Chemoprevention of colorectal cancer in inflammatory bowel diseases using routinely prescribed medications

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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- **Burr NE**, Lord R, Hull MA, et al. Decreasing Risk of First and Subsequent Surgeries in Patients with Crohn’s Disease in England from 1994 through 2013. Clin. Gastroenterol. Hepatol. 2018. The first author performed all the data analysis & wrote

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My own contributions, fully and explicitly indicated in the thesis, have been:

- Design of the thesis protocol.
- Ethics submissions.
- Design & conduct of the ResearchOne validation study.
- Design & conduct of the ResearchOne studies on the potential chemopreventative agents.
- Drafting all manuscripts. First author of all published research.

The other members of the group and their contributions have been as follows:

- Design of the study protocols (MAH, VS)
- Analysis of results (VS)
- Review of submitted manuscripts (MAH, VS)
- Design of the thesis (MAH, VS)

Abstract

Introduction

Colorectal cancer (CRC) is one of the most serious complications of colonic inflammatory bowel diseases. As with any disease, prevention is better than cure and there are several medications used for the condition itself or associated co-morbidity that are potential candidates for the chemoprevention of CRC.

Aims

- To scrutinise the available literature for the potential role of routinely prescribed medications for the chemoprevention of inflammatory bowel disease associated CRC (IBD-CRC).
- To validate the use of the ResearchOne primary care database for use in healthcare research.
- To describe the epidemiology of IBD-CRC cases in the ResearchOne primary care database.
- To assess the role of routinely prescribed medications in the chemoprevention of IBD-CRC within ResearchOne.

Methods

Two systematic reviews and meta-analyses were conducted to assess the role of folate and aspirin or non-aspirin non-steroidal anti-inflammatory agents in the chemoprevention of IBD-CRC. To validate the ResearchOne database, one hundred and forty-seven patients were consented and recruited from hospital IBD clinics and their primary care record was compared with the hospital records. A descriptive analysis was made of the ResearchOne

IBD cohort and trends in numbers of IBD-CRC were explored. Finally, a series of nested case control studies were performed to assess the potential role of routinely prescribed medications in preventing CRC in those with IBD. Potential adverse associations with these medications were also explored.

Results

From the limited available evidence, non-aspirin non-steroidal anti-inflammatory medications (NA-NSAID) or aspirin use does not appear to be chemopreventative for CRC in patients with IBD. Following meta-analysis, folate prescription was negatively associated with the development of IBD-CRC (HR 0.58, 95% CI 0.37 to 0.80). Based on the validation study, the ResearchOne database appears a valid resource for healthcare research. These data showed that IBD diagnoses were recorded in 98% of patients, 93% had the correct IBD subtype, and 85% had the first date of diagnosis accurate to within 12 months. In a series of nested case-control studies using the ResearchOne database, 5-ASA medications (OR 0.32, 95% CI 0.23 to 0.45), immunomodulators (OR 0.49, 95% CI 0.31 to 0.79), NA-NSAIDs (OR 0.68, 95% CI 0.49 to 0.95), non-aspirin antiplatelets (OR 0.41, 95% CI 0.20 to 0.84), and statins (OR 0.55, 95% CI 0.37 to 0.81) were negatively associated with IBD-CRC. Statins showed a potential dose association with high dose drugs having a lower odds of IBD-CRC. Statin lipophilicity also was important with lipophilic, but not hydrophilic drugs having a significant association. Being prescribed a statin medication was significantly associated with a reduced number of steroid prescriptions, reduced need for surgical resection one year after diagnosis and reduced odds of being prescribed an immunomodulator medication one year after diagnosis.

Conclusions

CRC remains an important complication of IBD. The routine prescription of 5-ASA drugs, statins or folate supplementation may have a role in the chemoprevention of this disease. Dedicated prospective studies in high-risk groups are now needed. The use of statins may have the additional benefit of controlling disease activity.

Table of Contents

List of Tables

List of Figures

Chapter 1
Introduction

Chapter 1: Introduction

In this chapter I will discuss the problem of CRC in those with inflammatory bowel diseases. I will describe the epidemiology of the disease, and strategies that have been proposed to deal with it. I will highlight the level of evidence to date for chemoprevention using routinely prescribed medications and the possibilities for future work. I will then describe population datasets used in epidemiological research, including the ResearchOne primary care dataset.

1.1 Inflammatory Bowel Diseases

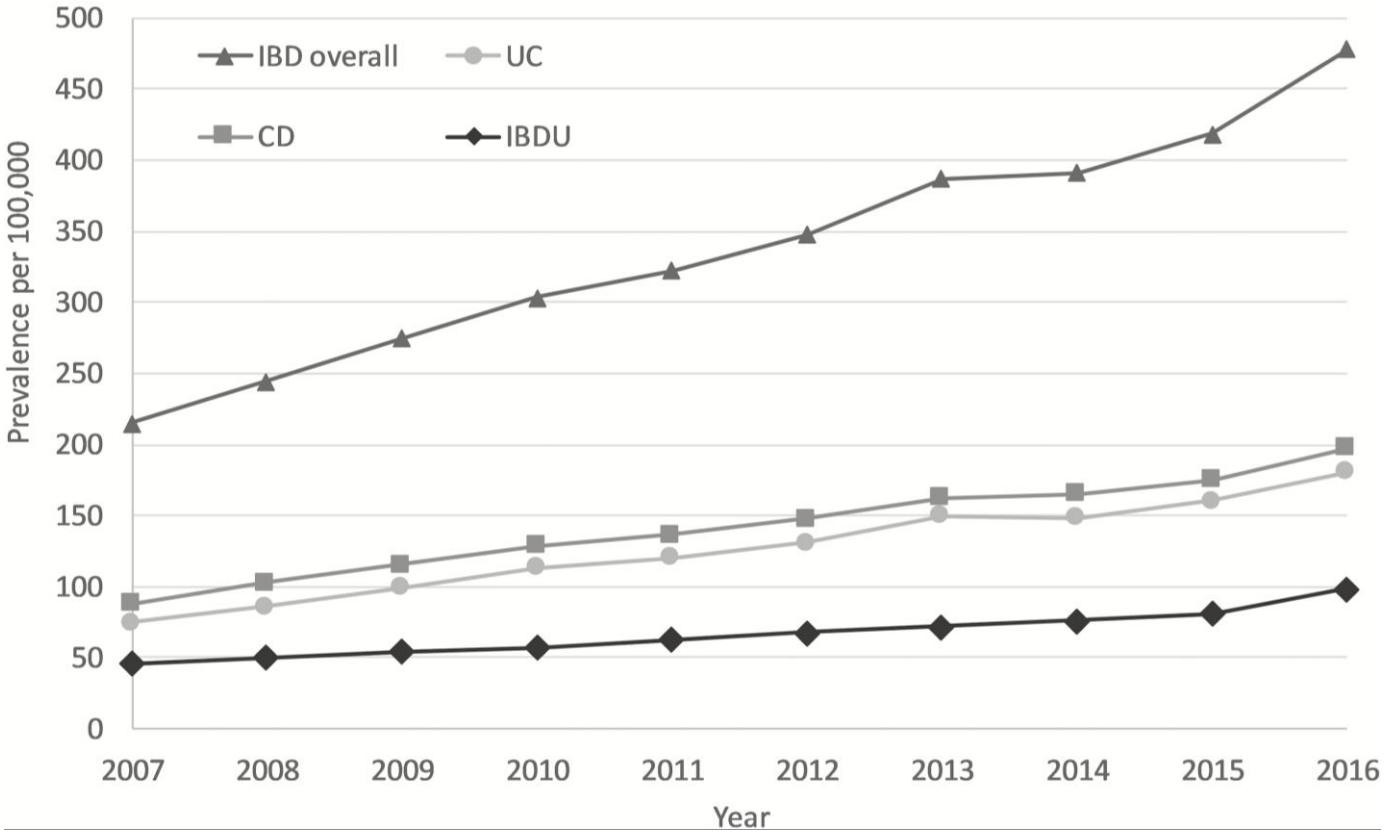
Inflammatory bowel diseases (IBD) are chronic diseases of the gastrointestinal tract with debilitating long-term sequelae and significant morbidity among those affected. The main types of IBD are ulcerative colitis (UC) and Crohn's disease (CD). UC causes continuous inflammation from the rectum to varying extents in the colon. CD causes transmural inflammation of the small and large bowel. Due to the transmural inflammation CD can be complicated by fibrotic strictures, which in turn can lead to luminal obstruction, perforations, abscesses and fistulae. A third category of IBD is indeterminate colitis, or IBD-unclassified (IBD-U) where no definitive categorisation of IBD can be made. Over time, often with more histological evidence, these individuals may be further classified as either CD or UC.

There is increasing evidence for genetic susceptibility to IBD. Contemporary studies have shown that 163 gene loci are associated with development of the diseases. (Jostins et al., 2012) IBD develops in these genetically predisposed individuals who develop an altered immune response to gastrointestinal microbes after an environmental trigger. (Xavier and Podolsky, 2007) Established environmental associations with the disease are: cigarette smoking, appendicectomy, diet, psychological stress, and vitamin D. (Ananthakrishnan,

2015) There are differences for CD and UC, with smoking being positively associated with CD and negatively with UC.

IBD can be diagnosed at any age, but most cases are diagnosed in childhood or early adulthood. (Loftus, 2004) There are modest sex differences with increased numbers of females being diagnosed with CD and a slight male predominance for UC. (Loftus, 2004) In the Western world the incidence of IBD started to rise rapidly in the mid-20th Century. At this time there was low prevalence of the disease. As IBD is typically diagnosed at a young age, has no known cure, and low mortality this has resulted in an exponential increase in prevalence of the diseases. (Ananthakrishnan, Kaplan and Ng, 2020) The combined prevalence of IBD is estimated at 396 per 100,000 population in the UK. (Stone, Mayberry and Baker, 2003) Recent population-based estimates from 2 large American insurance databases, encompassing over 60 million individuals, put the estimated prevalence at a higher rate at 478 per 100,000. This estimate translates to 1.2 million adults with the disease in the USA. (Ye et al., 2019) The prevalence of IBD is also increasing with the same study from American insurance populations showing a significant increase from 2007 to 2016 (Figure 1). The cost to the individual and healthcare systems of managing IBD in the Western world is considerable. There are increasing, expensive options in the treatment armamentarium for managing IBD, and as it affects people at working age the societal costs are large. In Europe there are an estimated 2.5 to 3 million people with IBD, with direct healthcare expenditure estimated at 4.6 to 5.6 billion euros. (Burisch et al., 2013).

Figure 1 Trend in adult IBD prevalence in the USA between 2007 and 2016. (Ye et al., 2019)



The peak age of incidence of CD is the third decade and UC incidence rises from the second decade and plateaus soon after. (Bernstein et al., 1999)

The precise aetiology of IBD remains unknown. There is a multifactorial development from an interaction between genetic susceptibility, environment, and immune dysfunction. Competing theories propose an abnormal immune response to a normal environment or an enhanced immune response to an abnormal environment. (Larabi, Barnich and Nguyen, 2020)Established risk factors for the development of IBD are white ethnicity, female sex, and positive family history. Primary sclerosing cholangitis is strongly associated with the development of IBD, with up to 90% of those with the condition developing UC. (Broomé et al., 1995)

In addition to the significant burden of illness affecting individuals in their prime productive years, the management of IBD is complex and resource intensive resulting in considerable health service use. (Hay and Hay, 1992) Hospital admission rates among patients with IBD, studied using the Hospital Episode Statistics (HES), showed that between 1989/1990 and 1999/2000 age-standardised admission rates for CD rose by 14 percent whilst admissions for UC rose by 6 per cent. (Lloyd et al.)

1.2 Colorectal Cancer in those with Inflammatory Bowel Diseases

Colorectal cancer (CRC) is one of the most serious complications of IBD. It is one of the most feared complications for those suffering with the conditions. (Lopez et al., 2016) Significant resource is spent on methods to prevent its development, detect early lesions and improve mortality. There are international guidelines on screening and surveillance for CRC in those with IBD from Britain (Cairns et al., 2010), Europe (Van Assche et al., 2013) and the United States, (Farraye et al., 2010) as well as an international collaboration and consensus statement in 2015. (Laine et al., 2015) Despite these resources and guidelines there is still some uncertainty about the current population risk of CRC, which groups should be

surveyed, the best method for surveillance, and the optimal interval between investigations. There is also a lack of evidence that surveillance prevents mortality in this population. (Bye et al., 2017)

1.3 Pathogenesis of IBD CRC

Cancer in the gastrointestinal tract results from several changes in epithelial cells. One of the first steps is often metaplasia, which is the change from one defined epithelium cell to another. (Humphries and Wright, 2008) This epithelium can be unstable and can further develop to dysplasia, the distortion of normal tissue architecture and cells. (Humphries and Wright, 2008)

There is accumulating evidence that cancers develop from a stem cell that accumulates the required genetic alterations for malignant potential. (Barker et al., 2009) This, cancer stem cell concept, (Clarke et al., 2006) suggests that a small number of these stem cells are able to divide and support a tumour.

The colonic mucosa is comprised of millions of finger like projections of epithelial cells called crypts. At the base of the crypts are a number of stem cells, which form the population of cells in the crypt lining. In certain environments stem cells can be lost resulting in one dominant cell lineage, called monoclonal cell expansion. For the number of crypts to increase during colon growth and development, or after destruction due to an insult such as colonic inflammation there needs to be a process of forming new crypts. This is called crypt fission, (Greaves et al., 2006) whereby one crypt is able to divide forming new identical crypts. If this is from an abnormal crypt with monoclonal cell lineage, the daughter crypts will have the same monoclonal lineage. This is the mechanism by which a single mutated cell lineage can expand to form a dysplastic lesion. The process usually takes many months to proceed but may be increased in inflammatory states with increased cell turnover. This is one

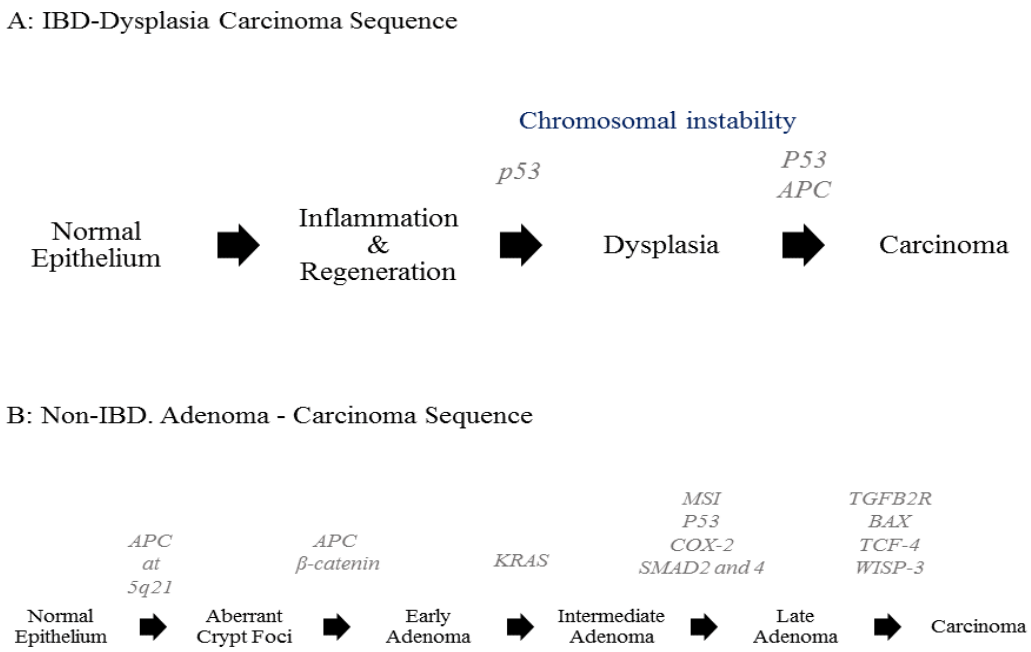
of the proposed mechanisms for the rapid growth of IBD-CRC. (Humphries and Wright, 2008; Wong et al., 2002)

IBD -associated CRC shares some similar molecular pathways with sporadic CRC, however there are also clear differences. Sporadic CRC develops along an adenoma – dysplastic polyp – malignancy sequence, with early loss of function of the adenomatosis polyposis coli (APC) tumour suppressor gene. (Vogelstein et al., 1988) The cellular mutations that occur later in sporadic CRC, such as loss of p53, occur much earlier in IBD CRC, (Leedham et al., 2009) with the loss of APC gene function occurring much later. This sequence of events may also progress much faster in IBD associated CRC.

Inflammation has been linked with cancer development. Various cytokines and chemokines are intimately involved with tumour growth and development. Tumour necrosis factor alpha (TNFα) is an inflammatory mediator whose expression is enhanced in several cancers including CRC and has been implicated in inflammatory infiltration, tumour angiogenesis, migration and invasion. (Waters, Pober and Bradley, 2013) Chronic inflammation is believed to be one of the main factors that drives carcinogenesis in IBD, which in turn leads to abnormal cell growth and DNA damage. (Murthy, Flanigan and Clearfield, 2002; Ullman and Itzkowitz, 2011)

Animal studies have shown that both the initiation and progression of neoplasia can be stimulated by inflammation. (Itzkowitz and Yio, 2004) Inflammation may play its role in carcinogenesis by exerting a “field effect” on the colonic mucosa. Analysis of mucosal specimens has shown that some of the molecular changes leading to carcinogenesis such as p53 mutations, (Brentnall et al., 1994) chromosomal, (Rabinovitch et al., 1999) and microsatellite instability (Willenbucher et al., 1999) can be present before the development of dysplasia, i.e. microscopically normal cells, or in areas of non-dysplastic colon in a patient with co-existing dysplasia or cancer.

Figure 1. Carcinoma sequence pathways for IBD associated colorectal cancer and sporadic colorectal cancer. (Matkowskyj et al., 2013)



The inflammatory bowel disease (IBD)–associated colorectal cancer pathway. Molecular changes in p53, followed by chromosomal instability, and finally b-catenin/WNT signalling (A). The adenoma-carcinoma sequence established in 1988 by Vogelstein (Vogelstein et al., 1988) as a stepwise progression of mutational activation of oncogenes and inactivation of tumour suppressor genes, resulting in cancer (B). Abbreviations: MSI, microsatellite instability.

1.4 Field carcinogenesis

The field carcinogenesis theory proposes that environmental and genetic factors contribute to a favourable environment for dysplasia and malignancy to develop. When synchronous (occurring at the same time) cancers are discovered they often share similar genetic mutations with each other. Field carcinogenesis is already well recognised in clinical practice for CRC. The risk of a proximal CRC is predicted by findings in the distal colon on sigmoidoscopy. (Imperiale et al., 2000; Levin et al., 1999) Patients with no lesions in their left colon are less likely to have right sided lesions as they have a less favourable colonic environment for carcinogenesis. The field carcinogenesis effect would explain some of the higher rates of synchronous, and metachronous (subsequent) cancers in patients with IBD.

Areas for potential improvement in early detection of IBD-CRC, may come in the identification of mutations and markers to identify those at greater risk of CRC. For sporadic colorectal cancer, optical detection of chromosomal instability, microsatellite instability and DNA methylation patterns are being developed with a view to using to them to risk-stratify patients. (Backman and Roy, 2013) It is worth bearing in mind, however that prospective studies of the effectiveness of these markers would be challenging in the IBD population due to the lower number of cases overall.

1.5 How IBD colorectal cancer differs from sporadic colorectal cancer

Those with IBD are at higher risk of synchronous and metachronous CRC. In a retrospective, single-centre series of surgical resections from patients with UC, 55% of specimens harboured synchronous dysplasia whilst 14% had synchronous malignancy. (Kiran et al., 2010) In a population study in the USA in 2012, there was a significantly greater number of metachronous malignancies in patients with IBD compared to those previously diagnosed with sporadic CRC (17% vs 12% respectively) (Gearhart et al., 2012)

IBD-CRC has worse outcomes than sporadic cancer. In a population analysis of individuals over the age of 65 in the US, cancer specific survival was worse for IBD-CRC than for sporadic counterparts with a mean survival of 33 months compared to 42 months. (Gearhart et al., 2012)

1.6 Epidemiology of IBD-CRC

Individuals with IBD are at increased risk of developing CRC, compared to those without the diseases. A landmark analysis for the increased risk came from Eaden *et al* in 2001. (Eaden, Abrams and Mayberry, 2001) Here, a cumulative incidence of 2% at 10 years and 8% at 20 years of follow-up was shown. There is now evidence that these estimates may have been overstated, but pooled population data still suggests an increased risk in UC with a pooled standardised incidence ratio of 2.4 (95% CI, 2.1 to 2.7). (Jess, Rungoe and Peyrin-Biroulet, 2012) Duration of the disease still appears to be one of the most important risk factors, the latest meta-analysis estimating the population risk of CRC in IBD at 0.8%, 2.2% and 4.5% after 10, 20 and >20 years of disease respectively. (Lutgens et al., 2013) For Crohn's colitis the risk of CRC is probably slightly lower than that for UC, the latest meta-analysis of population based studies reporting a standardised incidence ratio of 1.7 (95% CI, 1.01–2.5). (Lutgens et al., 2013)

1.7 Temporal trends of CRC in those with IBD

There have been recent conflicting data on whether the risk of IBD-CRC is declining. Studies from Sweden (Söderlund et al., 2009) and the USA (Herrinton et al., 2012) have reported an increase in IBD-CRC. A 2012 population-based study in Denmark has suggested a lower incidence of CRC than previously seen in patients with UC, and similar levels as the general population for patients with Crohn's colitis. (Jess et al., 2012) Contemporary evidence, from the largest cohort to date of ~96,000 individuals with UC from Sweden and Denmark showed an increased risk of CRC and death from CRC. The magnitude of the risk

is falling, but is still increased compared to a matched cohort from the general population. (Olén et al., 2020)

There are several potential reasons for a possible decline in CRC in this population. As colonic inflammation is one of the most strongly associated factors, better control of disease activity should plausibly reduce the malignant potential. There has also been a dramatic increase in the use of diagnostic tests in patients with IBD including colonoscopy, whether as a dedicated screening or surveillance procedure, or not. These tests may detect dysplasia, or pre-malignant polyps or lesions which may be removed that could reduce the number of incident cases of CRC. There has also been an increase in cross-sectional imaging in the form of computed tomography (CT) or magnetic resonance imaging (MRI) in these patients. This may also detect pre-malignant lesions that are removed and prevent subsequent CRC. Of course, the increase in investigations may also inflate the risk as cancers are diagnosed that would otherwise not have been detected.

Having considered these factors we must also bear in mind that there has been a decline in surgical interventions, such as pan-proctocolectomy in colitis patients. (Frolkis et al., 2013) This could have important implications over the coming years as it is likely that these patients, who would have been operated on, are at the greatest risk of CRC. These are individuals with the most severe, extensive disease, who are now aggressively managed with anti-inflammatory and immunosuppressive medications. They are more likely to have chronic inflammation, pseudopolyps, inflammatory polyps and colonic strictures which have all been associated with increased IBD-CRC risk. (Rutter et al., 2004a, 2004b) They are also receiving immunosuppressive medication that could adversely affect host anti-neoplastic mechanisms.

1.8 Risk factors for CRC in IBD

There are established risk factors for the development of colitis associated CRC. As mentioned, the duration of colitis is important and an increased risk after 10 and 20 years of disease has been consistently shown in studies from both referral and population cohorts. (Eaden, Abrams and Mayberry, 2001) There is however a high rate of cancers that develop earlier in the course of IBD as shown by a Netherlands population database study. (Lutgens et al., 2008) Here, 22% of cancer cases were diagnosed before 8 years, which is the cut-off for the start of routine screening in international guidelines. (Itzkowitz and Present, 2005)

The extent and activity of colitis are also implicated in the risk of developing CRC. Inflammation beyond the left side of the colon is associated with a 4.8 fold increase in the risk (Jess et al., 2005) and in a case-control study from a US referral population, histological inflammation was independently shown to increase the odds of developing CRC (OR 3.68; $p < 0.001$). (Rubin et al., 2013) Disease extent $\geq 50\%$ of the colon is also associated with increased risk of CRC. (Lutgens et al., 2014)

As with sporadic CRC, previous colonic dysplasia is also associated with future cancer risk. A meta-analysis of surveillance studies reported a nine-fold increase in the odds of developing cancer (OR 9.0, 95% CI: 4.0 to 20.5) when low grade dysplasia is detected on colonoscopy. (Thomas et al., 2007)

As well as the clinical features of the colitis, there are markers found at endoscopy that have been shown to predict the future risk of malignancy. Post-inflammatory polyps develop at the site of prior disease activity and mucosal inflammation. A United Kingdom referral centre study showed that the presence of these polyps was a marker for increased CRC (OR 2.14, 95% CI 1.24 to 3.70). (Rutter et al., 2004b) These polyps are not thought to have malignant potential (Kelly and Gabos, 1987) but are a marker of chronic disease activity and those at greater risk of CRC due to chronic inflammation. They also can make the detection and removal of subtle lesions more difficult. This makes the colon more

challenging to survey endoscopically so some pre-cancerous lesions, which could be removed, may be missed. As a result of these findings patients with multiple post-inflammatory polyps are advised to consider prophylactic colectomy in British society of gastroenterology (BSG) guidelines. (Cairns et al., 2010) Colonic strictures are also a poor prognostic endoscopic marker. From the same UK study such strictures were associated with an increase in the odds of developing CRC (OR 4.22, 95% CI 1.08 to 15.54). These strictures may be malignant themselves or be a marker of acute or chronic inflammation. Another important risk factor that has been consistently shown to be associated with colitis associated CRC is co-existent IBD and primary sclerosing cholangitis (PSC). (Broomé et al., 1995; Soetikno et al., 2002; Claessen et al., 2009)

When considering an individual risk profile, and the need for colonic surveillance, it is important to consider potential protective factors. A macroscopically normal colonoscopy is associated with a reduced chance of developing future CRC (OR 0.38; 0.19 to 0.73). (Rutter et al., 2004a)

1.9 Surveillance Colonoscopy for IBD related CRC

The goal of surveillance procedures is to detect early lesions to improve mortality from the disease. The number of colonoscopy procedures performed has increased dramatically in both the general population and individuals with IBD. This could lead to the detection of pre-malignant lesions, or early cancers that are more amenable to endoscopic or surgical resection and have better outcomes. This protective effect is recognised in sporadic CRC. (Nishihara et al., 2013)

There is considerable cost to both the individual and healthcare provider with regular surveillance colonoscopies, especially as colitis is often diagnosed at a young age. With certain risk factors, such as co-existent PSC, patients should be offered annual surveillance tests. The challenge is to identify those who are at the greatest risk and would benefit most

from surveillance tests, detect early dysplastic lesions that can then be either removed endoscopically or referred for surgical management. Issues that must be considered are the demand for the service, uptake from patients, how surveillance should be performed and what should be done if dysplasia or malignancy is detected.

1.9.1 Surveillance methods

Colonoscopy is the principal investigation used for the surveillance of IBD-CRC. Historically, multiple sequential biopsies were taken from the colonic mucosa to sample for invisible dysplasia. It is estimated that to achieve 90% detection of dysplasia 30-40 biopsies are necessary. (Ullman, 2005) Colonoscopy with pan-colonic dye spray, or chromoendoscopy is a method to try and improve dysplasia and cancer detection in IBD. This technique uses the application of dye to the colon wall via a spray catheter through the water jet channel of the colonoscope during the withdrawal of the instrument. The dyes that are used are typically methylene blue or indigo carmine. Application of the dye enhances subtle changes in the colon mucosa that can then be more easily detected, biopsied or removed.

