	-	-
3	71 (16)	41 (17)	30 (15)	0.66 [0.35–1.22]	-	-	-
2	74 (17)	37 (15)	37 (19)	0.90 [0.49–1.65]	-	-	-
1 (most deprived)	132 (30)	79 (32)	53 (26)	0.60 [0.36–1.03]	0.16	-	-
BMI (kg/m^2) groups							
20–24.9 (normal weight)	92 (23)	55 (25)	37 (20)	1.0	-	-	-
<20 (underweight)	8 (2)	5 (2)	3 (2)	0.89 [0.20–3.96]	-	-	-
25–29.9 (overweight)	150 (37)	73 (33)	77 (43)	1.57 [0.93–2.65]	-	-	-
30+ (obese)	153 (38)	89 (40)	64 (35)	1.07 [0.63–1.81]	0.69	-	-
Smoking status							
Never smoked	204 (48)	120 (52)	84 (44)	-	-	-	-
Ever smoked	219 (52)	111 (48)	108 (56)	1.39 [0.95–2.04]	0.09	1.34 [0.89–2.01]	0.15

CRP (mg/l)							
<3	120 (33)	64 (33)	56 (32)	-	-	-	-
≥3	248 (67)	131 (67)	117 (68)	1.02 [0.66–1.58]	0.93	-	-
Aspirin							
No	370 (83)	196 (81)	174 (87)	-	-	-	-
Yes	74 (17)	47 (19)	27 (13)	0.65 [0.39–1.08]	0.09	0.51 [0.29–0.89]	**0.02**
Statin							
No	268 (60)	149 (61)	119 (60)	-	-	-	-
Yes	176 (40)	94 (39)	82 (40)	1.09 [0.75–1.60]	0.65	-	-
ACE-inhibitor							
No	355 (80)	191 (79)	164 (82)	-	-	-	-
Yes	89 (20)	52 (21)	37 (18)	0.83 [0.52–1.33]	0.43	-	-

[1]*Adjusted for age, sex, smoking and aspirin use*

Table 4.5: The relationship between host factors and the incidence of non-advanced vs. advanced neoplasia

Baseline characteristics	Patients with neoplasia (%)	Non-advanced neoplasia[1] (%)	Advanced neoplasia[2] (%)	OR (univariable)	p-value
All patients	201	87 (43)	114 (57)		
Age (years)					
<55	29 (14)	13 (15)	16 (14)	1.0	-
55–64	68 (34)	31 (36)	37 (32)	0.97 [0.41–2.32]	-
65–74	100 (50)	42 (48)	58 (51)	1.12 [0.49–2.58]	-
75+	4 (2)	1 (1)	3 (3)	2.44 [0.23–26.3]	0.23
Sex					
Female	116 (58)	54 (62)	62 (54)	1.0	-
Male	85 (42)	33 (38)	52 (46)	1.37 [0.78–2.42]	0.28
Social deprivation quintile					
5 (least deprived)	50 (25)	26 (30)	24 (21)	1.0	-
4	31 (15)	12 (14)	19 (17)	1.72 [0.69–4.27]	-
3	30 (15)	11 (13)	19 (17)	1.87 [0.74–4.73]	-
2	37 (18)	17 (19)	20 (17)	1.28 [0.54–2.99]	-
1 (most deprived)	53 (26)	21 (24)	32 (28)	1.65 [0.76–3.61]	0.23
BMI (kg/m^2) groups					
20–24.9 (normal weight)	37 (20)	17 (21)	20 (20)	1.0	-
<20 (underweight)	3 (2)	2 (3)	1 (1)	0.43 [0.04–5.11]	-
25–29.9 (overweight)	77 (43)	38 (47)	39 (38)	0.87 [0.39–1.91]	-
30+ (obese)	64 (35)	23 (29)	41 (40)	1.52 [0.67–3.45]	0.42
Smoking status					
Never smoked	84 (44)	32 (39)	52 (48)	-	-
Ever smoked	108 (56)	51 (61)	57 (52)	0.69 [0.39–1.23]	0.21
CRP (mg/l)					
<3	56 (32)	22 (30)	34 (34)	-	-
≥3	117 (68)	52 (70)	65 (66)	0.81 [0.42–1.55]	0.52

Aspirin					
No	174 (87)	73 (84)	101 (89)	-	-
Yes	27 (13)	14 (16)	13 (11)	0.67 [0.30–1.51]	0.33
Statin					
No	119 (59)	43 (49)	76 (67)	-	-
Yes	82 (41)	44 (51)	38 (33)	0.49 [0.28–0.87]	**0.01**
ACE-inhibitor					
No	164 (82)	68 (78)	96 (84)	-	-
Yes	37 (18)	19 (22)	18 (26)	0.67 [0.33–1.37]	0.27

[1]*Refers to the finding of any small (<1cm) adenoma with no advanced features*
[2]*Refers to either an advanced adenoma (at least one of the following features: ≥1cm, HGD, villous histology) or an adenocarcinoma*

Table 4.6: The relationship between host factors and markers of the SIR

Baseline characteristics	All patients (%)	CRP <3 mg/l (%)	CRP ≥3 mg/l (%)	OR (univariable)	p-value	OR (multivariable)[2]	p-value
All patients[1]	368 (100)	120 (33)	248 (67)				
Age (years)							
<55	78 (20)	31 (26)	47 (19)	1.0	-	-	-
55–64	130 (36)	37 (31)	93 (37)	1.66 [0.92–2.99]	-	-	-
65–74	153 (42)	49 (41)	104 (42)	1.40 [0.79–2.47]	-	-	-
75+	7 (2)	3 (2)	4 (2)	0.88 [0.18–4.20]	0.49	-	-
Sex							
female	196 (53)	58 (57)	128 (52)		-	-	-
Male	172 (47)	53 (43)	120 (48)	1.23 [0.79–1.90]	0.36	-	-
Social deprivation quintile							
5 (least deprived)	80 (22)	36 (30)	44 (18)	1.0	-	1.0	-
4	61 (16)	23 (19)	38 (15)	1.35 [0.69–2.67]	0.39	1.09 [0.50–2.41]	0.81
3	62 (17)	20 (17)	42 (17)	1.72 [0.86–3.43]	0.13	1.41 [0.62–3.22]	0.42
2	60 (16)	14 (12)	46 (19)	2.69 [1.28–5.65]	**0.009**	2.33 [0.98–5.58]	0.06
1 (most deprived)	105 (29)	27 (22)	78 (31)	2.36 [1.27–4.39]	**0.007**	1.79 [0.88–3.64]	0.11
BMI (kg/m2)							
20–24.9 (normal weight)	73(22)	27 (24)	46 (21)	1.0	-	1.0	-
<20 (underweight)	7 (2)	4 (4)	3 (1)	0.44 [0.09–2.12]	0.31	0.59 [0.09–3.77]	0.58
25–29.9 (overweight)	125 (37)	56 (51)	69 (31)	0.72 [0.40–1.31]	0.28	0.69 [0.36–1.34]	0.28
30+ (obese)	128 (38)	24 (21)	104 (47)	2.54 [1.33–4.87]	**0.005**	2.72 [1.35–5.49]	**0.005**
Smoking Status							
Never smoked	171 (49)	72 (63)	99 (42)	-	-	-	-
Ever smoked	179 (51)	42 (37)	137 (58)	2.37 [1.49–3.76]	**<0.0001**	2.26 [1.33–3.84]	**0.003**
Aspirin							
No	305 (83)	111 (93)	194 (78)	-	-	-	-
Yes	63 (17)	9 (7)	54 (22)	3.43 [1.63–7.22]	**0.001**	2.59 [1.15–5.86]	**0.02**

Statin							
No	221 (60)	73 (61)	148 (60)	-	-	-	-
Yes	147 (40)	47 (39)	100 (40)	1.07 [0.69–1.68]	0.83	-	-
ACE-inhibitor							
No	296 (80)	101 (84)	195 (79)	-	-	-	-
Yes	72 (20)	19 (16)	53 (21)	1.45 [0.81–2.57]	0.21	-	-

[1]368 patients with CRP results
[2]Adjusted for social deprivation, BMI, smoking and aspirin use.

5 THE RELATIONSHIP BETWEEN COLORECTAL NEOPLASIA AND BODY COMPOSITION IN A BOWEL SCREENING POPULATION

5.1 Introduction

Elevated BMI, as a crude measure of obesity and adiposity, has been associated with an increased risk of CRC in large population-based studies (328-330). In general, the association appears to be stronger in males and in colon rather than rectal cancer (329, 331, 332) (279, 333). Additional measures of adiposity, such as elevated waist circumference (WC) and waist: hip ratio (WHR) have also been reported as risk factors for CRC (279, 333).

However, BMI, WHR and WC are crude surrogate markers of adiposity (329). Historically, adipose tissue was regarded as an energy storage site while contributing to body insulation and padding for physical protection. It is now accepted that adipose tissue is metabolically active and has an endocrine role, producing adipose-derived cytokines, commonly referred to as adipokines. The most well-known of these are leptin which regulates appetite, and adiponectin, which is an anti-inflammatory and insulin-sensitising hormone (285).

In descriptive terms, body fat can be divided into subcutaneous adipose tissue (SAT), which is located below the skin in the hypodermis, and visceral adipose tissue (VAT), the intra-peritoneal fat surrounding the abdominal organs. Surrogate markers of body fat mentioned previously, most notably BMI, do not account for the different distribution of adipose tissue. It has been suggested that adipose tissue distribution, rather than volume alone, may be an important determinant of CRC risk and previous reports have associated elevated VAT volume with the development of ischaemic heart disease, hypertension, insulin resistance and solid organ tumours (329) (334). Intersex comparisons have demonstrated that men generally have a higher volume of VAT than women, who often have a higher volume of SAT. For a given BMI, women typically carry 10% more body fat overall than men (285).

It is therefore plausible that higher levels of VAT in men may underpin the relationship between higher BMI, WC, WHR, male sex and an increased risk of CRC.

In addition, when considering pre-malignant disease, it is accepted that the majority of CRCs arise within colorectal adenomas as a result of the adenoma-carcinoma sequence (223, 280). In addition to CRC, obesity (according to BMI), has been associated with colorectal adenoma incidence with several meta-analyses demonstrating a positive but inconsistent correlation between the two (193, 297, 335) **(Chapter 3 and Chapter 4)**.

Moreover, there has been recent interest in the relationship between sarcopenia and CRC. Sarcopenia is characterised by progressive and generalised loss of skeletal muscle mass. It is associated with frailty, poor quality of life and comorbid disease (158). The condition has been associated with several chronic illnesses such as diabetes, renal failure and cardiovascular disease (336). There is evidence for the disproportionate loss of skeletal muscle tissue as an independent prognostic factor for both cancer-specific and overall survival in patients with CRC (337). However, there is little evidence pertaining to the role of sarcopenia in the early or pre-malignant stage of CRC.

The present study proposed that body composition, in particular, adipose tissue distribution, rather than overall adiposity (according to BMI) is an enhanced method with which to study the relationship between adiposity and colorectal neoplasia. Accordingly, the aim of this study was to examine the relationship between host characteristics, BMI, VAT, SAT, sarcopenia, and the incidence of colorectal neoplasia in a bowel screening population.

5.2 Methods

Study design and population

All population members aged between 50–74 years in Scotland are invited to take part in the SBoSP. The SBoSP has been described in detail previously (140) **(Section 1.2.2)**. Patients with comorbid disease who are unable to undergo colonoscopy as part of bowel screening, and those in whom colonoscopy is incomplete, are offered a CTC as an alternative. Patients undergoing CTC as part of the SBoSP in NHS GGC between July 2009 and February 2016 were eligible for inclusion.

Data collection

Patients must have undergone thorough colonic investigation by CTC as a minimum, and in most cases, an additional colonoscopy or flexible sigmoidoscopy was carried out either before or after the CTC. Following CTC, patients with suspected colorectal polyps or carcinoma underwent a colonoscopy to remove, biopsy, or clarify the CTC findings. Medical records and CTC images were accessed for all eligible patients. Age, sex, height, weight and BMI were recorded from medical records. Smoking status, aspirin or NSAID use, and socioeconomic deprivation were also recorded. Socioeconomic deprivation was assessed using the SIMD system, as outlined previously **(Chapter 3).**

Colonoscopy and pathology reports for each patient were reviewed to collect data on the number, size, and histopathological subtypes of colorectal neoplasia. Colorectal neoplasia was defined as either an adenomatous polyp of any subtype or invasive colorectal carcinoma. Advanced colorectal neoplasia was defined as either an advanced adenoma (at least one of; adenoma size ≥1cm, villous histology or HGD) or adenocarcinoma. In patients who had undergone colonoscopy before and after CTC, the results from all three tests were combined to give an overall outcome.

Body composition measurement using CT

Hounsfield Units and radiodensity

A CT scan builds images by sending a rotating beam of X-rays 360 degrees around a patient for multiple cycles. The pictures are based on the principle that X-ray absorption is variable depending on the tissue type it is passed through. Attenuation and absorption of the X-ray beam depend upon the thickness and composition of the tissues in the path of the beam, which reflects the radiodensity of the tissue (338). The Hounsfield scale is a quantitative scale for describing radiodensity and the corresponding units in this scale are Hounsfield Units (HU). The scale has two fixed points, where zero HU represents the radiodensity of distilled water, and -1000 HU represents the radiodensity of air when both are at standard temperature and pressure.

After scanning is complete, the image is reconstructed, HU are assigned to each pixel, and based on the Hounsfield scale, the radiodensity of the tissue represented in the pixel can be determined. The present study used previously validated HU attenuation thresholds of [-190 to -30 HU] and [-29 to +150 HU] as thresholds for adipose and skeletal muscle tissue, respectively (339).

