COLORECTAL CANCER IN PATIENTS WITH ULCERATIVE COLITIS.

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This work is dedicated to mum and dad

To write prescriptions is easy, but to come to an understanding of people is hard

Franz Kafka 1916

Hypothesis and outline of the thesis

Colorectal cancer is one of the most serious complications of ulcerative colitis but there are many areas of controversy surrounding the subject. The exact risk of colorectal cancer is unknown and remains a widely debated issue. The evidence for risk factors in the individual patient is scarce and needs further investigation. Patients with long-standing colitis are encouraged to participate in surveillance programmes involving regular colonoscopic examinations of the large bowel. The efficacy of such programmes is contentious as cancers are missed and some feel that the cancer risk is too small to justify their cost. The failure of screening may be due to poor patient knowledge concerning cancer risk, inadequate organization of surveillance programs and the clinical and technical difficulties of colonoscopies and biopsy interpretation. ***The hypothesis under investigation is that screening for colorectal cancer in ulcerative colitis is ineffective but may be improved by identifying and addressing issues responsible for its poor performance thereby allowing more cost-effective surveillance.***

To address this hypothesis, firstly, the risk of colorectal cancer (CRC) in ulcerative colitis (UC) was studied. In a meta-analysis of all 116 published studies that have reported CRC in UC the risk was determined as accurately as possible. The risk was estimated by decade of disease and was also defined in children. Where possible the incidence rate of CRC in UC in different countries was calculated and the analysis also determined how the risk has changed over time.

A retrospective case-control study of 204 patients across the United Kingdom investigated risk factors that may play a part in the development of cancer in colitis. Factors studied included aminosalicylate use, non-attendance at colonoscopy and hospital outpatient

clinics, smoking history, aspirin use, family history of sporadic colorectal cancer and the presence of primary sclerosing cholangitis. A statistical model was developed which identified the combination of factors which was most hazardous.

The development and validation of a self administered questionnaire evaluating patient knowledge in inflammatory bowel disease is reported. This is followed by an assessment of whether such knowledge differed in patients who had developed CRC as a complication of UC compared with those who had not. This helped ascertain whether patient education of the cancer risk could be a worthwhile strategy for cancer prevention. In a randomized prospective controlled trial of 124 patients the best method of improving patient knowledge was analyzed by comparing the efficacy of a video (scripted and produced by myself) with a simple information leaflet.

The first national audit of the screening and surveillance practices amongst consultant gastroenterologists assessed the adequacy of surveillance programs in the United Kingdom. The ability of pathologists with expertise in gastrointestinal disease versus general pathologists in grading colonic dysplasia was studied. This determined if specialist histopathology centres concentrating specifically on the interpretation of all surveillance colonoscopy biopsies from around the country would be of any benefit in a program to increase dysplastic case detection. To aid the histological diagnosis of dysplasia, the potential of a new marker of dysplasia and carcinoma (CYP1B1-an isoenzyme of cytochrome P450) was investigated using immunohistochemical techniques.

Abstract. Colorectal cancer in patients with ulcerative colitis.

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The magnitude of the colorectal cancer (CRC) risk in ulcerative colitis (UC) was determined in the first meta-analysis of all 116 studies reporting the risk. For any patient with UC the risk was 2% at ten years, 8% at twenty years and 18% after thirty years. The risk was greater in children, varied geographically and has fallen since 1955.

A case-control study of 204 patients across the United Kingdom demonstrated regular aminosalicylate therapy reduced cancer risk by 75% ($p<0.00001$). Mesalazine was particularly effective reducing risk by 81% ($p=0.006$). Visiting a hospital doctor more than twice a year and attending regular colonoscopies also reduced risk (84% and 78%). A family cancer history increased risk five fold.

A reliable, self administered questionnaire measuring patient knowledge was developed. No correlation was found between patient knowledge and the risk of developing CRC. A randomized controlled trial compared the efficacy of a video (scripted and produced by the author) vs. an information leaflet on patient knowledge. This established that both media improved knowledge (71% and 49%) but neither intervention was significantly more effective than the other.

The first nationwide audit of surveillance practices amongst gastroenterologists ascertained 94% of consultants practiced surveillance but it was extremely disorganized and considerable disagreement existed concerning the management of dysplasia.

An inter-observer variation study (examining histological slides) found specialist gastrointestinal *and* general pathologists were equally poor at grading dysplasia (Kappa =0.30 and 0.28 respectively).

A new immunohistochemical marker for dysplasia (CYP1B1) was investigated. Although CYP1B1 showed faint staining in dysplastic tissues, it was inconsistent and presently would not improve identification of dysplasia.

The CRC risk in UC is significant and may be modified through regular consumption of aminosalicylates. Resources may be better allocated at improving compliance with such medication and targeting surveillance on high risk patients. Standardization of surveillance through national guidelines is needed urgently.