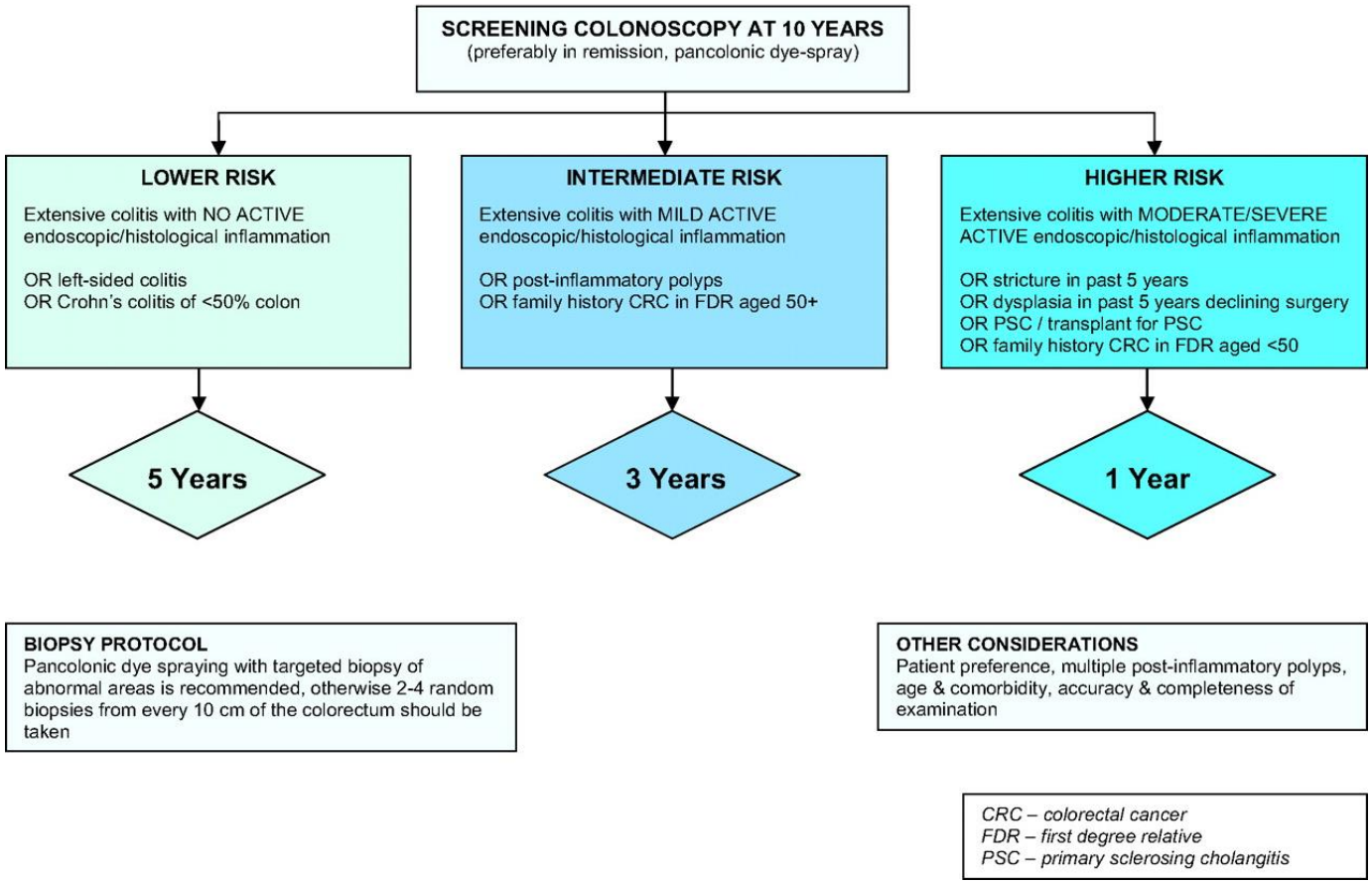
A systematic review and meta-analysis in 2019 of six randomised controlled trials (RCTs), and separately non-randomised observational studies, incorporating 10 studies in total showed chromoendoscopy was associated with detecting significantly more dysplasia than white-light endoscopy (RR 1.5, 95% CI 1.08 to 2.10), but not when compared to high-definition white light endoscopy (RR 1.36, 95% CI 0.84 to 2.18). (Feuerstein et al., 2019) Non-randomised studies showed a significant benefit for chromoendoscopy over both standard definition (RR 3.53, 95% CI 1.38 to 8.99) and high-definition white-light endoscopy (RR 3.15, 95% CI 1.62 to 6.13).

1.9.2 Current Surveillance Guidelines

CRC in IBD arises from dysplasia and progresses along an inflammation-dysplasia-malignancy pathway. In 2015 an international, multidisciplinary group convened to discuss

surveillance in IBD and drew up the SCENIC consensus guidelines. (Laine et al., 2015) There have been similar efforts from the European Crohn's and Colitis Organisation, (Van Assche et al., 2013) American Gastroenterology Society (Farraye et al., 2010) and the BSG, who published updated guidelines in 2010. (Cairns et al., 2010) The guidelines are consistent in their recommendations for regular colonic surveillance in high risk individuals, with the BSG recommending intervals of 1 year, 3 years, 5 years or no surveillance depending on the presence of certain risk factors (Figure 2).

Figure 2 British Society of Gastroenterology colitis surveillance guidelines, Cairns 2010 (Cairns et al., 2010)



1.10 Efficacy of Surveillance

In the general population, colonoscopy is effective in reducing the incidence and mortality from colorectal cancer through the detection and removal of pre-cancerous lesions and identifying early cancers that will be more amenable to treatment. (Nishihara et al., 2013) Individuals with colitis can be excluded from the UK bowel cancer screening programme due to the risk of a false positive stool-based blood screening test. Furthermore, even though there are societal guidelines advocating surveillance in the IBD population, there is no dedicated screening and surveillance programme for this group of patients.

There is sparse evidence of the efficacy of surveillance colonoscopy in the IBD population. Early reports showed no benefit from surveillance with random colonic biopsy, hampered by 40% non-attendance. (Lynch et al., 1993) Later studies from the 1990's suggested a potential benefit to surveillance. (Haggittii et al., 1993; Karlén et al., 1998) A recent study by Ananthrakrishnan *et al.* in 2014 explored the effects of colonoscopy on CRC incidence and survival from a US tertiary care population of patients with IBD. (Ananthakrishnan et al., 2014) Here, having a colonoscopy within 36 months was associated with a reduced likelihood of CRC (OR 0.56; 95% CI 0.39 to 0.80). Colonoscopy within the 6-36 months before diagnosis was also independently associated with reduced all-cause mortality (OR 0.34; 95% CI, 0.12 to 0.95) suggesting that the tests were effective in detecting early, treatable malignancies.

Further evidence for the use of surveillance colonoscopy came from the analysis of surveillance data from St Mark's Hospital in London. After analysing over 40 years of cohort data they showed increased detection of dysplasia and early cancers, reduced advanced cancer and a reduced colectomy rate for those undergoing surveillance. (Choi et al., 2015b) A Cochrane review of the efficacy of surveillance was conducted in 2017, and summarised the available evidence. (Bye et al., 2017) This included five observational studies and concluded

that there was less CRC following surveillance (1.83% vs 3.17%), less CRC related death (8% vs 22%), and more early CRC (16% vs 8% Duke's A or B). The overall quality of the included studies was graded as very low for all of the outcomes. Caution should be applied to any conclusions from this evidence and more work is needed.

We need to bear in mind that the reduction seen in incidence and mortality is an association and not necessarily a result of the colonoscopy. Other factors could be responsible for the reduction such as associated healthy behaviours, adherence to medications and more judicious reporting of red-flag symptoms in those patients who are more likely to attend for colonoscopy. For ethical and logistical reasons, a randomised controlled trial on surveillance colonoscopy is unlikely to be performed so we will have to rely on well-designed, retrospective population-based studies that can adjust for known risk factors and account for those who may not attend for screening and surveillance procedures.

1.11 Post-Colonoscopy Colorectal Cancer

Post-colonoscopy colorectal cancers (PCCRC) have been proposed as a key quality indicator of colonoscopy. (Kaminski et al., 2010) These tumours can either be due to a lesion that was not detected on the previous colonoscopy, or more rarely a rapidly growing malignancy. (Tollivoro et al., 2018) Studies from sporadic colorectal cancer have shown that these cancers are more likely to be in the right colon, more common in women, in older individuals and when procedures are not performed by experienced endoscopists. A recent population-based UK study has shown that the rate of CRC in the 6 to 36 month period following a colonoscopy is 7.4%. (Burr et al., 2019) The PCCRC-3yr rate for those with IBD was more than five times that of the general population at 36%. (Burr et al., 2019) Despite a significant improvement in PCCRC-3yr rates in people without the disease from 9% for colonoscopies in 2005 to 6.5% in 2013, the PCCRC-3yr rate in people with IBD remained constant throughout the study period (p=0.24).

A study by Wang *et al* in 2013 (Wang et al., 2013) showed that the rate of early or missed CRC in older patients was almost three times as high for patients with IBD compared with non-IBD patients, 5.7% for non-IBD patients, 15.1% for Crohn's disease and 15.8% for ulcerative colitis ($p<0.001$). These cancers were also less likely to be right sided ($p<0.05$). There should be some caution in interpreting this data as cancers in the older population are not likely to be representative of the whole age range of individuals with IBD.

There are several important considerations for the high rate of PCCRC in IBD. Firstly, as already explained CRC in IBD is different to sporadic CRC. The differences could account for more aggressive, fast growing cancers that occur within three years of a normal endoscopic test. Secondly, we know that post-inflammatory polyps and strictures are associated with increased incidence of cancer. These findings could either be misclassified as benign or distract the endoscopist from subtle lesions with dysplastic or malignant cells. Alternatively, the reason for not detecting pre-malignant lesions could plausibly be due to the fact that they can be flat and subtle adenomas requiring experience for detection. (Torres, Antonioli and Odze, 1998)

It is important to consider these high rates of PCCRC because attending for a colonoscopy and having a normal result is reassuring to both patients and clinicians. Patients may be less inclined to report symptoms at an early stage after a colonoscopy as usually they have observed the test, not seen a lesion and been reassured after the procedure that everything was normal.

1.12 Post-Colectomy Colorectal Cancer

Colectomy markedly reduces the future cancer risk. After undergoing a proctocolectomy and ileal pouch anal anastomosis there is a residual cancer risk of 0.5%. (Derikx et al., 2016) For those with an intact rectal stump the rate is 2%. (Derikx et al., 2016) One of the most important risk factors for future cancer risk seems to be the presence of

neoplasia before a resection. This would be in line with the “field carcinogenesis” theory described earlier. These patients should be considered in surveillance guidelines.

1.13 Chemoprevention of IBD associated CRC

As with any disease, prevention is better than cure. In the general, non-IBD population, there is the potential for chemoprevention against the development of sporadic adenomas and CRC. (Arber et al., 2008) For CRC in patients with inflammatory bowel disease, medications that are used to control luminal inflammation appear to have a protective effect with 6-mercaptopurine, azathioprine or methotrexate being associated with a reduced risk of developing CRC (OR 0.35; $p< 0.01$), (Rubin et al., 2013) Anti-TNF-α medications were not included in this study. 5-aminosalicylate (5-ASA) medications are the most prescribed medications for UC and colonic CD. For 5-ASA medications there has been conflicting evidence with some, but not all, studies showing a protective association. A meta-analysis by Velayos *et al.* including nine studies showed a 49% reduction in the odds of developing CRC (OR 0.51, 95% CI 0.37 to 0.69). (Velayos, Terdiman and Walsh, 2005) However, a meta-analysis of non-referral patients did not show a protective association (OR 0.95, 95 % CI 0.66 to 1.38). (Nguyen, Gulamhusein and Bernstein, 2012) There is generally a lack of research on the protective effects of other commonly prescribed medications that have a plausible biological role in chemoprevention against CRC. These include aspirin, (Flossmann and Rothwell, 2007) antiplatelet agents, non-aspirin non-steroidal medications (NA-NSAID), (Papagiorgis, 2015) statins, (Poynter and Gruber, 2005) calcium channel blockers, (Newmark, Wargovich and Bruce, 1984) and folate supplementation. (Mouzas, Papavassiliou and Koutroubakis, 1998)

1.13.1 The role of NSAIDs in the chemoprevention of CRC

There are plausible biological mechanisms for how NSAIDs may prevent CRC. NSAIDs inhibit cyclo-oxygenase-2 (COX-2) enzyme function which has been implicated in

several carcinogenic pathways including promoting tumour angiogenesis and inhibition of apoptosis. Laboratory studies have reported an over expression of COX-2 in CRC cells and COX-2 inhibitors prevented CRC cell growth *in-vitro.* (Dixon et al., 2013)

Several epidemiological studies have extolled the potential role for NSAIDs in preventing many solid tumours including: prostate, (Dasgupta et al.) oesophageal, (Duan et al., 2008) breast, (Agrawal and Fentiman, 2008) lung, (Harris, Beebe-Donk and Alshafie, 2007) ovary, (Bonovas, Filioussi and Sitaras, 2005) and hepatobiliary. (Grainge et al., 2009) One of the most consistent findings is that regular use of NSAIDs is associated with lower incidence of CRC (Vinogradova et al., 2007) and adenomatous polyps. These associations have also been observed in randomised controlled trials of NSAIDs in those with familial adenomatous polyposis syndrome, and high-risk of developing CRC, where treatment with sulindac resulted in regression in size and reduced numbers of adenomatous polyps. (Giardiello et al., 2002, 1993)

1.13.2 Aspirin

There are several plausible biological mechanisms for how aspirin use may prevent adenomatous polyp formation and CRC. The potential role in chemoprevention is likely to be through several integrated pathways rather than one mechanism in tumour prevention. (Drew, Cao and Chan, 2016) Aspirin works as an anti-inflammatory and antiplatelet agent. Its principal mechanism of action is through inhibiting rate limiting steps in the conversion of arachidonic acid to prostaglandins and eicosanoids namely: PGE_2, PGD_2, PGF_2, thromboxane A_2, and prostacyclin. (Drew, Cao and Chan, 2016) This is achieved through irreversible modification of cyclo-oxygenase (COX) enzymes. COX-2 is expressed in many tissues, and is overexpressed in CRC cells. (Dixon et al., 2013) The COX enzymes promote cell division, tumour angiogenesis and reduced cell death (apoptosis). Increased prostaglandin E2 (PGE_2) promotes carcinogenesis, and is seen in CRC cells. (Dixon et al., 2013; Pugh and Thomas,

1994) Another potential target for aspirin is through its effect on WNT-β-catenin signalling. Alteration of WNT signalling is seen in CRC. (Fearon, 2011) Aspirin modulates WNT signalling at multiple levels, including COX-2 and PGE_2 pathways, and the expression of key WNT target genes involved in CRC carcinogenesis. (Gala and Chan, 2015)

There is strong evidence supporting the potential role for aspirin in preventing sporadic CRC. (Dehmer et al., 2016; Flossmann and Rothwell, 2007) A consistent finding that has been observed in many observational studies. A meta-analysis, including over 9,000 individuals showed a 41% reduction in CRC risk for aspirin users (RR 0.59, 95% CI 0.54 to 0.64). (Cuzick et al., 2009) More recently Rothwell *et al*, analysed ~14,000 patients from RCTs investigating aspirin use and cardiovascular protection followed up for 20 years and found a reduced incidence of CRC (HR 0.76, 95% CI 0.60 to 0.96), and reduced mortality from CRC (HR 0.65, CI 0.48 to 0.88). (Rothwell et al., 2010a) There are also prospective data that aspirin is may prevent CRC after secondary analysis of trials investigating aspirin for prevention of cardiovascular disease. A meta-analysis of 3 such studies, analysing secondary data from prospective trials investigating aspirin for the prevention of cardiovascular disease showed that aspirin at a dose between 75 and 300mg reduced CRC risk significantly (HR 0.75, 95% CI 0.56 to 0.97). (Rothwell et al., 2010b) On the back of this compelling evidence, the United States Preventative Services Task Force have recommended aspirin as primary prevention against CRC for those aged between 50 and 60 years with greater than 10%, ten-year cardiovascular disease risk. (Bibbins-Domingo and U.S. Preventive Services Task Force, 2016)

1.13.3 Role of statins in chemoprevention of CRC

The 3-hydroxy-3methylglutaryl-coenzyme-A reductase inhibitors (statins) are a class of drug that were first identified in the 1970's, and have been approved for the treatment of hypercholesterolemia since the 1980's. (Oates, Wood and Grundy, 1988) Statins are used in

the primary and secondary prevention of cardiovascular disease and are one of the most widely prescribed medications in the world with up to 44% of American adults over the age of 65 years being prescribed them. HMG-CoA is involved in cholesterol synthesis, catalysing the rate limiting step in the mevalonate pathway. Mevalonate is a fatty acid which is essential in the biosynthesis of cholesterol and is formed from HMG-CoA by HMG-CoA reductase. Inhibition of HMG-CoA reductase by the small molecule statins, reduces cholesterol synthesis, resulting in lower levels of low-density lipoprotein cholesterol (LDL). (Demierre et al., 2005)

In addition to lowering cholesterol levels, statins have many potential chemopreventative effects through inhibition of the cell cycle, induction of apoptosis, inhibition of cytokines which can cause inflammatory tumours to proliferate, inhibition of tumour angiogenesis and suppression of tumour growth. (Katz, 2005) The mevalonate pathway is also up-regulated by a mutated p53 tumour suppressor gene, which is common in CRC. (Nielsen, Nordestgaard and Bojesen, 2012)

Statins have been shown to block tumour growth and proliferation *in vitro,* (Agarwal et al., 1999; Wächtershäuser, Akoglu and Stein, 2001) and statin use is associated with reduced incidence of many solid state tumours including: breast, (Ahern et al., 2011) prostate, (Platz et al., 2006) oesophageal, (Alexandre et al., 2014) and recently hepatobiliary cancers. (Liu et al., 2018) For sporadic CRC, a meta-analysis of 42 studies showed that statin use was associated with a modest reduction in the risk of developing CRC (RR 0.90, 95% CI 0.86 to 0.95). A meta-analysis of 6 studies including 13, 239 patients also showed a significant negative association between statin use and the development of CRC and advanced adenomas (RR 0.83, 95% CI 0.75 to 0.93). (Jung et al., 2016) Statin use, after a diagnosis of CRC is also associated with reduced CRC-specific mortality (adjusted HR 0.71, 95% CI 0.61 to 0.84). (Cardwell et al., 2014) Furthermore, a recent cohort study from Hong Kong has shown

that statins are associated with a significant reduction in PCCRC-3yr (HR 0.72, 95% CI 0.55 to 0.95). (Cheung et al., 2019)

1.13.4 Role of Antiplatelets in the chemoprevention of CRC

There is a much smaller body of evidence investigating whether antiplatelet agents, other than aspirin, have a chemopreventative effect on solid tumours.

Platelet function is principally for thrombosis and haemostasis but there is increasing experimental and epidemiological evidence for their role as amplifiers of chronic inflammatory processes. Over the past 20 years there has been accumulating evidence for the role of platelets in the direct stimulation of an inflammatory response. (Wecksler, 1992) The mechanisms for platelet derived inflammation are through the release of pro-inflammatory mediators including: platelet aggravating factor (PAF), Thromboxane A2, 12-hydroxyeicosatetraenoic acid (12-HETE), platelet derived growth factor (PDGF), intracellular platelet factor 4 (IPF-4) and transforming growth factor beta (TGF-β). (Collins and Rampton, 1997) A "reactive thrombocytosis" comprising a rise in platelet number, with changes in morphology and function is a marker of disease activity in chronic inflammatory conditions, including IBD. Patients with IBD are at risk of systemic thromboembolism with incidence ranging between 2 and 8%, rising to between 39 and 41% in post-mortem studies. (Murthy and Nguyen, 2011; Yuhara et al., 2013)

To date there is a lack of dedicated research on the potential role of antiplatelet agents as anti-inflammatory agents in IBD. They may also have a role in protecting against the development of IBD-CRC. As already discussed, IBD-CRC is likely to develop because of uncontrolled mucosal inflammation so as with other potential chemopreventative medications, if the inflammation is controlled then cancer might be prevented.

1.13.5 Role of folate in chemoprevention of CRC

Folate (vitamin B9) is the generic term for a group of compounds, including folic acid as a supplement, that are essential for numerous bodily functions. (Scaglione and Panzavolta, 2014) Folate deficiency in humans causes neural tube defects in embryos and megaloblastic anaemia in adults. Humans cannot synthesise folate, so it is obtained from foods such as leafy green vegetables, folic acid in supplements or food fortification, mandatory in the United States and Canada since 1998. There is a proposal for mandatory flour fortification in the UK that is under Government review. Folate has a role in DNA methylation and purine and thymidine synthesis for DNA and RNA (Choi and Mason, 2000) and folate deficiency has been implicated in carcinogenesis through permitting increased DNA damage and altering the expression of critical tumour suppressor and proto-oncogenes. (Kim, 1999) This is supported by experimental studies in rat models where folate deficiency has been shown to induce colorectal cancer and folate supplementation inhibits it. (Cravo et al., 1992; Kim et al., 1996) There is evidence for a "dual role" of folate in carcinogenesis whereby folate may prevent early cancers but causes harm if these lesions have formed. (Kim, 2007; Ulrich and Potter, 2006) These studies, in colorectal mouse models, showed that high levels of folate promoted carcinogenesis once microscopic, neoplastic foci had developed. (Song et al., 2000a, 2000b)

In spite of this, epidemiological studies have shown that reduced folate levels are associated with the development of several solid tumours including cervical, breast, pancreas, lung and colorectal cancer. (Freudenheim et al., 1991; Wien et al., 2012) Some of the most compelling evidence is for the potential protection against CRC, a recent meta-analysis of 27 papers showed a relative risk estimate reduction of 0.85 (95% CI 0.74 to 0.99) when comparing low *vs* high folic acid supplementation. (Kennedy et al., 2011) Patients with IBD are at increased risk of folate deficiency through inadequate nutritional intake, excessive intestinal loss and reduced absorption due to competitive inhibition by sulfasalazine use. (Potack and Itzkowitz, 2008; Swinson et al., 1981)

1.14 Potential adverse effects of chemoprevention agents

As well as the potential benefits for chemoprevention there are concerns about potential negative effects of aspirin and the NA-NSAIDs on the lower gastrointestinal tract. Adverse effects of NA-NSAIDs on the colon include a NSAID colonopathy with diaphragm-like stricturing and mucosal inflammation and ulceration, complicated diverticular disease including bleeding, (Strate et al., 2011) and microscopic colitis. (Laine et al., 2003; Abir et al., 2005) A possible association between the use of NSAIDs including aspirin and the onset or relapse of IBD has been repeatedly suggested. However, lack of controlled prospective trials make it difficult to draw definite conclusions. (Kefalakes et al., 2009; Maiden et al., 2005)

Aspirin use is associated with several side effects. The main concern is the risk of upper gastrointestinal bleeding and haemorrhagic stroke. Most studies using aspirin have not shown increased death rates from gastrointestinal bleeding suggesting that any bleeds related to aspirin are small and relatively insignificant. (Elwood P.C. Mustafa M. Almonte M. Morgan, 2012)

1.15 Primary care datasets in healthcare research

Electronic health records from primary care databases (PCD) are an important resource for healthcare research. The value of the databases for research purposes stems from the availability of information on “population-wide” data over a long period with detailed information on diagnoses and medication usage. There are many PCD databases available in the UK that have been validated and are widely used for healthcare research. These include the Clinical Practice Research Datalink (CPRD, formerly GPRD), QResearch and The Heath Improvement Network (THIN). (de Lusignan and van Weel, 2006; Horsfall, Walters and Petersen, 2013; Thiru, Hassey and Sullivan, 2003) They are becoming increasingly popular in

healthcare research with over 1,500 publications resulting from the CPRD alone since its inception.

1.15.1 GP coding

In the UK a new GP contract, incorporating a novel quality and outcomes framework (QOF), was introduced in 2004. This payment-by-results scheme required GPs to produce annual reports on several quality indicators to receive supplementary payments. Data items relating to conditions included in the QOF were prioritised and coded diligently to generate financial rewards for the GP practice. Studies have shown that pre- and post- contract recording changed to reflect the data items within QOF. (Campbell et al., 2009) There is therefore the potential that a disease not included in the GP contract may not be as accurately coded as those included in QOF. Another important point when considering GP coded entries is that they do not contain "rule out" codes which would override previous entries. As such it is possible that some patients may be misclassified if diagnoses have been subsequently updated. Patients may have two different entries for the same condition where diagnoses have been subsequently revised after addition of subsequent clinical information.

1.15.2 The ResearchOne primary care database

ResearchOne is a relatively new PCD that has become available for healthcare research. The patients are drawn from the SystmOne GP database that covers over 28 million patients throughout the UK. The population covered by SystmOne has increased from 8.4% of GP practices in 2008 to 17.8% of practices in 2011. (Kontopantelis et al., 2013) As of 2014 this database holds information for over 6 million patients. The GP practices on the database are spread throughout the UK, representing 85% of UK local authorities, and deprivations analyses of the database indicate that the patients are from a representative mix of the UK population. (Kontopantelis et al., 2013; Reeves et al., 2014) The data accrued in the ResearchOne database include demographic information (including patient's sex and year

of birth), clinical diagnoses, detailed prescription records, referrals to secondary care, and outcomes from hospital admission. Important, historical clinical diagnoses that occurred before the introduction of the electronic medical record are also coded retrospectively. The data quality of each entry into ResearchOne is measured against specific targets, developed by comparisons with external statistics, to ensure that research standards are met.

Chapter 2 Aims and Objectives

Chapter 2: Aims and Objectives

The aim of this thesis is to investigate the potential for the chemoprevention of IBD associated colorectal cancer. This will involve a systematic review of the literature to date and then, using primary care data, investigate whether there are associations between routine medication use and the development of IBD-CRC.

2.1 Chemoprevention of IBD-CRC

As already discussed, there are plausible mechanisms for the role of many medications in preventing IBD associated CRC. There have been several observational studies investigating the role of aspirin, non-aspirin non-steroidal medications and supplementation with folate. This evidence has not been synthesised, to date, and so the first two results chapters explore this potential by performing two systematic reviews and meta-analyses to investigate any association with the use of these medications and supplement.

2.2 Validation of the ResearchOne database

In order to investigate the potential for chemoprevention, large databases are required as the outcome of IBD-CRC is relatively rare and takes a long time to develop. As such, prospective studies or cohorts are not feasible and for the same reasons, prospective randomised studies would be difficult or impossible. There are now several large cohorts available for biomedical research that draw from primary care records. In the UK, most people are registered with a GP, and nearly all GPs maintain electronic healthcare databases. This means that exploring these rich datasets can give estimates of population level disease aetiology and outcomes. They include large numbers of people and span several decades and so are a good resource for investigating rare events, and long-term disease outcomes.

A novel primary care database is ResearchOne. A potential problem with using this resource is that it has not undergone data validation, which limits its utility. Before using this resource for chemoprevention work it is therefore important to perform a database validation

study. After the validation study the IBD and IBD-CRC cohorts within the ResearchOne database are described in detail with trends in incidence of IBD-CRC and description and analysis of aetiological factors associated with this disease.

2.3 Chemoprevention of IBD-CRC using the ResearchOne database.

The final results chapter involves several nested case-control studies to test the hypotheses that routinely prescribed drugs may be able to prevent IBD associated CRC. These include aspirin, NA-NSAIDs, statins, antiplatelets, 5-ASA, and immunomodulators.

Chapter 3 Systematic review and meta-analysis of the role of aspirin and non-aspirin non-steroidal anti-inflammatory drugs in the chemoprevention of IBD

Chapter 3: Systematic review and meta-analysis of the role of aspirin and non-aspirin non-steroidal anti-inflammatory drugs in the chemoprevention of IBD associated CRC.

In this chapter I will review the evidence for the potential role of aspirin and non-aspirin non-steroidal anti-inflammatory agents (NA-NSAIDs) in the chemoprevention of IBD associated colorectal cancer. After discussing the available evidence, I will describe a meta-analysis and pooled association size for the role of these drugs and, after discussing strengths and weaknesses of the evidence explore how this may affect future research and clinical practice.

3.1 Abstract

3.1.1 Aim

To determine whether aspirin or non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs) prevent colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD).

3.1.2 Methods

I performed a systematic review and meta-analysis. I searched for articles reporting the risk of CRC in patients with IBD related to aspirin or NA-NSAID use. Pooled odds ratios (OR) and 95% confidence intervals were determined using a random-effects model. Publication bias was assessed using funnel plots and Egger's test. Heterogeneity was assessed using Cochran's Q and the I^2 statistic.

3.1.3 Results

Eight studies involving 14,917 patients and 3 studies involving 1,282 patients provided data on the risk of CRC in patients with IBD taking NA-NSAIDs and aspirin respectively. The pooled OR of developing CRC after exposure to NA-NSAIDs in patients with IBD was 0.80 (95% CI, 0.39 to 1.21) and after exposure to aspirin it was 0.66 (95% CI 0.06 to 1.39). There was significant heterogeneity ($I^2 > 50\%$) between the studies. There was no change in the effect estimates on subgroup analyses of the population studied and after adjustment and matching for known confounders.

3.1.4 Conclusion

There is a lack of high-quality evidence on this important clinical topic. From the available evidence NA-NSAID or aspirin use does not appear to be chemopreventative for CRC in patients with IBD.