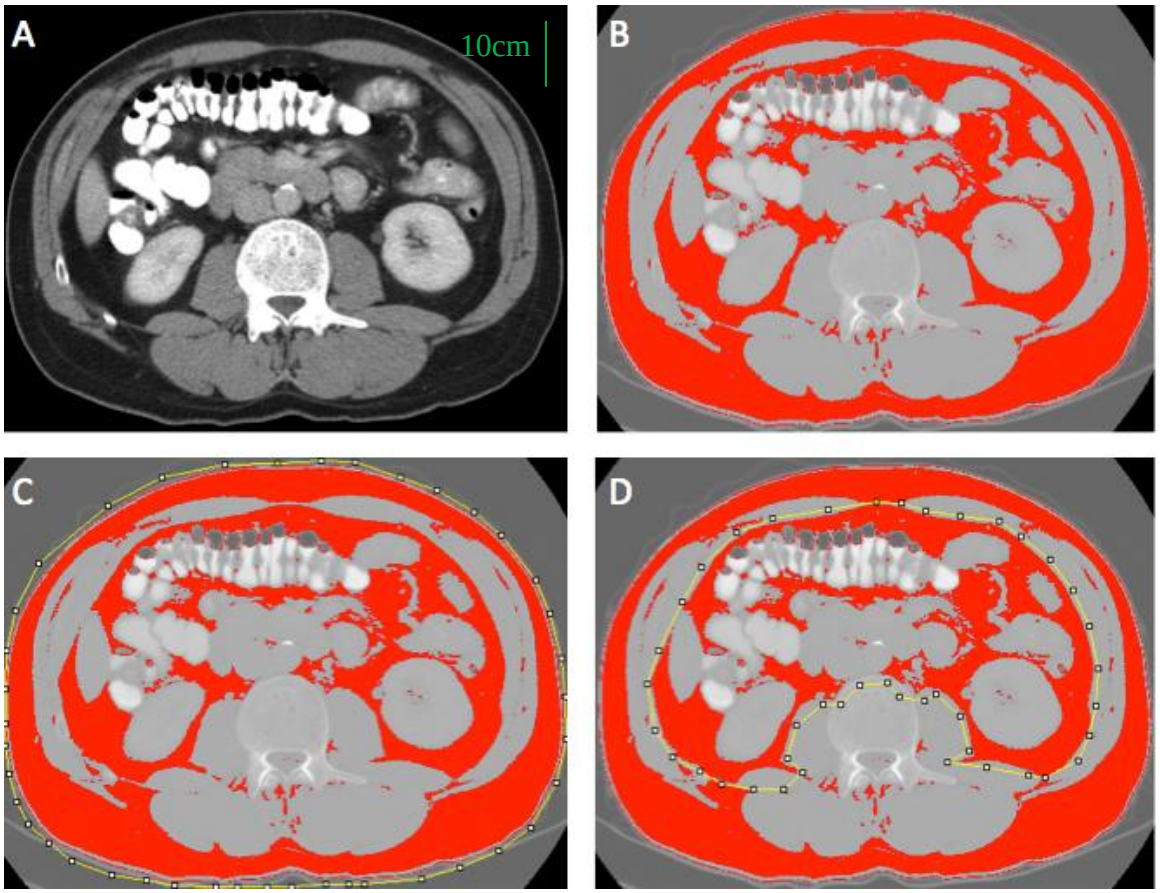
Measuring VAT, SAT and skeletal muscle area

CT images were viewed at the level of the 3rd and 4th lumbar vertebral interspace with the patient in the supine position (339). Scans with significant movement artefact or missing regions of interest were excluded. Medical imaging software was used for image analysis and the freely available software: NIH (National Institutes of Health), ImageJ version 1.46 was used to calculate body composition areas. This programme is available for download from https://imagej.nih.gov/ij/. The ImageJ programme and methods used in the present study have previously been validated against commercially available software (339). The primary investigator (DD) carried out all analysis using Image J. DD was trained in the use of this programme by two members of staff at the University of Glasgow (SM and RD) who

were highly experienced in its use. These two staff members had previously completed inter-rater reliability studies after training others on the use of the software and found good reliability. This indicated that the training methods were accurate and acceptable. The present study made use of published protocols to calculate the cross-sectional areas of VAT, SAT, and skeletal muscle (339, 340). VAT was defined as an area of intra-abdominal fat, bound by the parietal peritoneum with the paraspinal muscles and vertebral column excluded. SAT was defined as adipose tissue superficial to the peritoneal cavity, the bulk of which is also superficial to the abdominal and paraspinal muscles. Skeletal muscle area was defined as the total area of skeletal muscle comprising the abdominal wall, lumbar and paraspinal region.

In NHS GGC, medical images, including CTC, are stored as Digital Imaging and Communications in Medicine files (DICOM). These images can then be viewed using the Picture Archiving and Communication System (PACS). In order to export to ImageJ, the cross-sectional CTC slice was downloaded as a maximal resolution "Joint Photographic Experts Group" (JPEG) image from the PACS system. It was then opened with the ImageJ software, and attenuation thresholds specific for adipose and skeletal muscle tissue mentioned above were set (339). This instructed ImageJ to highlight the specific tissue types in isolation. **Figure 5.1** outlines the steps for measuring VAT (cm^2) and SAT (cm^2). **Figure 5.2** outlines the steps used to calculate the skeletal muscle area (cm^2).

Figure 5.1: An example of CT image analysis using NIH ImageJ software to calculate VAT and SAT



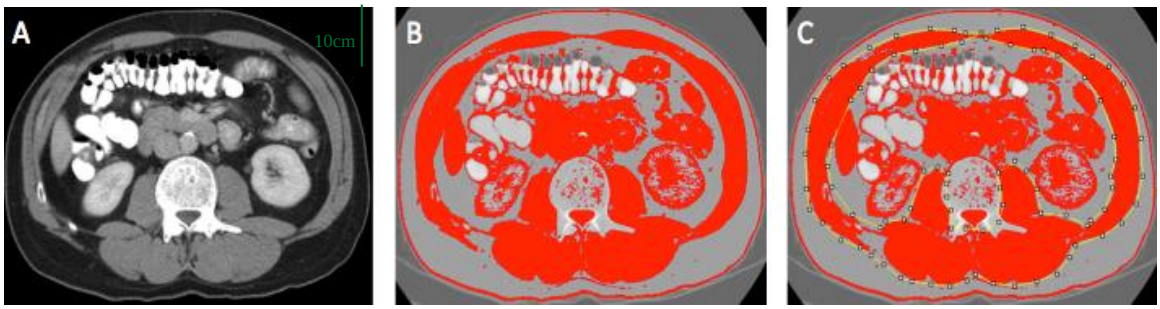
(A) The original CT image in JPEG format. A known distance of 10cm was set. This had been pre-marked in the PACS CT image viewer for accurate measurement.

(B) Tissue attenuation thresholds were set to selectively display adipose tissue [-190 to -30 HU].

(C)The polygon manual outline drawing tool was used to encompass the CT slice, and ImageJ was used to measure the area in red which represented the total adipose tissue area (TAT).

(D) Using the polygon manual drawing tool again, careful outlining of the peritoneal cavity was carried out, and ImageJ was used to calculate the area of adipose only within the outline. This represented the VAT area. A simple subtraction of the VAT area from the TAT area gave the SAT. (T–T - VAT = SAT).

Figure 5.2: An example of CT image analysis using NIH ImageJ software to calculate skeletal muscle area



(A) The CT image in JPEG had a known distance of 10 cm marked prior to capture from the primary image viewing software to enable accurate measurement. The image was then opened with ImageJ software.

(B) Thresholds in ImageJ were set to represent skeletal muscle tissue [-29 to +150 HU]. Muscle tissue was now highlighted in red.

(C) To exclude other tissue areas that are picked up at the same HU thresholds, the manual polygon tool was used to draw carefully round only the skeletal muscle area. This instructed ImageJ to only measure the skeletal muscle (red areas) within the selected boundaries and ensured an accurate measurement of the skeletal muscle area.

Study endpoints

Study endpoints for analysis were as follows:

1. The presence of any histologically confirmed colorectal neoplasia as part of the bowel screening process

2. The presence of any advanced colorectal neoplasia (advanced adenoma or adenocarcinoma) as part of the screening process

Preparation of data for analysis

Data were grouped, standardised, and categorised. Patients were allocated into one of four groups according to the WHO classification for BMI: normal weight (BMI 20–24.9) was used as the reference group. Further groupings were: underweight (BMI <20), overweight (BMI 25–29.9) and obese (BMI ≥30). Visceral obesity was defined as VAT area >160cm^2 for male patients and VAT area >80cm^2 for female patients according to established thresholds (341). SAT was normalised for height to obtain the subcutaneous fat index (SFI) (cm^2/m^2). High SFI was defined as ≥50 in men and ≥42 in women using thresholds defined by Dolan *et al.* (154) and Ebadi *et al.* (342). Skeletal muscle area was normalised for height to obtain the skeletal muscle index (SMI) (cm^2/m^2). Sarcopenia was defined as per Dolan and colleagues, which represents an SMI for a given BMI (154). Male patients with SMI <45.6 (if BMI ≤30) and SMI <56.8 (if BMI >30) were defined as sarcopenic. Similarly, female patients with SMI <39.1 (if BMI ≤30) and SMI <44.6 (if BMI >30) were defined as sarcopenic.

Statistical analyses

Comparisons of group characteristics at baseline in the present study were compared to those in the prospectively collected bowel screening cohort **(Chapter 4)**. Statistical analysis was carried out using a non-parametric independent samples median test for age, social deprivation and BMI. The χ^2 test was used for comparisons between these groups of the proportion of smokers, aspirin and NSAID users. In the principal analysis of outcomes, categorical variables were analysed using the χ^2 test, and ORs were calculated for an estimate of risk. Categorical variables with more than two groups were analysed using binary logistic regression, and the lowest quartile of each independent variable was selected as the reference group. Multivariable analysis was carried out using binary logistic regression. Covariates with a significance value of $p<0.1$ in the univariable were included in the multivariable analysis. A two-tailed p-value <0.05 was considered statistically significant in this study. All statistical analyses were carried out using IBM SPSS statistics version 24.0, IBM Co, Armonk, NY, USA.

5.3 Results

Study group characteristics

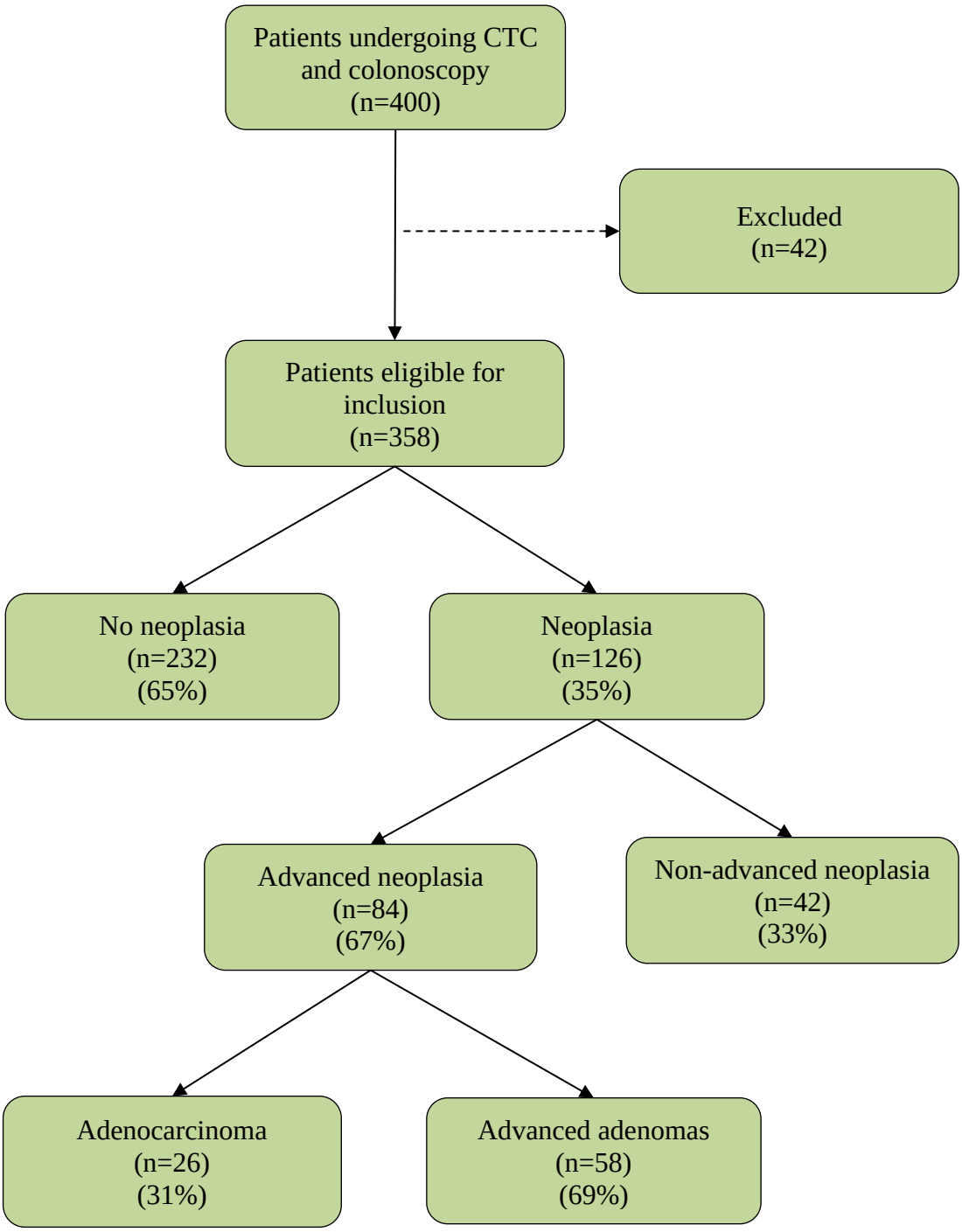
Between July 2009 and February 2016, 400 patients underwent CTC following a positive screening test as part of the SBoSP and were eligible for inclusion **[Figure 5.3]**. 89 (22%) were allocated directly to CTC, while 311 (78%) underwent CTC due to failed colonoscopy. 42 (10%) patients were excluded from the study **[Table 5.1],** leaving 358 for analysis**.**

The median age was 65 years [IQ range 59–71]. There were 121 (34%) males, and the study population was predominantly overweight with a median BMI of 27.8 [IQ range 24–33]. The baseline characteristics for the group in the present study were compared to those from the prospectively studied bowel screening group presented in **Chapter 4,** and the results are shown in **Table 5.2**. There were no statistically significant differences in age or BMI between the groups. The group in the present study comprised a higher proportion of females (66% vs. 53%, $p<0.001$), were more likely to suffer from socioeconomic deprivation ($p<0.001$), and were more likely to have been active or ex-smokers (66% vs. 52%, $p<0.001$). In addition, the present study group were more likely to be regular users of aspirin (29% vs. 17%, $p<0.001$) or NSAIDs (21% vs. 15%, $p<0.05$).