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Abbreviations

5-ASA	5-aminosalicylic acid
ABC	Avidin-Biotin complex
APC	Adenomatous polyposis coli
APES	Aminopropyl triethoxysilane
CCFA	Crohn's and Colitis Foundation of America
CCKNOW score	Crohn's and Colitis Knowledge score
CCQ-1	Charing Cross diabetes Questionnaire -1
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CICRA	Crohn's in Childhood Research Association
CKKT	Chambers kidney knowledge test
CRC	Colorectal cancer
DALM	Dysplasia associated lesion or mass
DCC	Deleted in colon cancer
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
GI	Gastrointestinal
HGD	High grade dysplasia
IBD	Inflammatory bowel disease
KDQ	Kidney disease questionnaire
KLH	Keyhole limpet haemocyanin
KQ	Knowledge questionnaire
LDS	Leicester Department of Surgery

LGD	Low grade dysplasia
McAb	Monoclonal antibody
MCQ	Multiple choice question
NACC	National Association of Crohn's and Colitis
NAT	N-acetyltransferase
NHS	National Health Service
NSAID	Non steroidal anti-inflammatory drug
OR	Odds ratio
PcAb	Polyclonal antibody
PSC	Primary sclerosing cholangitis
PYD	Person years duration
STn	Sialosyl-Tn antigen
TBS	Tris buffered saline
UC	Ulcerative colitis
WHO	World Health Organisation

Statement of attribution

The accompanying thesis submitted for the degree of Doctor of Medicine entitled: **Colorectal cancer in patients with ulcerative colitis** is based on work conducted by the author at the Leicester General Hospital mainly during the period between October 1st 1997 and September 30th 1999. None of the work has been submitted for another degree at this or any other University. All the work included was conducted by the author unless otherwise stated. In addition, all the work reported in this thesis is original unless otherwise acknowledged in the text or by references.

The new statistical techniques utilized in the meta-analysis (chapter 2) were developed and executed by Dr. Keith Abrams of the Department of Epidemiology and Public Health at Leicester University.

Dr Elizabeth Jackson assisted with data collection from the medical records of controls in the case-control study (chapter 3).

The immunohistochemistry (chapter 9) carried out in the assessment of a new marker of dysplasia was performed by the author in the laboratories of the Department of Pharmaceutical Sciences at De Montfort University under the supervision of Dr. Lesley Stanley. The generation and validation of the CYP1B1 antibody was conducted by Professor D. Burke and Dr Lesley Stanley at the De Montfort University and by workers in the Leicester Department of Surgery. The pathological interpretation of the immunohistochemical stain was performed by Dr Hugh MacKay at the Leicester General Hospital.

The case-control study (chapter 3) was approved by the Trent Multicentre Research Ethics Committee. The randomized controlled trial (chapter 6) was approved by the Leicestershire Ethics Committee.

Some of the work from this thesis has been published or accepted for publication:

Papers

Eaden JA, Abrams K, Mayberry JF. The Crohn's and Colitis Knowledge Score: A test for measuring patient knowledge in inflammatory bowel disease. American Journal of Gastroenterology 1999; 94: 3560-3566.

Eaden JA, Ward B, Mayberry JF. How British Gastroenterologists Screen for Colonic Cancer in Ulcerative Colitis: An Analysis of Performance. Gastrointestinal Endoscopy 2000; 51: 123-128.

J Eaden, K Abrams, A Ekbom E Jackson, J Mayberry. Colorectal Cancer Prevention in Ulcerative Colitis: a Case-Control Study. Alimentary Pharmacology & Therapeutics 2000; 14: 145-153.

Eaden JA, Mayberry JF. Colorectal Cancer Complicating Ulcerative Colitis: A Review. American Journal of Gastroenterology 2000 (in print).

Abstracts of presentations

Eaden JA, Ward B, Mayberry JF. How British Gastroenterologists Screen for Colonic Cancer in Ulcerative Colitis: An Analysis of Performance. Digestion 1998; 59 (Suppl 3): 145.

Tailor G, Ball MT, Burke MD, Eaden J, James RFL, Rolls S, Stanley LA. Detection of Cytochrome P450 CYP1B1 in Human Tumours Using Monoclonal Antibodies Against a C-Terminal Decapeptide. Human and Experimental Toxicology 1998; 17: 534.

Eaden JA, Abrams K, Ekbom K, Jackson E, Mayberry JF. Colorectal Cancer Prevention in Ulcerative Colitis: A Case-Controlled Study. Presented orally at the British Society of Gastroenterology, Glasgow, Spring 1999. Gut 1999; 44 (Suppl 1): W169.

Eaden JA, Abrams K, Mayberry JF. The true risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 1999; 44 (Suppl 1): T163.

Eaden JA, Abrams K, Mayberry JF. The Crohn's and Colitis Knowledge Score: A test for measuring patient knowledge in inflammatory bowel disease. Gut 1999; 44 (Suppl 1): T132.

Eaden JA, Shears J, Mayberry JF. Preventing bowel cancer in ulcerative colitis: a patients guide. Gut 1999; 44 (Suppl 1): V574.

Eaden JA, Abrams K, Mayberry JF. The Crohn's and Colitis Knowledge Score: A test for measuring patient knowledge in inflammatory bowel disease. Gastroenterology 1999; 116 (Suppl 2): G0233.

Eaden JA, Abrams K, Ekbom K, Jackson E, Mayberry JF. Colorectal Cancer Prevention in Ulcerative Colitis: A Case-Controlled Study. Poster of distinction at the American Gastroenterology Association, Orlando, 1999. Gastroenterology 1999; 116 (Suppl 2): G1739.