3.2 Introduction

As discussed, one of the most serious complications of inflammatory bowel disease (IBD) is the development of colorectal cancer (CRC). International society guidelines advocate regular surveillance colonoscopy examinations to identify malignant and pre-malignant lesions. (Cairns et al., 2010) These are resource intensive and not without risk. As such primary prevention of CRC in these patients is an attractive alternative. Several treatment modalities have been proposed as potential chemopreventative agents and studied mainly via retrospective case-control and cohort studies. (Subramanian and Logan, 2011) These include 5-aminosalicylic acid preparations, (van Staa, 2005; Eaden, 2003; Terdiman, 2011) ursodeoxycholic acid (in patients with concomitant PSC), (Low et al., 2010; Terhaar Sive Droste et al., 2006) thiopurine analogues, (van Schaik et al., 2012) aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs), and statins. (Poynter and Gruber, 2005)

There are plausible biological mechanisms for how NA-NSAIDs, and aspirin, may prevent CRC development in patients with IBD. In epidemiological, laboratory and clinical studies aspirin has consistently been shown to reduce the incidence of several tumours, including ‘sporadic’ CRC. (Rothwell et al., 2010b; Burr et al., 2014) The exact anti-neoplastic mechanism(s) of aspirin and NA-NSAIDs is not yet clear but several cell signalling pathways have been implicated as targets for COX-dependent and COX-independent mechanisms of action. (Wang and Dubois, 2010; Schrör, 2011) Aspirin use also appears to prevent CRC metastasis, as well as the risk of primary CRC. (Rothwell et al., 2012)

There are currently conflicting data on the putative role of NA-NSAIDs and aspirin in the prevention of IBD-CRC. I therefore performed a systematic review and meta-analysis in

order to identify if there is evidence that aspirin and NA-NSAIDs have chemopreventative activity against CRC in patients with IBD.

3.3 Materials and methods

I followed a pre-specified and peer-reviewed protocol; the PRISMA statement, a 27 item checklist deemed essential for reporting systematic reviews and meta-analyses of randomised controlled trials and observational studies. (Moher et al., 2009)

3.3.1 Search strategy

Multiple electronic databases were used including MEDLINE (1965 to July 2015), EMBASE (1974 to July 2015), ISI Web of Science (1945-July 2015) and the Cochrane Register of Controlled Trials. The MeSH search terms included were Inflammatory Bowel Disease AND CRC AND Aspirin OR NSAIDs. Free text terms and variations were used. No limits or language restrictions were applied. A recursive search of the bibliographies of relevant review articles and of the included studies was performed. Articles were assessed by two independent reviewers (NB and VS) to assess eligibility for inclusion. Any disagreements were resolved by consensus decision.

3.3.2 Study selection

Studies were eligible for inclusion if they reported on the risk of developing CRC in patients with IBD on either NA-NSAIDs or aspirin compared to a control population. Studies published only in abstract form were not included. Two reviewers (NB and VS) independently screened titles and abstracts identified by the preliminary searches to identify potentially eligible studies. Both reviewers independently assessed the full text articles of potentially relevant studies for inclusion in the pooled analysis. Data from included studies were independently extracted by two investigators (NB and VS). Information was collected on the characteristics of each included study (population studied, country of origin, study design, definition of drug exposure) and drug use including NA-NSAIDs, aspirin and

development of CRC. Agreement between the reviewers was greater than 95% and differences between the datasets were resolved by consensus decision.

3.3.3 Statistical Analysis

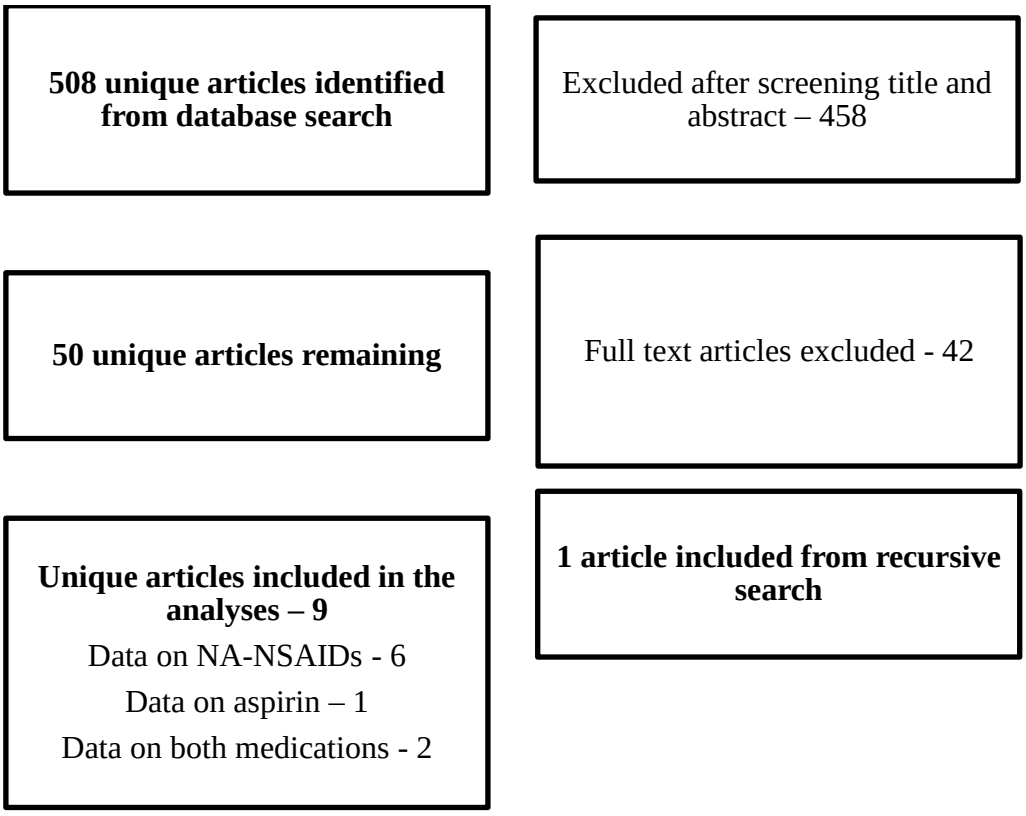
The odds ratio (OR) with 95% confidence interval (CI) of developing CRC in patients with IBD on aspirin or NA-NSAIDs compared with controls was extracted from the study. When insufficient (no information on odds ratio or drug exposure) data had been published, I contacted the study authors. As randomisation and blinding is not possible in observational studies and baseline differences between the groups can confound the results, I used the authors' ORs with adjustment for potential confounding factors wherever available. The pooled OR estimate was calculated from an inverse-variance-weighted average of the individual studies. (Yusuf et al.) A DerSimonian-Laird random effects model was used a priori. (DerSimonian and Laird, 1986) As a further sensitivity analysis a fixed effects model was used for comparison. Stata version 12 (StataCorp, College Station, Texas, USA), was used for all the data analysis.

Cochran's Q statistic was used to test heterogeneity among pooled estimates. (Cochran, 1954) Statistical heterogeneity was also measured by the I^2 statistic, which quantifies the proportion of inconsistency in individual studies that cannot be explained by chance. (Higgins et al., 2003) Values of I^2 equal to 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. To test for publication bias, I used a test for asymmetry of the funnel plot, proposed by Egger *et al*. (Egger et al., 1997) This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalised effect estimate (estimate divided by the standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate.

The quality of the primary studies assessing the risk of bias was evaluated using the Newcastle-Ottawa Scale for non-randomised studies (NOS). (Wells et al., 2000) Studies score for a maximum of 4 for selection, 2 for comparability and 3 for outcomes (cohort) or exposures (case-control). I regarded scores of 0-3 as low, 4-6 as medium and 7-9 as high methodological quality.

Pre-planned subgroup analyses were conducted to assess the following factors on the trial outcome and on the heterogeneity of the analyses: a) matching or adjustment for confounders (any or none) and b) the population studied (population-based or other).

Figure 3 Flow diagram of studies included in the systematic review of aspirin and NA-NSAIDs in preventing IBD-CRC



3.4 Results

The searches retrieved nine potentially relevant articles, of which three (Eaden et al., 2000; van Staa, 2005; Velayos et al., 2006) provided data on aspirin exposure and eight (van Staa, 2005; Velayos et al., 2006; Terdiman et al., 2007; Samadder et al., 2011; Bansal and Sonnenberg, 2013; Tang et al., 2010; Baars et al., 2011; Rubin et al., 2013) on NA-NSAID exposure and risk of CRC in patients with IBD. Figure 2 outlines the fate of the selected articles. The studies were either retrospective case-control, nested case-control or cohort studies by design and 5 (van Staa, 2005; Terdiman et al., 2007; Samadder et al., 2011; Bansal and Sonnenberg, 2013; Baars et al., 2011) included population-based analysis. Table 1 lists all the included studies and their characteristics. Authors of relevant papers were contacted for missing data, but no extra information was obtained. The quality assessment of the studies using the Newcastle Ottawa scale is also detailed in Table 1. Only three studies (Velayos et al., 2006; Bansal and Sonnenberg, 2013; Samadder et al., 2011) provided multivariate analysis of data for risk of developing CRC in IBD patients exposed to aspirin or NA-NSAIDs.

3.4.1 Cumulative risk of developing colorectal cancer in IBD patients exposed to NA-NSAIDs

Eight studies, including 14, 917 patients with IBD provided data on the risk of developing CRC after exposure to NA-NSAIDs. Using a random effects model, the pooled adjusted OR of developing CRC after exposure to NA-NSAIDs in patients with IBD was 0.80 (95% CI 0.39 to 1.21) (Figure 2). The heterogeneity between the studies was high (Cochran's Q = 38.15, p=0.00 and I^2=81.6%).

Table 1 Characteristics of the eligible studies in the meta-analysis of aspirin and NA-NSAIDs in the chemoprevention of IBD-CRC

Author	Design	Population	Definition of IBD	Drug exposure	Exclusion criteria	No. of patients	OR (95% CI)	Adjustment/matching *	NOS Quality assessment
Bansal, 1996(Bansal and Sonnenberg, 2013)	Case-control	US veterans' affairs	Clinical database	NSAID associated Diagnosis	Not specified	11446	0.84 (0.65-1.09)	adjusted for age, sex & ethnicity	6
Eaden, 2000(Eaden et al., 2000)	Case-control	UK hospital	Clinical, pathological and radiological records.	Prescribed 5-10 years before diagnosis.	Colorectal surgery, IBD diagnosed at time of cancer diagnosis	206	0.80 (0.21-2.98) Aspirin	non-adjusted	4
Van Staa, 2005(van Staa, 2005)	Nested case-control	UK general practice	Clinical records	Prescribed in the 6 months prior to diagnosis	Colorectal surgery, previous history of CRC	700	1.52 (0.7-3.25) (Aspirin) 0.80 (0.38-1.66) (NA-NSAID's)	non-adjusted	5
Velayos, 2006(Velayos et al., 2006)	Case-control	US hospital	Clinical, pathological and endoscopic records	2 records of use in notes	Previous CRC, IBD diagnosed at same time as CRC, incomplete data	376	0.3 (0.1-0.8) (Aspirin) 0.1 (0.03-0.5) (NA-NSAID)	matched on gender, duration of disease and extent of disease	8

Terdiman, 2007(Terdiman et al., 2007)	Case-control	US insurance claims	Clinical records	Prescribed in the year before diagnosis	Colorectal surgery	1536	0.97 (0.74-1.28)	non-adjusted	5
Tang, 2010(Tang et al., 2010)	Retrospective cohort	US hospital	Clinical database	Ever used	No colonic involvement of IBD	48	0.29 (0.03-2.75)	non-adjusted	5
Sammader, 2011(Samadder et al., 2011)	Case-control	N. Israel community	Patient questionnaires	Weekly for >3 years	Previous history of CRC	60	0.49 (0.07-3.32)	matched for age, gender & ethnicity	6
Baars, 2011(Baars et al., 2011)	Case-control	Netherlands nationwide pathology	Pathology reports	Ever used	IBD diagnosed at the same time as CRC	551	1.96 (0.72 -5.36)	non-adjusted	6
Rubin, 2013(Rubin et al., 2013)	Case-control	US hospital	Pathology reports	Not specified.	Incomplete records	200	1.84 (0.75-2.5)	non-adjusted	5

OR for CRC chemoprotective effect of non-aspirin non-steroidal (NA-NSAID) use in patients in IBD unless otherwise stated.

NOS – Newcastle-Ottawa Score. Note - for cohort studies was used only for the Tang et al study. The scale for case-control studies was used for the other studies.

Table 2 Subgroup analyses for studies reporting on risk of CRC in patients with IBD taking NA-NSAIDs

	Number of studies	Pooled OR (95% CI)
Matched y/n		
Matched/adjusted	3	0.47 (0.18 to 1.13)
None	5	1.04 (0.65 to 1.43)
Study location		
Hospital	6	0.92 (0.78 to 2.62)
Population	2	0.88 (0.72 to 1.04)

3.4.2 Sensitivity analysis and publication bias

Pre-planned subgroup analyses showed that there was no difference in the overall effect estimate when comparing the population studied or whether adjustment or matching for confounders was performed (Table 2). There was no heterogeneity among population-based studies (Cochran's Q=2.39, p = 0.79 and I^2=0%) but high heterogeneity between hospital-based studies (Cochran's Q=14.17, p < 0.05 and I^2=92%)). There was some funnel plot asymmetry compatible with publication bias (Figure 4). However, Egger's regression asymmetry test was non-significant (p = 0.56). The regression asymmetry test is probably underpowered as there are only 8 studies included in this meta-analysis. (Sterne et al., 2011)

3.4.3 Cumulative risk of developing CRC in IBD patients exposed to aspirin

Three studies, including 1,282 patients with IBD, provided data on risks of developing CRC after exposure to aspirin. The pooled adjusted OR of developing CRC after exposure to aspirin in patients with IBD was 0.66 (95% CI 0.06 to 1.39) (Figure 3). A random effects model was chosen a priori. The heterogeneity between the studies was high (Cochran's Q = 0.166 and I^2 = 44.4%). A fixed effects model was performed as a sensitivity test which changed the pooled adjusted OR to 0.41 (95% CI 0.08 to 0.74). I did not attempt to perform an analysis of publication bias or subgroup analyses as there were only three studies included in the final analysis.

Figure 4 Forest Plot of ORs and 95% CI for effect of NA-NSAIDs or aspirin on CRC development in patients with Inflammatory Bowel Disease. Random effects model

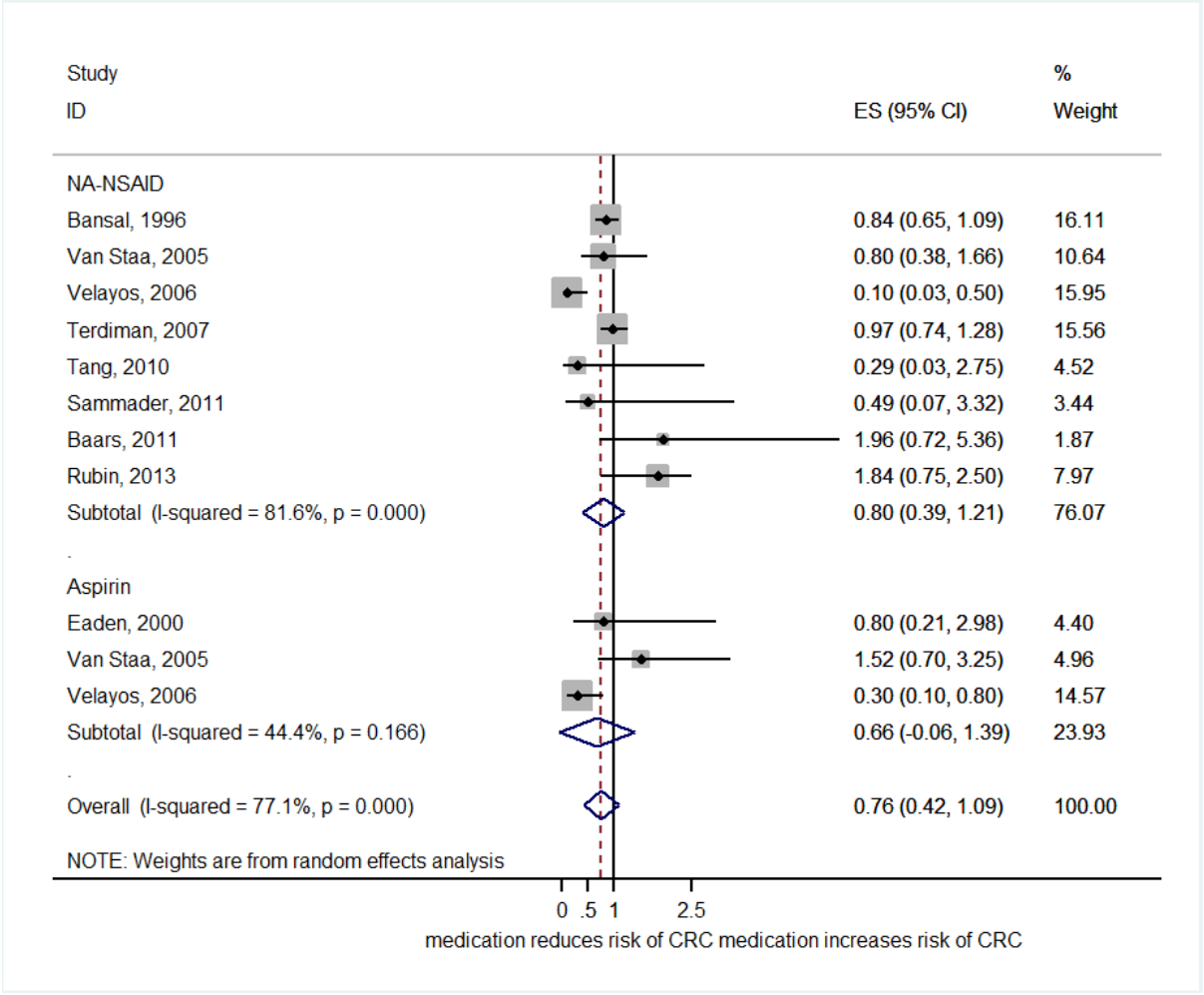
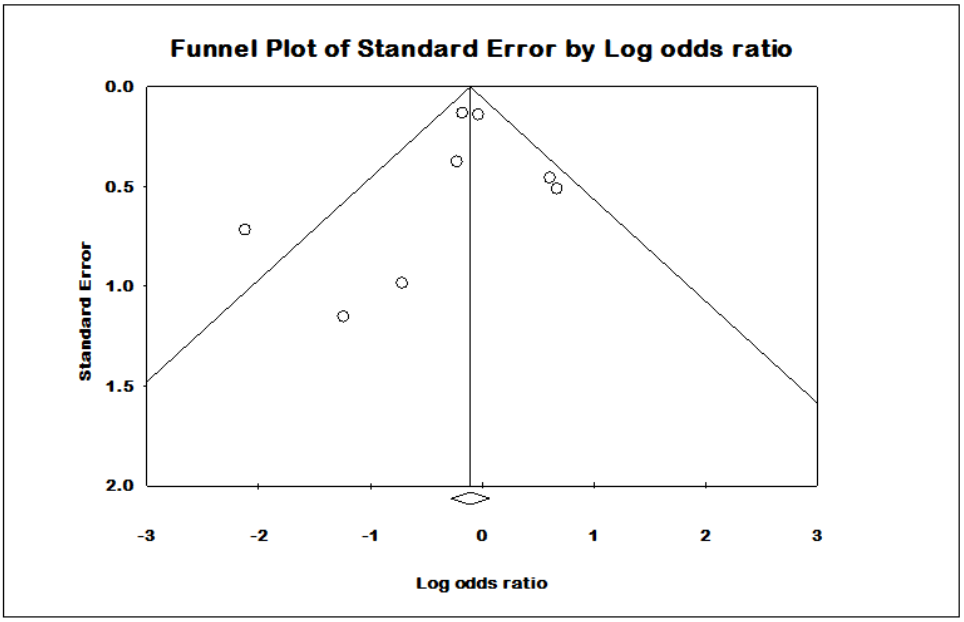


Figure 5 Funnel Plot for publication bias for studies looking at the odds ratio of developing colorectal cancer in patients with inflammatory bowel disease on non-aspirin non-steroids anti-inflammatory drugs (NA-NSAIDs).



3.5 Discussion

I present the first systematic review and meta-analysis of the effects of NA-NSAIDs and aspirin for CRC chemoprevention in patients with IBD to my knowledge. It is important to synthesise the available literature on this subject as CRC remains an important complication of IBD and NA-NSAIDs including aspirin have been consistently shown to have a protective effect in sporadic colorectal cancer. (Chubak et al., 2015; Friis et al., 2015) Nine retrospective studies were included that met the inclusion criteria, but unfortunately there have been no prospective randomised trials. There were only three studies that reported on aspirin use in patients with IBD associated cancer. I found no significant potential protective effect for NA-NSAIDs or aspirin against the development of CRC in IBD patients.

There are several limitations to this meta-analysis. All the included studies are retrospective and are therefore subject to inherent biases and confounding. Publication bias is another possible limitation as negative studies are less likely to be published and therefore not included in the analyses. However, I have attempted to reduce the possibility of publication bias by conducting an exhaustive search of the literature and did not limit inclusion of studies based on language. Most of the studies included in my analysis reported NA-NSAID and aspirin use as a secondary outcome measure and results from a multivariate analysis was provided only by three studies. (Velayos et al., 2006; Samadder et al., 2011; Bansal and Sonnenberg, 2013) The study with the most robust methodology from Velayos *et al*. (Velayos et al., 2006) reported a significant chemopreventative role for both NA-NSAIDs and aspirin. There were differences in the studies related to the definition of drug exposure and as these studies were all retrospective it was not possible to check compliance with the medication. A further limitation with studies of this type is confounding by indication. Aspirin and NA-NSAID use could be associated with another factor, such as another medical

condition, that is associated with colorectal cancer. It is not possible to adjust or correct for all such factors so this always must be borne in mind when interpreting such studies.

The dose and duration of drug exposure was not consistently recorded. An important consideration of chemoprevention against colorectal cancer is the duration of exposure to the medication. In the evidence for aspirin protecting against sporadic CRC a duration of >5 years conferred a 34% reduction in CRC risk. (Chan et al., 2012) The only study included here which took this into consideration was Eaden *et al.* (Eaden et al., 2000) where a prescription in the preceding 5-10 years before diagnosis was required for inclusion as positive exposure (Table 1). The dose of aspirin used was not stated in most of the studies, but it is likely to have been low dose as used in routine clinical practice in patients with cardiovascular risk factors, 75mg in the United Kingdom and 81mg in the United States. It is possible that a higher dose may be needed for chemoprevention of colitis-associated CRC. For example, a recent trial in patients with Lynch syndrome, a hereditary condition associated with high risk of CRC, demonstrated that high dose (600 mg daily) aspirin conferred protection against CRC. (Burn J. Mathers J. Bishop, 2012) Little information was provided about the timing and duration of exposure to aspirin and NA-NSAID's in any of the included studies. Aspirin and NA-NSAIDs may be unable to prevent the progression from dysplasia to cancer and could therefore be chemopreventative only in those with exposure to the drug from soon after onset of IBD and those with longer duration of exposure to the medication. Unfortunately, none of the studies included in this meta-analysis provided data on the timing of exposure to NA-NSAID or aspirin and the duration of IBD, to determine if early or long-term exposure was chemopreventative. The main outcome of interest was the development of CRC and not dysplasia which could support the argument that in some of the patients, CRC may have developed in those exposed to aspirin or NA-NSAIDs only after they had already developed colorectal neoplasia.

Adverse effects of NSAIDs on the gastrointestinal tract need to be considered in future studies as there is a potential increased incidence of disease flares with the use of NSAIDs, including aspirin.(Singh, Graff and Bernstein, 2009) This issue is still under debate as NSAIDs are often used for treatment of other conditions such as abdominal or musculoskeletal pain which are associated with flares of IBD. The NSAIDs therefore may be used after the flare has started to develop rather than being the cause of the IBD flare.

CRC remains an important complication of IBD. Current methods to reduce CRC in IBD are the use of colonoscopic surveillance or by prophylactic proctocolectomy. British Society of Gastroenterology guidelines advocate screening and surveillance colonoscopy which can result in annual tests for high risk patients. (Cairns et al., 2010) Chemoprevention is therefore an attractive proposition for these patients. NA-NSAIDs and aspirin remain biologically plausible targets for chemoprevention in IBD. As I have shown, the clinical evidence is limited. The available data are hampered by the fact that most of the studies include small numbers of patients and do not include adequate information on medication dose and duration. Potential chemoprevention agents are likely to take several years to display a protective effect as in the sporadic CRC population and this should be borne in mind in future studies. Prospective randomised chemoprevention trials are unlikely to be performed as the sample size required would be too large and therefore well-conducted epidemiological studies using prospectively recorded databases are needed to clarify the true effect of aspirin and/or NA-NSAIDs on the risk of CRC in patients with IBD.

Chapter 4 Systematic review and meta-analysis of the role of folate in the chemoprevention of IBD associated CRC

Chapter 4: Systematic review and meta-analysis of the role of folate in the chemoprevention of IBD associated CRC

In this chapter I will review the evidence for the potential role of folate supplementation in the chemoprevention of IBD associated colorectal cancer. After discussing the available evidence, I will describe the meta-analysis and pooled association size for folate and, after discussing strengths and weaknesses of the evidence and describe the impact of these findings.

4.1 Abstract

4.1.1 Aims

To evaluate the role of folic acid supplementation in colorectal cancer (CRC) chemoprevention in patients with inflammatory bowel disease (IBD).

4.1.2 Background

CRC is a serious complication of IBD. Folic acid supplementation has been shown to be chemopreventative in sporadic CRC. Patients with IBD are at risk of folate deficiency though intestinal malabsorption and competitive inhibition by concurrent sulfasalazine use. To date there have been several studies reporting on folic acid supplementation in patients with IBD and CRC.

4.1.3 Study

I searched electronic databases for studies reporting folic acid use and CRC incidence in patients with IBD. I produced a pooled Hazard Ratio (HR) with 95% confidence intervals (CI) using a random effects model. Pre-planned subgroup analyses were performed to explore for any potential sources of heterogeneity.

4.1.4 Results

Ten studies reporting on 4,517 patients were included. I found an overall protective effect for folic acid supplementation on the development of CRC, pooled HR 0.58 (CI 95% 0.37 to 0.80). There was low to moderate heterogeneity amongst studies, $I^2 = 29.7\%$. Subgroup analyses suggested that folic acid use was protective in hospital-based studies, studies from North America and those that were performed before folate fortification of foods in 1998.

4.1.5 Conclusion

CRC remains an important complication of IBD. Chemoprevention is an attractive strategy and folic acid as a cheap, safe and well tolerated supplement may have a role.

Focussed prospective studies are required in high risk groups to explore this association further and try and define whether there is a protective causal relationship between folate and IBD-CRC.

4.2 Introduction

As already discussed, chemoprevention of IBD-CRC is an attractive target as medical and surgical treatment of neoplasia is associated with substantial morbidity and mortality.

Folate (vitamin B9) is the generic term for a group of compounds, including folic acid as a supplement, that are essential for numerous bodily functions. (Scaglione and Panzavolta, 2014) Folate deficiency in humans causes neural tube defects in embryos and megaloblastic anaemia in adults. Humans cannot synthesise folate, so it is obtained from foods such as leafy green vegetables, folic acid in supplements or food fortification, mandatory in the United States and Canada since 1998. Folate has a role in DNA methylation and purine and thymidine synthesis for DNA and RNA (Choi and Mason, 2000) and has been implicated in carcinogenesis through permitting increased DNA damage and altering the expression of critical tumour suppressor and proto-oncogenes. (Kim, 1999) This is supported by experimental studies in rats where folate deficiency has been shown to induce CRC and folate supplementation inhibits it. (Cravo et al., 1992; Kim et al., 1996) There is evidence for a "dual role" of folate in carcinogenesis whereby folate may prevent early cancers but cause harm if these lesions have formed. (Kim, 2007; Ulrich and Potter, 2006) These studies, in mice with CRC, showed that high levels of folate promoted carcinogenesis once microscopic, neoplastic foci had developed. (Song et al., 2000a, 2000b)

Epidemiological studies have shown that reduced folate levels are associated with the development of several solid tumours including cervical, breast, pancreas, lung and CRC. (Freudenheim et al., 1991; Wien et al., 2012) Some of the most compelling evidence is for CRC, a recent meta-analysis of 27 papers showed a relative risk estimate reduction of 0.85 (95% CI 0.74 to 0.99) when comparing low vs high folic acid supplementation. (Kennedy et al., 2011) Individuals with IBD are at increased risk of folate deficiency through inadequate

nutritional intake, excessive intestinal loss and reduced absorption due to competitive inhibition by sulfasalazine use. (Potack and Itzkowitz, 2008; Swinson et al., 1981)

4.2.1 Aims

There have been several studies reporting the effect of folic acid supplementation on the chemoprevention of CRC in those with IBD but the results to date remain inconclusive. The aim of this study was to perform a comprehensive review and meta-analysis to see if there is evidence for the use of folic acid in chemoprevention against CRC in patients with IBD.