Study outcomes

Study outcomes are displayed in **Figure 5.3.** Of the 358 patients included, 126 (35%) were diagnosed with colorectal neoplasia. Among these, 84 (67%) had advanced neoplasia. Of those with advanced neoplasia, 26 (31%) had adenocarcinoma, and 58 (69%) had an advanced adenoma (in the absence of CRC). From the CTC group overall (n=400), 7% of patients (n=26) were found to have an adenocarcinoma.

Figure 5.3: Outcomes following colonoscopy and CTC



Outcome: Any colorectal neoplasia

The relationship between colorectal neoplasia incidence and non-body composition host characteristics

Results are shown in **Table 5.3**. On univariable analysis, male sex was associated with the presence of colorectal neoplasia, OR 2.17 [95% CI; 1.38–3.41, p<0.01]. This remained significant on multivariable analysis, OR 2.35 [95% CI; 1.47–3.77, p<0.001] when adjusting for age and visceral obesity. Neither advancing age, social deprivation, elevated BMI, smoking, aspirin or NSAID use were significantly associated with colorectal neoplasia incidence.

The relationship between colorectal neoplasia incidence and body composition

Results are shown in **Table 5.3.** On univariable analysis, visceral obesity was associated with colorectal neoplasia, OR 2.69 [95% CI; 1.46–4.98, p<0.01]. This relationship persisted on multivariable analysis when adjusting for age and sex, OR 2.79 [95% CI; 1.48–5.25, p<0.01]. Neither high SFI nor sarcopenia were associated with colorectal neoplasia incidence.

The relationship between visceral adiposity and adenoma number

Results are shown in **Table 5.4**. There was no significant relationship between increasing visceral adiposity and adenoma number.

Outcome: Advanced colorectal neoplasia

The relationship between advanced colorectal neoplasia incidence and non-body composition host characteristics

Results are shown in **Table 5.5.** Older age was associated with a reduced risk of advanced neoplasia when adjusting for SFI with an OR of 0.93 [95% CI; 0.87–0.99, $p<0.05$]. None of the other host characteristics were associated with advanced colorectal neoplasia.

The relationship between advanced colorectal neoplasia incidence and body composition

Results are shown in **Table 5.5.** A high SFI was associated with an increased risk of advanced neoplasia, OR 5.1 [95% CI; 1.55–16.73, $p<0.01$]. This observation remained following adjustment for age in the multivariable model, OR 6.28 [95% CI; 1.79–21.98, $p<0.01$]. Neither visceral obesity nor sarcopenia were associated with advanced neoplasia.

5.4 Discussion

The present study reports on the association between host factors, CT-derived measures of body composition, and the incidence of colorectal neoplasia within the SBoSP. The results indicate that male sex and visceral obesity are independently associated with an increased risk of colorectal neoplasia. There was no association between elevated BMI or sarcopenia and colorectal neoplasia incidence.

It is generally accepted that central adiposity, measured by WC and WHR, is associated with poor health outcomes, particularly with regards to cardiovascular disease, although the association with BMI is inconsistent (343). Systematic reviews have shown an association between increased WC and increased risk of developing CRC (344). Furthermore, in a large population study, BMI was associated with only a modest increase in the risk of colon cancer, HR 1.10 [95% CI; 1.07–1.13] and a borderline association with rectal cancer, HR 1.04 [95% CI; 1.00–1.08] (59). These results are mirrored by other researchers who agree that WC and WHR demonstrate stronger correlations with colorectal neoplasia than BMI (345). BMI and WC are used as surrogate markers of adiposity, although it is now more evident that adipose tissue distribution, rather than volume, may be an important determinant of CRC risk (329). It is plausible, therefore, that the association between WC, WHR and CRC may reflect visceral adiposity. The present study supports this suggestion by reporting that visceral obesity resulted in an almost 3-fold increase in the risk of colorectal neoplasia after adjustment for age and sex **[Table 5.3]**.

A number of studies have investigated the relationship between VAT and colorectal neoplasia. 12 of the largest are summarised in **Table 5.6** (345-356). The majority of these studies report similar results to the present study. Five of the 12 studies reported a positive association with elevated VAT, but not elevated BMI, and colorectal neoplasia incidence (346, 349-351, 356). This finding supports the suggestion that visceral obesity could be a

superior method of measurement when examining the relationship between colorectal neoplasia and adiposity. Similar observations have been reported in recent meta-analyses (286, 287).

To our knowledge, no previous studies investigating the relationship between body composition and colorectal neoplasia have been conducted within a bowel screening population similar to ours. In addition, the vast majority of studies mentioned above **[Table 5.6]** were conducted in Southeast Asia with only two in the USA (352, 354). Thus, the applicability of previous work to a western population, particularly a screening cohort, is debatable and highlights the importance of our results.

The mechanisms underpinning the association between visceral obesity and colorectal neoplasia in the present study are not clear. It is likely that the mechanisms are complex. Several are biologically plausible. It has been suggested that VAT is metabolically more active than SAT. Relative to SAT, it is thought that higher volumes of VAT results in elevated levels of circulating pro-inflammatory cytokines such as IL-6 and TNF-α. Furthermore, elevated VAT volume is thought to promote insulin resistance and the bioavailability of insulin-like growth factor-1 (IGF-1). Recent work has demonstrated a correlation between CT-derived measurements of VAT and both inflammatory and angiogenic biomarkers such as CRP and vascular endothelial growth factor (VEGF) in patients with CRC (357). It is believed that the pro-inflammatory, pro-proliferative, insulin-resistant environment promoted by VAT may play a role in the formation and growth of colorectal neoplasia (287, 347). This theory is supported by previous work, demonstrating that insulin and insulin-like growth factors are associated with the development and progression of adenomatous polyps (352).

Inflammatory cytokines released by adipose tissue such as leptin and adiponectin may play an additional role in the formation and promotion of colorectal neoplasia. In particular,

adiponectin is noted for its anti-diabetic and anti-inflammatory properties and is lower in obese patients, and those with CRC according to a previous meta-analysis (358) (192). However, the precise mechanisms of these interactions are likely to be complex and remain poorly understood.

The present study reported that male sex was associated with colorectal neoplasia. It is plausible that the association is mediated through visceral obesity, especially given that median VAT area was higher in males than females (264.9 cm^2 vs. 157.2cm^2, $p<0.0001$), which has been reported previously (285).

Adenoma number is a risk factor for adenoma recurrence **(Chapter 3)** and is regarded as a high-risk finding based on the BSG adenoma surveillance guidelines **(Section 1.4.7)** (15). The present study sought to determine if visceral adiposity influenced adenoma number in a similar manner to incident neoplasia **[Table 5.4]. N**o statistically significant relationship was identified making it difficult to draw firm conclusions.

The present study also sought to investigate the relationship between body composition and advanced neoplasia. In those with any neoplasia, high SFI was associated with the presence of advanced neoplasia. This remained significant when adjusting for both BMI and visceral obesity. The reason for this finding is not clear; however, previous studies have reported that VAT decreases in the later stages of CRC (347). This would be consistent with cancer cachexia. It may be that VAT is potentially adenoma-promoting in the early stages as per the results of the present study, but its volume and influence decrease as adenomas progress towards advanced neoplasia and cancer, such that VAT becomes less influential than SFI. Further work comparing body composition measures in a group of patients with pre-malignant disease and those with established CRC may be of value in examining this theory further.

In a study by Im *et al.* (2018), the researchers reported that increased VAT area is associated with incident colorectal neoplasia but not with recurrent colorectal neoplasia after polypectomy (346). The researchers followed patients for a median of 43 months to determine if any patients developed a subsequent adenoma. The findings suggested the effect of VAT on adenoma formation may not have an influence on adenoma formation during the 43-month follow up. The study did note that elevated VAT was associated with incident adenomas, which are likely to have developed over a prolonged period. As such, it is plausible that the effects of VAT are slow-acting and prolonged, possibly spanning decades. If this is the case, there may be a window of opportunity for clinical intervention.

Reports on sarcopenia and its effect on chronic disease and cancer are gaining interest. With respect to CRC, sarcopenia has been associated with poor cancer-specific and overall survival (359). However, limited work has been conducted to examine the role of sarcopenia during the pre-malignant and early stages of CRC. The present study did not detect an association between sarcopenia and the incidence of any, or advanced colorectal neoplasia. Therefore, it would appear that visceral obesity is more likely to drive the early and pre-malignant stage of CRC than sarcopenia, which remains relevant in established cancer. The findings of the present study suggest that sarcopenia plays a marginal role in early or pre-malignant disease when visceral adiposity is more relevant. These results contrast with two recent studies from South Korea. They concluded that sarcopenia was associated with advanced adenomas when compared with those who were non-sarcopenic (336, 360). However, there are a number of methodological differences between the present study and those from South Korea where younger patients were recruited (40+ years and 50+ years), excluded patients with a positive FOB test, and used the Asian-Pacific region criteria to define obesity (BMI ≥25) (336). Moreover, the researchers used bioelectrical impendence to measure muscle mass and calculate sarcopenia, rather than the widely validated CT-derived measures. Neither of the studies examined patients in a bowel screened population.

Therefore, the varied methodology and selection criteria limit the extent to which these studies and the present study are comparable.

The present study compared the baseline group characteristics with those from **Chapter 4,** which included consenting patients attending for bowel screening for whom data were collected prospectively. There were no differences in age or BMI between these two groups **[Table 5.2]**. The present study group consisted of a significantly higher proportion of females, ex or current smokers, as well as aspirin and NSAID users. In addition, they were likely to suffer higher levels of socioeconomic deprivation. It is appreciated that the colonoscopy procedure itself can be more difficult to perform in females with a lower completion rate compared to males (361). Thus, it is unsurprising that the current group, who are undergoing CTC mostly as a result of incomplete colonoscopy, has a higher proportion of females. In addition, many of the patients in the present study underwent CTC for a first-line investigation as they were deemed unfit for colonoscopy due to comorbid disease. Thus, it is unsurprising that the comorbid group in the present study were likely to be regular aspirin or NSAID users, ex, or current smokers, and socially and economically deprived. These factors are often associated with poorer health outcomes, as compared to a voluntary study group such as those presented in **Chapter 4**.

Moreover, although there are a number of features that potentially make the present study group unique, they are still drawn from the participants of the SBoSP. Given that the BMI of both groups is similar, it is likely that the findings of the present study in relation to body composition and incidence of neoplasia can still be generalised to a standard bowel screening group.

Strengths and limitations

The present study has a number of strengths. To our knowledge, it is the first study carried out on a bowel screening cohort similar to the SBoSP. This enhances its validity in screening groups. Previous studies have predominantly been conducted in Southeast Asia where demographics are different compared to western populations, particularly in terms of BMI and adiposity. Furthermore, these studies tended to have younger patients and patients were often those who attended for a standard health check-up rather than screening. In contrast, the present study provides real-world data with respect to a bowel screening population.

There were limitations, however, in that by using JPEG rather than DICOM files for body composition measurements, it was not possible to measure muscle quality, and in particular, myosteatosis which is an emerging area of interest in CRC research (154). In addition, a significant number of patients had CTC as their first-line investigation due to multiple comorbidities that rendered them unfit for colonoscopy. It could be construed that this group may be slightly less representative of standard SBoSP patients; however, the 7% cancer diagnosis rate in this group mirrors that in the SBoSP nationally (165).

Final conclusions and further work required

The results of the present study demonstrate that visceral obesity may be a significant risk factor for incident colorectal neoplasia. It is likely that body fat distribution is a superior measure to BMI for studying the relationship between adiposity and colorectal neoplasia. Sarcopenia, although relevant as a prognostic indicator in established CRC, is not associated with pre-malignant disease. However, further work comparing measures of body composition in a pre-malignant population and those with established cancer would be of interest. The present study supports lifestyle changes that aim to reduce overall adiposity and methods which could specifically target visceral adiposity as a primary prevention strategy for colorectal neoplasia. Further large studies in western populations would be

beneficial, particularly those designed to investigate the relationship between myosteatosis and colorectal neoplasia incidence.