Eaden JA, Abrams K, Mayberry JF. The true risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gastroenterology 1999; 116 (Suppl 2): G1738.

Abrams KR, Eaden JA, Mayberry JF. Estimating the risk of colorectal cancer in ulcerative colitis: a meta-analysis of heterogeneously reported studies.. Abstracted at the International Society for Technology Assessment in Health Care. Edinburgh 19th-23rd June 1999.

Stanley LA, Tailor G, Ball MT, Eaden J, James RFL, Rolls S, Burke MD. Expression of Cytochrome P450 CYP1B1 in the Early Stages of Colon Tumour Development. Abstracted at the European Conference on Screening and Early Detection of Cancer. Vienna, November 1999.

Eaden JA, Abrams K, Shears J, Mayberry JF. A Randomized Controlled Trial Comparing the Efficacy of a Video and Information Leaflet vs Information Leaflet Alone on Patient Knowledge About Surveillance and Cancer Risk in Ulcerative Colitis. Abstracted at the British Society of Gastroenterology, Birmingham, 2000. Gut 2000 (in print).

Eaden JA, Abrams, McKay H, Denley H, Mayberry JF. Inter-Observer Variation Between General vs Specialist Gastrointestinal Pathologists When Grading Dysplasia in Ulcerative Colitis. Abstracted at the British Society of Gastroenterology, Birmingham, 2000. Gut 2000 (in print).

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Chapter 1.

Review of the Literature.

Summary

This chapter consists of a review of the literature relevant to the work in this thesis and is divided into five sections. It begins with a description of ulcerative colitis, its epidemiology and aetiology, pathological and clinical features, medical management and prognosis. Section two goes on to discuss colorectal cancer as a complication of ulcerative colitis, examining the magnitude of the risk and associated factors. The third section deals with how this risk may be modified through patient education. It is followed by a detailed review of the recommended practices for colorectal cancer surveillance along with their efficacy and cost effectiveness in ulcerative colitis. Section five defines the significance of dysplasia as a marker of malignancy and reviews other markers which may be used to complement dysplasia.

Section 1.

Ulcerative colitis.

Ulcerative colitis is a chronic relapsing and remitting disease of the colon that almost invariably affects the rectum and extends proximally for a variable distance. In 1859 Samuel Wilks was the first clinician to recognize that not all colitis was due to dysentery when he described the 'morbid appearances in the intestine of Miss Isabella Bankes' at a celebrated murder trial. (1) However, it was not until the classical descriptions by Sir Arthur Hurst in 1921 that the disease entity was fully accepted. (2)

1.1 Case Definition.

In any epidemiological investigation of a disease it is of primary importance to correctly identify all people with the condition in a defined population. This allows valid comparisons of data between countries and between studies. International diagnostic criteria have been agreed for ulcerative colitis, (3,4) which permit accurate case definition. They are based on clinical symptomatology, histology and radiological findings. Despite this, differentiation between Crohn's disease and ulcerative colitis remains a problem in around ten percent of patients who have indeterminate colitis. (5) Case definition is also hampered by the existence of acute self-limiting colitis and other conditions which may mimic ulcerative colitis such as ischaemia and infection. Diagnostic verification of disease is thus a crucial aspect of epidemiological studies and cancer risk studies.

The criteria of case definition outlined by Truelove and Witts in 1955 (6) allows accurate inclusion of patients in epidemiological studies. They include:

(i) an acceptable clinical history, namely passage of blood and mucus with or without diarrhoea

(ii) a history of remission or relapse or a chronic continuous course with no symptom - free intervals for a period of 3-6 months and

(iii) at least one endoscopic examination showing features characteristic of inflammatory changes and histopathological features of ulcerative colitis.

No patient should be admitted to a study on the basis of physician definition of disease alone or simply on the basis of the clinical history.

1.2 Epidemiology and Aetiology.

Ulcerative colitis is more common in Western Europeans and North Americans with an incidence varying from six to fifteen cases / 100,000 population / year (7-10) and the prevalence of the disease in the community is approximately twelve times this figure. The incidence has remained remarkably steady between the 1950's and the 1990's. The prevalence is similar in Scandinavia and the disease is now reported with increasing frequency in Asia, Africa and South America.

Colitis primarily affects young adults between twenty and forty years old but it may present at any age. Women tend to be affected more often than men but recent studies have failed to find a sex difference. (11) There is some evidence of an ethnic variation in the disease. Several studies have all shown an increased risk for ulcerative colitis in Jews living in Western communities with a prevalence of 37.1 / 100,000. (12-14) However, in Israel itself the prevalence is lower than in non-Jews in the United States or Western Europe. Moreover, in Israel, American and European-born Jews have double the incidence of those born in Africa, Asia or Israel. (15) This implies that environmental factors such as diet and smoking may counteract racial or ethnic factors.