4.3 Materials and Methods

I followed pre-specified and peer-reviewed MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for reporting systematic reviews and meta-analyses of observational studies. (Stroup, 2000)

4.3.1 Search strategy

Separate electronic database searches were performed on MEDLINE (1946 to September 2015) and EMBASE (1947 to September 2015). Further searches were conducted on The Cochrane Library for systematic reviews and assessment evaluations and the National Health Service (UK) Economic Evaluation Database to September 2015. I also searched ISI Web of Science to capture conference abstracts and proceedings. The search terms used were inflammatory bowel diseases, Crohn's disease, ulcerative colitis, colorectal neoplasms and folic acid. Medical subject heading (MeSH), free text terms and variations were used. No limits or language restrictions were applied. I performed a recursive search of the literature by reviewing the bibliographies of the relevant articles identified from the search strategy. Articles were assessed by two independent reviewers (NB and VS) to assess eligibility for inclusion. Any disagreements were resolved by consensus decision.

4.3.2 Study selection

Studies were eligible for inclusion if they reported on the risk of developing CRC in patients with IBD on folic acid supplementation compared to a control population. Two reviewers (NB and VS) independently screened titles and abstracts identified by the preliminary searches to identify potentially eligible studies. Both reviewers independently assessed the full text articles of studies for inclusion in the pooled analysis. Data extraction was performed by two investigators (NB and VS) and included the characteristics of the study (population studied, country of origin, study design, definition of drug exposure) and medication use including folic acid supplementation and development of CRC. Agreement between the reviewers was greater than 95% and differences between the datasets were resolved by discussion.

4.3.3 Statistical Analysis

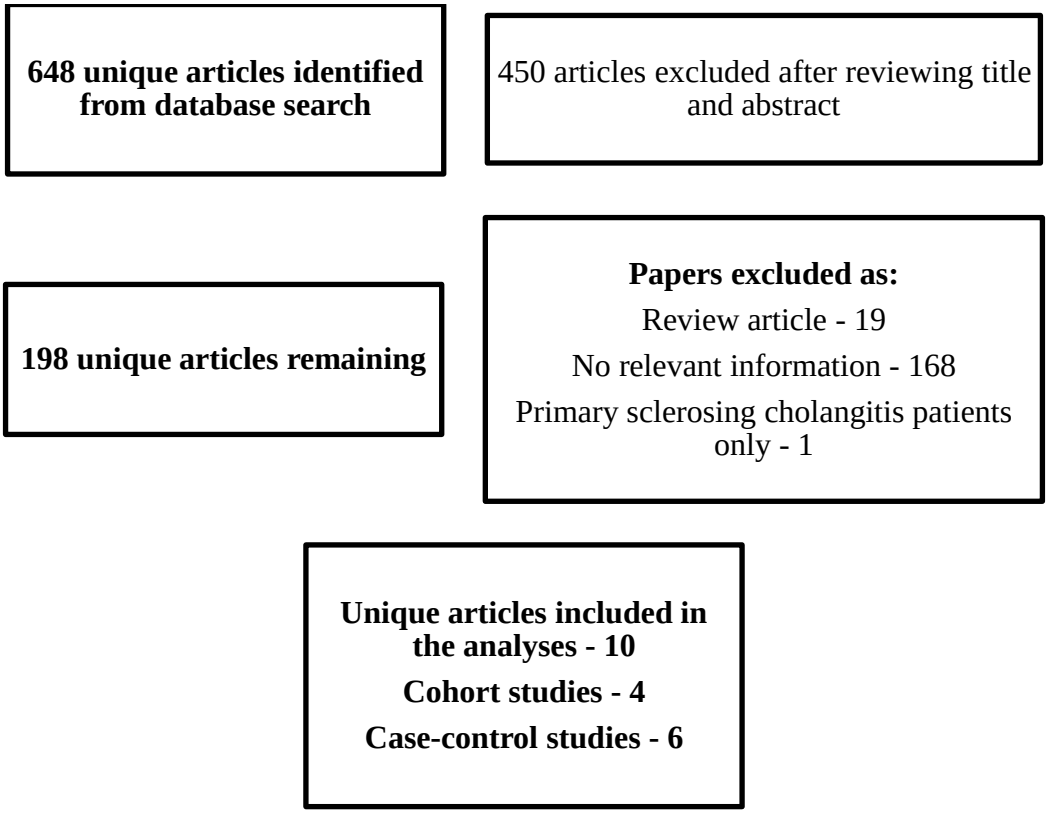
The effect size with 95% confidence intervals (CI) of developing CRC in IBD patients with and without folic acid supplementation was extracted from each study. Where possible I extracted HR with 95% confidence intervals. If the desired data was not reported in the study I converted the effect size estimates to a consistent HR format using methods outlined by Parmar *et al*, 1998 (Parmar, Torri and Stewart, 1998) using the Microsoft Excel spreadsheet produced by Tierney *et al*, 2007. (Tierney et al., 2007)

As randomisation and blinding is not possible in observational studies and baseline differences between the groups can confound the results, I used the authors' HR with adjustment or matching for potential confounding factors wherever available. A DerSimonian-Laird (DerSimonian and Laird, 1986) random effects model was used *a priori* for pooling the HRs. I subsequently performed a fixed effects model as a sensitivity test. I also used the Cochran's Q statistic to test heterogeneity among pooled estimates. (Cochran, 1954) Statistical heterogeneity was further measured by the I^2 statistic, which quantifies the

proportion of inconsistency in individual studies that cannot be explained by chance.

(Higgins et al., 2003)

Figure 6 Flow chart of included studies in the systematic review and meta-analysis of the role of folate medications in the chemoprevention of IBD-CRC



Values of I^2 equal to 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. As a further sensitivity test, I excluded studies with significant heterogeneity to see if there was a change in the overall observed effect. To test for publication bias, I used a test for asymmetry of the funnel plot proposed by Egger *et al.* (Egger et al., 1997) This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalised effect estimate (estimate divided by the standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate.

The quality of the primary studies assessing the risk of bias was evaluated using the Newcastle-Ottawa Scale for non-randomised studies (NOS) (Wells et al., 2000). Studies score a maximum of 4 for selection, 2 for comparability and 3 for outcomes (cohort) or exposures (case-control). I regarded scores of 0 to 3 as low, 4 to 6 as medium and 7 to 9 as high methodological quality.

4.3.4 Subgroup analyses

Pre-planned subgroup analyses were performed to explore potential sources of heterogeneity by assessing the influence of several factors on the overall effect estimate. These were 1) outcome studied (CRC or any dysplasia), 2) whether the study reported outcomes after matching or adjustment (yes vs no), 3) the population studied (hospital based or population-based), 4) whether the study was performed before introduction of folate fortification (pre or post 1998), 5) NOS study quality ($\geq$7 vs <7) and 6) geographic location of study (North America vs Europe). All analyses were conducted using Stata statistical software (version 12, Stata Corp, College Station, TX).

Table 3 Characteristics of the studies included in the systematic review and meta-analysis of the role of folate medication in the chemoprevention of IBD-CRC

Author, year	Design	Population	IBD	Duration of IBD	Neoplasia	Folic acid exposure	Study size (cases/controls)	HR (95% CI) AD	HR (95% CI) CRC	Matching criteria	Newcastle-Ottawa Score for quality
Lashner, 1989(Lashner et al., 1989)	Cohort	US hospital	UC†	> 7yrs	AD	0.4mg or 1mg, ever used	88 (29/59)	0.41 (0.19-0.88)		None	7
Lashner, 1997(Lashner et al., 1997)	Cohort	US hospital	UC†	> 8yrs	CRC or AD	0.4mg or 1mg, > 6 months.	97 (29/68)	0.59 (0.28-1.24)	0.44 (0.66-1.24)	None	7
Rutter, 2004(Rutter et al., 2004a)	Case-control	UK hospital	UC	> 8yrs	CRC or AD	"any"	42 (14/28)	0.74 (0.13-4.16)	0.54 (0.05-6.28)	Gender, duration of disease, extent of disease	7
Siegel, 2006(Siegel and Sands, 2006)	Case-control	US hospital	CC	All patients	CRC	"any"	54 (27/27)	1.00 (0.04-2.48)		Gender, duration of disease	7
Velayos, 2006(Velayos et al., 2006)	Case-control	US hospital	UC	"chronic"	CRC	"any"	376 (188/188)	0.79 (0.48-1.32)		Gender, duration of disease, extent of disease	6
Gupta, 2007(Gupta et al., 2007)	Cohort	US hospital	UC	> 7yrs	CRC* or AD	"any"	**	0.90 (0.50-1.60)	1.30 (0.40-3.70)	None	7

Tang, 2010(Tang et al., 2010)	Case-control	US hospital	UC or CD	All patients	CRC	1mg, ever used.	48 (18/30)	0.23 (0.09-0.58)	None	7
Baars, 2011(Baars et al., 2011)	Case-control	Netherlands nationwide pathology database	UC or CD	All patients	CRC	"any"	551 (159/392)	0.83 (0.05-1.38)	None	6
Van Schaik, 2012(van Schaik et al., 2012)	Cohort	Netherlands nationwide insurance database	UC or CD	> 6 months	CRC*	"any"	2578 (28/2550)	2.11 (0.45-9.94)	None	9
Rubin, 2013(Rubin et al., 2013)	Case-control	US hospital	UC	All patients	AD	"any"	199 (59/140)	0.77 (0.46-1.28)	Age, duration of disease, extent of disease	7

Abbreviations used: UC - ulcerative colitis, CD - Crohn's disease, CC - Crohn's colitis, AD - any dysplasia, CRC - colorectal cancer

HR - hazard ratio.

† pancolitis

* advanced neoplasia

** some patients excluded as missing data, unknown number

4.4 Results

The search strategy and results are shown in figure 5. Ten studies were included in the meta-analysis which reported on 638 cases of IBD associated CRC. (Lashner et al., 1989, 1997; Rutter et al., 2004a; Velayos et al., 2006; Siegel and Sands, 2006; Gupta et al., 2007; Tang et al., 2010; Baars et al., 2011; van Schaik et al., 2012; Rubin et al., 2013) Of note, the study by Shetty *et al*. (Shetty et al., 1999) was not included as it included only patients with co-existing primary sclerosing cholangitis. The individual study details are shown in table 3. There was variation in study design (case-control or cohort), sample size, location, population studied and the reporting on dose and duration of folic acid use. Folic acid was the primary measure in 2 of the studies, (Lashner et al., 1989, 1997) the remainder reporting it as a secondary outcome measure. The overall study quality was high with 8 of the 10 studies having a NOS score of ≥7 (table 1). Pooling of the effect estimates from the studies (Figure 6) resulted in a HR of 0.58 (CI 95% 0.37 to 0.80). This result was maintained when performing a fixed effect model analysis, pooled HR 0.51 (CI 95% 0.36 to 0.66). I performed a series of planned subgroup analyses (Table 4). Folic acid use was protective in hospital rather than population-based studies, studies conducted in the United States of America, high quality studies, unmatched studies and studies conducted before the introduction of food fortification in 1998.

To test for publication bias, I constructed a funnel plot (Figure 7). There was some asymmetry in the funnel plot suggesting that there may be some publication bias. Egger's regression asymmetry test however was not significant (p = 0.83). Publication bias does remain a possibility as there were only 10 studies in the analyses and in this scenario the ability of Egger's test to detect a potential bias is limited.

Figure 7 Hazard ratios (HR) and 95% confidence intervals for folic acid as a chemopreventative agent against the development of CRC in IBD. Random effects model.

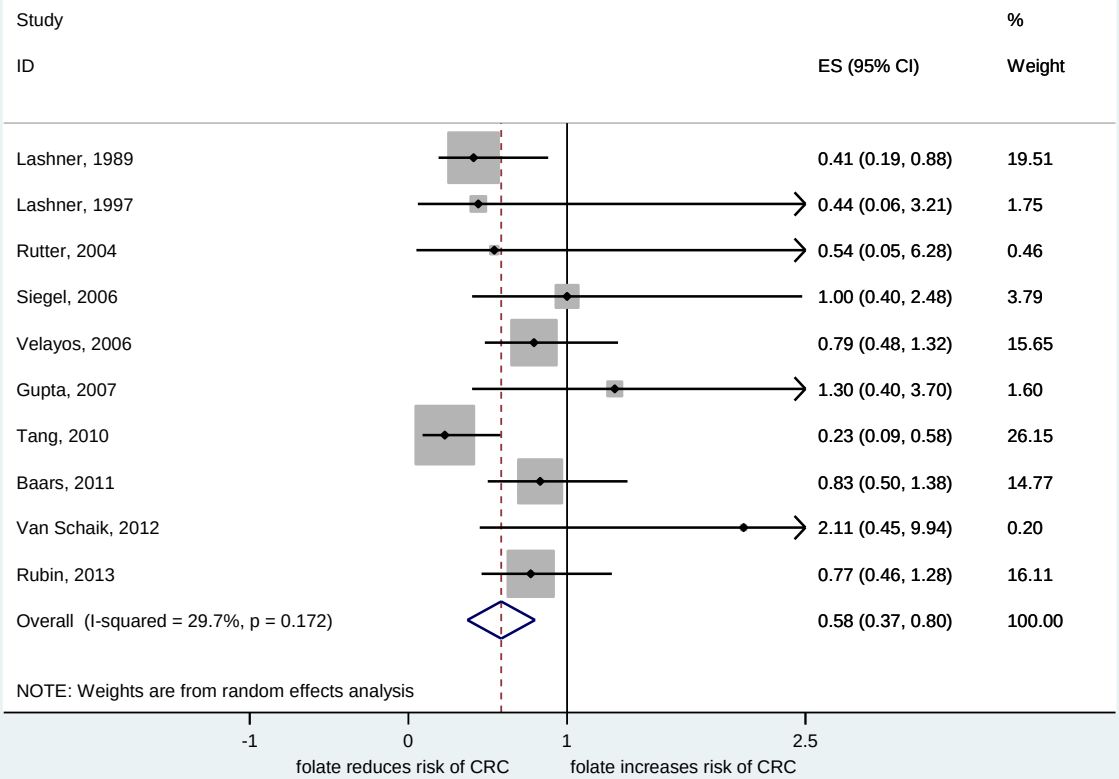


Figure 8 Funnel plot of studies evaluating folic acid in the chemoprevention of CRC in patients with IBD.

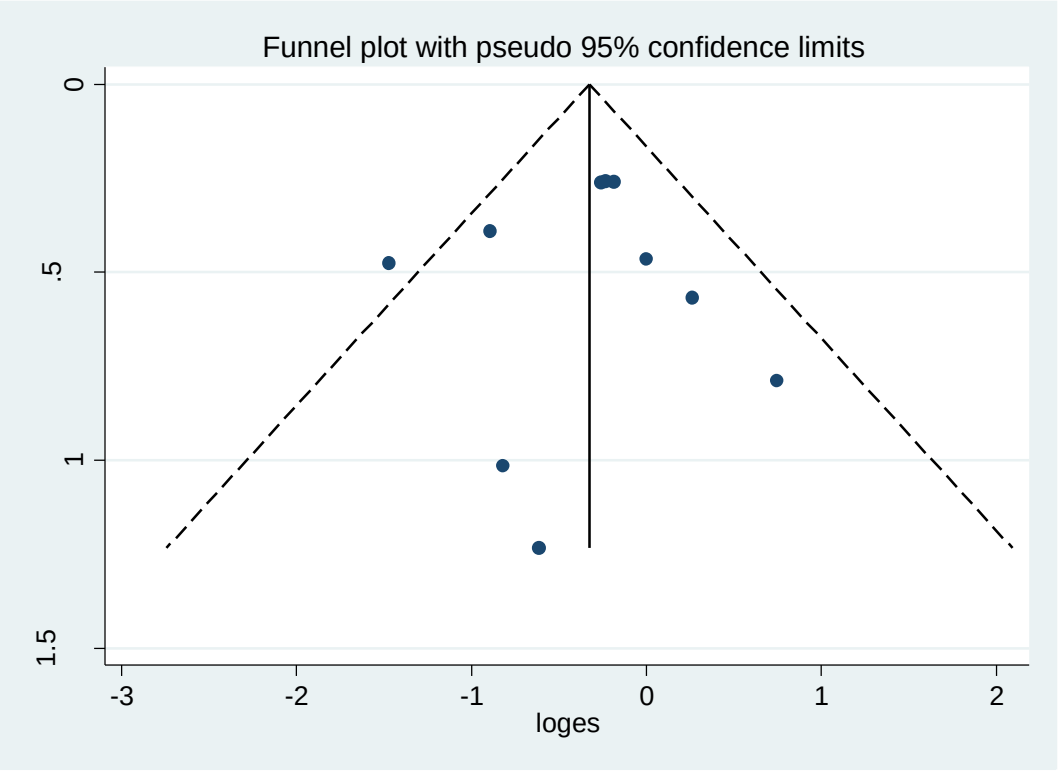


Table 4 Subgroup analyses in the chemoprevention of IBD-CRC by folate medications

	Number of studies	Pooled HR (95% CI)	Heterogeneity		
			Cochran's Q	p-value	I^2 (%)
Dysplasia					
CRC	5	0.62 (0.41-0.83)	2.96	0.56	
Any dysplasia	8	0.63 (0.31-0.94)	10.88	0.14	35.7
Matched y/n					
Matched/adjusted	4	0.80 (0.52-1.08)	0.17	0.98	
None	6	0.54 (0.28-0.79)	9.38	0.10	46.7
Study location					
Hospital	8	0.58 (0.37-0.79)	11.53	0.12	39.3
Population	2	0.84 (0.40-1.28)	0.28	0.60	
Folate fortification					
Before	2	0.47 (0.20-0.75)	0.36	0.55	
After	5	0.66 (0.32-1.00)	11.05	0.03	63.8
Study quality					
NOS ≥7	8	0.47 (0.26-0.67)	7.37	0.29	18.6
NOS <7	2	0.83 (0.56-1.10)	0.10	0.95	
Geographic location					
US	7	0.58 (0.36-0.81)	11.48	0.08	47.7
Europe	3	0.84 (0.41-1.26)	0.29	0.87	

NOS – Newcastle-Ottowa scale

4.5 Discussion

I have shown that there is a significant negative association with folic acid supplementation and CRC incidence in patients with IBD. There was however marked variation in study design, so more work is needed to substantiate this association. The potential effect of folic acid has been more rigorously investigated for sporadic colorectal cancer (Kennedy et al., 2011) but there is a paucity of data in the IBD population who are not only at greater risk of CRC but also folate deficiency. This review builds on the initial work by Lashner *et al.* in 1989 (Lashner et al., 1989) and 1997 (Lashner et al., 1997) where non-significant reductions in CRC lead to some physicians advocating the use of folic acid as a chemopreventative agent in the UC population. (Potack and Itzkowitz, 2008)

There are several important limitations to this analysis. All of the studies are retrospective and are subject to inherent biases associated with case-control and cohort studies. (Mann, 2003) Importantly they are unable to control for all possible confounding factors and indeed some of the studies included here report unadjusted and unmatched results. Important confounders that should be considered in future studies are family history of sporadic CRC, frequency of consultation and colonoscopy, smoking, obesity, other medications or supplements known to affect sporadic colorectal cancer risk. IBD-associated factors of extent, duration and severity of disease should also be included. It is important to stress that the results seen are association only and a causal effect of folate on preventing IBD-CRC cannot be assumed based on these results. There may be other confounding factors associated with folic acid use that have not been accounted for in the retrospective studies included. One such associated factor is that patients taking health supplements are known to cluster healthy behaviours which may reduce their CRC risk. (McNaughton et al., 2005). It may be an associated healthy behaviour, that is responsible for the reduced incidence of CRC rather than the folate supplementation. A further consideration is the indication for folate

prescription, and whether it is this indication, rather than the prescription that has an influence on CRC risk. Folate medication is prescribed for several conditions that may be associated with IBD-CRC risk. Folic acid is co-prescribed with the folate antagonist methotrexate, which is prescribed in chronic inflammatory conditions, to prevent deficiency. As discussed, chronic colonic inflammation is associated with IBD-CRC risk (Rutter et al., 2004a) so the methotrexate co-prescribed with the folic acid may be responsible for the negative association. I was not able to explore this in the studies involved in the meta-analysis. However, methotrexate is not commonly used in colonic IBD due to lack of efficacy (Wang et al., 2015) so I would not expect this to account for all of the association seen. Folic acid supplementation is given to young women hoping to conceive. Young age and female sex are associated with a reduction in CRC (Johnson et al., 2013b) so this may contribute to some of the negative association seen. Chronic alcoholism is one of the principal reasons for folate deficiency, (Allen, 2008) but a meta-analyses of risk factors for sporadic CRC did not show any association between alcohol intake and CRC. (Johnson et al., 2013a) Alcohol use is associated with smoking, and smoking is positively associated with CRC. This interaction may mean that folate prescription is associated with an increased CRC population risk due to the positive association with alcohol and smoking. Overall, these potential confounding factors need to be considered, and there are positive and negative associations with CRC risk and folate supplementation. This highlights the need for further confirmatory studies, and ideally prospective controlled trials, that although difficult and expensive to conduct can provide more definitive evidence of any chemopreventative role of folate. There was significant variation in design of the studies included in our analyses. To account for some of the important differences I performed a series of subgroup analyses (Table 4). Due to the low numbers of studies in some of the subgroup arms these results should be interpreted with caution. I found that hospital-based patients had potential protection from folic acid

supplementation, which would be expected as these patients are likely to have more significant disease burden from their IBD with increased inflammation and subsequent malignant potential. There was also a difference in association when comparing studies performed before and after folate fortification in the United States of America in 1998. When comparing studies before and after the introduction of folate the effect estimate changed from 0.47 (95% CI 0.2 to 0.75) to 0.66 (95% CI 0.32 to 1.00). Although only a slight change in the effect estimate there is a borderline loss of statistical significance and the effect estimate change supports our biological hypothesis as the control populations after 1998 are likely to be receiving greater amounts of folate through food fortification. The protective effect was maintained when analysing high quality studies, NOS >7. This would support the effect being a true association as the better-quality studies would be expected to have less bias and confounding through increased methodological rigor.

Meta-analyses are subject to publication and reporting bias and it is possible that some of the 24 studies not included (Figure 5) did not report on folic acid use in their analyses as it showed no association. There may also be some dedicated studies which showed negative results that have not been published. To reduce the potential for any publication bias I did an exhaustive literature search which included the "grey literature" and did not have any language restrictions. To check for publication bias, I produced a funnel plot along with Egger's regression asymmetry test. The funnel plot had some asymmetry; however, Egger's test was non-significant. While this does not exclude the possibility of publication bias, the extensive search of the literature performed reduces the risk of relevant published articles being excluded in this analysis. Another problem when analysing non-prescription supplements such as folate is not being able to account for "over the counter" use. This use would, however, lead us to underestimate the true effect as patients taking these supplements would most likely be counted as controls in the studies included. Unfortunately,

most of the studies did not report on the dose of folate or duration of use. As such I was unable to calculate any dose or time response gradients which would strengthen an aetiological hypothesis. As with sporadic CRC, higher doses of folate may lead to a greater chemopreventative effect. (Kennedy et al., 2011) Future studies should attempt to quantify folate exposure to aid these analyses.

CRC remains an important and serious complication of both UC and colonic CD. There are plausible mechanisms for the chemopreventative effects of folate through its essential role in DNA replication and cell division. A deficiency in tissues with rapidly dividing cells, such as colonic epithelium, can result in ineffective DNA synthesis and repair, altered expression of critical tumour suppressor genes and proto-oncogenes and subsequent carcinogenesis. (Choi and Mason, 2000; Kim, 2004, 1999)

Chemoprevention remains an attractive option for patients with IBD to prevent dysplasia, reduce the burden of surveillance colonoscopy and reduce the need for proctocolectomy in patients with UC. The ideal chemopreventative agent would be safe, well tolerated, inexpensive and have a role in suppressing inflammation and malignant transformation (Lakatos and Lakatos, 2008) and folic acid fits these criteria. Any further reduction to the risk of CRC in IBD is welcomed and folic acid supplementation, as a safe intervention, may be an attractive option if further focused population-based studies on this topic confirm the findings of this meta-analysis.

Chapter 5 Validation study of the ResearchOne primary care database for use in IBD research

Chapter 5: Validation of the ResearchOne Primary care database for use in IBD research.

In this chapter I will describe a validation study of the ResearchOne dataset undertaken at Leeds Teaching Hospitals NHS Trust.

5.1 Abstract for the validation study

5.1.1 Background

Electronic health records from primary care databases are an important resource for biomedical research. They allow the analysis of large cohorts, long-term trends and investigation into rare outcomes. The SystmOne primary care database is one of the largest in the United Kingdom (UK) and includes clinical records from ~ 2,700 UK general practices. ResearchOne is an ethically approved dataset that comprises a subset of ~6 million individual clinical records from SystmOne.

Despite the growing use of electronic datasets there are uncertainties around data quality and completeness. Data are sparse on the validity of chronic disease diagnoses within primary care databases and the SystmOne database has not been externally validated to my knowledge before this project.

5.1.2 Methods

I recruited individuals from the IBD out-patient clinic at Leeds Teaching Hospitals NHS Trust, UK. The latest IBD diagnosis was recorded, namely; UC, CD or IBD-unclassified, the date of first diagnosis, first GI resectional surgery after an IBD diagnosis and the type of surgery performed. The hospital records were compared with primary care recorded entries, taking the hospital clinical and histopathological records as the reference standard. In the primary analyses the accuracy of diagnoses recorded on the SystmOne primary care database was investigated, as a secondary outcome I included other primary care databases and reported pooled results. I calculated the proportion of individuals with accurate

clinical data on the primary care databases, and those with a recorded date accurate to within 12 months.

5.1.3 Results

147 adults with a hospital diagnosis of IBD were included. One hundred patients had primary care records held on the SystmOne database. The only other PCD included was EMIS, with the remaining 47 patients. For SystmOne: IBD diagnoses were recorded in 98% of patients, 93% had the correct IBD subtype, and 85% had the first date of diagnosis accurate to within 12 months. GI surgical resections were recorded in 91% of cases, recorded as the correct procedure type in 81% of cases and the procedure date was correct to within 12 months in 95% of cases. There was no difference when comparing results between SystmOne and EMIS

5.1.4 Conclusions

I have shown that IBD and surgical diagnosis codes, present in a hospital medical record, are recorded in over 90% of those with IBD in the primary care database SystmOne. This gives confidence in using this resource for healthcare research into IBD.

5.2 Introduction

Electronic health records from primary care databases (PCD) are an important resource for biomedical research. They allow the analysis of large research cohorts, long-term trends and investigation into rare outcomes. In the United Kingdom (UK) they enable research studies of population cohorts as >98% of UK residents are registered with a GP as the gatekeeper for healthcare services. (Lis and Mann, 1995)

ResearchOne is one such database which was created in 2014, and includes de-identified clinical records on ~6 million patients from the SystmOne database. (Burr et al., 2018b) Despite the growing use of electronic datasets as research tools there are uncertainties around data quality, data completeness and the potential for unrecorded confounding factors to introduce bias. Any compromise in the quality, or completeness of the data could result in spurious conclusions being drawn. It is therefore important that before studies are performed using these datasets, the data is checked for validity. Data are sparse on the validity of chronic disease diagnoses within primary care databases and the SystmOne database has not been externally validated to our knowledge to date.

5.1 Potential validation methods

There are several methods that have been employed to validate PCDs. Studies have compared results from observational studies performed on a PCD with results from randomised controlled trials with the same hypothesis. This may not always be appropriate as the populations enrolled within clinical trials do not always reflect a more general population due to inclusion criteria within the studies. Further methods of validation have been undertaken to compare PCD data with National validated registries such as National cancer registries and UK hospital episode statistics (HES). The potential problem with this method is that the episodes recorded in cancer registries and hospital procedures are not usually included in GP quality performance measures and prioritised for coding. Another validation

method is to compare results from one dataset with a similar PCD. This, again, has been used to compare other UK databases such as CRPD and THIN (Reeves et al., 2014) and has shown good concordance. Another validation method has been to use GP questionnaires to compare PCD with hospital letters and discharge summaries also held on the PCD, although not coded. This method is limited by the response rate from the GP and the quality and quantity of data sent through to them from secondary care. Rare diseases, and those predominantly managed in secondary and tertiary care centres are most likely to be misclassified on GP databases as the entries are transposed from discharge summaries and clinical letters. They are also less likely to be included in the GP contract codes. It is therefore important that PCD data for such conditions is validated in order to use these data for research purposes.

To date there has been no prior validation study of the data held within the SystmOne and therefore the ResearchOne PCD to my knowledge.

5.1.1 Aim

Here, I explore the validity of IBD diagnoses within the SystmOne primary care database in individuals recruited from hospital out-patient clinics.