Table 5.1: Reasons for exclusion from the study

Reason for exclusion	n
Total exclusions	42
• Lost to follow-up: inadequate or unavailable information in the medical notes	13
• Poor CTC picture quality. Movement artefact, metal or otherwise implants and picture blurring rendering inaccurate tissue area measurements	10
• Technical difficulty rendering CTC unreliable. Failure to carry out faecal tagging, poor bowel prep, inadequate colonic distension if mentioned in report	7
• Patient unable to tolerate CTC. Unable to hold gaseous distension	2
• Died soon after CTC prior to follow-up colonoscopy	2
• Patient refusal for post-CTC colonoscopy to determine the histology of detected polyps	2
• Polyp excised but inadvertently lost at colonoscopy. No histopathological data available	2
• Known previous colonic resection (malignant or benign indication)	2
• Poor views and technical failure on both colonoscopy and CTC. Thus, non-diagnostic tests	1
• Missing pathology reports from excised and retrieved polyps	1

Table 5.2: A comparison of baseline characteristics between the present study group and volunteers from a prospectively studied bowel screening group in the same geographical region (Chapter 4)

Variable	Prospectively studied bowel screening group[1]	Present study group	p-value
All patients			
Age (median; years)	63	65	0.07
Female sex (%)	53	66	**<0.001**
Social Deprivation (median)[2]	3082	2223	**<0.001**
BMI (median; kg/m^2)	28.1	27.8	0.45
Active or ex-smokers (%)	52	66	**<0.001**
Aspirin users (%)	17	29	**<0.001**
NSAID users (%)	15	21	**<0.05**

[1]*See Chapter 4*
[2]*As per SIMD ranking*

Table 5.3: The relationship between colorectal neoplasia incidence and host characteristics including CT-derived body composition

Baseline characteristics	All patients (%)	No neoplasia (%)	Any neoplasia (%)	OR (univariable)	p-value	OR (multivariable)[1]	p-value
All patients	358 (100)	232 (65)	126 (35)				
Age (years)							
<55	49 (14)	37 (16)	12 (9)	1.0	-	-	-
55–64	125 (35)	84 (36)	41 (33)	1.51 [0.71–3.19]	-	-	-
65–74	154 (43)	93 (40)	61 (48)	2.02 [0.99–4.18]	-	-	-
75+	30 (8)	18 (8)	12 (10)	2.06 [0.77–5.47]	**0.05**	1.03 [0.99–1.06]	0.06
Sex							
Female	237 (66)	168 (72)	69 (55)	-	-	-	-
Male	121 (34)	64 (28)	57 (45)	2.17 [1.38–3.41]	**0.001**	2.35 [1.47–3.77]	**<0.001**
Social deprivation quintile							
5 (least deprived)	61 (18)	33 (15)	28 (23)	1.0	-	-	-
4	39 (11)	29 (13)	10 (8)	0.41 [0.17–0.98]	-	-	-
3	48 (14)	26 (11)	22 (18)	0.99 [0.47–2.13]	-	-	-
2	73 (21)	53 (24)	20 (16)	0.45 [0.22–0.91]	-	-	-
1 (most deprived)	125 (36)	82 (37)	43 (35)	0.62 [0.33–1.15]	0.19	-	-
BMI[2] (kg/m^2)							
20–24.9 (normal weight)	71 (25)	48 (27)	23 (22)	1.0	-	-	-
<20 (underweight)	18 (6)	10 (5)	8 (7)	1.67 [0.58–4.79]	-	-	-
25–29.9 (overweight)	81 (28)	50 (27)	31 (30)	1.29 [0.66–2.52]	-	-	-
30+ (obese)	116 (41)	73 (41)	43 (41)	1.23 [0.66–2.29]	0.59	-	-
Visceral obesity *(all sexes)*							
No	77 (22)	62 (27)	15 (12)	-	-	-	-
Yes	281 (78)	170 (73)	111 (88)	2.69 [1.46–4.98]	**0.001**	2.79 [1.48–5.25]	**0.001**

High SFI[3] *(all sexes)*							
No	34 (12)	20 (11)	14 (13)	-	-	-	-
Yes	252 (88)	160 (89)	92 (87)	0.82 [0.39–1.70]	0.59	-	-
Sarcopenia[3] *(all sexes)*							
No	137 (48)	89 (49)	48 (46)	-	-	-	-
Yes	149 (52)	92 (51)	57 (54)	1.15 [0.71–1.86]	0.57	-	-
Smoking status							
Never smoked	118 (34)	74 (33)	44 (36)	-	-	-	-
Ever smoked	228 (66)	149 (67)	79 (64)	0.89 [0.56–1.42]	0.63	-	-
Aspirin[4]							
No	247 (71)	157 (69)	90 (73)	-	-	-	-
Yes	103 (29)	69 (31)	34 (27)	0.86 [0.53–1.39]	0.54	-	-
NSAIDs[5]							
No	277 (79)	175 (77)	102 (82)	-	-	-	-
Yes	73 (21)	51 (23)	22 (18)	0.74 [0.42–1.29]	0.29	-	-

[1]Adjusted for age, sex and visceral obesity
[2]BMI data available for 286 patients
[3]Data available for 286 patients for SFI and sarcopenia since height data not available for all patients
[4]Regular low dose aspirin use
[5]Regular use of NSAIDs including diclofenac, naproxen, ibuprofen, celocoxib, rofecoxib, indomethacin

Table 5.4: The relationship between visceral adiposity and adenoma number

VAT	All adenoma patients[1] (%)	1–2 adenomas (%)	≥3 adenomas (%)	OR (univariable)	p-value
All patients	100 (100)	86 (86)	14 (14)		
VAT quartiles					
Q1 (0–109.9 cm^2)	16 (16)	15 (17)	1 (7)	1.0	-
Q2 (110–180 cm^2)	22 (22)	16 (19)	6 (43)	5.63 [0.60–52.4]	0.13
Q3 (180.1–256.9 cm^2)	26 (26)	23 (27)	3 (21)	1.96 [0.19–20.6]	0.58
Q4 (>256.9 cm^2)	36 (36)	32 (37)	4 (29)	1.88 [0.19–18.2]	0.59

[1]*Excluding patients with cancer*

Table 5.5: The relationship between advanced colorectal neoplasia and host characteristics including CT-derived body composition

Baseline characteristics	All patients with neoplasia (%)	Non-advanced neoplasia (%)	Advanced neoplasia (%)	OR (univariable)	p-value	OR (multivariable)[1]	p-value
All patients	126 (100)	42 (33)	84 (67)				
Age (years)							
<55	12 (9)	2 (5)	10 (12)	1.0	-	-	-
55–64	41 (33)	13 (31)	28 (33)	0.43 [0.08–2.25]	-	-	-
65–74	61 (48)	20 (47)	41 (49)	0.41 [0.08–2.05]	-	-	-
75+	12 (10)	7 (17)	5 (6)	0.14 [0.02–0.96]	**0.07**	0.93 [0.87–0.99]	**0.04**
Sex							
Female	69 (55)	21 (50)	48 (57)	-	-	-	-
Male	57 (45)	21 (50)	36 (43)	0.75 [0.36–1.58]	0.45	-	-
Social deprivation quintile							
5 (least deprived)	28 (23)	9 (22)	19 (23)	1.0	-	-	-
4	10 (8)	3 (7)	7 (8)	1.11 [0.23–5.30]	-	-	-
3	22 (18)	10 (25)	12 (15)	0.57 [0.18–1.80]	-	-	-
2	20 (16)	7 (17)	13 (16)	0.89 [0.26–2.96]	-	-	-
1 (most deprived)	43 (35)	12 (29)	31 (38)	1.22 [0.43–3.45]	0.69	-	-
BMI (kg/m^2)							
20–24.9 (normal weight)	23 (22)	10 (30)	13 (18)	1.0	-	-	-
<20 (underweight)	8 (8)	5 (15)	3 (4)	0.46 [0.19–2.41]	-	-	-
25–29.9 (overweight)	31 (29)	6 (18)	25 (35)	3.21 [0.95–10.79]	-	-	-
30+ (obese)	43 (41)	12 (37)	31 (43)	1.99 [0.69–5.74]	0.24	-	-
Visceral obesity *(all sexes)*							
No	15 (12)	6 (14)	9 (11)	-	-	-	-
Yes	111 (88)	36 (86)	75 (89)	1.39 [0.46–4.20]	0.56	-	-

High SFI *(all sexes)*							
No	14 (13)	9 (27)	5 (7)	-	-	-	-
Yes	92 (87)	24 (73)	68 (93)	5.1 [1.55–16.73]	**0.004**	6.28 [1.79–21.98]	**0.004**
Sarcopenia *(all sexes)*							
No	48 (46)	15 (46)	33 (46)	-	-	-	-
Yes	57 (54)	18 (54)	39 (54)	0.99 [0.43–2.25]	0.97	-	-
Smoking status							
Never smoked	44 (36)	15 (37)	29 (35)	-	-	-	-
Ever smoked	79 (64)	26 (63)	53 (65)	1.05 [0.48–2.30]	0.89	-	-
Aspirin[2]							
No	90 (73)	29 (69)	61 (74)	-	-	-	-
Yes	34 (27)	13 (31)	21 (26)	0.77 [0.34–1.75]	0.53	-	-
NSAIDs[3]							
No	102 (82)	33 (79)	69 (84)	-	-	-	-
Yes	22 (18)	9 (21)	13 (16)	0.69 [0.27–1.78]	0.44	-	-

[1]Adjusted for age and SFI
[2]Regular low dose aspirin use
[3]Regular use of NSAIDs including diclofenac, naproxen, ibuprofen, celocoxib, rofecoxib, indomethacin

Table 5.6: Studies reporting on the association between colorectal neoplasia and visceral adiposity

Author	Year	Country	Design	n	VAT measurement	Independent variable	Dependent variable	VAT associated with colorectal neoplasia	BMI associated with colorectal neoplasia	Statistical ratios (OR, HR)
Schoen *et al.* *(352)*	2005	USA	Cohort study with data from RCT	458	CT L4–L5 interspace	VAT volume	Incident adenoma	No	No	Adjusted OR 0.87 [0.47–1.6, p=0.52] for 4th quartile vs. 1st
Oh *et al.* *(351)*	2008	South Korea	Observational case-control	200	CT from L4–L5 interspace	VAT area quartiles. Lowest quartile as the reference group	Incident colorectal neoplasia	Yes (but no dose-dependent relationship)	No	Adjusted OR 4.07 [1.01–16.43, p<0.05] for 4th quartile vs. 1st
Yamaji *et al.* *(355)*	2009	Japan	Case-control	1205	CT derived at the level of the umbilicus	VAT area quartiles. Lowest quartile as the reference group	Incident adenoma	Borderline	Yes	Adjusted OR 1.46 [1.03–2.06, p=0.06] for 4th quartile vs. 1st
Kang *et al.* *(348)*	2010	South Korea	Cross-sectional case-control	2244	CT derived at level of the umbilicus	VAT area quintiles lowest quintile as the reference group	Incident adenoma	Yes	Not measured	Adjusted OR 3.09 [2.19–4.36, p<0.001] for 5th quintile vs. 1st
Nam *et al.* *(350)*	2010	South Korea	Observational cohort	3933	CT derived from 50mm above and below the umbilicus	VAT volume at four pre-set thresholds	Incident adenoma	Yes	No	Adjusted OR 1.43 [10.6–1.94, p<0.05] for highest vs. lowest VAT volume group

Summers *et al. (354)*	2012	USA	Observational case-control	1233	CT from top L2– bottom L3	VAT area quintiles lowest quintile as the reference group	Incident adenoma, or advanced adenoma	Yes	Not measured	Unadjusted OR 2.06 [1.36–3.13, p< 0.001] for 5th quintile VAT vs. 1st quintile
Chloe *et al. (345)*	2013	South Korea	Case-control	1264	CT derived at level of the umbilicus	VAT area quartiles. Lowest quartile as the reference group	Incident early CRC	No	Borderline (BMI only associated as p for trend)	Adjusted OR 0.82 [0.47–1.46, p = 0.51] for 4th quartile vs. 1st
Nagata *et al. (349)*	2014	Japan	Observational case-control	1328	CT derived at level of the umbilicus	VAT area quartiles. Lowest quartile as the reference group	Incident adenoma	Yes	No	Adjusted OR 1.90 [1.16–3.13, p<0.01] for 4th quartile VAT vs. 1st
Yamaji *et al. (356)*	2014	Japan	Observational cohort of asymptomatic subjects	907	CT derived at level of the umbilicus	VAT area quartiles. Lowest quartile as the reference group	Incident adenoma	Yes	No	Adjusted OR 2.42 [1.46–4.03, p<0.001] for 4th vs. 1st quartile
Seo *et al. (353)*	2017	South Korea	Observational cohort	309	L 3–4 interspace	VAT area quartiles. Lowest quartile as the reference group	Incident adenoma	Yes	Not measured	Adjusted OR 2.81 [1.02–7.73, p<0.05] for 4th quartile vs. 1st
Im *et al. (346)*	2018	South Korea	Observational case-control	1163	CT derived at level of the umbilicus	VAT area quintiles lowest quintile as the reference group	Incident adenoma	Yes	No	Adjusted HR 2.16 [1.26–3.71, p<0.01] for 5th quintile VAT vs. 1st
Jung *et al. (347)*	2018	South Korea	Observational case-control	551	CT derived at level of the umbilicus	VAT area quartiles. Lowest quartile as the reference group	Incident adenoma, early or late-stage CRC	Y for adenoma, No for CRC	Not measured	Adjusted OR 3.90 [2.11–7.20, p<0.001] for 4th quartile vs. 1st

6 THE INCIDENCE, IMPLICATIONS AND RISK FACTORS FOR INCIDENTAL EXTRACOLONIC FINDINGS AT CT COLONOSCOPY IN A BOWEL SCREENING POPULATION

6.1 Introduction

All members of the population aged from 50–74 years in Scotland are invited to take part in the SBoSP. The SBoSP has been described in detail previously **(Section1.2.2)**. The screening programme accounts for 18% of all CRCs encountered in clinical practice in Scotland (140). Between November 2015 and October 2017, just over 1 million people in Scotland were screened for CRC with 20,000 (2%) returning a positive screening test (186). Approximately 16,000 (80%) of those with a positive screening test attended for colonoscopy (186).

Not all colonoscopies in the screening programme are successfully completed and approximately 5-10% of cases end in failure to visualise the caecum (362). Public Health Scotland now release Key Performance Indicator (KPI) reports for bowel screening outcomes biannually, with the latest reporting an overall colonoscopy completion rate of 96% (95% for females, 98% for males) (165).

In addition, a proportion of patients are deemed unsuitable for colonoscopy due to either comorbid disease, the high burden of full bowel preparation or the inability to tolerate the procedure. In these cases, CTC can serve as an alternative for investigating the large bowel **(Section 1.1.5 and Section 1.2.5)**. Published data report that approximately 2% of screened patients undergo CTC as their first-line investigation, rising to 9% in some centres (363) (364). CTC is a CT-based radiological scan specifically designed to examine the colon and rectum and was first introduced in 1994 **(Section 1.1.5.1)** (105). The test is increasingly used as a completion investigation in bowel screening programmes where colonoscopy has failed.

Studies have reported that for larger colonic lesions (≥1cm) and CRC, the sensitivity of CTC is comparable to colonoscopy (106). Nonetheless, a key consideration of CTC is the inadvertent detection of an incidental extracolonic finding (ECF); the advantage of this being the potential to encounter important abdominal, pelvic or lung base abnormalities that otherwise would have been undetected. However, these ECFs may trigger further investigation, potentially by invasive means, and may ultimately be found to be benign. This can result in additional resourcing costs and trigger unnecessary patient anxiety.

Several studies have examined the prevalence and monetary cost of ECFs at CTC. These mainly considered symptomatic patients undergoing CTC in Korea (365), Australia (366, 367) and the USA (368), but similar studies on asymptomatic patient populations have been carried out in the USA (108, 171, 369). However, in the UK, to our knowledge, only one study reports the prevalence and cost impact of ECFs at CTC (169). This study was published in 2006 prior to the rollout of the bowel screening programme. It examined a symptomatic population from a fast track bowel cancer clinic (169).