The aetiology of ulcerative colitis remains unknown and is likely to be multifactorial. The main suggestions as to its cause include infection, an allergic response to dietary components, immune reaction to bacterial or self antigens and an abnormality of the epithelial cells lining the gut. Environmental factors which may also play a part include smoking and the oral contraceptive pill. (16)

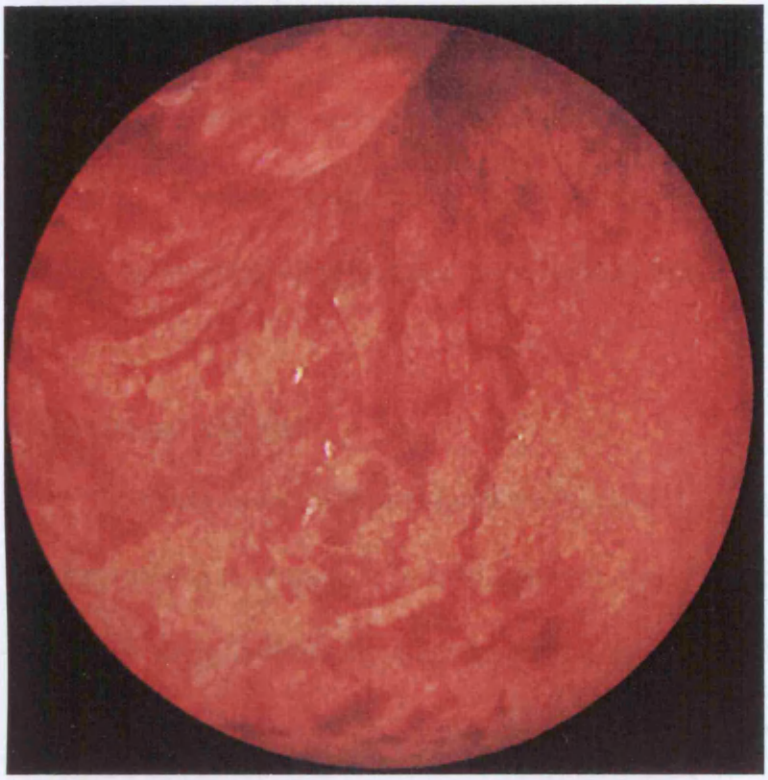
1.3 Genetics.

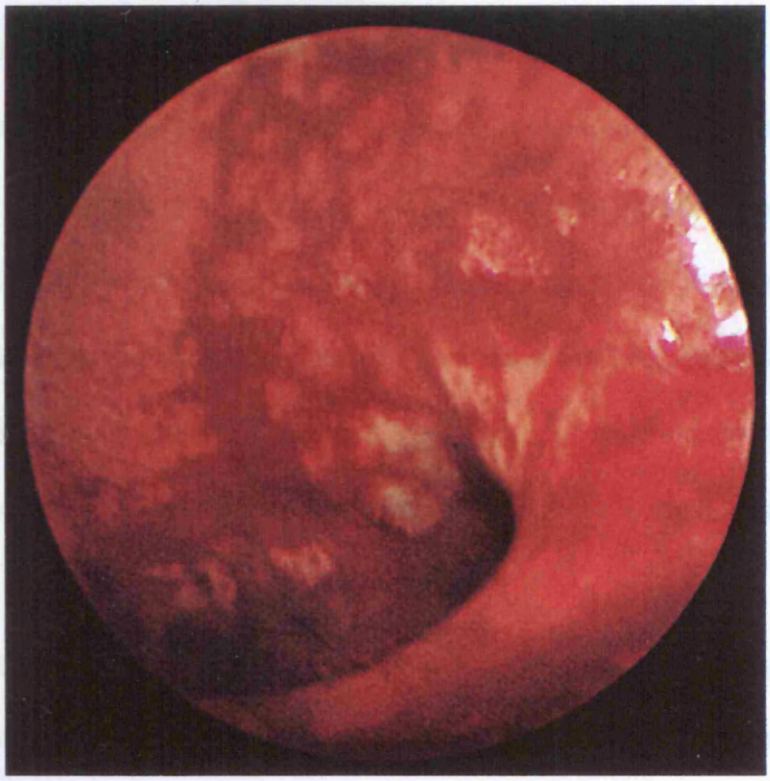
A familial incidence of ulcerative colitis has been recognized for many years with approximately ten to twenty percent of patients having at least one other family member affected. (17) The general consensus is that most of the familial association is within first degree relatives. Other affected family members may have either Crohn's disease or ulcerative colitis, although the majority will have ulcerative colitis. A recent twin study by Tysk (18) demonstrated a much greater genetic influence in Crohn's disease compared to ulcerative colitis as only one of sixteen pairs of monozygotic twins was concordant for UC and all twenty dizygotic pairs were discordant.

1.4 Pathological and Histological Features.

The macroscopic features are usually most severe in the rectum and extend proximally for a variable distance around the colon. With mild inflammation the mucosa is hyperaemic, oedematous and granular (Figure 1.1). With severe disease an acute dilatation of the colon can develop where the bowel is thin and congested and this may lead to perforation. In most patients with severe disease punctate ulcers are seen which enlarge and extend to the lamina propria. In long-standing disease pseudopolyps may occur as a result of exuberant epithelial regeneration. In remission the mucosa may look normal but over the years it becomes atrophic and featureless, which is accompanied by shortening and narrowing of the colon. Fibrosis is uncommon and strictures are rare.

Figure 1.1. Abnormal colonic mucosa in ulcerative colitis.