5.2 Materials and methods

Patients were recruited from IBD out-patient (OP) clinic attendances at Leeds Teaching Hospital NHS Trust, UK. Written, informed consent was obtained by members of the research team (NB, VS). Information was recorded on IBD type, CD, UC or indeterminate colitis (IBD-U). The first recorded date of IBD diagnosis was obtained from hospital clinical records, including clinic letters, and histopathology results. Surgical information was recorded for the first gastrointestinal resection and the type of operation performed. Operations were classified as small bowel resection, ileo-colonic resection, colonic resection and total colectomy. The hospital records were taken as the reference standard for the study.

Primary care recorded entries were taken as the first recorded Read code entry for IBD and the number, type and date of the first recorded, IBD-related surgery. Where there were multiple different Read code entries for IBD I classified the IBD diagnoses as follows;

- CD – CD Read codes only or IBD-U followed by CD Read code.
- UC – UC Read codes only or IBD-U followed by UC Read code.
- IBD-U – IBD-U Read codes only or a combination of CD & UC Read codes.

Patient records from SystmOne were used for my primary analyses. In my secondary analyses I recorded information from any other different primary care databases and pooled the data. I aimed to recruit 100 patients with IBD, and data held on the SystmOne primary care database. This is in line with previous validation studies from different datasets (Aberra et al., 2005; Herrett et al., 2010) and would give enough patients to draw a meaningful conclusion about the accuracy of the database.

5.2.1 Statistical analyses

Continuous variables were presented as medians with interquartile range (IQR) for non-parametric and means with standard deviations (SD) for parametric variables. I compared the percentage accuracy between the SystmOne database and all other recorded primary care databases using a paired t-test.

I considered p values of <0.05 to be statistically significant. I used Stata 14 (StataCorp LP, College Station, TX, USA) for all our analyses.

5.2.2 Ethical statement

The study was approved by the North West - Liverpool Central Research Ethics Committee and the NHS health research authority (REF: 16/NW0076). Approval documents are included in the appendix (Appendix 4)

5.3 Results

I recruited and consented 147 patients with IBD from outpatient clinics at Leeds Teaching Hospitals NHS Trust (Table 5). Of these, 100 patients were registered with a SystmOne GP practice and included in the primary results. From the hospital histological diagnoses there were 62 patients with CD, 35 with UC and three with indeterminate colitis. There were 23 individuals who had undergone a GI surgical resection for IBD, 61% of these were ileo-colonic resections (Table 5).

The results of the validation are shown in Table 6. IBD diagnoses were recorded in 98 (98%) individuals' SystmOne GP records. The type of IBD was correct in 93% of individuals with no difference between SystmOne and all other GP computer systems ($p = 0.50$). The IBD diagnosis was within 6 months for 76% and within 12 months for 85% of individuals. Again, there was no difference between SystmOne and other GP computer systems ($p = 0.88$ and $p = 0.77$, respectively). Individuals who had undergone surgery was recorded in 91% of patient's primary care records. The surgery type was correct in 81% of cases. The surgery date was accurate within 6 months in 90% of cases and within 12 months in 95% of cases.

Table 5 Inflammatory bowel disease patients and gastrointestinal surgery resections included in a validation study of the SystmOne primary care database.

	SystmOne, n (%)	SystmOne and EMIS combined, n (%)
Inflammatory bowel disease	100	147
Crohn's disease	62 (62)	86 (58)
Ulcerative colitis	35 (35)	57 (39)
Indeterminate colitis	3 (3)	4 (3)
Surgery	23	32
Small bowel resection	2 (9)	2 (6)
Ileo-colonic resection	14 (61)	22 (69)
Colonic resection	0 (0)	1 (3)
Total colectomy	7 (30)	7 (22)

Table 6 Validation of inflammatory bowel disease diagnoses held within the primary care databases SystmOne, and pooled primary care databases compared to the reference standard of hospital medical records.

	SystmOne, n (%)	SystmOne and EMIS combined, n (%)
IBD diagnoses		
IBD diagnosis recorded in primary care record	98 (98)	144 (98)
IBD diagnosis correct, n (%)	92 (93)	137 (94)
Difference in IBD diagnosis date, median days (IQR)	38 (4 - 188)	34 (6 - 194)
IBD diagnosis date correct within 6 months, n (%)	75 (76)	110 (75)
IBD diagnosis date correct within 12 months, n (%)	84 (85)	123 (84)
Surgical diagnoses		
First GI surgery recorded on primary care record, n (%)	21 (91)	28 (88)
First GI surgery type correct, n (%)	17 (81)	22 (79)
Difference in surgery date, median days (range)	0 (0 - 2922)	0 (0 - 2922)
First GI surgery date correct within 6 months, n (%)	18 (90)	24 (92)
First GI surgery date correct within 12 months, n (%)	19 (95)	25 (96)

IBD – inflammatory bowel disease; GI – Gastrointestinal; IQR – inter-quartile range.

5.4 Discussion

There is increasing use of PCDs for epidemiological research studies into population health. There is a need to validate these databases for the accuracy of clinical data within them to justify their continued use. Here I have shown that the SystmOne database has good accuracy for IBD diagnoses and associated GI resectional surgery that are recorded in hospital notes.

There have been previous studies examining the validity of UK primary care databases employing different methodologies to give a positive predictive value of a primary care recorded entry. (Soriano et al., 2001; Herrett et al., 2010) My results are in concordance with a study by Lewis *et al* who compared GPRD primary care data with data from GP questionnaires. (Lewis et al., 2002) Here, IBD diagnoses were shown to be accurate in 92% of cases. A systematic review and meta-analysis of diagnostic coding in UK primary care computerised datasets found an overall median accuracy of 89%, which is also in line with my results. (Herrett et al., 2010) I have also shown that the dates of diagnoses are accurate to within 12 months. This is an important finding as epidemiological investigations using primary care datasets will often seek to investigate long-term outcomes in longitudinal, observational studies. It is important therefore to have an accurate start point to investigate the clinical disease course.

Previous studies have used computerised searches of primary care data or questionnaires to general practitioners to confirm cases, often without additional information from hospital records. This introduces a potential bias as primary care practitioners are validating their own clinical entries. My study uses hospital data as the reference standard. IBD is typically diagnosed and managed in secondary care after endoscopy and histology (Mowat et al., 2011) so I believe that this is a robust way of confirming a diagnosis of IBD.

I selected consecutive patients from out-patient clinic lists on different days and expect the results of this study to be generalisable to the remainder of the SystmOne database and other UK databases as SystmOne GPs are not pre-selected and should be representative of primary care practitioners.

I included a relatively small sample size of 100 patients from the SystmOne database, and only 23 of these had undergone a GI surgical resection for IBD which may limit the accuracy of the final estimates for our secondary outcome. A systematic review of validation studies of a similar dataset, the General Practice Research Datalink (now called the Clinical Practice Research Datalink) in 2010 included 347 studies. (Herrett et al., 2010) Here, the median number of cases reviewed was 104, which is consistent with my study. A further limitation is that I could not verify the positive predictive value of the accuracy of IBD diagnoses on primary care records as I approached the validation from secondary care records. This is an important consideration for IBD diagnoses that are made in primary care. However, I expect this scenario to be unlikely for conditions such as IBD that are typically diagnosed after colonoscopy, performed in secondary care centres with subsequent management being co-ordinated through dedicated hospital clinics. Studies have shown that over a third of patients are solely managed in secondary care services in the UK. (Stone, Mayberry and Baker, 2003) The latest estimates, albeit from the 1990's, showed that there were only 26 consultations per 100,000 population per year for IBD related symptoms in primary care which strengthens my hypothesis that most cases of IBD are managed predominantly in secondary or tertiary care settings. (Clinical Effectiveness and Evaluation Unit, 2014)

CD can occur at any location in the GI tract and UC at different colonic locations. This level of detail is not recorded in primary care databases, so I was unable to further explore location of IBD in this study.

5.5 Conclusions

There is increasing use of large-scale population datasets for epidemiological research. A concern with using these datasets is the accuracy of information held in them. Here, I have shown that IBD diagnoses recorded in hospital records are correct for 93% of patients on the SystmOne database, giving validity to research studies using this data source. ResearchOne is a novel, ethically approved dataset that comprises a subset of ~6million individual clinical records from SystmOne. This information is de-identified and so cannot be externally validated but I expect our results to be generalisable to this dataset as the records are not pre-selected for inclusion. IBD is typically diagnosed and managed from secondary care facilities in the UK. It is reasonable to assume that other chronic diseases will have similar coding accuracy to the estimates I have made for IBD.

Chapter 6 Description of the IBD cohort in the ResearchOne database

Chapter 6: Description of the IBD cohort in the ResearchOne database

In this chapter I will describe the IBD cohort obtained from the ResearchOne primary care dataset and used for the remainder of the analyses in this thesis. I will also describe the aetiological factors associated with IBD-CRC and furthermore describe the trends in diagnosis of CRC in this population.

6.1 Data sources and participants

The primary care database ResearchOne was used for this study. (www.researchone.org) This is described in detail in prior chapters but includes information from the electronic health records of approximately 6 million individuals (>10% of the total population) in England.

6.1.1 Inclusion and exclusion criteria

I included all adults (>18 years old) at the extraction date (14th September 2014) with a Read code for IBD in their primary care record (Appendix 1). Individuals were classified as CD and ulcerative colitis UC when only Read codes for these IBD subtypes were recorded. I defined a third category of IBD-U as those with a specific code for this entity or where there were both codes for UC and CD in the individual's GP medical record. For all individuals, I extracted a defined set of data items, including; date of birth (mm/yyyy), sex, date of death (mm/yyyy), GP registrations, Index of Multiple Deprivation (IMD) of residence, (Noble, Mclennan and Wilkinson, 2007) diagnoses of IBD and relevant comorbidities (including smoking status), ethnicity, and prescriptions (including repeat prescriptions). British National Formulary (https://www.evidence.nhs.uk/formulary/bnf/current (accessed April 2014)) headings and subheadings were used to identify the medication classes. Individuals were followed up from their IBD diagnosis to either death or the extraction date.

I defined an incident cohort as those who had been diagnosed with IBD at least twelve months after joining a ResearchOne practice. This excludes prevalent cases where the date of

diagnosis may be less accurate. This also allows the capture of continuous prescription and clinical data from the date of entry into the ResearchOne database.

6.1.2 Covariates

Age at diagnosis was categorised into groups as follows: < 30 years, 31 to 40, 41 to 50, 51 to 60, 61 to 70, and over 70 years. Duration of IBD was categorised as follows: 0 to 2 years, > 2 years to 4 years, > 4 years to 6 years, > 6 years to 8 years, > 8 years to 10 years, and > 10 years. Individuals were also classified into cohorts depending on the year of IBD diagnosis to account for changes in disease phenotype and management that might affect outcomes. Year of diagnosis cohorts were as follows: before 1993, from 1994 to 2000, from 2001 to 2007, and from 2008 to 2014.

Social deprivation score was included as five groups, based on equal quintiles of the IMD score. A higher IMD score equates to more deprivation and has been shown to correlate with increased morbidity and all-cause mortality in the UK. (Marmot et al., 2010) To account for co-morbidity I produced an estimate of the Charlson score (Charlson et al., 1987) using Read codes for each of the seventeen weighted disease categories included in the original score. I calculated a similar, weighted score and used a cut off of ≥ 2 as a modest estimate of co-morbidity. Smoking history was recorded as ever smoked, never smoked and smoking data missing. The hierarchy of smoking data was: 0 “never smoked”, 1 “missing smoking data”, and 2 “ever smoked”. This ordering for the hierarchy was used as it is assumed that some of individuals with missing smoking data will have smoked. I adjusted for known surrogate markers of CD severity including corticosteroid medications given within ninety days of IBD diagnosis (Peyrin-Biroulet et al., 2012) and also immunomodulator use, namely azathioprine, 6-mercaptopurine and methotrexate. (Picco et al., 2009)

6.1.3 IBD-CRC epidemiology cohort

I included all individuals with a Read code diagnosis for CRC (Appendix 2). Individuals who had undergone a colectomy for UC were excluded as they have much reduced chance of developing CRC. I described the demographics of the IBD-CRC using the covariates listed above. Again, as above I created an incident cohort comprising those who were diagnosed with IBD at least one year after joining a ResearchOne GP practice. To explore the geographical spread of the IBD population held within the ResearchOne database I plotted the location of each general practitioner location with an individual with an IBD diagnosis.

6.1.4 Trend analysis

I explored the trend in cancer cases depending on the year of IBD diagnosis to see if there has been any change in the rate of diagnosis over time. I used chi^2 for trend as a significance test. The numerator in this analysis was the number of CRC cases diagnosed in a particular time period. The denominator was the total number of living IBD cases within each time period excluding those who had an earlier coded entry for CRC. I performed a subgroup trend analysis of only those diagnosed after the year 1990 as I used 1990 as a cut-off for the start of the year cohorts.

Any change in the trend in diagnosis of IBD-CRC in the ResearchOne database throughout the study period is likely to be associated with the overall age of the ResearchOne cohort. This is because increasing age is a such a strong risk factor for the development of CRC. To display this association, I produced a line graph of the mean age of the alive, registered cohort throughout the study period from 1990. Again, chi^2 for tend was used as a significance test.

6.1.5 Ethical statement

ResearchOne has received a favourable opinion from National Health Service (NHS) Research Ethics Committee (REC) (11/NE/0184) and the UK National Information Governance Board for Health and Social Care. Our study has NHS REC (14/WM/01/26) and local research and development (GA14/11077) approval. Approval documents are included in the appendix. (Appendix 4)

6.2 Results

6.2.1 Description of the ResearchOne IBD cohort

There were 17,883 adults (>18 years) with a diagnosis of IBD, (6,077 CD, 9,442 UC and 2,364 with indeterminate colitis). Full characteristics are shown in table 7. For all IBD subtypes there was a small difference in sex, with 51% of the cohort being female. When stratified by IBD subtype there was a difference for CD with 54% being female ($p < 0.01$). For UC there were significantly more males, 52% ($p < 0.01$). The median duration of IBD for those included was 9 years (IQR 4 to 15 years) for our entire cohort and 7 years (IQR 3 to 12 years) for our incident cohort, diagnosed at least one year after joining a ResearchOne practice. I plotted the geographical location of General Practices in the United Kingdom with patients with IBD and included on the ResearchOne database. (Figure 9) This shows that the cohort is distributed throughout the UK, with predictable concentrations in areas with known, high population densities, such as the South East of England and London area. There is also a cluster of increased density in Northern England.

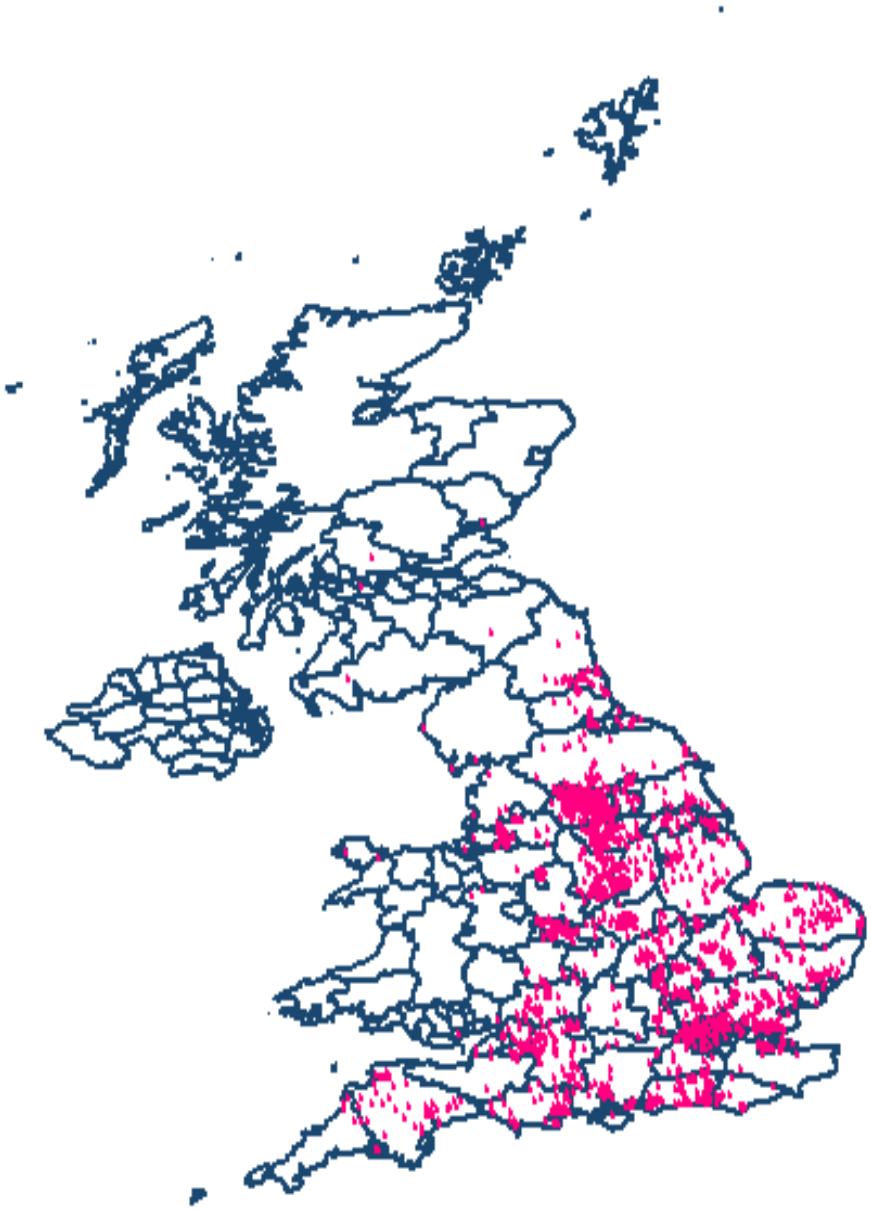
Table 7 Table of characteristics of the IBD population held within the ResearchOne Primary care database. Entire cohort and incident cohort.

		Entire cohort		Incident cohort	
		n	%	n	%
Total		17,883		10889	
IBD subtype	Crohn's disease	6077	34.0	3517	32.3
	Ulcerative colitis	9442	52.8	5641	51.8
	Indeterminate colitis	2364	13.2	1731	15.9
Sex	Male	8784	49.1	5396	49.6
	Female	9099	50.9	5493	50.4
Age at diagnosis	under 20 years	5445	30.4	2294	21.1
	over 20 to 30 years	3535	19.8	1983	18.2
	30 to 40 years	2931	16.4	1996	18.3
	50 to 60 years	2416	13.5	1775	16.3
	60 to 70 years	1898	10.6	1512	13.9
	over 70 years	1658	9.3	1329	12.2
Year of IBD diagnosis	before 1993	2526	14.1	629	5.8
	after 1993 to 2000	2260	12.6	1036	9.5
	after 2000 to 2007	5907	33.0	3683	33.8
	after 2007 to 2014	7190	40.2	5541	50.9
IBD duration (years)	0 to 2 years	1392	7.8	1196	11.0
	> 2 years to 4 years	2194	12.3	1782	16.4
	> 4 years to 6 years	1948	10.9	1451	13.3
	> 6 years to 8 years	1928	10.8	1361	12.5
	> 8 years to 10 years	1699	9.5	1140	10.5
	> 10 years	8722	48.8	3959	36.4
Smoking	Never smoked	8834	49.4	5307	48.7
	Smoking data missing	1038	5.8	595	5.5
	Ever smoked	8011	44.8	4987	45.8
IMD income category	Most affluent	3587	20.1	2052	18.8
	2	3618	20.2	2224	20.4
	3	3551	19.9	1983	18.2
	4	3562	19.9	2292	21.0
	Least affluent	3565	19.9	2338	21.5
Charlson score ≥ 2	No	14433	80.7	8724	80.1
	Yes	3450	19.3	2165	19.9

IBD – inflammatory bowel disease; IMD – index of multiple deprivation.

Incident cohort is those diagnosed at least one year after joining a ResearchOne GP practice

Figure 9 Map of the United Kingdom with location of GP practices with IBD patients held within the ResearchOne primary care database



Each dot represents a general practice in the United Kingdom with a patient with IBD in the ResearchOne primary care database. The solid boundaries represent administrative counties in the UK.

6.2.2 Characteristics of the ResearchOne IBD-CRC dataset

The demographics of the ResearchOne IBD-CRC dataset is shown in Table 8. After restricting those who had a colectomy, there were 250 cases of colorectal cancer and 16,434 controls, without the disease, with a median IBD duration of 9 years. In the incident cohort of patients with IBD there were 146 cases of CRC and 10,183 controls without CRC, with a median IBD duration of seven years. More of the CRC cases were male (60% versus 40% female). When stratified by age category at diagnosis of IBD, CRC cases were younger ($p < 0.01$). There were more individuals with CRC and a history of smoking in both the entire (48% in cases versus 44.9% in controls) and incident (50.7% in cases versus 45.6% in controls), with 7.2% of CRC cases with missing smoking data in the entire cohorts and ~6% missing data in all other groups. Deprivation scores were comparable in the entire and incident cohorts, with a higher proportion in the most affluent and least affluent groups for CRC cases. In the entire cohort 36% of CRC cases (n = 90) were diagnosed with less than eight years of recorded disease, taken as their first recorded entry of IBD in their primary care record. In the incident cohort this proportion was even higher with 51% (n = 74) being diagnosed with less than eight years of recorded disease. Comorbidity scores were significantly higher in CRC cases in both the entire and incident cohorts.

Table 8 Demographics of the IBD CRC cohort and incident cohort within the ResearchOne primary care database

		Entire cohort					Incident Cohort				
		Controls		Colorectal cancer cases			Controls		Colorectal cancer cases		
		n	%	n	%	p-value	n	%	n	%	p-value
Total		16434		250			10183		146		
IBD type	Crohn's disease	5729	34.9	72	28.8		3363	33.0	43	29.5	
	Ulcerative colitis	8446	51.4	148	59.2		5156	50.6	81	55.5	
	Indeterminate colitis	2259	13.7	30	12.0	0.05	1664	16.3	22	15.1	0.51
Sex											
	Male	8027	48.8	150	60.0		5013	49.2	87	59.6	
	Female	8407	51.2	100	40.0	<0.01	5170	50.8	59	40.4	0.01
Year of IBD diagnosis	Before 1993	2127	12.9	74	29.6		546	5.4	14	9.6	
	1993 - 2000	2008	12.2	25	10.0		926	9.1	11	7.5	
	2000 - 2007	5389	32.8	82	32.8		3369	33.1	66	45.2	
	2007 - 2014	6910	42.0	69	27.6	<0.01	5342	52.5	55	37.7	<0.01
Age at diagnosis	under 20 years	4929	30.0	46	18.4		2156	21.2	9	6.2	
	> 20 to 30 years	3262	19.8	30	12.0		1871	18.4	10	6.8	
	30 to 40 years	2698	16.4	38	15.2		1859	18.3	18	12.3	
	50 to 60 years	2232	13.6	36	14.4		1650	16.2	26	17.8	
	60 to 70 years	1762	10.7	47	18.8		1408	13.8	39	26.7	
	> 70 years	1551	9.4	53	21.2	<0.01	1239	12.2	44	30.1	<0.01
IBD duration (years)	0 to 2 years	1353	8.2	22	8.8		1162	11.4	19	13.0	
	> 2 years to 4 years	2117	12.9	26	10.4		1724	16.9	19	13.0	
	> 4 years to 6 years	1865	11.3	24	9.6		1389	13.6	20	13.7	
	> 6 years to 8 years	1820	11.1	18	7.2		1287	12.6	16	11.0	

	> 8 years to 10 years	1582	9.6	20	8.0		1069	10.5	16	11.0	
	> 10 years	7697	46.8	140	56.0	0.07	3552	34.9	56	38.4	0.78
Smoking	Never smoked	8093	49.2	112	44.8		4967	48.8	64	43.8	
	Smoking data missing	966	5.9	18	7.2		568	5.6	8	5.5	
	Ever smoked	7375	44.9	120	48.0	0.32	4648	45.6	74	50.7	0.47
IMD income category	Most affluent	3256	19.8	68	27.2		1898	18.6	38	26.0	
	2	3315	20.2	41	16.4		2075	20.4	23	15.8	
	3	3276	19.9	49	19.6		1868	18.3	26	17.8	
	4	3306	20.1	38	15.2		2164	21.3	25	17.1	
	Least affluent	3281	20.0	54	21.6	0.02	2178	21.4	34	23.3	0.13
Charlson score ≥ 2	No	13308	81.0	182	72.8		8182	80.3	105	71.9	
	Yes	3126	19.0	68	27.2	<0.01	2001	19.7	41	28.1	0.01

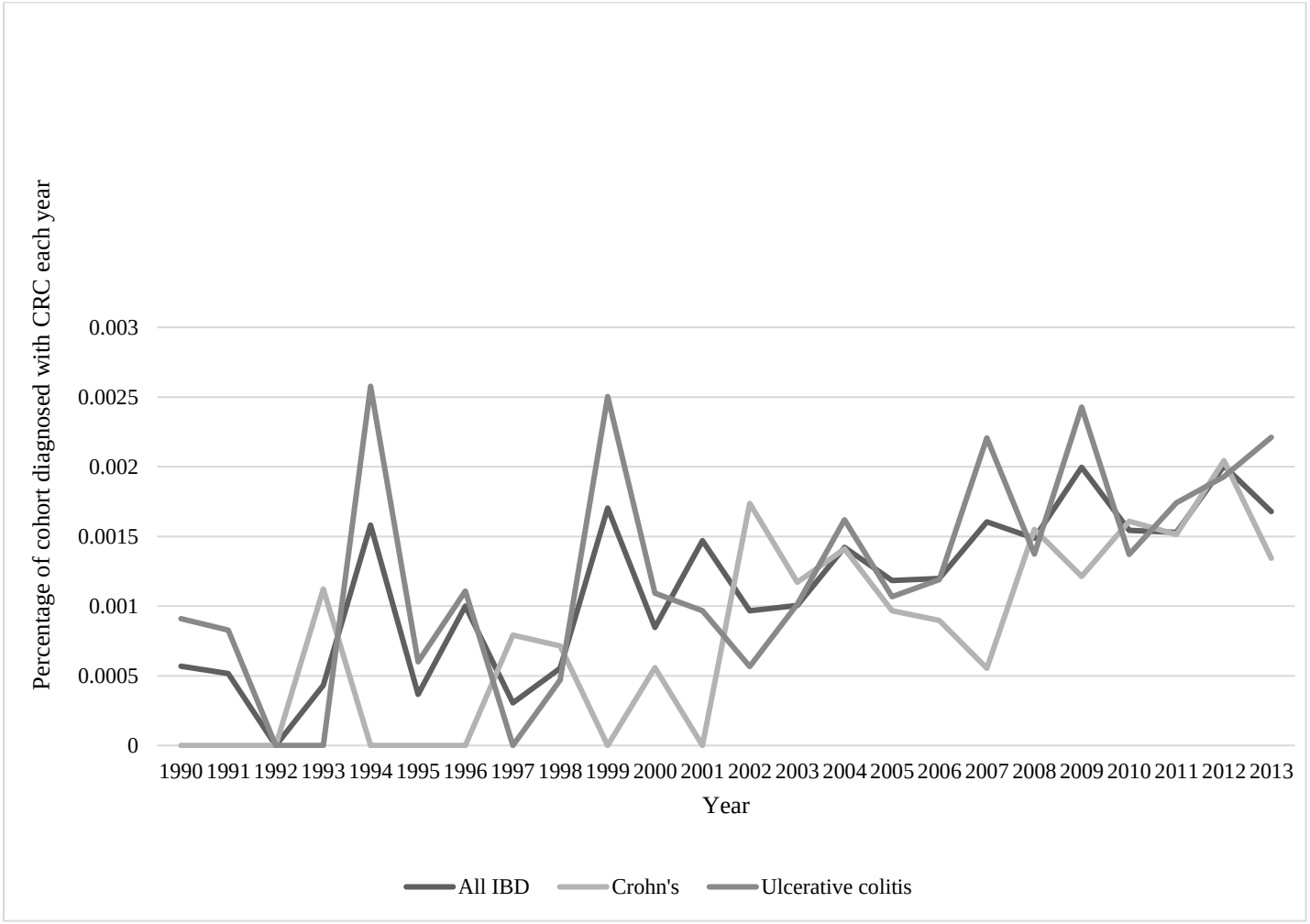
IBD – inflammatory bowel disease; IMD – index of multiple deprivation.