Within the bowel screening population, patient characteristics such as age, sex, social deprivation, obesity and measures of body composition may be linked to extracolonic pathology. As such, the present study is the first to report the incidence, implication and risk factors for ECFs at CTC in patients undergoing CTC within the SBoSP.

6.2 Methods

Subjects, inclusion and exclusion criteria and data collection

All patients who underwent CTC between July 2009 and February 2016 as part of the SBoSP in NHS GGC were eligible for inclusion. CTC was performed in screening patients deemed unfit for colonoscopy and in patients who had already undergone an incomplete or suboptimal colonoscopy. Data were collected from medical records including age, sex, BMI, smoking status, indication for CTC and socioeconomic deprivation. Socioeconomic deprivation was assessed using the SIMD system described previously **(Chapter 3)** (268). Measures of body composition were calculated as described previously **(Chapter 5)**.

CTC reports were scrutinised, and both colorectal findings (CRF) and ECFs from CTC colonoscopy (incomplete or otherwise) were recorded. Incidental ECFs were only included if they were documented in the official radiological report. CRFs were included as relevant only if they were subsequently clarified by colonoscopy. Patient medical notes and previous scans were examined in order to ensure only new, previously undocumented ECFs were included. Colonoscopy reports were matched to the CTC findings.

Classification of CRFs and ECFs

CRFs and ECFs were recorded using the CT Colonography Reporting and Data System (C-RADS) (171, 370). The C-RADS system classes CRFs and ECFs simultaneously (171); CRFs are classed as C_0 to C_4 and ECFs are classed E_0 to E_4 by C-RADS using a hierarchical system. The C-RADS classification system with clinical examples are displayed in **Table 6.1** and **Table 6.2.** In patients where multiple ECFs were identified, a hierarchical system was used where the only most significant finding was included in the analysis.

CRFs follow-up

CRFs $C_{2–4}$ were investigated by colonoscopy if clinically feasible and appropriate according to the C-RADS criteria **[Table 6.1]**. The subsequent colonoscopy and corresponding pathology reports were examined to confirm the presence and nature of any significant CRFs.

ECFs follow-up

According to the C-RADS classification for ECFs **[Table 6.2]**, only E_{3-4} findings require follow-up. However, some clinicians exercised clinical judgement by choosing to investigate some E_2 and E_1 on a case by case basis. For this reason, patient medical notes, pertaining to ECF-based follow-up, were examined for every patient regardless of the C-RADS classification. The following clinical encounters were recorded as follow-up.

1. **Outpatient appointment**
    a. Consultant clinic
    b. Nurse-led clinic
2. **Further radiological procedure**
    a. CT scan
    b. Ultrasound (US) scan
    c. MRI scan
3. **Invasive procedure**
    a. Endoscopy
    b. Biopsy
    c. Blood sampling
4. **Other tests**
    a. Bone scan or other non-specific tests
5. **Day surgery procedures**
    a. Operative
    b. Endoscopic
6. **Inpatient stay**
    a. Either surgical or non-surgical treatment

Specific exclusion criteria

Patients with ECFs on CTC but without documented follow-up were identified and excluded. There were no other specific exclusion criteria.

Cost analysis of benign disease

The monetary cost of investigating subsequent benign disease was calculated. A previous UK study in 2006 reported on the NHS costs with regards to CTC in symptomatic patients (169). The researchers estimated the cost based on the NHS reference costs manual for 2004 (now archived) (371). Since matters of healthcare budgeting in Scotland are devolved to the Scottish Government, the present study reports on costs (in British Pounds; £) specific to the NHS in Scotland. Public Health Scotland, and specifically the Information Services Division, hold and maintains data relating to health finance (372). This includes the Scottish health service costs manual, referred to as the "cost book". The data are collated annually and are the only source of published NHS costs for Scotland (372). The cost book for the year ending 31st March 2017, published on the 21st November 2017, was the most up-to-date report available at the time of writing. Costs were calculated based on those published for the GGC health board, and where costs were only published for specific hospitals rather than on a regional level, Glasgow Royal Infirmary (GRI) was chosen as the base hospital. In the interests of transparency, a detailed description of how monetary costs were calculated is outlined below.

Specific methodology for costing of services and investigations

In determining the cost of a radiological investigation, the cost book for radiology services was accessed (373). The total gross expenditure per modality was divided by the total number of examinations in the year to provide an estimated cost per procedure, with the cost of a consultant or nurse-led outpatient appointment determined on a "per attendance" basis (374). Patients allocated an appointment that did not attend were included in the cost analysis since the cost is still incurred by the health service in these cases. Inpatient and day-case

surgery costings were available and were grouped by speciality (374). Inpatient costs were calculated as the total cost per speciality per year and divided by the number of inpatients. Direct costing for endoscopy was not available; thus, endoscopy was classed as a gastroenterology day-case procedure (374). Direct laboratory service costs were available for pathological reports, clinical genetics and medical physics (375). Other laboratory works were not available on an itemised basis; therefore the cost of one blood test or non-itemised laboratory work was estimated as the cost for laboratory tests for a single day as an inpatient in GGC, with all specialities considered equal (374). The costs estimated in the present study reflect those incurred in hospital care settings only. It was not possible to accurately determine the number, if any, of primary care consultations in relation to ECFs.

Statistical analyses

Statistical analyses were carried out to assess the relationship between patient characteristics and the likelihood of detecting ECFs. Standard WHO categories for BMI were used for grouping**.** Age thresholds were selected based on established and validated age ranges used to stratify risk in CRC patients. A χ^2 test was performed to determine statistical significance, and ORs were calculated to estimate risk. A p-value was calculated using a linear by linear approach where more than two groups were analysed from a single independent variable. In order to obtain ORs, binary logistic regression was used to compare categorical variables with two or more groups against a reference group. Any variables with $p<0.1$ on univariable analysis were included in the multivariable model. In all analyses, a two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were carried out using IBM® SPSS® Statistics version 22 (SPSS Inc., Chicago, IL, USA).

6.3 Results

Study population

400 patients underwent CTC during the study period and were eligible for inclusion. 6 patients were lost to follow-up and were excluded leaving 394 patients in the analysis. The study group comprised of 146 (37%) males, the median age was 65 years [IQ range 59–71], and median follow-up time was 72 months [IQ range 46–86]. The indications for CTC in the present study are shown in **Table 6.3.** 92 (23%) patients underwent CTC as their first-line investigation, and 302 (77%) proceeded to CTC after failed colonoscopy.

CRFs by patient

Outcomes are shown in **[Figure 6.1]** Based on CTC findings confirmed by colonoscopy, 45 (11%) patients had significant CRFs (C-RADS $C_{2–4}$); of these patients, 36 (9%) were diagnosed with an adenoma and 9 (2%) with CRC.

ECFs by patient

Outcomes are shown in **[Figure 6.2]** In considering the whole study group, 244 (62%) patients were found to have a total of 368 ECFs**.** A breakdown of all 368 ECFs by severity are shown in **Table 6.4**. Considering only the 244 patients with ECFs, 179 (73%) patients had low significance C-RADS E_2 findings, 33 (14%) had moderately significant C-RADS E_3 findings, and 32 (13%) had highly significant C-RADS E_4 findings **[Figure 6.2]**. In the overall study group (n=394), 179 (45%) patients had low significance C-RADS E_2 findings, 33 (8%) had moderately significant C-RADS E_3 findings, and 32 (8%) had highly significant C-RADS E_4 findings.

Figure 6.1: Outcomes from CTC in relation to CRFs

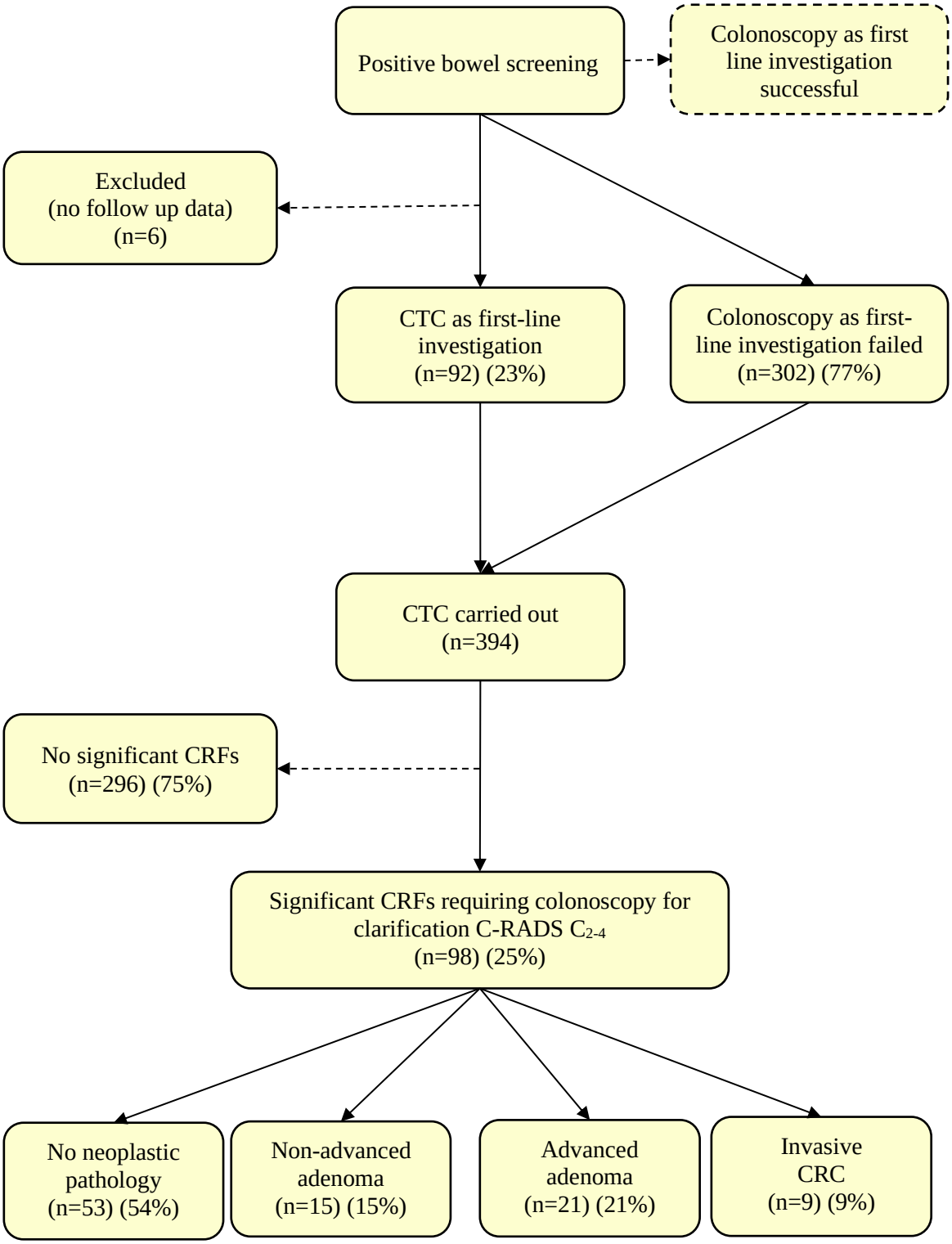
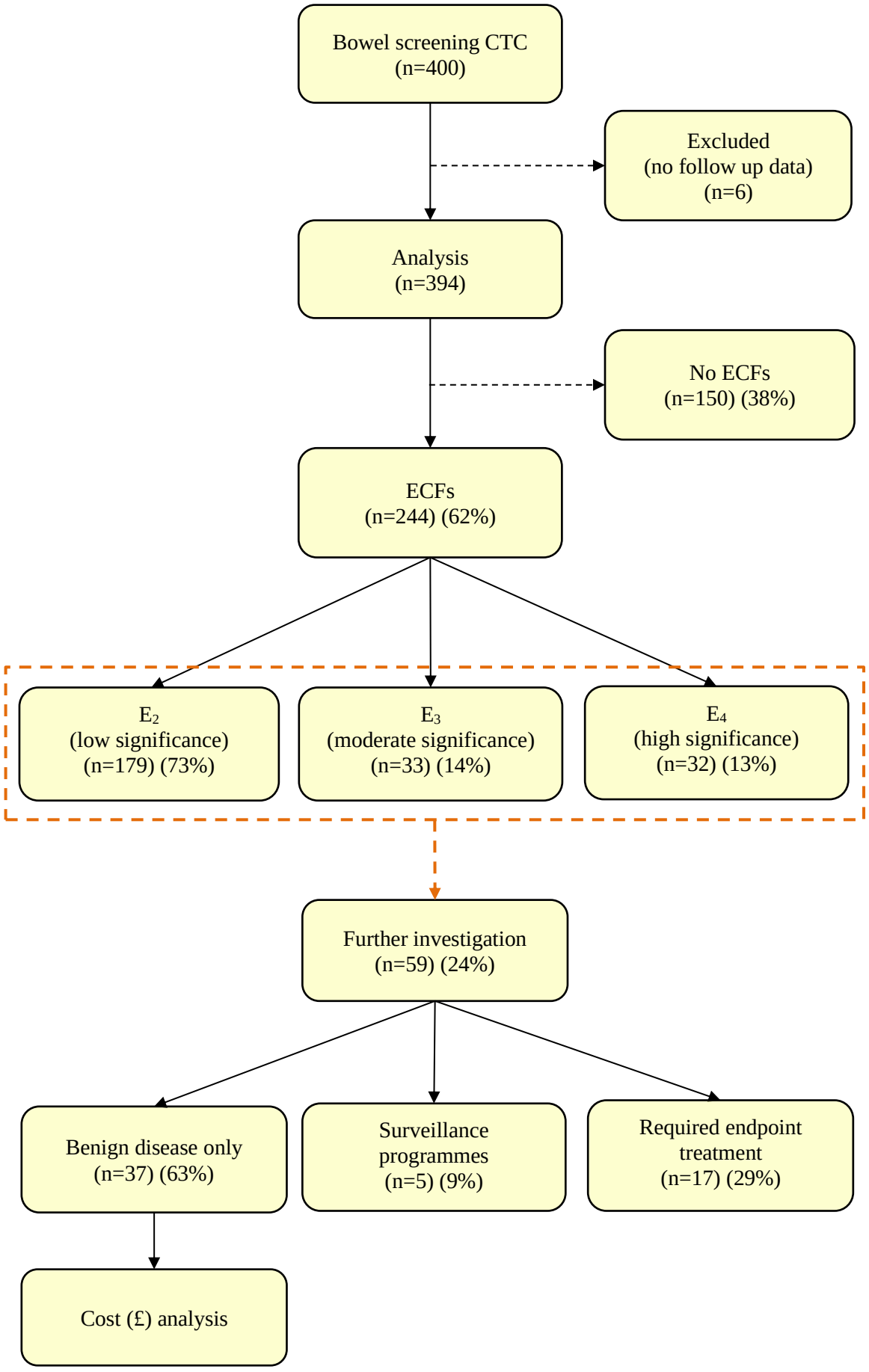


Figure 6.2: Outcomes from CTC in relation to ECFs



Outcomes, investigations and treatments related to incidental ECFs

In considering the study group as a whole (n=394), 59 (15%) patients required further investigation for incidental ECFs [**Figure 6.2].** This represented 24% of the 244 patients with ECFs. 17 (29%) patients required endpoint treatment as a direct result of ECFs, and 5 (9%) were entered into radiological surveillance programmes. Of the 5 patients entered into surveillance programmes, 3 were entered into a programme of regular abdominal aortic aneurysm (AAA) surveillance, 1 underwent regular review of a common iliac artery stenosis, and 1 was entered into CT surveillance for lung nodules. Of the 17 (29%) patients requiring endpoint treatment, 10 required major surgery. There were 3 AAA repairs, 2 pulmonary lobectomies, 1 small bowel resection, 1 colonic resection (non-neoplastic colovaginal fistula), 1 de-functioning colostomy (non-neoplastic colovesical fistula), 1 nephrectomy and 1 hysterectomy. 3 patients began chemotherapy or radiotherapy for metastatic malignancy (breast, gastric, lung), 2 underwent endoscopic therapy including ERCP, while 2 patients (1 with Crohn's disease and 1 with benign prostatic hyperplasia) began lifelong medications.