Microscopically the changes are predominantly confined to the mucosa. The lamina propria is oedematous and capillaries are dilated and congested. There is an inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, macrophages, eosinophils and mast cells. Neutrophils invade the epithelium leading to cryptitis and crypt abscesses with goblet cell depletion. Features suggesting chronicity include distorted crypt architecture, crypt atrophy, basal lymphoid aggregates and a chronic inflammatory infiltrate.

1.5 Symptoms and Signs.

The prevalence of asymptomatic colitis may be as high as 34/100,000 (19), but when present the major symptoms include diarrhoea, rectal bleeding, the passage of mucus and abdominal pain. Generally their severity correlates with the severity of the disease. However, a lag phase often occurs between the onset of inflammatory changes in the mucosa and the development of symptoms as active disease may be found at sigmoidoscopy in patients who are clinically asymptomatic. In addition a delay in diagnosis may be compounded by late presentation as symptoms have usually been present for weeks or even months by the time a patient presents. The disease can arise suddenly with no obvious cause or it may begin after a documented infection (e.g. salmonella) where the infection may have revealed pre-existing silent disease or may have been the initiating factor. It may also present as intermittent episodes of diarrhoea and bleeding that were not of sufficient severity to cause the patient to seek medical attention. Disease of moderate or severe activity can lead to systemic symptoms including weight loss, fever, shortness of breath, ankle swelling and fatigue.

Few abnormal signs are exhibited with mild disease and patients can appear deceptively well. Tachycardia and a tender colon can be the only abnormal signs but many

with severe disease look ill with evidence of weight loss and depletion of salt and water. Such patients may be febrile and clinically anaemic and dependent oedema secondary to hypoproteinaemia can occur. Some patients develop oral candidiasis or aphthoid ulceration and clubbing may also be seen in chronic disease.

1.6 Assessment of disease severity.

The severity of disease can be assessed by various techniques but the original criteria of Truelove and Witts (6) remain a valuable guide and are simple and easy to use (Table 1.1).

1.7 Medical management.

Corticosteroids were introduced in the 1950's and they dramatically affected disease management along with the improved supervision of fluid and electrolyte balance. The classical trial of cortisone acetate was conducted in 1955 by Truelove and Witts (6) and provided the first controlled evidence that corticosteroids were beneficial in treating active disease. Since then they have been proven to be beneficial orally as well as when used as topical treatments in the form of retention enemas, foams and suppositories. Both oral cortisone and prednisolone have been shown to be ineffective in maintaining remission (20) and so prolonged therapy is contraindicated because of side effects which include weight gain, hair growth, hypertension and osteoporosis.

Table 1.1. Truelove and Witts' disease severity index. (6)

Mild disease	Diarrhoea < 4 times per day
	Small amounts of microscopic blood
	Apyrexial
	Normal pulse
	No severe anaemia
	ESR not raised (<30mm/h)
Severe disease	Diarrhoea > 6 times per day
	Macroscopic blood in stool
	Temperature > 37.5° or > 37.8° on 2 out of 4 days
	Pulse > 90 bpm
	Anaemia (Hb < 75% normal)
	ESR raised (> 30 mm/h)

Moderately severe disease is defined as intermediate between severe and mild.

Another major milestone in the treatment of ulcerative colitis had been the introduction of sulphasalazine by Nana Svartz in 1941. (21) The drug consists of 5-aminosalicylic acid (5-ASA), which is the major active component, linked to sulphapyridine by an azo bond. Once in the colon bacteria split the azo bond to release the two components. The use of this drug as a maintenance therapy has reduced the relapse rate four fold but for active disease sulphasalazine is less effective than corticosteroids. (22) Its suppressive effect on the disease is maintained over many years. (23) However, the incidence of adverse effects is high and can be divided into dose-dependent and dose-independent reactions. (24) Dose-dependent effects include nausea, vomiting, anorexia, folate malabsorption, headache and alopecia. Non-dose related effects include hypersensitivity rashes, haemolytic anaemia, agranulocytosis, hepatitis, fibrosing alveolitis, reversible male infertility and colitis.

Orally administered 5-ASA's are readily absorbed from the jejunum and therefore two types of delivery systems have been developed to obtain higher concentrations of the drug in the colonic lumen. The first is to coat the 5-ASA with a resin that is pH sensitive e.g. mesalazine with Eudragit S (Asacol) or L (Salofalk) coating. The second is to link the 5-ASA with another molecule by an azo bond (e.g. balsalazide). There are also slow release preparations such as Pentasa. These new salicylate drugs have been shown to be as effective as sulphasalazine, both for treating active ulcerative colitis and maintaining remission. (24,25) Topical treatments with sulphasalazine or mesalazine (retention enemas and suppositories) can be used for left sided colitis and proctosigmoiditis and are effective for both active disease and maintenance.

Azathioprine and 6-mercaptopurine have been the most widely used forms of immunosuppression. Their major value is in the management of chronic active disease (in

which they can have a steroid sparing effect) and in the maintenance of remission. Cyclosporin has also been used in ulcerative colitis. (26) It appears to have little effect in severe colitis when given orally but favourable results have been reported for intravenous usage.