Incident cohort is those diagnosed at least one year after joining a ResearchOne GP practice

6.3 Trend in CRC diagnosis

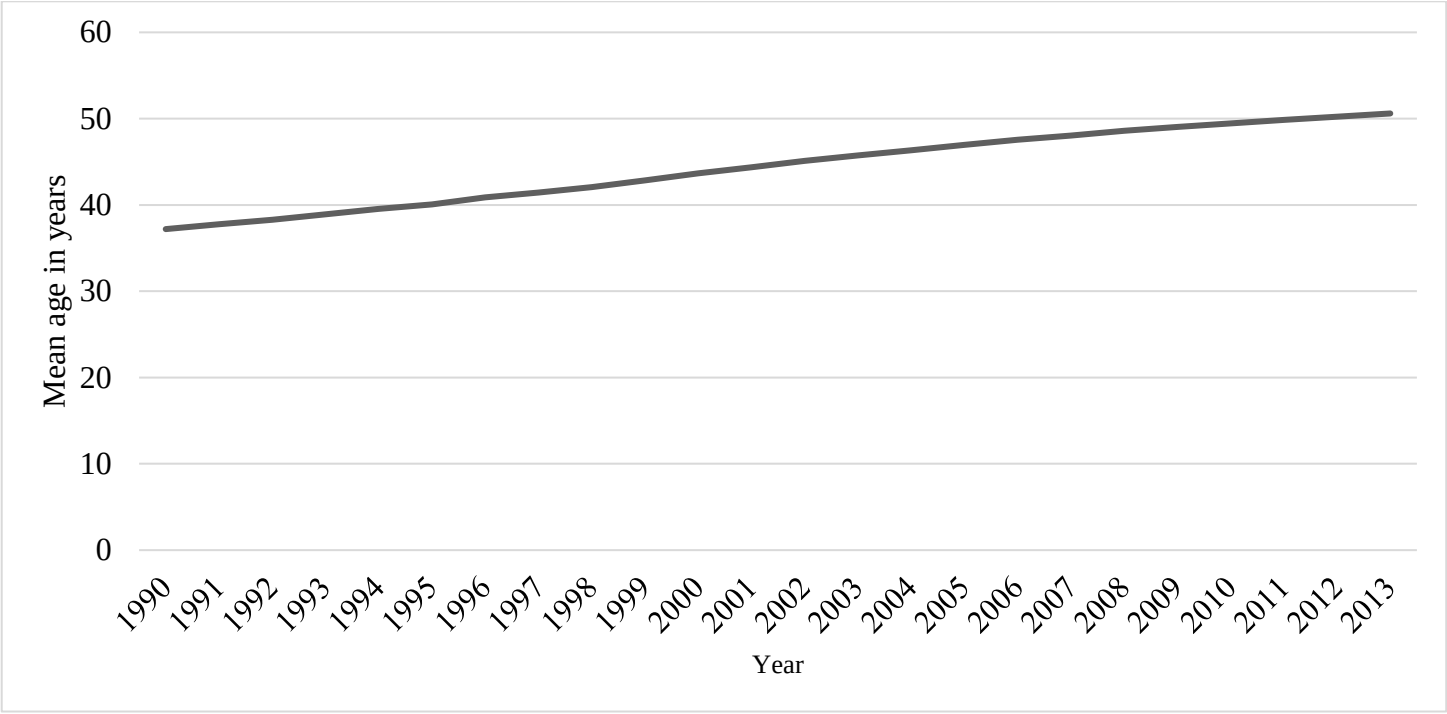
Figure 10 shows the trend in diagnosis of CRC in our IBD cohort each year, with separate trend lines for each IBD subtype. There has been an increase in CRC cases in the ResearchOne database through the study period from 1990 to 2013 for each IBD subtype. This did not reach significance for those with UC but was significant for all CD and all IBD combined (Chi^2 for trend $p < 0.05$). Figure 11 shows the mean age of the ResearchOne IBD cohort over the same time period. There was a significant increase throughout the time period from an average age of 37 years in 1990 to 51 years in 2013 (Chi^2 for trend $p < 0.05$).

Figure 10 Proportion of the ResearchOne IBD cohort diagnosed with CRC each year: Stratified by IBD subtype



IBD subtype	Chi² for trend
All IBD	0.04
Crohn's	0.02
Ulcerative colitis	0.07

Figure 11 Mean age of those alive and registered in the ResearchOne database 1990 to 2013



Note: Chi^2 for trend ($p < 0.05$)

Entire cohort used

6.4 Discussion

Here, I have confirmed associations with IBD-CRC and male sex, increasing age, increasing disease duration and increased co-morbidity. The overall number of IBD-CRC cases in the ResearchOne database is increasing over time but the average age of the cohort is also increasing which is likely to be attributing to the increase in CRC.

There have been several recent studies that have attempted to estimate the risk of CRC in those with IBD and compare it to the "sporadic" CRC population. Many of the results are heterogenous because of the varied populations used and mixes of primary and secondary care studies. Increased risk estimates from previous studies are at anywhere between 1 and 30 times compared to the general population. (Lutgens et al., 2013; Castano-Milla C. Chaparro M. Gisbert J.P. et al., 2014; Laukoetter et al., 2011; Eaden, Abrams and Mayberry, 2001)

There are varying reports on the temporal trends of IBD-CRC. A Danish study indicated that the incidence of CRC in those with UC may be decreasing. (Jess et al., 2012) This was also shown in a systematic review and meta-analysis in 2013, (Castano-Milla C. Chaparro M. Gisbert J.P., 2014) which showed a decreased incidence rate from 4.29/1000 patient years for studies in the 1950's to 1.21/1000 patients years for studies since 2000. These results may be affected by the rate of colectomy in the different countries. Historically, these rates have been higher in Scandinavian countries which could explain some of the reduced rates in these jurisdictions. (Frolkis et al., 2013) However, in line with the small but significant increase seen in this study, results from the USA and Sweden show a small increase in the rate. As the prevalence of IBD is increasing worldwide, regardless of whether there are small changes in the temporal incidence either way, there will be an increased prevalence and overall burden of IBD-CRC. It therefore remains important to characterise risk-factors for the disease to target appropriate screening and surveillance strategies.

I have shown that those with longer disease duration were more likely to develop IBD-CRC with 56% of cases having disease for longer than ten years compared to 47% of controls. Duration of disease is an established risk factor for IBD-CRC, as prolonged inflammation leads to the increased chance of mutations that can lead to malignancy. (Adami et al., 2016) A landmark study from Eaden *et al.* from studies pre-dating the year 2000 showed that cumulative CRC incidence was 8% by 20 years and 18% by 30 years of disease. (Eaden, Abrams and Mayberry, 2001) More contemporary results report much more conservative estimates with a meta-analysis of four population based studies estimating a risk of 0.8% at 10 years, 2.2% at 20 years and 4.5% after > 20 years. (Lutgens et al., 2013) I have also shown that a large proportion of IBD-CRC cases were diagnosed before eight years of recorded disease, 36% in the entire cohort and 51% in the incident cohort. This is an important observation as societal guidelines advocate a screening colonoscopy after 8, or 10 years of disease duration. (Lamb, 2019; Cairns et al., 2010) It is difficult to accurately determine the true duration of disease in routine collected datasets from primary or secondary care as they rely on the first recorded entry in a medical record. The mucosal inflammation from IBD may be present for a prolonged period before a patient presents to primary or secondary care and ultimately undergoes investigation such as endoscopy to confirm the diagnosis. This date may be erroneously recorded as the onset time of disease, when the true onset may have been months or years earlier.

The finding that a large proportion of IBD-CRC occurs in those without longstanding colitis (< eight years of disease) is in line with prior studies. In a study from St Mark's Hospital in the UK, and a Danish population cohort, duration of disease was not shown to be an independent risk factor for the development of IBD-CRC. (Choi et al., 2015a; Jess et al., 2012) These results taken together with our own could have an implication on societal guidelines for the timing of the initial screening test, and interval for further surveillance.

Currently the recommendation for an index test at eight to ten years and then up to five-yearly based solely on duration may not be appropriate. A further study from the St Mark's group investigated the potential effects of colonic inflammation, and cumulative inflammatory burden on the development of IBD-CRC. (Choi et al., 2019) In this study, the cumulative inflammatory burden was calculated by multiplying the average inflammation score on consecutive colonoscopies by the length of surveillance interval. From a cohort of 97 IBD-CRC cases they showed that an increase in the mean severity of inflammation score over the preceding 5 colonoscopies was significantly associated with increasing risk of CRC with a HR of 2.2 per 1-unit increase ($p < 0.001$). This is intuitive as it is the presence of longstanding inflammation that is the likely driver of malignant transformation. As most of these studies pre-date the widespread use of more aggressive treatments to control inflammation, and reduce risk, these may still overestimate the true risk if IBD-CRC. Those with mucosal healing, and quiescent disease are unlikely to be at any greater risk than the background population. Future guidelines should incorporate the duration of active inflammation and not just the duration since diagnosis. This could be classified as the cumulative inflammatory burden as in the St Marks study above. (Choi et al., 2019)

In my results, cases of IBD-CRC were older at diagnosis in both the entire cohorts and incident-1yr cohorts, with over 40% (entire) and over 50% (incident) being over the age of 60 at diagnosis compared to 20% and 25% of those without CRC. Increasing age is an established risk factor for sporadic CRC and is also seen in IBD-CRC. As I did not have a control group of sporadic CRC, I was unable to compare relative risk of CRC in different age groups compared to the risk in each of these age groups in those without IBD. In prior meta-analyses the pooled standard incidence ratio of IBD-CRC was 8.2 amongst those less than 30 and 1.8 in those older than 30. (Lutgens et al., 2013) Young age at onset of IBD is associated with higher risk of CRC. A Danish population-based study estimated the increased risk at

43.8 for those with IBD diagnosed between the ages of 0 and 19. The SIR was 2.65 for those diagnosed between ages 20-39 and lower for those diagnosed after the age of 60 years. (Jess et al., 2012)

I have shown that male sex is a significant risk factor associated with the development of IBD-CRC. This is consistent with prior studies. In the same Lutgens meta-analysis of contemporary studies in 2012 there was a pooled increased standardised incidence ratio of IBD-CRC of 1.9 in men and 1.4 in women. (Lutgens et al., 2013)

I did not find a significant positive association between a recorded history of smoking and IBD-CRC in any of our analyses. This is consistent with other studies investigating IBD-CRC. (Velayos et al., 2006) A potential theory is that smoking, and in particular nicotine may suppress colonic inflammation. (Pullan et al., 1994; Sandborn, 1997)

Using primary care data is useful for estimating population risks of disease, as secondary or tertiary care data are likely to include those with more advanced, aggressive disease with a higher risk of CRC. Primary care populations, such as here, are more likely to give a closer approximation of the true incidence, as they should include a greater spectrum of disease. I censored those who had undergone a colectomy before a diagnosis of CRC, as this would affect our risk estimate as these patients are highly unlikely to develop CRC.

I was unable to investigate associated risk factors for IBD-CRC due to lack of detail in the ResearchOne database. These include; extent of disease, severity of disease, family history, obesity and history of primary sclerosing cholangitis.

The increased incidence of IBD-CRC could be due in part to lead-time bias. IBD patients are more likely to undergo regular investigations of their colon either as part of IBD disease assessment or surveillance for CRC. This can lead to overdiagnosis, in detecting CRC incidentally that would never have manifested otherwise. This bias is particularly important

in survival analyses conducted on similar datasets. Another reason for an apparent increase in IBD incidence through the study period could be explained by the increasing age in the cohort. There was a significant increase in the average age throughout the study period, so this is likely to have an influence on the increase in IBD-CRC. Future analyses should consider age standardised incidence ratios to explore this association further.

Whilst duration of disease is an important association with IBD-CRC, there were a large number who developed CRC before 8 years from the first recorded diagnosis which has implications for future surveillance guidelines. The ResearchOne IBD cohort shares characteristics with established cohorts of IBD and IBD-CRC cases which gives confidence in using it as a resource for epidemiological research. The limitations of using these resources is that diagnoses are recorded from primary care and are not verified. Ideally, linked datasets would be made available that would combine the rich population data, and prescription data with hospital clinical records to include more disease specific data to define any associations more precisely.

Chapter 7. Chemoprevention of CRC in Inflammatory bowel disease using routinely prescribed drugs

Chapter 7: Chemoprevention of CRC in Inflammatory bowel disease using routinely prescribed drugs

7.1 Introduction

The aim of these nested case-control studies was to investigate if there is an inverse association between the use of routinely prescribed drugs and the development of IBD-CRC. Demonstrating such an association would emphasise the need to record these drugs in future studies investigating IBD-CRC and support their assessment as chemopreventative agents in prospective randomised controlled trials in patients at high risk of the disease.

7.2 Methods

7.2.1 Data sources and participants

The primary care database ResearchOne was used for this study. (www.researchone.org) As described, ResearchOne holds de-identified clinical and administrative information from the electronic health records of approximately 6 million individuals (>10% of the total population) in England. For this study I used the IBD-CRC dataset as described in Chapter 6.

7.2.2 Drug use definitions

Drug use was taken from recorded prescriptions in the ResearchOne database before a diagnosis of CRC for cases and in the entire follow up period for control. I defined drug users and non-users based on the number of independent prescriptions of each drug that they had been issued. Drug users were those with at least 3 prescriptions of each drug. A prescription from primary care in the UK is typically for a 28 day course. (Foy et al., 2016) Aspirin, statins and antiplatelet medications are typically prescribed for chronic disease and so I would not routinely expect these to be discontinued. Additionally, individuals were only defined as drug users if they had been prescribed the medication for at least one year before a diagnosis of CRC for enough time to have elapsed to exert any potential chemopreventative effect. Non-users were those who had never been prescribed the drug, had less than 3

prescriptions in total, or had been prescribed the drug for less than one year as a conservative definition. This may reduce any associations identified, but it is expected that at least a year of drug use would plausibly be required to prevent early cancer development. I used a dichotomous definition of low and high dose of statins depending on whether the medication strength was greater or ≤ than one "defined daily dose" of the drug. The defined daily dose is an international unit that aids comparison of drugs in the same class. One defined daily dose is taken as the average maintenance daily dose of a medication. (Wertheimer, 1986) Where an individual had been prescribed both low and high dose statins, they were restricted from the subgroup analyses. The statins were also further divided into lipophilic and hydrophilic drugs. Where an individual had been prescribed both lipophilic and hydrophilic statins, they were restricted from the subgroup analyses to try and determine whether there was a different association depending on the drug lipophilicity.

7.2.3 Drugs included.

I included all forms and versions including generics and originator equivalents of each medication class as follows:

- Aspirin.
- Non-aspirin antiplatelet drugs included: clopidogrel, dipyridamole, and ticagrelor.
- NA-NSAIDs included: diclofenac, ketoprofen, etoricoxib, etodolac, azaproprazone, piroxicam, ibuprofen, celecoxib, sulindac, lumaricoxib, mefenamic acid, meloxicam, nabumetone, naproxone, etodolac, etoricoxib, fenbrufen, flurbiprofen, indomethacin, rofecoxib, tolfenamic acid, and voltarol.
- Statins:
    - Lipophilic statins included: simvastatin, lovastatin, atorvastatin, and fluvastatin.

    - Hydrophilic statins included: pravastatin and rosuvastatin.

- 5-aminosalicylate medications included: balsalazide, colazide, mesalazine, olsalazine and sulfasalazine. These were then categorised depending on the preparation type into: “Oral”, “rectal”, and “oral or rectal”.
- Immunomodulator medications included: azathioprine, 6-mercaptopurine, and methotrexate.
- Corticosteroids included: budesonide, prednisolone, methylprednisolone, and hydrocortisone.

7.2.4 Covariates

All covariates were as defined in Chapter 6 and included: date of birth, IBD subtype (UC, CD and indeterminate), sex (male, female), Year of IBD diagnosis in 7-year cohorts, Age at IBD diagnosis in 10-year bands, IBD duration in years in 2-years bands, smoking status (never smoked, smoking data missing, and ever smoked), IMD score (1-5), and Charlson co-morbidity score ≥ 2.

7.2.5 Nested case control analyses

To explore the potential role of these medications in preventing IBD-CRC I performed a series of nested case-control analyses. CRC cases were defined by a Read code entry for CRC in their ResearchOne medical record. Controls were those without an entry for the disease. A matched case control study was used to control the influence of known confounding variables. A nested case-control study design with matching has been shown to be an efficient design that can be used to provide unbiased risk estimates. (Breslow, 1996) There are several advantages to using this approach as cases and controls are sampled from the same population, exposures are measured prior to the outcome occurring and cases are matched to controls at the time of the outcome event.

7.2.6 Statistical analysis

To increase the precision of any association, CRC cases were randomly matched with up to 10 controls, without a recorded entry for CRC, to form the analysis cohort. The matched analysis was used to try and account for the influence of several important confounding factors that might bias the results. After matching, a conditional estimate of the odds ratio for each medication was calculated. The matching variables used in the model were: IBD subtype, sex, age at IBD diagnosis cohort, duration of IBD in years cohort, year of IBD diagnosis cohort, smoking history, and corticosteroid use within 90 days of diagnosis. I excluded cases where no matches could be found. These variables may be associated with developing IBD-CRC and were available for use with this ResearchOne dataset. Matching using these variables was used to try and produce phenotypically similar individuals in the case and control groups. Matching analyses were performed using Stata version 14 (*Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

After matching, univariate analyses were conducted to compare characteristics between case and control groups. Conditional logistic regression analyses were then performed to produce adjusted OR with 95% CI for IBD-CRC, adjusting for any of the variables that remained unbalanced after the matching process.

7.2.7 Safety of chemopreventative medications

In order to be considered as a routinely used chemoprevention agent it is important that each medication is tolerated with an acceptable risk profile. I performed a series of safety analyses using three outcomes as markers of adverse results from the use of these medications as follows:

Independent steroid prescriptions

I used independent prescription of corticosteroid medications as a surrogate marker for a flare of inflammatory bowel disease activity. A similar definition, has been validated in

a prior study investigating the relationship between season of the year and flare of IBD. (Lewis et al., 2004) In the Lewis study, exclusions were made for those with another condition which may necessitate the use of steroids. This was not possible in my study as all the relevant Read codes were not available for such an analysis. An independent prescription of steroids was defined as a prescription of any corticosteroid medication after a period of four months with no such prescription. The last 14 days prior to a flare were excluded as it is impossible to say with certainty with routinely collected data, when a person enters a period of remission. From the primary care data held in ResearchOne, it is often difficult to determine exactly when a patient completes a course of steroids. In the Lewis *et al.* study, (Lewis et al., 2004) using the same definition for prescription of corticosteroid medications, a validation study was undertaken. Here, they completed a GP survey involving 150 IBD patients who received a new prescription for corticosteroids, the positive predictive value of a new prescription for steroids to identify an acute flare of inflammatory bowel disease was 85% (82 of 96).

Surgery

I defined a new surgery as the presence of a Read code for GI resectional surgery (Appendix 1) occurring one year after starting a medication namely aspirin, NA-NSAIDs, or statins. A time period of one year was allowed so that any potential adverse effect had time to develop. I did not include Read codes for perianal operations, including fistula surgery as these may not be related to IBD disease activity. I also excluded codes for reversal, or revision, of a previous ileostomy or colostomy as this is likely to represent planned surgery to repair the stoma site, rather than for disease activity. (Failes et al., 1979) In the validation study (Chapter 5) I found that surgical diagnoses were correct in 91% of cases and the date was correct to within 12 months in 95% of cases.

New prescription of an immunomodulator medication

I defined a new prescription of an immunomodulator as any prescription of a thiopurine or methotrexate one year after starting a medication, namely aspirin, NA-NSAIDs, or statins.

7.2.8 Statistical methods for the safety analyses

To ensure that there was correction for relevant variables, I matched cases being prescribed each medication of interest with one control, not prescribed the medication based on several previously defined variables, namely: age at diagnosis of IBD in 10 year bands, type of IBD, duration of IBD, IBD diagnosis cohort in bands, comorbidity score, sex, deprivation, and smoking status, and whether corticosteroids were prescribed within 90 days of diagnosis or not. The matching was to try and ensure that phenotypically similar individuals were accounted for. Conditional logistic regression was then performed to calculate OR with 95% CI to compare the odds of each safety outcome for cases prescribed a medication of interest and matched controls without such a prescription. Variables included in the model were those that remained unbalanced after the matching process.

7.2.9 Sensitivity analysis

I composed an incident cohort by excluding those with a date of diagnosis within twelve months of joining a ResearchOne practice to exclude prevalent cases where the date of diagnosis may be less accurate. This also allows the capture of continuous clinical and prescription data from the date of entry into the ResearchOne database. All the analyses were repeated on this incident cohort. Separate analyses were performed for CD and UC

7.3 Results

I identified 17,883 individuals with IBD in the entire cohort. After removing 1,199 who had undergone a colectomy without developing CRC, 16,684 were included in the analysis dataset; 5,729 with CD, 8,446 with UC and 2,259 with indeterminate colitis. There were more females (8,407 versus 8,027). 37.7% had ever smoked (Table 9). The median average duration of IBD was 9 years. The full description of the CRC cases and controls is as detailed in Chapter 6.

7.3.1 Matched cohort, 10 controls for each case

The characteristics of the matched cohort are shown in table 9. I aimed to match 10 controls without CRC for each case with the disease. The cohort included 1,432 controls and 211 cases with a median IBD duration of 12 years. I was unable to find successful matches for 39 (16%) of cases. The matching success rate is shown in table 10. Despite matching, in the entire cohort there were significant differences with more CRC cases with indeterminate colitis, diagnosed in early or late cohorts, younger at age of diagnosis, and with shorter duration of IBD. These variables were then included in the matching model for the conditional logistic regression. The incident cohort comprised 746 controls and 119 cases of CRC, with a median IBD duration of 8 years. After matching there were significant differences with more CRC cases in the later diagnosis cohorts, and more at older age of diagnosis, so these variables were including in the logistic regression model for the incident cohort.

Medication use for the matched entire cohort, and matched incident cohort is shown in Table 11. CRC cases were significantly less likely to have been prescribed oral 5-ASA drugs, immunomodulator drugs, and high dose statins or ($p < 0.05$). There were no significant associations seen for aspirin, NA-NSAIDs, non-aspirin antiplatelet drugs, low dose statins, or

lipophilic or hydrophilic statins analysed individually. Similar associations were seen in the incident cohort apart from no significant association for immunomodulators.

7.3.2 Conditional logistic regression analyses

Table 12 shows the results for the adjusted conditional logistic regression for the entire cohort and incident cohort. CRC cases were significantly more likely to be prescribed 5-ASA medications, immunomodulators, NA-NSAIDs, NA-antiplatelet drugs, any statin, high dose statins and lipophilic statins, all $p < 0.05$. The only change in association for the incident cohort was a borderline association with NA-antiplatelets and IBD-CRC ($p = 0.05$), and no association seen for NA-NSAIDS. There were no significant associations for aspirin, low dose statins, or hydrophilic statins when prescribed alone.

I performed subgroup analyses for CD and UC separately. For CD, significant negative associations were seen for 5-ASA medications in the entire and incident cohorts, $p <0.01$. Immunomodulators only had a significant association in the entire cohort. NA-NSAIDs had a significant negative in the entire cohort and a borderline association in the incident cohort. There were no significant associations observed for any of the remaining drugs (Table 13). For UC, significant negative associations were observed for 5-ASA drugs in the entire and incident cohorts ($p <0.01$). There was a significant negative association for aspirin in the incident cohort ($p <0.01$), but not the entire cohort. NA-antiplatelet medications were significantly negatively associated with IBD-CRC in the entire but not incident cohort. Any statin had a significant negative association in both cohorts, with an apparent dose response and greater association size in higher dose statin prescription in both cohorts. Lipophilic, but not hydrophilic statins showed a significant negative association. For UC, there were no significant associations for immunomodulators, or NA-NSAIDs. (Table 14)

Table 9 Demographics of the chemoprevention entire cohort and incident cohort. Matched cohort (1:10)

		Entire cohort					Incident (1yr) cohort				
		Controls		Colorectal cancer cases			Controls		Colorectal cancer cases		
		n	%	n	%	p-value	n	%	n	%	p-value
Total		1432		211			746		119		
IBD subtype	Crohn's disease	369	25.8	58	27.5		186	24.9	31	26.1	
	Ulcerative colitis	1007	70.3	237	112.3		515	69.0	76	63.9	
	Indeterminate colitis	56	3.9	16	7.6	0.04	45	6.0	12	10.1	0.22
Sex	Male	822	57.4	126	59.7		417	55.9	72	60.5	
	Female	610	42.6	85	40.3	0.53	329	44.1	47	39.5	0.35
Year of cancer diagnosis	before 1993	593	41.4	70	33.2		165	22.1	13	10.9	
	1993 - 2000	130	9.1	19	9.0		53	7.1	8	6.7	
	2000 - 2007	410	28.6	62	29.4		277	37.1	50	42.0	
	2007 - 2014	299	20.9	60	28.4	0.05	251	33.6	48	40.3	0.04
Age at diagnosis	under 20 years	342	23.9	42	19.9		85	11.4	7	5.9	
	> 20 to 30 years	343	24.0	30	14.2		139	18.6	10	8.4	
	30 to 40 years	230	16.1	31	14.7		124	16.6	14	11.8	
	50 to 60 years	220	15.4	33	15.6		153	20.5	23	19.3	
	60 to 70 years	172	12.0	38	18.0		144	19.3	34	28.6	
	> 70 years	125	8.7	37	17.5	<0.01	101	13.5	31	26.1	<0.01
IBD duration (years)	0 to 2 years	60	4.2	15	7.1		56	7.5	12	10.1	
	> 2 years to 4 years	76	5.3	18	8.5		71	9.5	14	11.8	
	> 4 years to 6 years	88	6.1	16	7.6		68	9.1	13	10.9	
	> 6 years to 8 years	86	6.0	16	7.6		65	8.7	15	12.6	

	> 8 years to 10 years	83	5.8	16	7.6		55	7.4	12	10.1	
	> 10 years	1039	72.6	130	61.6	0.03	431	57.8	53	44.5	0.18
Smoking	Never smoked	689	48.1	95	45.0		338	45.3	53	44.5	
	Smoking data missing	28	2.0	9	4.3		11	1.5	2	1.7	
	Ever smoked	715	49.9	107	50.7	0.09	397	53.2	64	53.8	0.98
IMD income category	Most affluent	357	24.9	58	27.5		185	24.8	31	26.1	
	2	238	16.6	34	16.1		120	16.1	19	16.0	
	3	295	20.6	41	19.4		138	18.5	21	17.6	
	4	215	15.0	31	14.7		123	16.5	19	16.0	
	Least affluent	327	22.8	47	22.3	0.96	180	24.1	29	24.4	1
Charlson score ≥ 2	No	1127	78.7	156	73.9		584	78.3	87	73.1	
	Yes	305	21.3	55	26.1	0.11	162	21.7	32	26.9	0.21

IBD – inflammatory bowel disease; IMD – index of multiple deprivation.
Matching variables: Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis

Table 10 Matching success rate , 1 CRC to 10 controls without CRC in the ResearchOne IBD database

211 out of 250 cases matched.

Number of successful control matches	n	%
0	39	15.6
1	22	8.8
2	18	7.2
3	13	5.2
4	14	5.6
5	14	5.6
6	13	5.2
7	6	2.4
8	8	3.2
9	6	2.4
10	97	38.8

Matching variables: Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis.

Table 11 Medication use in the Medication use in the ResearchOne chemoprevention matched cohort (10:1)

		Entire cohort					Incident (1yr) cohort				
		Controls		Colorectal cancer cases			Controls		Colorectal cancer cases		
		n	%	yes	%	p-value	n	%	yes	%	p-value
Oral 5-ASA	No	429	30.0	119	56.4		199	26.7	75	63.0	
	Yes	1003	70.0	92	43.6	<0.01	547	73.3	44	37.0	<0.01
Immunomodulator	No	1144	79.9	188	89.1		605	81.1	105	88.2	
	Yes	288	20.1	23	10.9	<0.01	141	18.9	14	11.8	0.06
Non-aspirin NSAID	No	905	63.2	147	69.7		431	57.8	79	66.4	
	Yes	527	36.8	64	30.3	0.07	315	42.2	40	33.6	0.08
Aspirin	No	1157	80.8	168	79.6		579	77.6	96	80.7	
	Yes	275	19.2	43	20.4	0.69	167	22.4	23	19.3	0.45
Non-aspirin antiplatelet	No	1323	92.4	202	95.7		683	91.6	113	95.0	
	Yes	109	7.6	9	4.3	0.08	63	8.4	6	5.0	0.20
Any statin	No	1049	73.3	164	77.7		521	69.8	91	76.5	
	Yes	383	26.7	47	22.3	0.17	225	30.2	28	23.5	0.14
Low dose statin *	No	1160	92.0	172	89.6		587	91.6	95	88.0	
	Yes	101	8.0	20	10.4	0.26	54	8.4	13	12.0	0.22
High dose statin *	No	1150	91.2	184	95.8		575	89.7	104	96.3	
	Yes	111	8.8	8	4.2	0.03	66	10.3	4	3.7	0.03
Lipophilic statin **	No	1060	77.6	166	81.0		528	74.8	92	80.0	
	Yes	306	22.4	39	19.0	0.28	178	25.2	23	20.0	0.23
Hydrophilic statin **	No	1355	99.2	203	99.0		699	99.0	114	99.1	

Yes	11	0.8	2	1.0	0.80	7	1.0	1	0.9	0.90

* Those with low and high dose statin prescribed were restricted (n = 190)
** Those prescribed lipophilic and hydrophilic statins restricted (n = 72)

NA-NSAID – non-aspirin non-steroidal anti-inflammatory drug; 5-ASA – 5-aminosalicylic acid; immunomodulators include thiopurine medications and methotrexate.