Cost analysis relating to benign ECFs

37 (63%) patients who had further investigations for ECF were subsequently found have benign disease **[Figure 6.2]**, and these patients required a combined total of 112 clinical encounters **[Table 6.5]**. These included 46 outpatient appointments at the cost of £8,441, 5 invasive procedures (1 inpatient surgery, 1 day case surgery and 3 endoscopies) at the cost of £5,301, 43 radiological investigations at a cost of £3,405 and 18 laboratory tests at a cost of £442. The total estimated cost of investigating was ultimately benign disease over the study period was £17,589.

Host characteristics and the risk of ECFs

Table 6.6 displays the relationship between host characteristics and the risk of finding ECFs at CTC. Older patients were more likely to have ECFs ($p<0.05$). There was a linear relationship between advancing age and the risk of ECFs with OR 1.90 [95% CI; 1.03–3.52, $p<0.05$] and 2.49 [95% CI; 1.00–6.17, $p<0.05$] for those aged 65–74 years and ≥75 years respectively, when compared with those aged <55 years. There were no associations between other host characteristics and the risk of finding ECFs at CTC.

6.4 Discussion

The present study is the first to report the prevalence, cost and potential risks factors for incidental ECFs at CTC as part of a UK bowel screening programme. The results suggest that incidental ECFs are common and more frequently diagnosed in older patients. Moreover, although the majority of ECFs are of little clinical significance, a proportion require further investigation at a cost to the healthcare service. Furthermore, the likelihood of detecting important colorectal pathology by CTC as part of a bowel screening programme is lower than the likelihood of detecting ECFs.

CTC use is expected to increase

CTC remains an important adjunct to, or in some cases as an alternative to colonoscopy when performed as part of a bowel screening programme. The use of CTC continues to increase as it becomes more accessible and in the future patients may be allowed to choose this investigation modality following positive bowel screening (376). This would only be feasible if the patient was adequately counselled with regards to the risks and benefits of each procedure. In England and Wales, current guidelines do not recommend that patient choice should be considered a valid reason to refer for CTC (377). Furthermore, in England and Wales, bowel screening now begins at 50 years as opposed to the 60 years cut-off used previously, bringing the guidelines in line with Scotland (378). This will draw many more patients into screening and potentially CTC. For this reason, considering the implications of this test as part of screening is becoming more significant.

The advantages and disadvantages of CTC within a bowel screening population

CTC offers a number of advantages over colonoscopy. The examination is quicker, does not require the use of sedation and is generally well-tolerated. Generally, bowel preparation is milder, and there is no absolute requirement for intravenous contrast, thus reducing the risk of anaphylaxis (376). Many patients report CTC as more comfortable than colonoscopy

(105). The required dose of radiation for CTC is significantly lower than that used in standard CT scanning because of the high contrast between the air-filled colonic lumen and soft tissue (105). In addition, the risk of colonic perforation is low based on high volume studies (379, 380). Any test used for screening purposes must carry a low risk of returning false negative results since it is crucial not to miss pathology. A recent systematic review suggested that CTC is less sensitive for the overall detection of colonic lesions compared with colonoscopy (66.8% vs. 80.3% respectively) (106). Nonetheless, when considering larger polyps (≥1cm), sensitivity is comparable (91.2% vs. 92.9% for CTC and colonoscopy, respectively). When considering CRC only, large studies have reported a sensitivity of 96.1% [95% CI; 93.8%–97.7%] for CTC vs. 94.7% [95% CI; 90.4%–97.2%] for colonoscopy (381). The above studies would suggest that, when required, CTC can serve as an attractive substitute for colonoscopy in a bowel screening programme as larger polyps and cancer are unlikely to be missed.

The prevalence of ECFs

A consequence of CTC is the high prevalence of incidental ECFs and the subsequent costs to the patient and healthcare service. In the present study, ECFs were detected in a significant proportion of patients (62%), which is similar to the data in previously published reports where ECF detection rates range from 46–69% (108, 169, 368, 382). In the present study, 59 (15%) patients proceeded to further investigation as a result of ECF detection. Previous reports of potentially significant ECFs have ranged from 10–37%, while outlying studies have reported this to be as high as 45% (108, 171, 368, 369, 383-386) (365). The present study found that 32 (8%) patients had highly significant (C-RADS E_4) findings **[Figure 6.2]**, including malignancy and arterial aneurysmal disease which mirrors previous reports of 2–10% (108, 171, 383, 384, 386). The finding that 32 (8%) patients in the present study were found to have highly significant ECFs could form an argument in favour of CTC. However, this should be conducted with care since closer inspection determined that only around half

(4% of the entire cohort) of these patients went on to require treatment as a result. Therefore, although it appeared that the yield of important ECFs overall was relatively low, it is accepted that the value allocated to this finding is subjective. Furthermore, several of the more significant ECFs included metastatic malignancy that was unsuitable for curative intent treatment. It is questionable whether the finding of late-stage metastatic malignancy is of any physical or psychological benefit to the patient. Another consideration are the 5 (1%) patients who, as a result of ECFs, were entered into long-term surveillance programmes for lung nodules and vascular disease. The cost-effectiveness of surveillance programmes, outside of national screening, which is usually local-guideline driven, remains unclear.

The prevalence of ECFs vs. useful CRFs

Another key consideration when offering a patient CTC is to balance any potential disadvantages of detecting ECFs with the likelihood of yielding important CRFs, specifically colorectal neoplasia. This is especially important when a CTC is conducted as a completion test after a colonoscope may have been used to visualise as far as the splenic flexure, thus covering the region where 70% of colorectal malignancies are usually found. It follows that in this situation, the likelihood of finding additional colorectal pathology with a completion CTC is likely to be low at the outset. This is supported by the findings of the present study. Within a bowel screening cohort, the primary aim is to examine the colon and rectum. As such, any test should be justified with respect to the potential yield of useful pathology. The present study showed that in the overall cohort, 45 (11%) patients had significant CRF (neoplastic) detected by CTC and confirmed by colonoscopy. This is broadly similar to previous reports of 14% for low-risk symptomatic patients (387), but substantially lower than the 32% of symptomatic high-risk (for CRC) patients (382). Crucially, it is also much lower than the combined standard colonoscopy yield for adenomas and cancer (approximately 40% in the SBoSP; (375). This indicates that any additional yield of useful

CRF from a completion CTC in asymptomatic screening patients is low when compared with symptomatic and standard bowel screening patients.

CRF yield vs. ECF and patient consent

In the present study, the relatively low colorectal pathology yield of 11% mentioned above can be compared to the 15% of patients who required additional investigation for ECFs, the majority (63%) of which were subsequently benign. Therefore, the likelihood of significant ECFs is higher than useful CRFs in this bowel screening cohort and must be considered when consenting patients for a CTC. It should be made clear to patients that they are subject to a 15% chance of ECFs which may cause anxiety and require further investigation versus the 11% chance of finding colonic neoplastic pathology, the majority of which are benign. Despite this, several patients may be willing to accept the risks, given that 4% of the present study group had significant ECFs that required endpoint treatment.

In terms of consenting a patient for CTC, the above information amounts to a significant volume for a layperson as it is reasonably complex information. A significant number of patients in a screening cohort are elderly with comorbid disease. They may struggle to grasp or fully understand the implications of what they are consenting to. In this scenario, a significant responsibility remains with the clinician ordering the test who must use a balanced judgment to assess the risk: benefit ratio of that test for the specific patient on a case by case basis. Of particular interest in the present study was the finding that almost a quarter of patients (23%) had CTC as a first-line investigation, and the most common indication in these patients was a lack of fitness for colonoscopy. Thus, it is important to justify sending patients who are unfit for a colonoscopy, and therefore unlikely to be surgically fit, for a CTC whose primary aim is to detect colorectal malignancy but may, detect more ECFs.

Symptomatic vs. asymptomatic patients

Another key consideration for the care provider ordering a CTC relates specifically to the population for its intended use. In symptomatic patients, where clinical manifestations are largely non-specific (e.g. abdominal pain, a minor rectal bleed or change in bowel habit), the decision for CTC is easier to justify given its added benefit as a diagnostic test for the extracolonic organs. In fact, in a large study of 10,000 participants, the rate of extracolonic cancers diagnosed by CTC was higher than that of CRC at 0.35% vs. 0.21%, respectively (388). Furthermore, a UK study mentioned previously investigated the prevalence of ECFs and CRFs in high-risk symptomatic patients referred for CTC and reported that 32% had significant CRFs (14% CRC, 19% adenoma(382). In this situation, any additional ECF detected would be acceptable, given the prevalence of useful CRF. This patient group differs from the asymptomatic bowel screening cohort in the present study, where the likelihood of ECFs should be balanced more cautiously with the lower likelihood of CRFs.

The additional monetary cost of ECFs

Colonoscopy is the investigation of choice in the SBoSP, although it is accepted that CTC is a safe and suitable alternative (389). Nonetheless, the present study calculated the additional cost to the NHS from the investigation of benign ECFs to be £17,589, or an additional £45 per CTC. This reflects only a modest increase in cost, but may underestimate the true figure as discussed later. This is the first study to our knowledge that reports specifically on the additional costs of investigating subsequently benign disease. Previous studies in the USA have reported the additional cost of investigating ECFs as approximately $34–50 per CTC (108, 368). However, both studies considered the cost of additional, ECF-related, radiological tests only. Moreover, both studies calculated the cost of investigating any significant ECF regardless of whether they were benign or not. As such, it is difficult to draw comparisons with the present study, especially considering the differences between the private and public-funded healthcare systems of the USA and UK.

To date, only one previous study has estimated the cost of ECFs in the UK. Xiong *et al.,* in 2006, examined the CTC reports for patients referred from a "fast-track" CRC clinic and reported a higher estimated ECF-related cost of £153 per CTC (169) than the present study. However, their results are not comparable to the present study as the researchers calculated the cost to investigate and treat all ECFs, rather than calculating the cost of subsequently benign disease only. Nonetheless, it is of interest to compare this with the £45 additional cost (per CTC) of investigating only benign findings in the present study. It would seem reasonable that the additional £108 be spent on providing treatment for those who require it and who may benefit from the ECF findings.

The additional non-monetary costs of ECFs

Non-monetary costs of additional investigation related to ECFs include patient anxiety. In some cases this can be significant (390). In a publicly-funded health service such as the NHS, the undertaking of any voluntary screening test that potentially impacts on cost and patient anxiety should be carried out with caution. It should be considered that at the beginning of the bowel screening process, a patient is only initially consenting for an investigation of their colon and rectum, not their full abdomen and lung bases as would be the case with CTC. The present study was unable to capture the cost to patients in terms of anxiety and the potential discomfort of further investigations including endoscopy, biopsy, radiological investigation and, in some cases, surgical intervention. One patient in the present study underwent a laparotomy for what was found later to be benign disease. A diagnosis of ECFs that requires further investigation and is ultimately benign is akin to a false-positive result at bowel screening. A Scandinavian study by Brasso and co-workers demonstrated that patients suffered a similar degree and duration of anxiety when given a false positive bowel screening result compared with a true positive result (168). Although normal levels of anxiety returned by 12 months, these findings suggest there is a psychological impact as a result of false-positive results.

In contrast to this are the results of a study in 2014 by Plumb and co-workers (391). They used face-to-face interviews and interactive laptop presentations to assess the attitude of 50 healthcare professionals and 79 patients to false-positive ECFs at CTC. The interviews and interactive presentations used in the study were designed for participants to consider the implications of both false-positive results and subsequent investigations. Interestingly, although this was a small study in terms of numbers, the researchers found that patients were prepared to accept a high (99.8%) rate of additional imaging or invasive testing after CTC to reap the benefits of a potential early diagnosis of extracolonic malignancy (391). These results suggest that the impact of ECFs on patient anxiety is less of a concern than previously thought, and closer inspection may be of benefit.