Colitis limited to the distal colon which is refractory to standard or immunosuppressive therapy may be treated with several other agents. These include acetarsol (an arsenical compound in suppository form) which was first shown to be of value by Connell et al in 1965. (27) This was later confirmed by Forbes et al who demonstrated clinical remission in patients with 'intractable' proctitis. (28) Butyrate enemata may also be worth trying in patients with refractory left sided colitis as some trials have yielded promising results (29) although true blinding of butyrate treatment is very difficult because of its characteristic strong odor. Ulcerative colitis is largely a disease of nonsmokers and several randomized controlled trials have been conducted to determine whether nicotine may be beneficial in its treatment. It has been shown to be effective in the treatment of patients with active ulcerative colitis (30,31) but is no better than placebo in maintaining remission. (32) Heparin has also been used to treat corticosteroid-resistant ulcerative colitis. (33) The rationale for its use is based on potentially anti-inflammatory effects including inhibition of neutrophil elastase and inactivation of chemokines. The results from early studies are encouraging with some evidence of a therapeutic effect when given both intravenously (33) and subcutaneously. (34)

1.8 Complications.

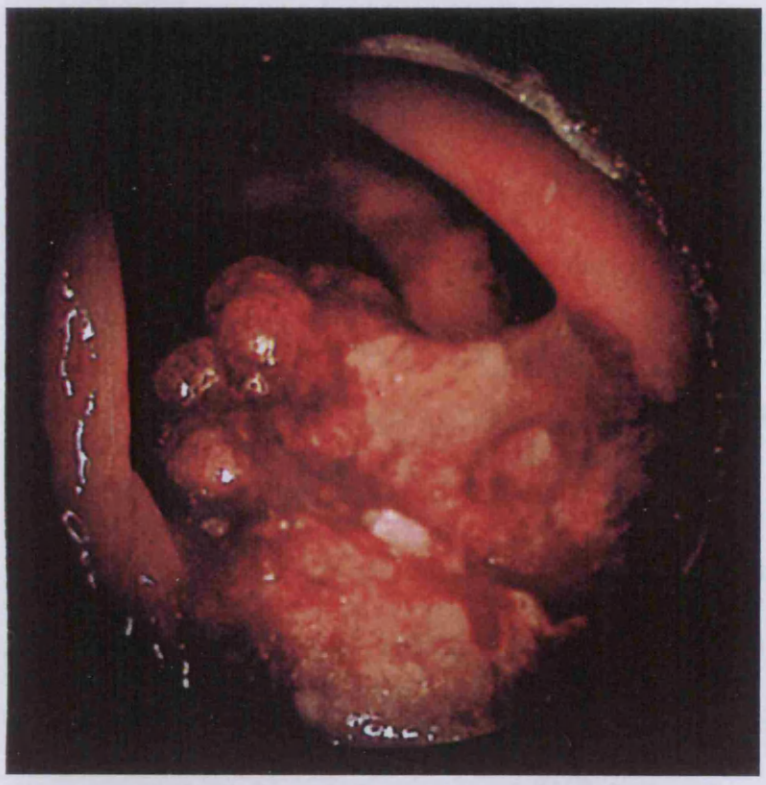
Patients with ulcerative colitis occasionally develop anal fissures, perianal abscesses or hemorrhoids but the occurrence of extensive perianal lesions is more suggestive of

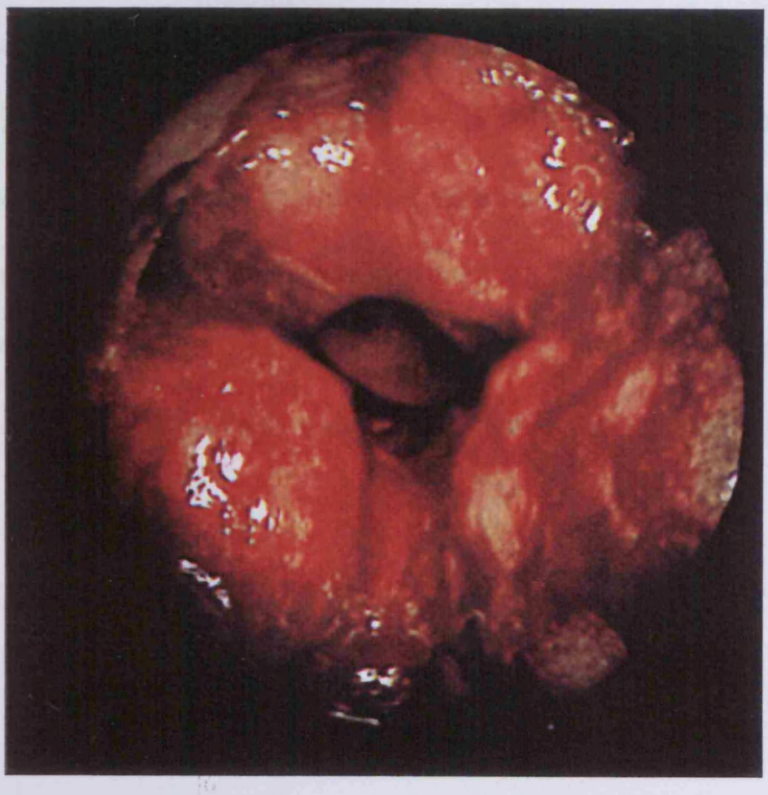
Crohn's disease. Significant haemorrhage is associated with severe attacks of the disease and if a patient requires six to eight units of blood within 24 to 48 hours and are still bleeding, urgent colectomy must be considered.