Matching variables: Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis

Table 12 Conditional logistic regression analysis of medication use and risk of subsequent IBD-CRC in the ResearchOne matched cohort

	Entire cohort †				Incident (1yr) cohort ‡			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
Oral 5-ASA	0.32	0.23	0.45	<0.01	0.15	0.09	0.27	<0.01
Immunomodulator	0.49	0.31	0.79	<0.01	0.65	0.34	1.24	0.34
Non-aspirin NSAID	0.68	0.49	0.95	0.02	0.68	0.43	1.08	0.10
Aspirin	0.72	0.48	1.08	0.11	0.40	0.22	0.72	<0.01
Non-aspirin antiplatelet	0.41	0.20	0.84	0.02	0.41	0.16	1.02	0.05
Any statin	0.55	0.37	0.81	<0.01	0.42	0.25	0.72	<0.01
Low dose statin	1.01	0.58	1.75	0.98	0.84	0.38	1.86	0.67
High dose statin	0.34	1.59	0.74	<0.01	0.26	0.09	0.76	0.01
Lipophilic statin	0.60	0.40	0.90	<0.01	0.45	0.25	0.80	<0.01
Hydrophilic statin	0.72	0.14	3.62	0.69	0.46	0.05	4.58	0.50

Matching	Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis
Adjustment for †	IBD subtype, IBD duration in 2-year cohorts, Cohort year of diagnosis, Age at diagnosis cohort in bands
Adjustment for ‡	IBD duration in 2-year cohorts, Age at diagnosis cohort in bands
*	Anyone prescribed low and high dose drug restricted
**	Anyone prescribed lipophilic and hydrophilic statins restricted

Table 13 Conditional logistic regression analysis of medication use and risk of subsequent IBD-CRC in the ResearchOne matched cohort. Entire cohort, Crohn's disease

	Entire cohort †				Incident (1yr) cohort ‡			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
Oral 5-ASA	0.31	0.16	0.61	<0.01	0.11	0.03	0.44	<0.01
Immunomodulator	0.28	0.11	0.75	0.01	0.27	0.55	1.36	0.11
Non-aspirin NSAID	0.34	0.16	0.73	<0.01	0.35	0.12	1.00	0.05
Aspirin	1.08	0.44	2.68	0.87	0.44	0.11	1.72	0.24
Non-aspirin antiplatelet	1.15	0.31	4.34	0.83	0.63	0.11	3.51	0.60
Any statin	0.68	0.26	1.75	0.42	0.52	0.15	1.76	0.29
Low dose statin	1.44	0.40	5.17	0.58	1.35	0.28	6.45	0.70
High dose statin	0.54	0.11	2.67	0.45	0.39	0.04	4.15	0.44
Lipophilic statin	0.94	0.36	2.44	0.91	0.83	0.24	2.85	0.76
Hydrophilic statin								

Matching	Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis
Adjustment for †	IBD subtype, IBD duration in 2-year cohorts, Cohort year of diagnosis, Age at diagnosis cohort in bands
Adjustment for ‡	IBD duration in 2-year cohorts, Age at diagnosis cohort in bands
*	Anyone prescribed low and high dose drug restricted
**	Anyone prescribed lipophilic and hydrophilic statins restricted

Table 14 Conditional logistic regression analysis of medication use and risk of subsequent IBD-CRC in the ResearchOne matched cohort. Entire cohort, Ulcerative colitis

	Entire cohort †				Incident (1yr) cohort ‡			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
Oral 5-ASA	0.34	0.23	0.51	<0.01	0.17	0.88	0.31	<0.01
Immunomodulator	0.67	0.38	1.15	0.15	0.99	0.48	2.07	0.99
Non-aspirin NSAID	0.83	0.56	1.25	0.38	0.82	0.47	1.41	0.47
Aspirin	0.71	0.44	1.16	0.17	0.42	0.21	0.84	0.01
Non-aspirin antiplatelet	0.28	0.10	0.80	0.02	0.34	0.10	1.19	0.09
Any statin	0.58	0.37	0.91	0.02	0.42	0.22	0.79	0.01
Low dose statin	0.96	0.5	1.84	0.91	0.75	0.28	2.00	0.57
High dose statin	0.39	0.16	0.96	0.04	0.34	0.1	1.19	0.09
Lipophilic statin	0.63	0.39	1.01	0.06	0.47	0.24	0.92	0.03
Hydrophilic statin	0.62	0.07	5.59	0.67				

Matching	Age at diagnosis cohort in bands, IBD subtype, IBD duration in 2-year bands, comorbidity score, sex, IMD quintile, smoking status, steroid prescription within 90 days of diagnosis
Adjustment for †	IBD subtype, IBD duration in 2-year cohorts, Cohort year of diagnosis, Age at diagnosis cohort in bands
Adjustment for ‡	IBD duration in 2-year cohorts, Age at diagnosis cohort in bands
*	Anyone prescribed low and high dose drug restricted
**	Anyone prescribed lipophilic and hydrophilic statins restricted

7.3.3 Adverse outcomes

I performed a series of nested case control analysis to compare adverse outcomes of independent steroid prescriptions, and surgery or immunomodulator prescription at least one year after being prescribed each medication. I used a matched analysis, 1 control for every case of CRC. Matching variables were age at diagnosis in cohorts, IBD subtype, co-morbidity score, gender, deprivation score, smoking status, and whether steroids were prescribed within a year of diagnosis. The case and control groups were balanced after matching with no significant differences for any of the matching variables.

Being prescribed a NA-NSAID medication was significantly associated with an increase in the number of independent steroid prescriptions (OR 1.28, 95% CI 1.18 to 1.39). Being prescribed aspirin (OR 0.87, 95% CI 0.78 to 0.96), or a statin (OR 0.65, 95% CI 0.59 to 0.71) was associated with a reduction in the number of independent steroid prescriptions. (Table 15)

Being prescribed aspirin was associated with lower odds of undergoing a surgical resection one year after IBD diagnosis (OR 0.53, 95% CI 0.40 to 0.71), as was being prescribed a statin (OR 0.44, 95% CI 0.34 to 0.57). NA-NSAIDS had no association (OR 0.87, 95% CI 0.73 to 1.04). (Table 16)

Being prescribed aspirin (OR 0.57, 95% CI 0.46 to 0.71), or statin medication (OR 0.78, 95% CI 0.66 to 0.93), was significantly associated with a reduced odds of being prescribed an immunomodulator medication with one year of IBD diagnosis. Being prescribed a NA-NSAID medication had no association (OR 0.98, 95% CI 0.86 to 1.12). (Table 17)

Table 15 Odds of increasing number of independent steroid prescriptions depending on prior prescription of NA-NSAIDs, aspirin, or statin medication. Matched 1 case with 1 control.

	Entire cohort				Incident cohort			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
NA-NSAID	1.31	1.17	1.46	<0.01	1.53	1.37	1.7	<0.01
Aspirin	1	0.86	1.17	0.97	0.89	0.72	1.11	0.3
Statin	0.63	0.58	0.68	<0.01	0.63	0.57	0.7	<0.01

NA-NSAID – non-aspirin non-steroidal anti-inflammatory drug.

Matching variables: age at diagnosis in cohorts, IBD subtype, co-morbidity score, gender, deprivation score, smoking status, and whether steroids were prescribed within a year of diagnosis.

Groups balanced, with no statistical differences after matching.

Table 16 Odds of surgical resection at least 1 year after being prescribed a given medication. Matched 1 case with 1 control.

	Entire cohort				Incident cohort			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
NA-NSAID	0.87	0.73	1.04	0.13	1.96	1.47	2.61	<0.01
Aspirin	0.53	0.4	0.71	<0.01	0.89	0.58	1.36	0.58
Statin	0.44	0.34	0.57	<0.01	1	0.67	1.48	1

NA-NSAID – non-aspirin non-steroidal anti-inflammatory drug.

Matching variables: age at diagnosis in cohorts, IBD subtype, co-morbidity score, gender, deprivation score, smoking status, and whether steroids were prescribed within a year of diagnosis.

Groups balanced, with no statistical differences after matching

Table 17 Odds of being prescribed an immunomodulator medication at least 1 year after being prescribed a given medication. Matched 1 case with 1 control.

	Entire cohort				Incident cohort			
	Odds Ratio	95% Confidence Intervals		p-value	Odds Ratio	95% Confidence Intervals		p-value
		Lower	Upper			Lower	Upper	
NA-NSAID	0.98	0.86	1.12	0.82	1.07	0.88	1.3	0.52
Aspirin	0.57	0.46	0.71	<0.01	0.76	0.56	1.03	0.08
Statin	0.78	0.66	0.93	<0.01	0.76	0.6	0.98	0.03

NA-NSAID – non-aspirin non-steroidal anti-inflammatory drug.

Matching variables: age at diagnosis in cohorts, IBD subtype, co-morbidity score, gender, deprivation score, smoking status, and whether steroids were prescribed within a year of diagnosis

Groups balanced, with no statistical differences after matching

7.4 Discussion

In this analysis of over 16,000 individuals I have shown that regular use of 5-ASA drugs is consistently negatively associated with IBD-CRC. Statins showed a similar negative association, particularly lipophilic statins and there was an apparent dose response with high dose statins showing a greater negative association with IBD-CRC. Further, in the adverse events analysis statin or aspirin prescriptions were associated with fewer adverse events.

5-ASA is the most used medication for the treatment of UC and is frequently used in colonic CD. There has been considerable interest in 5-ASA as a chemoprophylactic drug in IBD following publication of observational epidemiological data from case control series suggested that regular 5-ASA use reduce the risk of IBD-CRC. (Eaden et al., 2000) There is substantial biological plausibility for this role, as 5-ASA has been demonstrated in pre-clinical models of carcinogenesis to suppress several of the hallmarks of cancer: sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. (Hanahan and Weinberg, 2011) 5-ASA can induce cell cycle arrest in multiple CRC cell lines, antagonise β-catenin signalling (which is dysregulated in majority of CRC), suppress the COX-2/PGE_2 axis, potentiate PPARγ signalling with subsequent upregulation of tumour suppressor PTEN and enhance replication fidelity. (Stolfi et al., 2013) There has been conflicting observational evidence between population-based and referral populations for its potential role in the chemoprevention if IBD-CRC. In a meta-analysis of population based, non-referral centre studies incorporating four studies (608 CRC cases and 2177 controls), 5-ASA use was not associated with a reduced incidence of IBD-CRC (OR 0.95, 95% CI 0.66 to 1.38). (Nguyen, Gulamhusein and Bernstein, 2012) However, two recent meta-analyses have provided further evidence for the chemoprophylactic properties of 5-ASA for IBD-CRC. In their 2016 meta-analysis of 9 population based and 17 referral centre based studies, involving 1958

IBD-CRC cases and 13492 controls, Qiu et al found a protective effect of 5-ASA against IBD-CRC (OR 0.58, 95% CI 0.45 – 0.75). (Qiu et al., 2016) Interestingly, whilst the effect was lost in the analysis of population-based studies, a protective effect was demonstrated for patients with UC (OR 0.23, 95% CI 0.09 – 0.6) but not for patients with CD (OR 0.37, 95% CI 0.12 – 1.14); 5-ASA was not shown to reduce risk of IBD-CRC for patients with CD, neither in the population-based or referral centre-based analyses, although a pooled analysis did demonstrate a protective benefit if a trial reporting neoplasia as CRC or dysplasia was excluded (OR 0.48, 95% CI 0.26 – 0.88). A further meta-analysis by Bonovas et al of 5-ASA and IBD-CRC involving 2,137 cases of IBD-CRC across 31 studies (12 population-based, 19 referral-centre based) reported an overall risk reduction of CRC or dysplasia of 43% (RR 0.57, 95% CI). (Bonovas et al., 2017) They found the inverse relationship between 5-ASA use and IBD-CRC was significant amount both population-based (RR 0.70, 95% CI 0.52 – 0.94) and referral-centre studies (RR 0.46, 95% CI 0.34 – 0.61). Interestingly, whilst 5-ASA was protective for patients with UC, the risk reduction in patients with CD was weaker and non-significant (RR 0.76, 95% CI 0.43 – 1.33). In my results there was a similar protective association for both CD and UC IBD subtypes with prescription of oral 5-ASA medications. Here, with data taken exclusively from a primary care population, it provides further evidence that 5-ASA has chemoprophylactic properties against IBD-CRC. Current guidelines from the European Crohn's and Colitis Organisation, recommend that 5-ASA medications should be considered for all those with UC (Magro et al., 2017) because of their potential chemopreventative effects although this strategy is yet to be endorsed by other societal guidelines.

The inverse association between high-dose statin use and IBD-CRC is consistent with previous cohort studies, Anathakrishnan and colleagues, analysing a cohort of >11,000 IBD patients reported age-adjusted OR of 0.35 (0.24 – 0.53). The antineoplastic mechanisms

underpinning this association are not fully understood but are likely to, at least in part, be the result of inhibition of the mevalonate biosynthetic pathway and subsequent suppression of downstream mediators including isoprenoids. Depletion of isoprenoids is associated with enhanced apoptosis, inhibition of cellular proliferation and inhibition of angiogenesis in models of tumorigenesis. (Bardou, Barkun and Martel, 2010) Isoprenoids are required for post-translational modification of small GTPases including Ras, which is commonly mutated in tumours. Ras is dependent on prenylation for its membranous translocation and subsequent signalling activity. Accordingly, in preclinical models of cancer, atorvastatin has been shown to decrease membrane-bound Ras. (Beckwitt, Shiraha and Wells, 2018)

Lipophilic statins (at any dose) but not hydrophilic statins (at any dose) were associated with an inverse risk of IBD-CRC, with in pooled cases of IBD and UC alone, albeit a borderline association in the entire cohort. Similar findings for chemoprevention depending on statin lipophilicity have been observed in a Swedish cohort of patients with chronic viral hepatitis: lipophilic statin use but not hydrophilic statin use was associated with a significant reduction in hepatocellular carcinoma cases. (Simon et al., 2019) Beckwitt and colleagues reported that lipophilicity of statins was directly related to efficacy in suppressing tumour cell growth in preclinical models of breast, prostate, brain and melanoma tumours, (Beckwitt, Shiraha and Wells, 2018) replicating data from pancreatic cell lines. (Hao et al., 2019) Further, using the azoxymethane/dextran sodium sulphate (AOM/DSS) murine model of colitis-induced colorectal cancer, Yasui and colleagues demonstrated that the lipophilic statin pitavastatin suppressed the number of neoplastic lesions through activation of apoptosis and modulation of mucosal inflammation, oxidative stress and cellular proliferation. (Yasui et al.) It is uncertain whether statins have a different effect depending on the colonic location of the tumour. Unfortunately, tumour site was not available in this dataset and so this question was beyond the realm of this study. In a large cohort study examining the relationship

between statin use and risk of sporadic post-colonoscopy CRC, Cheung and colleagues demonstrated in their stratified analysis that statin use was associated with a lower risk of PCCRC in the proximal colon, but not the distal colon. (Cheung et al., 2019) This raises the possibility that statins may exert more of an effect on tumours arising from the serrated pathway which are more commonly found in the proximal colon. (Lytras, Nikolopoulos and Bonovas, 2014) IBD-CRC is also found more commonly in the proximal colon but at present this potential mechanism is not clear, particularly as IBD-CRC tumours are biologically different to those arising from the serrated pathway. These questions should be addressed in future studies.

Here, the adverse outcome analysis demonstrated that statins are associated with improved outcomes for those with IBD with reduced numbers of independent steroid prescriptions, reduced surgery, and reduced prescriptions of immunomodulator medications within a year of starting a statin. There are conflicting observational clinical data on the potential association between statins and IBD outcomes. However, there is a growing body of preclinical data that suggests that statins may have beneficial immunomodulatory effects in several conditions including IBD by modulating antigen presenting function of immune cells, T-lymphocyte function, inflammatory cell migration and effects on nitric oxide. (Côté-Daigneault et al., 2016) Experimental work has shown that atorvastatin promoted the expansion of myeloid derived suppressor cells, and supressed T-cell response by nitric oxide production both in vivo and in vitro. (Lei et al., 2016) Data from animal models, including AOM/DSS and trinitrobenzene sulfonic acid murine models of colitis, have shown that statins mediate intestinal cytokine/chemokine profile, decrease lymphocyte adhesion, modify intestinal flora and may have a role in fibrosis. (Côté-Daigneault et al., 2016) A further study showed that the addition of atorvastatin attenuated 2,4,6-trinitrobeneze sulfonic acid (TNBS)-induced colitis in mice. (Rashidian et al., 2016)

To date, clinical data aimed at determining impact of statin on IBD outcomes has yielded mixed results, mainly based on retrospective observational data with no comprehensive prospective trials, systemic reviews or meta-analyses to my knowledge. One retrospective study showed that statin users had reduced need for steroids and anti-TNF-α medication and had improved outcomes. (Crockett et al., 2012) There is conflicting observational evidence that statin use may protect against the onset of IBD. (Ungaro et al., 2014; Khalil et al., 2015) In a retrospective case-control study from the USA, statin use was significantly negatively associated with pouch related complications and antibiotic use in those with a J-pouch and ileo-anal anastomosis. (Kaimakliotis et al., 2017) To date there is not a large body of evidence and there are yet to be any comprehensive prospective studies. A small single arm study of ten patients with CD showed that the use of atorvastatin reduced inflammatory markers in those with CD. (Grip, Janciauskiene and Bredberg, 2008) However, An Indian RCT of low dose atorvastatin therapy (20mg) versus placebo, was associated with worse clinical outcomes in mild to moderate UC. (Dhamija et al., 2014)

The possible protective association with statins and IBD-CRC, and association with fewer negative outcomes raises the possibility of a dual purpose for these medications in IBD management. Furthermore, IBD is associated with an increased risk of coronary artery disease. (Bernstein, Wajda and Blanchard, 2008) This seems to be largely driven by a chronic inflammatory state as there is increasing evidence that acute phase proteins, such as C-reactive protein (CRP) are important risk factors for coronary artery disease. CRP deposits in the artery wall during atheromatous plaque formation and promotes low density lipoprotein uptake. (Zwaka, Hombach and Torzewski, 2001) Traditional risk factors for coronary artery disease such as hyperlipidaemia, smoking, obesity and type 2 diabetes are not consistently associated with coronary artery disease in the IBD population. (Gandhi et al., 2012) Controlling luminal inflammation, therefore, seems important not just for reducing direct

consequences from bowel injury and inflammation, but also protecting against cardiovascular morbidity and early mortality.

I did not demonstrate a consistent negative association with aspirin use and the prevention of IBD-CRC. There was a significant negative association in the incident cohort for all IBD combined UC, but no association in the other subgroups. Aspirin has plausible biological mechanisms for preventing carcinogenesis, many of which are shared with 5-ASA (Stolfi et al., 2013) and there is substantial epidemiological evidence that aspirin use is associated with reduced risk of multiple primary cancers including sporadic CRC. (Rothwell et al., 2010a) Prospective RCTs have reported that high-dose aspirin reduces polyp burden in individuals with the familial cancer syndrome familial adenomatous polyposis (Burn et al., 2011a) and halved the incidence of CRC in patients with Lynch syndrome. (Burn et al., 2011b) Aspirin may have no effect on IBD-CRC but there could be other explanations for the absence of an association seen here. Aspirin use is available over the counter in the UK, so it is possible that not all aspirin use was be captured by this study, with some of the controls potentially taking the medication. This would dilute any association. Secondly, aspirin use has been shown to have potential negative effects on the GI tract, including GI bleeding, so it is plausible that its use is discouraged by physicians managing those with IBD. I would not necessarily expect a difference between cases and controls, but low use in this IBD cohort may mean that this study was underpowered to detect a difference. It is speculative, but plausible, those with the longest disease duration, and most severe disease may have more encounters with secondary care physicians where they may be more likely to be advised not to take aspirin or NA-NSAID medications. Lastly, the chemoprophylactic effects of aspirin is dose dependent, much in the same way that the chemoprophylactic benefit of 5-ASA is seen at doses >1.2g/day, (Qiu et al., 2016; Bonovas et al., 2017) with benefits seen at doses > 100mg/day. (Rothwell et al., 2010a) Given that most prescriptions for aspirin in the UK are

for secondary prevention of cardiovascular disease at 75mg daily, this dose may be insufficient to confer a chemoprophylactic benefit. I did not have a sufficient number of patients taking regular aspirin at more than 75mg per day to explore this. The potential association for aspirin does warrant further investigation but may need more detailed clinical note reviews than is possible with population-based primary care data.

My meta-analysis did not find a significant association with aspirin or NA-NSAIDs. (Burr, Hull and Subramanian, 2016a) A recent network meta-analysis investigated the association of 14 potential chemopreventative medications in high risk individuals, with a previous history of colorectal cancer in a non-IBD population. (Dulai et al., 2016) Network meta-analysis allows the ranking of medications, estimating the chance that a particular treatment is "best". (Salanti, Ades and Ioannidis, 2011) NA-NSAIDs (OR 0.37, 95% credible interval 0.24 to 0.53), and aspirin (OR 0.71, 95% credible intervals 0.41 to 1.23) were significantly better than placebo with NA-NSAIDs being ranked the highest.

There was more consistent evidence found for non-aspirin antiplatelet medications. Significant negative associations were observed in both cohorts for all IBD cases, and the entire cohort for UC with a trend towards significance in the incident cohort for UC. There was no association seen for CD alone. Antiplatelets may have a role in CRC chemoprevention through modifying the tumour microenvironment. Activated platelets release inflammatory mediators, growth factors, and angiogenic factors which may be associated with increased risk of CRC. (Patrignani and Patrono, 2016) There is also some evidence that platelets can alter the host local immune response to CRC, which may facilitate cancer growth and metastatic potential. (Contursi et al., 2017; Xu, Yousef and Ni, 2018) There is some observational data that antiplatelets may have a role in preventing sporadic CRC. A study of over 15,000 CRC cases and 60,000 controls showed a 20% reduction in CRC associated with clopidogrel prescription (OR 0.8; 95% CI 0.69 to 0.93). (Rodríguez-

Miguel et al., 2018) There is a lack of data for IBD-CRC, but the results shown here taken together with the laboratory data, and observational data with sporadic CRC show that this may be another option for chemoprevention. Again, more work is needed.

Strengths and weaknesses

I included a large sample size of over 16,000 individuals in our entire cohort and 10,000 in our incident cohort. In the nested case control analyses, IBD duration was 9 years and 7 years in our entire cohort and incident cohort respectively. This should be a reasonable time to expect any chemopreventative association to be detected and a long enough follow up for adverse events to occur.

A strength of this study is that the study cohort is likely to be representative of the full clinical spectrum of IBD as over 98% of UK residents are registered with a GP. (Herrett et al., 2010) Previous studies have shown that Read code entries were >90% accurate in an analysis of IBD in a similar UK primary care database, the General Practice Research Datalink (now called the Clinical Practice Research Datalink). (Lewis et al., 2002) Furthermore, the ResearchOne database has now been validated with IBD diagnoses recorded in 98% of cases. (Burr et al., 2018a) Studies using secondary or tertiary care data are likely to have an inherent referral bias, typically including those with more severe disease, which is relevant because risk of IBD-CRC is proportional to extent and severity of disease. (Rutter et al., 2004a) I was able to include several variables in the matching model that are associated with CRC, including: co-morbidity, social deprivation, gender, age at diagnosis, duration of disease, and smoking history. A further strength is that aspirin, statins and antiplatelet medications are typically prescribed for chronic diseases and so I would not routinely expect these to be discontinued.

There are limitations to this study. The results relate to the prescription of drugs and I do not know whether these prescriptions were obtained or taken as instructed. However, non-adherence would weaken any associations.

Drug use may be the cause or the effect of potential residual confounding factors. There may be uncontrolled variables which may be responsible for an association bias. Risk factors for sporadic CRC not controlled for include family history, history of polyposis syndromes, and acromegaly. I was also unable to correct for obesity as body mass index measurement is not recorded consistently and may relate to CRC. Future studies should record such anthropometric information. The matched, nested case control design allows correction for known confounders for IBD-CRC that were available in the ResearchOne dataset. This design can introduce bias as the matching process could create a sample of controls that matches the cases but is not representative of the IBD population as a whole. This would shift the drug exposure frequency toward that in the cases and dilute any association found. This bias is a consideration here, as I was unable to find a suitable matched control for 29 cases of CRC. Results from the study are therefore only generalisable to those included in the study.

I used a dichotomous exposure of ever and never having been prescribed each drug and did not have information on duration and cumulative dose exposure. Demonstrating dose and time-response effects would help support a causal relationship and suggest if any of these drugs could be used as chemoprevention in high-risk groups. I did not have phenotypic data on disease extent and the use of anti-TNFα medication which is typically used in more severe disease and may be a potential confounder. It is administered from hospital specialists, so prescribing data is not consistently available in primary care databases. However, widespread use for maintenance therapy was not adopted in the UK until 2010 (NICE. Guidance and guidelines., 2010) and between 2002 and 2010 episodic treatment was available but uptake

was low. Less than 3% of those with IBD in the UK were prescribed an anti-TNFα in 2010. (Bardhan et al., 2010) In the UK immunomodulator drugs are typically commenced from secondary care clinics with monitoring for any potential intolerance or adverse side effects. (Lamb, 2019) The medications are then usually continued through primary care prescriptions and so will be captured in ResearchOne. The analyses could also be subject to multiple analyses bias where significant associations will be observed by chance alone. I used a restrictive p-value of <0.01 as a level of significance which will limit this potential bias but for all the analyses this bias should be considered, and results be taken as association and not causal for reduction in IBD-CRC.

7.5 Conclusions

In summary, I report an inverse association between regular use of 5 -ASA drugs and statins in the development of IBD-CRC. As there is biological plausibility for a chemoprotective effect of these medications, further aetiological studies are required to determine whether the associations are consistent and hence likely to be causal. If this inverse association is consistent then investigation of these medications as potential chemopreventative agents for those at high risk of developing IBD-CRC in clinical trials would be justified. Furthermore, this work has shown that aspirin and statins may have a role in controlling disease activity and reducing the steroid prescriptions.

The use of statins in an anti-inflammatory and anti-neoplastic role is attractive as they are cheap, with a good safety profile and may confer additional health benefits. My results add weight to this, and there is justification for targeted clinical trials, for primary prevention or as an adjunct to conventional oncological treatments.

Chapter 8 Discussion

Chapter 8: Discussion

IBD is a common disease with population prevalence estimates at ~0.4% in the West. (Molodecky et al., 2012) It is life-long, with onset in early age, and is associated with excess morbidity and early mortality. One of the most serious complications is CRC. As with any disease prevention is better than cure and it is important to determine whether routinely prescribed medications, that are safe and well tolerated, have a role.

This work has shown that there is the potential for routinely prescribed medications to prevent IBD-CRC. In Chapter 4, a systematic review of the existing literature and meta-analysis has shown that folate may have a role. (Burr, Hull and Subramanian, 2016b) In Chapter 7, promising associations are seen for several routinely prescribed medications including: 5-ASA medications, high-dose statins, lipophilic statins and potentially non-aspirin antiplatelet medications. Importantly, statins were also associated with less independent steroid prescriptions, that when calculated in a similar way, has a positive predictive value of 85% for predicting a flare of IBD in a prior validation study. (Lewis et al., 2004) I have replicated findings from review of the existing literature in Chapter 3, that aspirin, or NA-NSAIDs do not appear to have a chemopreventative effect in IBD-CRC as they do in sporadic CRC. Thiopurine medications show no association although results from observational data, including here, should be taken with caution as these studies have inherent bias and are likely to be confounded by indication. Those with the most severe disease, and greater risk of CRC are also more likely to be prescribed a thiopurine.

An important finding is that the data held within ResearchOne is accurate when compared to a gold-standard of a multitude of hospital record sources. Primary care databases are a rich resource of healthcare data and are extremely useful for exploring rare, or long-term outcomes where prospective studies are not feasible. Confidence is required in the data before applying any results to clinical practice or when planning randomised trials. Whilst

other resources have been validated, this is the first study using ResearchOne data. Results were consistent with prior reports from other data sources and validation methods. This should give confidence in using the ResearchOne database for epidemiological and aetiological studies, particularly those in IBD.