Risk factors for detecting ECFs

Given that careful consideration must be made regarding the potential implications to the healthcare service and patients with ECFs, determining an "at-risk" population would be useful to aid decision making. In patients with a high risk of ECFs but a large burden of disease, clinicians may decide that the additional burden of potential ECFs would not be beneficial to the patient. For this reason, the present study sought to determine an "at-risk" patient population. Advancing age was associated with increased risk of ECFs. Those aged 65 years or older were approximately twice as likely to have ECFs than those younger than 65 years ($p<0.05$). This is in agreement with previously published work (367). BMI, visceral obesity, sarcopenia, social deprivation and smoking were not associated with a higher incidence of ECFs. Therefore, the present study can only suggest advancing age as a risk factor for ECFs. Clinicians should take this into account when considering the possible burden of ECFs on older patients prior to requesting a CTC.

Strengths and limitations

The present study is the first to report the implications and costs of ECFs as a result of CTC in a UK bowel screening population, addressing an important and relevant topic. There were minimal patients lost to follow-up, allowing the use of an almost complete data set for analysis. The present study benefitted from an extended follow-up period (median 72 months) thus enabling adequate time for completion of follow-up investigations to resolution.

There are a number of limitations, however. The present study may underestimate the monetary cost of post-CTC investigations since data collection was only available from the role out of the SBoSP in 2009 to date of censor in August 2018. Some patients, such as those undergoing long-term surveillance, may continue on this path lifelong, or at some point require invasive investigation (e.g. CT-guided biopsy for indeterminate lung lesions). This prolonged follow-up is not captured in the present study. In addition, the retrospective nature of the present study meant it was unable to account for any associated primary care attendances, additional radiological reporting time, or hidden costs such as administration and transport. Furthermore, the present study was unable to quantify the non-monetary costs of ECFs to patients such as travel inconvenience, lost working hours, loss of productivity, anxiety, and discomfort from investigations. Nor was the present study able to estimate how long any anxiety persisted. Finally, patients being investigated by CTC as an alternative or adjunct to colonoscopy are likely to have a higher burden of comorbid disease and may be less representative of a standard bowel screening cohort.

Final conclusions and future work required

CTC is likely to remain as a commonly utilised test within the UK Bowel Screening Programmes. It is feasible that its use will increase, both as technology advances and radiological tests improve, and as a result of an ageing population that is increasingly unfit for colonoscopy. The present study highlights some of the issues arising from the decision to offer CTC to patients in a bowel screening cohort, and in particular, those who are asymptomatic. Furthermore, the present study reports that ECFs are very common and more likely with advancing age. Within a bowel screening population, the incidence of ECFs may be higher than the useful yield of colonic findings at CTC. The implications of this in terms of further investigation, should be carefully discussed with the patient as part of the consent process. CTC as a test should be used judiciously in screening patients. Clinicians should have an awareness of the potential additional cost to both the healthcare service and the patient, both in financial terms and in terms of morbidity.

Table 6.1: C-RADS classification and examples of CRFs at CTC

C-RADS classification	Explanation and examples
C_0 Inadequate study	Inadequate preparation, inadequate insufflation
C_1 Normal colon or benign lesion	No polyp >5mm, recommend routine screening with CTC or colonoscopy in 5 years
C_2 Intermediate polyp or indeterminate finding	Polyps 6–9mm, <3 in number, recommend CTC surveillance or colonoscopy and polypectomy
C_3 Polyp, possibly advanced adenoma	Polyps ≥1cm, ≥3 polyps with each 6–9mm, recommend colonoscopy with polypectomy
C_4 Colorectal mass, likely malignant	Lesion compromises bowel lumen, shows extracolonic invasion, recommended surgical review

Table 6.2: C-RADS classification and examples of ECFs at CTC

C-RADS classification	Explanation and examples
E_0 Limited examination	**Excluded scan** Scan compromised by artefact, evaluation of extracolonic tissues limited
E_1 Normal examination or anatomic variant	**No ECFs** Extracolonic abnormalities visible, no workup indicated
E_2 Clinically unimportant finding	**Low significance minor findings** Benign conditions that do not require further medical therapy or additional work-up • Calcifications • Granulomas • Diverticulosis • Simple organ cysts • Hernias without strangulation, obstruction or concerning features • Pleural thickening • Benign prostatic hypertrophy • Accessory spleen • Benign bony lesion • Bony degeneration and osteoarthritis • Fatty liver • Old renal infarction • Uterine fibroids • Simple ovarian cysts
E_3 Likely unimportant, incompletely characterised	**Intermediate significance moderate findings** Conditions not requiring immediate therapy but may require further investigation, clarification, monitoring or intervention at a later date • Simple calculi • Intermediate cysts • Pulmonary fibrosis • Pulmonary nodules • Inguinal hernia • Uterine myoma • Endometriosis • Pelvic fluid collection • Liver cirrhosis • Liver haemangioma • Bile duct dilatation
E_4 Potentially important finding	**High significance major findings** Lesions requiring immediate intervention and/or urgent investigation • A solid organ mass • Adrenal mass >3cm • Aortic aneurysm >3cm • Aortic dissection • Lymphadenopathy >1cm • Cardiomegaly • Pericardial effusion • Fistulation • Abscess • Small bowel infarction • Small bowel obstruction • Obstructing ureteric calculi • Complex ovarian cyst or adnexal mass • Lytic bone lesions

Table 6.3: Indications for CTC as part of the bowel screening process

Reason for CTC	n (%)
All patients	**394 (100)**
CTC after a failed colonoscopy	**302 (77)**
• Technical failure to complete colonoscopy	190 (63)
• Patient discomfort resulting in the withdrawal of consent	59 (19)
• Poor bowel preparation resulting in inadequate views or failure to progress colonoscopy	45 (15)
• Inadequate views	8 (3)
CTC as the first-line investigation	**92 (23)**
• Comorbidities resulting in an unreasonable risk of complications or technical difficulty	55 (14)
• Indication for CTC not clear from medical notes	13 (3)
• Patient choice/refusal for standard colonoscopy	12 (3)
• Previous failed optical colonoscopy either due to patient discomfort or technical difficulty	10 (3)
• Serious complication from previous standard colonoscopy (perforation)	1 (0.5)
• Patient unable to tolerate full bowel prep for standard colonoscopy	1 (0.5)

Table 6.4: Incidental ECFs on CTC by C-RADS criteria

C-RADS	All ECFs[1]	n (%)
		368 (100)
E_4	**High significance major findings**	**32 (9)**
	• Abdominal aortic aneurysm (AAA)	5
	• Lung mass, suspected malignancy	4
	• Complex adnexal mass (suspicious)	4
	• Bony lesion (possible metastases)	3
	• Renal mass (suspicious)	3
	• Organ-to-organ fistula	2
	• Pancreatic mass (suspicious)	2
	• Small bowel mass/abnormality (suspicious)	2
	• Pelvic collection	1
	• Peri-colic collection	1
	• Spinal stenosis	1
	• Stomach mass	1
	• Abnormal gallbladder	1
	• Pulmonary arteriovenous malformation (bleeding risk)	1
	• Hydronephrosis (new/unexplained)	1
E_3	**Intermediate significance moderate findings**	**45 (12)**
	• Adnexal cystic lesion (benign)	9
	• Biliary duct dilatation (new/unexplained)	7
	• Osteopenia/osteoporosis	5
	• Lung nodules (indeterminate)	4
	• Atypical renal cysts (more likely benign)	3
	• Bulky uterus (indeterminate cause)	2
	• Common iliac artery stenosis (new)	2
	• Thickened endometrium	1
	• CBD stones	1
	• Abdominopelvic lymphadenopathy	1
	• Abnormal appearance of the common bile duct	1
	• Dermoid cyst	1
	• Breast tissue density (indeterminate)	1
	• Gastric polyp	1
	• Liver hypodense lesions (undefined)	1
	• Lytic bony lesion (low suspicion)	1
	• Non-aortic small vascular aneurysm	1
	• Pancreatic cyst (low suspicion)	1
	• Prostatic enlargement	1
	• Splenic artery aneurysm	1
E_2	**Low significance minor findings**	**291 (79)**
	• Liver cysts (benign)	40
	• Cholelithiasis	39
	• Renal cysts (benign)	38
	• Spinal degenerative change (bony or disc)	32
	• Fatty liver	31
	• Hiatus hernia	30
	• Adrenal adenoma	15
	• Renal calculi	8
	• Inguinal hernia	9
	• Uterine fibroids	6

• Ventral abdominal wall hernia	7
• Spinal wedge fracture	6
• Renal cortical scarring	5
• Spondylolisthesis	5
• Chronic pancreatitis	3
• Pleural plaques (chronic)	3
• Benign prostatic enlargement	2
• Haemangioma of liver	2
• Small bowel diverticulum	2
• Duodenal lipoma	1
• Renal atrophy	1
• Splenic atrophy	1
• Rib fracture	1
• Duplex kidney	1
• Neurofibroma	1
• Meckel's diverticulum	1
• Gastric diverticulum	1

[1]244 patients had a total of 368 ECFs

Table 6.5: Itemised cost of the clinical workup for subsequently benign ECFs

Clinical encounter	n	Method / coding used to calculate cost	Per item (£)	Total (£)
All clinical encounters	**112**			**17,589**
Outpatient appointment	**46**			**8,441**
Gynaecology	19	Consultant outpatient clinic per visit NHS GGC	201	3,819
General Surgery	15	Consultant outpatient clinic per visit NHS GGC	162	2,430
Urology	5	Consultant outpatient clinic per visit NHS GGC	145	725
Radiology[1]	2	Consultant outpatient clinic per visit NHS GGC	199	398
Haematology	2	Consultant outpatient clinic per visit NHS GGC	266	532
Neurosurgery	1	Consultant outpatient clinic per visit NHS GGC	200	200
Vascular Surgery	1	Consultant outpatient clinic per visit NHS GGC	175	175
Breast	1	Consultant outpatient clinic per visit NHS GGC	162	162
Invasive test/treatment	**5**			**5,301**
Endoscopy[2]	3	Day case gastroenterology per case NHS GGC	654	1,962
Inpatient surgery[3]	1	Inpatient gynaecology per case NHS GGC	2,549	2,549
Day case surgery[4]	1	Day surgery general surgery per case NHS GGC	790	790
Radiology investigation	**43**			**3,405**
US[5] Scan	20	US scan Glasgow Royal Infirmary	48	960
CT[5] Scan	12	CT scan Glasgow Royal Infirmary	77	924
MRI[5] Scan	6	MRI Glasgow Royal Infirmary	180	1,080
Isotope bone scan	2	Gamma camera Glasgow Royal Infirmary	150	300
Plain x-ray/mammogram	2	Classed as "other radiology" NHS GGC	47	94
DEXA Scan[6]	1	Classed as "other radiology" NHS GGC	47	47
Laboratory tests	**18**			**442**
Blood tests	14	Laboratory cost per day as inpatient NHS GGC	25	350
Tissue biopsy[7]	4	Cost per examination of specimen NHS GGC	23	92

[1]Classed as "medical other" outpatient clinic in costing book
[2]Included diagnostic and therapeutic endoscopy
[3]Laparotomy and ovarian cystectomy
[4]Open lymph node biopsy
[5]Abbreviations as previously defined
[6]Dual energy x-ray absorptiometry (DEXA)
[7]Cost to examine the specimen does not include the cost of collecting the specimen

Table 6.6: The relationship between host characteristics and the incidence of ECFs at CTC

Baseline characteristics	All patients (%)	No ECFs (%)	ECFs (%)	OR (univariable)	p-value
All patients	394 (100)	244 (62)	150 (38)		
Age (years)					
<55	55 (14)	28 (19)	27 (11)	1.0	-
55–64	135 (34)	52 (35)	83 (34)	1.66 [0.88–3.11]	-
65–74	170 (43)	60 (40)	110 (45)	1.90 [1.03–3.52]	-
75+	34 (9)	10 (6)	24 (10)	2.49 [1.00–6.17]	**0.03**
Sex					
Female	248 (63)	92 (61)	156 (64)	-	-
Male	146 (37)	58 (39)	88 (36)	0.89 [0.59–1.36]	0.60
BMI[1] (kg/m^2) groups					
20–24.9 (normal weight)	75 (24)	30 (25)	45 (23)	1.0	-
<20 (underweight)	22 (7)	9 (7)	13 (7)	0.96 [0.37–2.53]	-
25–29 (overweight)	90 (29)	40 (33)	50 (26)	0.83 [0.45–1.55]	-
30+ (obese)	127 (40)	43 (35)	84 (44)	1.30 [0.72–2.35]	0.41
Visceral obesity (*all sexes*)					
No	79 (23)	30 (24)	49 (22)	-	-
Yes	272 (77)	95 (76)	177 (78)	1.14 [0.68–1.92]	0.62
High SFI[2]					
No	38 (13)	16 (16)	22 (12)	-	-
Yes	246 (87)	87 (84)	159 (88)	1.33 [0.66–2.66]	0.42
Sarcopenia[2]					
No	131 (46)	50 (49)	81 (45)	-	-
Yes	153 (54)	53 (51)	100 (55)	1.17 [0.72–1.89]	0.54
Social deprivation quintile					
5 (least deprived)	68 (18)	22 (15)	46 (19)	1.0	-
4	45 (12)	15 (10)	30 (13)	0.96 [0.43–2.13]	-
3	60 (15)	22 (15)	38 (16)	0.83 [0.39–1.72]	-
2	79 (20)	35 (23)	44 (18)	0.60 [0.31–1.18]	-
1 (most deprived)	137 (35)	56 (37)	81 (34)	0.69 [0.38–1.28]	0.13
Smoking status					
Never smoked	133 (35)	46 (31)	87 (37)	-	-
Ever smoked	249 (65)	101 (69)	148 (63)	0.78 [0.50–1.20]	0.25
CTC first-line test[2]					
No	302 (77)	193 (71)	109 (73)	-	-
Yes	92 (23)	51 (21)	41 (27)	1.42 [0.89–2.29]	0.14
Intracolonic findings					
Nil	349 (89)	132 (88)	217 (89)	1.0	-
Adenoma	36 (9)	17 (11)	19 (8)	0.68 [0.34–1.35]	-
Cancer	9 (2)	1 (1)	8 (3)	4.87 [0.60–39.35]	0.13

[1]Data available for 314 patients
[2]Data reliant on height measurement. Available for 284 patients
[3]CTC first-line in those who went straight to CTC without a prior colonoscopy

7 CONCLUSIONS AND FUTURE WORK

7.1 Overview of thesis

Colorectal cancer has been associated with a number of risk factors. Some of these risk factors are modifiable, while others are not. In order to minimise CRC incidence, an understanding of the risk factors themselves and how they might be modified is of high importance. From the outset of this research project, it was clear that colorectal adenomas, as pre-malignant entities, are modifiable risk factor for CRC.