An acute dilatation of the colon complicates about five percent of acute attacks and can be triggered by hypokalaemia or the administration of opiates. The most dangerous but rare local complication is perforation with a mortality rate for perforation complicating toxic megacolon as high as sixteen percent. (35) About fifty percent of cases of acute dilatation recede with medical therapy alone but urgent colectomy is required for those who do not improve or deteriorate.

Colorectal cancer (Figure 1.2) has been recognized as the most serious long term complication of ulcerative colitis since the 1930's and cancer surveillance is one of the most difficult areas in the management of colitis. Although the 'true' cancer risk is unknown, patients with colitis are estimated to have an approximately 11-fold increased risk for colorectal cancer compared with the general population (36) and there is a marked variation in the magnitude of the risk according to duration and extent of disease. Cancers usually arise as flat lesions rather than developing from adenomatous polyps which makes them difficult to detect at an early stage. (37) Early work (38,39) showed that colitic cancers are more evenly distributed around the colon than the non-colitic, but a more recent study does indicate a predilection for the left colon. (40) In addition there is a higher incidence of multiple cancers in ulcerative colitis compared with the general population and cancers in ulcerative colitis tend to be less well differentiated. Many aspects of cancer in colitis are controversial and the whole subject will be reviewed in detail later in this chapter.

Figure 1.2. Colorectal cancer complicating ulcerative colitis.





1.9 Course and Prognosis.

Eighty percent of patients with ulcerative colitis have intermittent attacks of their disease but the length of remission varies from a few weeks to many years. Ten to fifteen percent will pursue a chronic continuous course whereas the remainder will have a single severe first attack which requires urgent colectomy. (41) In a large study from Copenhagen only one percent of patients had no relapses during the 18 years following presentation. (42) However, it is worth noting that in this study the case definition could have included patients who only had a single episode of bloody diarrhoea and therefore did not have a definite diagnosis of ulcerative colitis. (43)

The extent of disease partly determines severity and therefore the course of the disease. Patients with total colitis are more likely to have severe attacks than those with limited disease. However, patients who present with proctitis may subsequently extend their disease, a study by Powell-Tuck showed that 29% had done so after nineteen years. (44)

Mortality due to ulcerative colitis diminished dramatically with the introduction of corticosteroids and the use of maintenance therapy with sulphasalazine. For a severe attack, mortality has fallen from 37% in 1963 (41) to less than 1% in 1978 (45), which includes cases who died during emergency colectomy. (11) Recent series have shown a normal life expectancy, although there is a slight but significantly increased mortality (2%) in the first year after diagnosis. (42,45,46) A recent population based study of over 1,000 cases in Leicestershire had similar results with an overall standardized mortality ratio of 0.93 (95% CI 0.75 to 1.14). (47)

Section 2.

Colorectal Cancer in Ulcerative Colitis.

Burrill Crohn and Herman Rosenberg reported the first case of adenocarcinoma complicating ulcerative colitis in 1925. (48) Numerous published reports have since confirmed the increased risk in individuals with chronic ulcerative colitis. Overall mortality associated with ulcerative colitis has declined markedly since Edwards and Truelove reported a mortality rate of 35% at twenty years of follow-up. (41) Now life expectancy does not differ significantly from the general population. This decline in mortality is probably related to improved surgical techniques, antibiotics and the use of corticosteroids and 5-aminosalicylates. However, it is now likely that a significant number of deaths amongst patients with ulcerative colitis will be caused by colorectal cancer. As more effective anti-inflammatory and immunosuppressive agents are developed to treat inflammatory bowel disease, the need for colectomy for refractory disease *may* diminish and the issue of cancer risk will be of increasing importance in the long term care of ulcerative colitis patients. Cancer risk is also of considerable concern to many patients with ulcerative colitis. (49)

1.10 Epidemiology of colorectal cancer risk.

Although it is clear that patients with long-term ulcerative colitis have an increased risk of developing colorectal cancer, this risk has been difficult to estimate. Initial studies from referral centres did not reflect experience in the general population. In more recent years, population-based data have been reported, although these studies are difficult or nearly impossible to perform in many areas of the world. Early studies suggested that the mean time from diagnosis of ulcerative colitis to the development of cancer varied from ten

to twenty-five years. (50-52) However, it is likely that many of these patients had ulcerative colitis for many years before the diagnosis was established. In general, it appears that the risk of developing colon cancer within the first seven to ten years of the onset of colitis is negligible compared with age matched controls.

However, the reported cumulative cancer incidence of colorectal cancer after 25 to 35 years of disease has ranged from 3.1% to 43%. (53,54) Practitioner and hospital based studies report a cumulative colorectal cancer incidence that varies from 5.5% to 21% after twenty years of disease, (36,41,55-59) primarily in patients with pancolitis. In general these studies reflect the referral biases associated with reports from tertiary care centres. Other reasons for the wide range of results reported in these studies will be reviewed in detail in chapter two.