Performing detailed studies such as these is important in the understanding of the natural history of diseases. Large-scale, accurate, population-based datasets such as ResearchOne provide a valuable research resource for these goals. Here I have shown that the proportion of those with IBD developing CRC is significantly increasing. I have also confirmed established risk factors for the disease including male gender, duration of disease, comorbidity, and immunomodulator use which is likely to be a proxy marker for more advanced disease with more mucosal inflammation. Establishing these risk factors is important when developing guidelines for screening and surveillance of this population to utilise scarce resources most appropriately and not expose people to potentially unnecessary investigations that are not without risk.

I have also confirmed that whilst duration of disease is important, there are also a large number of people who develop cancer before the recommended start date for screening and future surveillance at eight to ten years. This is important to consider in future guidelines.

8.1 Future research targets

There is a need to further explore the negative associations demonstrated here, with high-dose and lipophilic statins and IBD-CRC. The first step would be to perform a systematic review and meta-analysis of the available evidence, incorporating the results from this study. To my knowledge there are only a small number of studies investigating the potential role of statin medication as potential chemopreventative agents. These have been conflicting, but with the addition of the results here there may be enough data to explore this

association further. This would define any association more precisely and could form the basis for a prospective randomised investigation.

Inflammation is one of the most important aetiological factors in IBD-CRC, and perhaps the only modifiable risk factor. There have been significant advances in the treatment options to promote mucosal healing, and histological remission is now the endpoint in some new treatment trials. (Darr and Khan, 2017) Plausibly, this should reduce the potential for malignant transformation. (Saxena, Limdi and Farraye, 2017) To date, there is scant research investigating any association with biological and small molecule drugs and the development of IBD-CRC. Large cohorts, including registry data could be used to explore these outcomes, particularly anti-TNFα medications which have now been widely used since 2010 and should have had enough time to exert a potential chemopreventative effect. These investigations are important. The use of biological and small molecule drugs is likely to reduce the use of surgery to cure aggressive, longstanding disease. Colonic surgery obviously reduces the potential for developing colon cancer. These individuals are likely to be at a higher inherent risk of cancer with the most aggressive disease. Defining a negative association would add weight to the goal of mucosal healing, over clinical remission as proposed by some jurisdictions. (Darr and Khan, 2017) Chemoprevention of colorectal cancer in IBD might be added as an extra benefit of pursuing this goal. A potential first target for prospective studies would be high-risk cohorts, such as those with co-existent PSC, previous low-grade dysplasia or a strong family history of sporadic CRC.

In summary, there is hope for the chemoprevention of IBD-CRC and 5-ASA drugs statins, and folate supplementation are attractive targets. There have been many new additions to the therapeutic armamentarium for colonic IBD in recent years including new biological medications such as anti-integrin and janus kinase inhibitors. Luminal inflammation is one of the strongest risk factors for the development of IBD-CRC. There is

additional hope that with improved control of disease activity the burden of this important disease may be reduced. There are also further advancements with detection through high definition chromoendoscopy and the ability to resect cancerous and pre-cancerous lesions through endoscopic mucosal resection and dissection so the model may move to preventative colonoscopy removing cancerous precursors similarly to the reduction of sporadic CRC by the judicious removal of adenomatous polyps.

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doi:10.1161/01.CIR.103.9.1194.

List of Abbreviations

5-ASA	5-aminosalicylic acid
AOM/DSS	Azoxymethane/dextran sodium sulphate
APC	adenomatosis polyposis coli
BNF	British National Formulary
BSG	British society of Gastroenterology
CD	Crohn's disease
CI	Confidence interval
COX	Cyclo-oxygenase
COX-2	Cyclo-oxygenase-2
CPRD	Clinical Practice Research Datalink
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
DNA	Deoxyribose nucleic acid
GI	Gastrointestinal
GP	General practitioner
HES	Hospital episode statistics
HMG-Co-A	3-hydroxy-3methylglutaryl-coenzyme-A reductase inhibitors
HR	Hazards ratio
IBD	Inflammatory bowel diseases
IBD-CRC	Inflammatory bowel disease associated colorectal cancer
IBD-U	IBD unclassified
IMD	Index of Multiple Deprivation
IPF-4	Intracellular platelet factor 4
MeSH	Medical subject heading
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NA-NSAIDs	Non-aspirin non-steroidal anti-inflammatory drugs
NHS	National health service
NOS	Newcastle Ottowa scale
NSAID	Non-steroidal anti-inflammatory drug
OP	Outpatient
OR	Odds ratio

PAF	Platelet aggravating factor
PCCRC	Post-colonoscopy colorectal cancer
PCD	Primary care database
PDGF	Platelet derived growth factor
PSC	Primary sclerosing cholangitis
QOF	Quality and outcomes framework
RCT	Randomised controlled trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
RR	Relative risk
TGF-β	Transforming growth factor beta
THIN	The Heath Improvement Network
TNBS	Trinitrobenzene sulfonic acid
TNFα	Tumour necrosis factor alpha
UC	Ulcerative colitis
UK	United Kingdom
USA	United states of America

Appendices

Appendix 1 Read codes (CTV3) for inflammatory bowel diseases used in the study

Read code (CTV3)	Description	Study definition
J40..	Regional enteritis - Crohn's disease	Crohn's disease
J4002	Crohn's disease of terminal ileum	Crohn's disease
J4003	Crohn's disease of the ileum unspecified	Crohn's disease
J4004	Crohn's disease of the ileum NOS	Crohn's disease
J4010	Crohn's colitis	Crohn's disease
J4011	Crohn's proctitis	Crohn's disease
J401z	Crohn's disease of the large bowel NOS	Crohn's disease
Jyu40	[X]Other Crohn's disease	Crohn's disease
X302t	Crohn's ileitis	Crohn's disease
XaK6D	Exacerbation of Crohn's disease of large intestine	Crohn's disease
XE0af	Crohn's disease of the large bowel NOS	Crohn's disease
XE2QL	Crohn's disease	Crohn's disease
J410.	Ulcerative colitis confined to rectum and sigmoid colon	Ulcerative colitis
J4100	Ulcerative ileocolitis	Ulcerative colitis
J4102	Ulcerative rectosigmoiditis	Ulcerative colitis
J4103	Ulcerative colitis confined to rectum	Ulcerative colitis
J410z	Ulcerative proctocolitis NOS	Ulcerative colitis
Jyu41	[X]Other ulcerative colitis	Ulcerative colitis
XaK6E	Exacerbation of ulcerative colitis	Ulcerative colitis
XaYzX	Ulcerative pancolitis	Ulcerative colitis
XaZ2j	Left sided ulcerative colitis	Ulcerative colitis
XE0ag	Ulcerative colitis	Ulcerative colitis
X303k	Indeterminate colitis	Indeterminate colitis
XE0ae	Inflammatory bowel disease	Indeterminate colitis

Appendix 2 Read code definitions for colorectal cancer

Read code CTV3 code	Definition
9C52.	Malignant neoplasm rectum, rectosigmoid junction and anus NOS
B11y.	Malignant neoplasm of caecum (& carcinoma)
B120.	Malignant neoplasm of splenic flexure of colon
B13..	Malignant tumour of colon
B130.	Malignant neoplasm of ascending colon
B131.	Malignant tumour of transverse colon
B132.	Malignant neoplasm of sigmoid colon
B133.	Malignant neoplasm of colon NOS
B134.	Malig neop other site rectum, rectosigmoid junction and anus

B136.	Malignant tumour of ascending colon
B13z.	Malignant neoplasm of colon (& NOS)
B14..	Malignant neoplasm of other specified sites of colon
B140.	Malignant tumour of rectosigmoid junction
B141.	Malignant neoplasm of rectum (& carcinoma)
B142.	Malignant neoplasm of hepatic flexure of colon
B143.	Malignant neoplasm of transverse colon
B803.	Carcinoma in situ of colon
B8031	Carcinoma in situ of transverse colon
B8033	Carcinoma in situ of sigmoid colon
B803z	Carcinoma in situ of colon NOS
B804.	Carcinoma in situ of rectum and rectosigmoid junction
B8041	Carcinoma in situ of rectum
X78gK	Malignant tumour of intestine
X78gM	Carcinoma of caecum
X78gN	Malignant tumour of large intestine
X78gO	Adenocarcinoma of colon
X78Nj	Tumour of caecum
X78Np	Tumour of colon
X78Nu	Tumour of hepatic flexure
X78OA	Tumour of sigmoid colon
X78OE	Tumour of rectosigmoid junction
X78OI	Tumour of rectum
X78OK	Adenocarcinoma of rectum
Xa34H	Carcinoma of sigmoid colon
Xa84V	Adenocarcinoma of sigmoid colon
XaDc5	Carcinoma of ascending colon
XaDc6	Carcinoma of transverse colon
XaDc7	Carcinoma of descending colon
XaDc8	Carcinoma of hepatic flexure
XaFrJ	Local recurrence of malignant tumour of rectum
XaFro	Metastasis from malignant tumour of colon
XE1vU	Malignant tumour of caecum
XE1vV	Malignant neoplasm of colon NOS
XE1vW	Malignant tumour of rectum
XE1xd	Ca colon NOS
XE1xh	Carcinoma of the rectosigmoid junction
XE1xj	(Ca rectum) or (rectum carcinoma)
XE1xL	Carcinoma of colon
XE1xT	Ca sigmoid colon
XE1xX	Ca ascending colon

Appendix 3 Read code definitions for gastrointestinal surgery

Read code (CTV3)	**Surgery definition**
77210	Abdominoperineal excn rectum & end colostomy (& named vars)
Y21ld	Abdominoperineal resection

YMGtu	Abdominoperineal resection
Y21lY	Abdominoperineal resection rectum
XaDto	Ant resect rectum stapled anast sigmoid to anus with J pouch
77213	Anterior resection of rectum and anastomosis NEC
77214	Anterior resection of rectum and exteriorisation of bowel
XaFza	Anterior resection of rectum with anastomosis
77212	Anterior resection rectum + staple anastomosis colon-rectum
Y21lf	AP resection
Y21le	AP resection of rectum
7642	Bypass of ileum
7642z	Bypass of ileum NOS
X20X5	Caecal operation
76483	Closure of perforation of ileum
76352	Closure of perforation of jejunum
X20XD	Colectomy
77172	Colectomy and anastomosis NEC
77170	Colectomy and end-to-end anastomosis of colon to colon NEC
XE0DC	Colectomy and exteriorisation of bowel NEC
77173	Colectomy and ileostomy NEC
77171	Colectomy and side-to-side anastomosis of ileum to colon NEC
X20XF	Colectomy NEC
7717z	Colectomy: [other NOS] or [NEC] or [hemi- NEC] or [Rankin]
Xa9Zk	Colon and caecum operations
XaA11	Colonic pouch operations
X20XO	Colostomy NEC
X20XN	Colostomy operation
XE0DJ	Construction of permanent colostomy
Xa85G	Construction of sigmoid colostomy
XE0DI	Construction of temporary colostomy
76452	Creation defunctioning ileostomy (& [Brooke] or [split])
76450	Creation of continent ileostomy
XE0D2	Creation of defunctioning ileostomy
X20XR	Creation of ileal pouch

XaB0q	Creation of ileo-anal J-shaped pouch
XaB0p	Creation of ileo-anal pouch
7645	Creation of ileostomy
7645z	Creation of ileostomy NOS
XaFB4	Creation of loop ileostomy
X20WX	Creation of permanent ileostomy
76451	Creation of temporary ileostomy
XE0MS	Excision large intestine (& colectomy)
XaBAY	Excision of caecum
XaBC6	Excision of colocutaneous fistula
XaA14	Excision of colonic pouch
XE0D1	Excision of ileum NOS
7716z	Excision of sigmoid colon NOS
Xa3u1	Excision small intestine
Xa3ty	Excision small intestine NOS
7712z	Extended excision of right hemicolon NOS
X20XH	Extended left hemicolectomy
7712	Extended right hemicolectomy
77121	Extended right hemicolectomy and anastomosis ileum to colon
77122	Extended right hemicolectomy and anastomosis NEC
77120	Extended right hemicolectomy and end-to-end anastomosis
XaA10	Extended right hemicolectomy and ileostomy
77123	Extended right hemicolectomy and ileostomy HFQ
X20XE	Hemicolectomy NEC
YaaPj	Ileal resection and ileostomy
YabAT	Ileal resection sample
76403	Ileectomy and anastomosis of ileum to colon
76403	Ileectomy and anastomosis of ileum to colon
76402	Ileectomy and anastomosis of ileum to ileum
XaB9j	Ileectomy and ileostomy
Xa9Tw	Ileectomy NEC
Y21hD	Ileocaecal resection
YahIf	Ileocolic resection

Xa858	Ileostomy operation
XE0D0	Ileum operations
764z.	Ileum operations NOS
7632	Jejunostomy operations
763..	Jejunum operations
XaBAc	Laparoscopic sigmoid colectomy
XaBAd	Laparoscopic transverse colectomy
XaZVW	Laparoscopically assisted right hemicolectomy
XaBAe	Laparoscopic-assist right hemicolectomy (?AND/OR[colectomy])
7715	Left hemicolectomy
7715	Left hemicolectomy
77151	Left hemicolectomy & end-to-end anastomosis colon to colon
77152	Left hemicolectomy and anastomosis NEC
77154	Left hemicolectomy and exteriorisation of bowel NEC
77153	Left hemicolectomy and ileostomy however further qualified
XaFzV	Left hemicolectomy with anastomosis
XaFzW	Left hemicolectomy with stoma
77150	Left hemicolectomy+end to end anastomosis of colon to rectum
7717	Other excision of colon
XE0DD	Other excision of colon NOS
7713	Other excision of right hemicolon
7713z	Other excision of right hemicolon NOS
XE0DH	Other exteriorisation of colon
XE0DM	Other exteriorisation of colon NOS
771Rz	Other operation on colon NOS
764Bz	Other operation on ileum NOS
771R.	Other operations on colon
XE0D6	Other operations on ileum
XE0D3	Other specified creation of ileostomy
7640y	Other specified excision of ileum
764y.	Other specified operations on ileum
7717y	Other specified other excision of colon
7713y	Other specified other excision of right hemicolon

7648y	Other specified other open operation on ileum
771Ry	Other specified other operation on colon
XaMM1	Other specified subtotal excision of colon
7711y	Other specified total excision of colon
7710y	Other specified total excision of colon and rectum
77101	Panproc/colec
XE0DA	Panproctocolectomy anast ileum to anus & pouch creation HFQ
77102	Panproctocolectomy and anastomosis of ileum to anus NEC
77102	Panproctocolectomy and anastomosis of ileum to anus NEC
77100	Panproctocolectomy and ileostomy
Xa9U1	Parks panproctocolectomy
Xa9Zi	Partial colectomy
XE0MW	Partial colectomy (& sigmoid)
77175	Partial colectomy NEC
Xa7vg	Partial jejunectomy
76304	Partial jejunectomy and anastomosis of duodenum to colon
76303	Partial jejunectomy and anastomosis of jejunum to ileum
YaoCv	Perineal resection rectum HFQ
7710	Proctocolectomy
7710	Proctocolectomy
77103	Proctocolectomy NEC
77103	Proctocolectomy NEC
YMKgo	Rectum-abdominoperin resection
XS7fq	Repair of colon
XaB4f	Repair of ileum
XaBDA	Repair of perforated colon
XaB4e	Repair of small intestine
Yaonr	Resection of ileo-colic anast
Y21dr	Resection of ileum
7640	Resection of ileum
Y21dg	Resection of jejunum
7630	Resection of jejunum
YaaHp	Resection of small intestine

YaaDQ	Resection of terminal ileum
XaB19	Resection of terminal ileum
X20XQ	Restorative proctocolectomy
X20XI	Right hemicolectomy
77131	Right hemicolectomy & side-to-side anast ileum-transv colon
77132	Right hemicolectomy and anastomosis NEC
XaFzS	Right hemicolectomy and anastomosis of ileum to colon
77133	Right hemicolectomy and ileostomy however further qualified
77130	Right hemicolectomy+end to end anastomosis of ileum to colon
77130	Right hemicolectomy+end to end anastomosis of ileum to colon
Yae6r	Salvage AP resection of rectum
X20XM	Segmental colectomy
X20Wd	Segmental excision of small intestine
7716	Sigmoid colectomy
77160	Sigmoid colectomy & end-to-end anastomosis ileum to rectum
77162	Sigmoid colectomy and anastomosis NEC
77161	Sigmoid colectomy and anastomosis of colon to rectum
XaBC1	Sigmoid colectomy and colostomy
77164	Sigmoid colectomy and exteriorisation of bowel NEC
XaBBq	Sigmoid colectomy and ileostomy
77163	Sigmoid colectomy and ileostomy however further qualified
XaFzX	Sigmoid colectomy with anastomosis
XaFzY	Sigmoid colectomy with stoma
YaVc0	Small bowel resection
764..	Small intestine operations (& ileum)
76481	Strictureplasty of ileum
XaL6I	Sub ex colon rectum creation colon pouch anastom colon anus
XaL6K	Subtot exc colon creation colonic pouch anastom colon rectum
X20XG	Subtotal colectomy
XaFzR	Subtotal colectomy with anastomosis
XaBC2	Subtotal colectomy with ileorectal anastomosis
XaBBy	Subtotal colectomy with ileosigmoid anastomosis
XaMM2	Subtotal excision of colon NOS

YabAW	Terminal ileum resection sample
7711	Total colectomy
77111	Total colectomy
XaBCE	Total colectomy
XaBCH	Total colectomy
77110	Total colectomy & ileo-rectal anastomosis (& Hampton)
XE0DB	Total colectomy and anastomosis of ileum to rectum
XaBCD	Total colectomy and ileostomy
77112	Total colectomy and ileostomy NEC
7710z	Total excision of colon and rectum NOS
7710z	Total excision of colon and rectum NOS
7711z	Total excision of colon NOS
7714	Transverse colectomy
77142	Transverse colectomy and anastomosis NEC
77141	Transverse colectomy and anastomosis of ileum to colon
XaBBm	Transverse colectomy and ileostomy
77143	Transverse colectomy and ileostomy HFQ
XaFzT	Transverse colectomy with anastomosis

Appendix 4 Documentation for the validation study of the ResearchOne database. Includes ethical approvals, patient information sheet, consent form and GP letter.

NHS
Health Research Authority

North West - Liverpool Central Research Ethics Committee
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 020 71048008

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

22 February 2016

Dr Nicholas Burr
Clinical Research Fellow in Gastroenterology
Leeds Institute for Biomedical and Clinical Sciences
St James's University Hospital
Leeds
LS9 7TF

Dear Dr Burr

Study title:	**Validation of the SystmOne GP database for the use in healthcare research**
REC reference:	**16/NW/0076**
IRAS project ID:	**196065**

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Carol Ebenezer, nrescommittee.northwest-liverpoolcentral@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters	1	14 January 2016
IRAS Application Form [IRAS_Form_19012016]		19 January 2016
Participant consent form	4	16 February 2016
Participant information sheet (PIS)	6	16 February 2016
Research protocol or project proposal [Protocol]	4	21 December 2015
Summary CV for Chief Investigator (CI) [N Burr CV]	1	14 January 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0076	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp.

Mrs Julie Brake
Chair

Email:nrescommittee.northwest-liverpoolcentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to:

Anne Gowing, Leeds Teaching Hospitals NHS Trust

The Leeds Teaching Hospitals NHS Trust

Patient

UNIVERSITY OF LEEDS

information sheet

Version 6

IRAS - 196065

Date 16/02/2016

Validation of the SystmOne Primary Care Database for the use in healthcare research.

A study to compare general practice records with hospital medical records for patients with inflammatory bowel disease.

Chief Investigator – Dr Nick Burr, Specialist Registrar in Gastroenterology. Leeds Teaching Hospitals NHS Trust.

1. Invitation

You are invited to take part in this study for people with inflammatory bowel disease treated at Leeds Teaching Hospitals NHS Trust. The investigators want to know if the data held in medical records at the hospital in Leeds is similar to information held by your General Practitioner on their computer system. Before you decide to take part in this study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the purpose of this study and why have I been chosen?

The purpose of this study is to determine whether the information held on hospital records is the same as the information held on General Practice computer system databases. This is very important as General Practice databases can be extremely useful in conducting research studies into the long term effects of diseases and medications. It is very important that the data held on these databases is accurate before conducting the research studies.

You have been selected to take part as you have a condition called inflammatory bowel disease. We will compare the diagnosis records of inflammatory bowel disease from Leeds Teaching Hospital with your GP records to see if the information is consistent. The information will contain no personal details and only the records related to your inflammatory bowel

disease diagnosis will be used. We will assign an anonymous, unique number to your record after the data has been combined to ensure you cannot be identified.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part in the study, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

4. What will happen to me if I continue to take part?

If you decide to take part in this study we will compare your medical records from the hospital with your General Practitioner's medical records. We will do this by using your NHS number, which is a unique number already assigned to you. The same number is used on your GP medical records. It is important for you to know that we will not ask for any other information from your GP records other than those listed below.

- Type of Inflammatory bowel disease.
- Date of inflammatory bowel disease diagnosis.
- Admission to hospital for a complication of inflammatory bowel disease.
- Flare-up of your inflammatory bowel disease.
- Any operation for your inflammatory bowel disease.

Please note that we will not use this information for any other purpose than to check whether the information on the GP record is similar to that recorded in hospital medical records. Your information will **not** be shared, or made available to anyone not involved with this study. If you want more information then please contact a member of the study team:

- Email - nick.burr@nhs.net.
- Tel – (0113) 206 8691

5. Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the research team. Nowadays all studies are monitored and audited by the study sponsor (University of Leeds) or by external government agencies. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. Your medical information will all be held on secure, password protected computers at Leeds University. Your study files that undergo statistical analysis will be anonymised. Research publications that arise from this study will never contain any personal or identifiable details about you. Your data will be kept in a secure location at the University of Leeds for 5 years after the study has completed in line with European Guidelines after which point they will be destroyed.

6. What are the potential disadvantages of taking part?

We do not envisage any disadvantages in taking part in this study.

7. What are the potential benefits of taking part

Taking part in this study will give credibility to the use of the ResearchOne database for healthcare research. This will be of benefits to patients and their clinicians as this resource has the potential to provide important information on the long-term consequences of diseases and medical treatments.

8. Involvement of the general practitioner/family doctor (GP)

We will notify your general practitioner that you are taking part in this study.

9. Expenses and payments.

Participation in this study will not cost you anything, nor will you be paid.

10. Who is organising and funding the research and where was it reviewed?

The study is being conducted within this institution by Dr Nick Burr, Specialist registrar within the gastroenterology department at Leeds teaching Hospitals NHS Trust. The study has been designed by a group of inflammatory bowel disease researchers. The study is being co-coordinated by the University of Leeds. This study was given a favourable ethical opinion for conduct in the NHS by the National research ethics service. The conduct of this study at Leeds Teaching Hospitals has been authorised. If you have any complaints or concerns about the conduct of this research study, please discuss this with a member of the research team. If you are not satisfied, please contact the Patient Advisory and Liaison Service (Trust PALS).

- Tel: (0113) 2066261 - Available during normal working hours only (9:00am to 4:30pm Monday to Friday).
- Tel: (0113) 2067168 - For queries outside of normal working hours, please leave a voicemail.
- E mail: patientexperience.leedsth@nhs.net

11. How will the results of the research be made available to me?

After completion on the study we will produce a summary of the study findings which can be obtained by contacting the principal investigator.

- Email - nick.burr@nhs.net.
- Tel – (0113) 206 8691

Thank you for taking the time to consider this study.

A copy of this information sheet and signed consent form will be given to you to keep.

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

Version 1

Date 14.01.2015

IRAS - 196065

Dear Doctor.

RE: Validation of the SystmOne primary care database for the use in healthcare research.

Patient Name and DOB

I am writing to inform you that your patient has agreed to participate in the above clinical trial at (Leeds Teaching Hospitals NHS Trust). This study is to validate the use of SystmOne primary care research database. This will improve the quality and applicability of this resource for healthcare research. To perform this study we will compare medical records from hospital outpatient clinics with that held on SystmOne.

I have enclosed a copy of the Patient Information Sheet for your reference, however if you have any queries or require further information please contact Dr N Burr, Gastroenterology SpR Leeds Teaching Hospitals NHS Trust, nick.burr@nhs.net. Tel – 0113 206 8691.

Yours sincerely,

Dr Nick Burr

Encs: Patient Information Sheet, version 5 date 29/12/15

Appendix 4. ResearchOne Ethical and National Information Governance Board reviews

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1
TEDCO Business Centre
Room 002
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3564
Facsimile: 0191 428 3432

04 October 2012

Dr Christopher J Bates
TPP
Mill House
Troy Road
Horsforth
Leeds
LS18 5TN

Dear Dr Bates

Title of the Research Database: **ResearchOne**
REC reference: **11/NE/0184**

Thank you for your letter (sent by Samantha Crossfield), responding to the Committee's request for further information on the above research database and submitting revised documentation

The further information has been considered on behalf of the Committee by the Chair

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation as revised.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Databases set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter	Dr Christopher Bates	18 June 2011
Other: List of Stored Data Items		
Other: Data Protection Registration	Dr John Parry (TPP)	

Other: System Level Security Policy	May 2011	
Other: Response from NIGB	Natasha Dunkley (NIGB Approvals Manager)	03 October 2012
Other: GP Poster	Version 1.0	03 October 2012
Participant Information Sheet: Information for Healthcare Providers	Version 1.0	03 October 2012
Participant Information Sheet: Information Leaflet for Patients	Version 1.0	03 October 2012
Protocol for Management of the Database	Version 1.0	01 June 2011
REC application	IRAS Version 3.1 76446/224560/9/964	20 June 2011
Response to Request for Further Information	Samantha Crossfield (TPP)	
Summary of Research Programme(s)		

Research governance

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research databases. There is no need to inform Local Research Ethics Committees.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Annual Reports. Please refer to the attached conditions of approval.
c) Amendments. Please refer to the attached conditions of approval.

11/NE/0184	Please quote this number on all correspondence

Yours sincerely

(pp)

Mr Chris Turnock
Chair

E-mail: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: *Approval conditions*

Copy to: *Ms Samantha Crossfield, TPP*

NIGB

Ethics and Confidentiality Committee
On behalf of the Secretary of State for Health

5th Floor, Skipton House
80 London Road
London
SE1 6LH
Tel: (020) 7004 1539
Email: ecapplications@nhs.net

Dr Christopher J Bates
TPP
Mill House
Troy Road
Horsforth, Leeds
LS18 5TN

Samantha.crossfield@tpp-uk.com

03 October 2012

Dear Dr Bates

Establishment of the TPP ResearchOne Database

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. It is the applicant's responsibility to ensure they are compliant with any other relevant legal frameworks and constraints over the use of data. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions.

Secretary of State decision

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined the following:

1. The application does not require a recommendation of support in order to proceed, on the basis there is no disclosure of identifiable data

2. Future linkages involving the transfer of identifiable data to or from the database should seek support before proceeding.

Context

This application from TPP set out the establishment of a pseudonymised research database. Advice was sought from the Committee on whether this application required a recommendation of support.

ECC advice

NIGB

Ethics and Confidentiality Committee
On behalf of the Secretary of State for Health

Members had previously reviewed this application, and provided initial feedback, requesting responses to a number of clarifications. These focused on whether identifiers would be processed at any point. These clarifications were welcomed by the Committee, and it was agreed all responses were satisfactory, as summarised below:

1. The link database and ResearchOne databases will be held in separate data centres, and both will be accessible to the technical team only
2. Postcode is automatically converted to sector level via an automated process
3. Dates of birth and death are similarly reduced to year and month automatically
4. Free or narrative text will not be included within the data extraction. The letter indicated that there might be possibility of controlled text fields, however, members were clear that this should not be identifiable to the patient or anyone associated with the patient
5. Data transfer from SystmOne to ResearchOne is stated to be an automated process with no manual intervention
6. De-identified sexual and mental health data items will be included; terminations data will not be extracted.
7. Marital status psychiatric, NJR data and flags showing military affiliations will be excluded.
8. Read code diagnoses showing under 5 will be suppressed / not transferred.
9. System rebuilds will automatically remove those who have recently dissented from inclusion
10. The aim would be to ideally increase lay involvement
11. Linkages to HES will be undertaken using pseudonymisation software so that there is no disclosure to or from HES of identifiers
12. Any future linkages involving the transfer of identifiable data to or from the research database is likely to require a legal basis, such as support under these Regulations.

Please do not hesitate to contact me if you have any queries following this letter.

Yours sincerely

Natasha Dunkley
NIGB Approvals Manager