Logic dictates there are two ways in which this risk factor can be modified. Firstly, by reducing primary adenoma incidence and secondly, by reducing recurrence in those who have undergone polypectomy. Identifying risk factors for adenoma incidence and recurrence and setting out to modify and mitigate them is likely to be of benefit in reducing subsequent CRC incidence.

Although previous work has been conducted examining the influence of various risk factors for incident and recurrent colorectal adenomas, there is significant heterogeneity between study designs. At the time of writing this thesis, there was a lack of uniform agreement on which risk factors are most relevant, the magnitude of their effect, the interaction between them, and the applicability of the results to different populations. This explains why post-polypectomy guidelines are in constant evolution and may demonstrate why those from the UK, EU and USA differ. Therefore, contributing to the knowledge base in this important and costly topic was of value.

In Scotland, adenomas are most commonly identified as a result of the bowel screening programme. Post-polypectomy surveillance is costly to both the patient and to healthcare services. Screening was still largely in its infancy in Scotland at the start of this research period having been rolled out in 2009. Examining the factors associated with adenoma

incidence and recurrence in this specific group; the better to target finite resources, was desirable. The literature was notable in that a sizeable body of work examining adenoma risk factors originated in the USA and Southeast Asia. There are clear social, demographic, physical and racial differences between patients from Southeast Asia and the UK, and more specifically, the Scottish population. As such, the validity of these studies as a guide to adenoma risk factors, their modification, and post-polypectomy surveillance, within a West of Scotland bowel screening population is questionable.

At the beginning of this period of research, the current BSG guidelines for post-polypectomy surveillance recommended follow-up colonoscopy based solely on the size and multiplicity of colorectal adenomas found at the index colonoscopy (15). It was unclear to what extent it was possible to detach the host from the adenoma; therefore, an examination of the association between adenoma incidence and recurrence, and non-adenoma host factors such as age, sex, BMI, social deprivation and body composition was of interest.

Chapter 1 provided an overview of CRC, summarising the implicated risk factors, treatment, and prognostic indicators. CRC screening was discussed, including the rationale, outcomes and risks of screening. Moreover, a detailed overview of the classification, natural history, suspected risk factors and management of adenomatous polyps of the colon and rectum was outlined.

Chapter 2 explored the relationship between host factors and their influence on colorectal adenoma recurrence after polypectomy; the aim of which was to quantify the association between age, sex, BMI and adenoma recurrence. These three variables were selected as they represent host characteristics that are quantifiable and could be used to group patients for a personalised screening and post-polypectomy surveillance schedule. An attempt was made to identify an “at-risk” group which would allow optimal utilisation of surveillance colonoscopy in a selected group of individuals with the highest risk of developing future

adenomas, advanced adenomas, or cancer. The results are presented as a systematic review and meta-analysis, which pooled raw data available in the published literature. The meta-analysis suggested that worldwide, advancing age, male sex and higher BMI were risk factors for adenoma recurrence. However, there were limitations with significant heterogeneity between study design, sample population and reporting of results. This questioned the validity of the results in a West of Scotland population. Nonetheless, the findings did present an argument for host factors to be considered in future surveillance guidelines.

With this in mind, the work presented in **Chapter 3** was designed to examine the role of host characteristics in identifying a high-risk group for adenoma and advanced adenoma recurrence in a representative UK screening population. This was conducted by collecting original data from the first round of the West of Scotland Bowel Screening Programme, the benefit of which was an extended median follow-up time of >6 years. In addition, Chapter 3 also explored the association between adenoma-specific factors and the risk of recurrence, since adenoma size and multiplicity are included in UK post-polypectomy guidelines. The analysis suggested that a higher adenoma number was associated with recurrence at surveillance but not advanced adenoma recurrence. In addition, the presence of advanced adenomas at baseline was associated with subsequent advanced adenomas at follow-up. However, the analysis did not support the incorporation of host factors into existing surveillance guidelines with the results supporting the current BSG guidelines. Nonetheless, the research did suggest that patients with advanced adenomas, in addition to those with multiple and large adenomas, should be considered as high-risk for surveillance purposes. Importantly, the results support the new inclusion and definition of "advanced adenomas" in the latest 2020 BSG surveillance guidelines that were published during the latter stages of thesis preparation (392). Finally, although the present study did not find an association between BMI and adenoma recurrence, there was evidence of a weak association between

BMI and the development of subsequent advanced adenomas. Based on this, and given the modifiable nature of BMI as well as other measures of body composition, further evaluation of this relationship was warranted, which formed the basis of **Chapters 4** and **5**.

The main aim of **Chapter 4** was to gain insight into the determinants of initial colorectal neoplasia formation as opposed to recurrence. Of particular interest was the SIR. It is well established that systemic inflammation is associated with poor prognosis and survival in established CRC. However, the stage at which this systemic inflammation can modify the cancer development pathway, and the mechanisms that underpin it, are complex and not fully understood. This chapter examined the relationship between host characteristics, colorectal neoplastic incidence, and the SIR, with a focus on pre-malignant disease. A prospective cross-sectional study was designed to gather data over a two-year period to determine these relationships. The study found evidence for an association between advancing age and colorectal neoplasia. In addition, when adjusting for age, smoking and CRP, subjects taking aspirin were less likely to have neoplasia, a finding which has previously been reported in a wide-ranging systematic review (393). A link between clinically detectable systemic inflammation and neoplasia incidence was not found. It is likely that the level of inflammation during the pre-malignant disease stage is at a low level and may not be detected clinically. However, it is plausible that this low-grade inflammation contributes to genetic damage in the pre-malignant stage and thereafter, a tumour promoting effect leading to established cancer. In the initial stages of this project, there was consideration given to host characteristics strongly associated with CRC (e.g. advanced age, male sex and higher BMI). Logic suggests there was a linking mechanism between these host factors, the development and progression of neoplastic lesions, and the SIR appeared to be a plausible link. The results demonstrated that systemic inflammation at a clinically detectable level was significantly associated with higher BMI, smoking and possibly with increased socioeconomic deprivation. There was no demonstrable evidence for a direct link

between host factors, systemic inflammation and neoplasia. The use of a cross-sectional study design to examine systemic inflammation may be suboptimal, and further work could be considered to explore this.

Chapter 5 examined the relationship between CT-derived body composition and colorectal neoplasia in a bowel screening population. The results of the meta-analysis in **Chapter 2** suggested higher BMI was associated with colorectal neoplasia in the form of adenoma recurrence, yet work in **Chapter 3,** and **Chapter 4** failed to replicate this finding in a bowel screening population, potentially as a result of varying patient demographics, as mentioned previously. However, having noted that higher BMI was associated with systemic inflammation in **Chapter 4,** and given the known links between inflammation and cancer, it was considered that adiposity might still be associated with early neoplastic formation and that BMI was not the optimal measurement. Accordingly, work to explore the relationship between adiposity in different body compartments and colorectal neoplasia was undertaken. The results presented in **Chapter 5** showed that visceral obesity was associated with increased colorectal neoplasia incidence, even when the data were adjusted for age and sex. VAT is known to be associated with metabolic disturbance and cardiovascular disease. It is therefore likely that hormones synthesised in this tissue play a part in early genetic damage and neoplasia formation. In addition, sarcopenia is a feature of established CRC and cancer cachexia. The results did not support an appreciable association between sarcopenia and colorectal neoplasia in this population. The study group however, were largely patients with pre-malignant adenomas rather than established neoplasia. It is likely that this feature becomes more evident during the transition from the pre-malignant disease to established cancer.

In conducting research for **Chapter 5,** the resource burden of the bowel screening programme was noted. Despite the benefits of screening, there are risks involved, and the question arose as to what extent screening should be pursued at all costs? During the analysis

of CTC scans for **Chapter 5** it was noted that the patient being deemed unfit for colonoscopy was often an indication for the utilisation of CTC. Patients deemed unfit, or borderline, for colonoscopy would not likely be fit for subsequent curative intent cancer treatment. This raised the question as to whether investigating these patients was the most efficient use of limited resources.

Chapter 6 sought to estimate the prevalence, outcomes, and costs of ECFs in an asymptomatic bowel screening population, the first study of its kind in the UK. The detection of a significant number of ECFs is a problem of particular note in a bowel screening population where the aim is to examine the colon and rectum specifically. When volunteering for screening, a patient is only consenting to have their colon and rectum investigated at the outset. However, although 11% of patients were found to have significant colorectal findings, 15% were actually found to have significant ECFs that required additional workup. The majority of these were subsequently found to be benign. This chapter concluded that careful consideration and consenting is important when offering a patient any test to screen the colon and rectum that will also screen the entire abdomen and lung bases, with a higher chance of detecting non-colorectal, indeterminate disease. Patients must be made aware of the disadvantages of this approach and the potential useful yield, while clinicians need to be aware of the potential burdens on both healthcare resources and their patients before proceeding to CTC as a screening test, in a largely unfit population.

7.2 Future work

This thesis is an examination of the interplay between the pre-malignant neoplasm and the host, the better to prevent neoplastic formation and recurrence. **Chapter 3** indicated that adenoma factors seemed to be stronger predictors of future risk than host factors and, therefore, future work should focus more specifically on the adenoma. The consideration of this has, in part, led to the launch of the Integrated Technologies for Improved Polyp Surveillance (INCISE) project; a multi-million-pound project, led by the University of Glasgow and NHS GGC. The aim of the project is to combine the latest developments in digital pathology with genomic and transcriptomic analyses of excised polyps. The INCISE project will utilise machine learning to develop a risk-stratification tool to better determine the need for follow-up colonoscopy after polypectomy. During the period of thesis preparation, the BSG released their updated 2020 guidelines on post-polypectomy surveillance. For the first time, as a marked deviation from the 2010 guidelines, it is notable that specific adenoma features (e.g. HGD) are included in the definition of an advanced adenoma for risk stratification (392). This further highlights the need for ongoing examination of the pre-malignant polyp and how it may aid prediction of future risk (394).

Moreover, UK guidelines for post-polypectomy surveillance have historically considered all adenomas of the colon and rectum as one entity for screening, risk stratification and surveillance purposes. This is unchanged in the most recent guidelines. However, it is known that the acquisition of mutations appear to vary between tumours of the colon and rectum. Their management differs substantially, especially with regards to neoadjuvant and adjuvant treatment. Although data were not available to examine this during the present study period, future work may consider colon and rectal adenomas as separate entities. This may enable the separate study of their behaviour both in isolation and in combination with host characteristics. It may be that rectal adenomas and colonic adenomas should be treated

separately, given the disparity in incidence between CRCs of the proximal and distal portions of the colon or rectum.

The relationship between the SIR and early, largely pre-malignant disease was explored in **Chapter 4**. No association was found between systemic inflammation and the presence of colorectal neoplasia. Nonetheless, during thesis preparation, a well-conducted study was published in 2020, suggesting that elevated CRP was associated with colorectal adenomas incidence (395). The researchers report the OR of finding a colorectal adenoma as 1.71 [95% CI; 1.12–2.62, $p<0.05$] in males and 2.86 [95% CI; 1.26–6.49, $p>0.05$] in females when comparing the highest quartile CRP group to the lowest. The results were even more pronounced when considering advanced adenomas. The researchers used 23,000 patients with laboratory CRP measurements to validate a predicted CRP model based on patient characteristics. They achieved consistent results when using either laboratory or predicted CRP measurements.

Therefore, further examination of the relationship between systemic inflammation and pre-malignant disease is warranted. Ethical approval for an extension of the study time frame in the prospective study reported in **Chapter 4** was granted during the writing of this thesis. Ongoing data are being collected on CRP, BMI, host characteristics and bowel screening outcomes. This will enable further detailed analyses with enhanced study numbers and follow-up. Additional data are also being collected regarding dietary habits, and faecal samples for calprotectin have been requested. These data will enable future expansion of the work presented in **Chapter 4** to include a more in-depth analysis of the association between systemic inflammation, local intra-colonic inflammation, dietary habits and early colorectal neoplasia.

Building on the results of **Chapter 5** which examined the relationship between body composition and colorectal neoplasia, it would be useful to compare the characteristics of

this screening group who are largely pre-malignant, with those who have established cancer. Exploring body composition differences between patients with pre-malignant disease and established cancer could enable a further understanding of the changes that take place during this transition, paving the way for further studies to evaluate the precise mechanisms that underpin this relationship.

The clear association between visceral obesity and colorectal neoplasia reported in **Chapter 5**, indicates that there may be a "teachable moment" for bowel screening patients. The relationship between visceral obesity and metabolic syndrome is well known. A recent large epidemiological study in South Korea suggested that metabolic syndrome is associated with CRC development independently from sex, HR 1.22 [95% CI; 1.20–1.24] (396). The researchers note that the association is stronger in males than in females and that abdominal obesity, according to WC using an Asia-Pacific cut-off, is a leading risk factor (397). However, it is not clear to what extent abdominal obesity is associated with or reflects visceral obesity in this population. Further studies examining this relationship would be useful.

In addition, the well-established links between visceral obesity and metabolic syndrome, non-insulin dependent diabetes and cardiovascular disease suggest that targeted diet and exercise regimes to reduce visceral obesity specifically may be a worthwhile interventional option(398). Indeed, this is an area of active research where the potential benefits may extend beyond CRC prevention to other comorbid diseases. Of interest, a recent report discussed the elevated incidence of major cardiovascular events (MACE) in survivors of CRC (399). The increased prevalence of MACE may limit the ongoing improvement in overall survival. The researchers examined a cohort of 2,839 CRC survivors, within 10 years of diagnosis. They determined that while BMI was of limited use in predicting MACE, visceral adiposity and muscle radiodensity were predictors of risk. Further work in this field and development

of a cancer-specific MACE scoring system could allow physicians to refine risk management for this growing population of cancer survivors.

The fight against colorectal cancer is an ongoing one, however it is encouraging to observe the extensive effort and resources that are dedicated to reducing incidence and mortality from this disease. It is hoped that the work carried out in this thesis, its continuation, and the recent extensive funding secured by the University of Glasgow will contribute positively to the improvement of colorectal cancer services for patients in the future.

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