Several population based studies mostly from northern European countries have reported the cumulative risk of colorectal cancer ulcerative colitis. Although these results may not be applicable to other populations, the studies are not limited by tertiary referral centre bias. These population-based studies estimate the cumulative risk of colorectal cancer complicating extensive colitis from 1.8% at twenty-five years (54) to 30% at thirty-five years. (60) In the largest study of a population-based cohort of 3,117 patients in Sweden there was a 30% cumulative incidence of colorectal cancer at thirty-five years after the diagnosis of the disease. (60) For patients less than the age of forty at the onset of pancolitis, the cumulative risk of colorectal cancer was 5% and 13% at twenty and twenty-five years respectively.

In marked contrast, Langholz et al reported an overall cumulative incidence of only 3.1% at twenty-five years and a calculated lifetime risk of 3.5% for individuals with ulcerative colitis compared with 3.7% for the Danish population. (54) The reason for this

discrepancy in cancer risk is unclear but may be related partly to a very high colectomy rate in the Danish population. There was a 32% overall colectomy rate at twenty years and a 40% colectomy rate at twenty-five years for patients with pancolitis.

A more detailed account of the potential methodological biases that have been encountered by physicians when aiming to quantify the risk of colorectal cancer in ulcerative colitis will be discussed in chapter two. Chapter two also presents a comprehensive assessment of a meta-analysis of all published studies reporting a colonic cancer risk in ulcerative colitis in order to estimate the true risk.

1.11 Risk factors affecting the incidence of colorectal cancer in ulcerative colitis.

There are several independent risk factors important in the development of colorectal cancer in ulcerative colitis and table 1.2 shows the relative importance of each in contributing to this risk.

1.11.1 Extent of disease.

Most cancers complicating ulcerative colitis arise in patients with extensive or total disease. There is general agreement that there is little or no increased risk associated with proctitis or procto-sigmoiditis (54) while left-sided colitis carries an intermediate cancer risk. For example, in a combined British and Swedish study (61) the excess risk observed in patients with pancolitis was 19.2 and for those with left-sided disease the risk was 2.75. Similarly, in a separate Swedish study (60) the relative risk for pancolitis was 14.8 and the relative risk for proctitis was 1.7 with the relative risk for left-sided colitis being 2.8. This

Table 1.2. The importance of various risk factors in the development of cancer in ulcerative colitis.

Risk Factor	Relative Importance
Long disease duration	++++
Extent of colonic involvement	++++
Young age at disease onset	++
Presence of stricture	++
Presence of fistula	NK
Presence of primary sclerosing cholangitis	+/-

NK = Not Known

From Choi PM, Kim WH. Colon cancer surveillance. Gastroenterology Clinics of North America 1995; 24: 671-687.

was associated with an overall cumulative incidence of colorectal cancer of 5% for left-sided colitis. The exception to this was a cumulative incidence of cancer in left-sided colitis of 12% at thirty years for those patients who received a diagnosis of ulcerative colitis between the ages of 15 and 29.

The development of cancer in left-sided colitis may not be as frequent as those in pancolitis during the first two decades, (62) but the incidence in these two groups is virtually equal by the fourth decade of disease. (56) The data related to the risk of left-sided colitis should be viewed cautiously because of variability in the definition of left-sided colitis and the methods used to determine extent of disease. The definition of left-sided colitis varies from study to study and has included patients with disease to the splenic flexure in some reports, but in others included patients with disease to the hepatic flexure. In addition, most studies gathered data from the pre-colonoscopic era, relying on single- or double-contrast barium enemas to assess extent of disease. Even in the colonoscopic era, the histological extent of involvement has generally not been reported. It is therefore nearly impossible to be confident in assessments of risk in cases where the disease extends proximal to the rectum but is less than pancolitis.

1.11.2 Duration of disease.

Colorectal cancer is only rarely encountered when the total duration of disease is less than eight to ten years, but thereafter the risk of cancer rises at approximately 0.5% to 1.0% per year. (63) A large Swedish series reported 65 cancers in patients with pancolitis during 13,241 patient-years of follow-up (one cancer every 203 years) from diagnosis of colitis. (60) Lennard-Jones' study showed that among patients with extensive colitis no cancers were detected in 1,406 patient-years during the first decade, one in 137 patient-

years during the second decade and one in 103 patient-years thereafter. (64) The annual risk for a patient with extensive colitis is thus estimated to be about one in 125 during the period 10-25 years after onset. (65)

1.11.3 Severity and time course of inflammation.

Although it is likely that colorectal cancer development is related to the underlying inflammatory process, no study has convincingly shown that severity of disease correlates with inflammation. The reasons may be twofold. First, patients with severe disease that is unsuccessfully treated with medical therapy are likely to have a colectomy early in the course of their disease. Secondly, the technical difficulties involved with tracking disease severity (by clinical or histological data) in retrospective studies on large populations are quite formidable. The relative risk for cancer of the colon apparently remains constant with time when controlled with an age-matched (that is, ageing) population. (36) This implies that there is no simple causal relationship between chronic inflammation and cancer risk. This is supported by early work showing the distribution of cancers complicating ulcerative colitis, which unlike the colitis itself, do not seem to have any predilection for the distal colon. (38,39) Similarly, if there were a simple relationship between inflammation and cancer, there should be a higher incidence of rectal cancer in patients with proctitis. There is evidence from one series that patients with chronic continuous colitis have a greater risk of cancer than those with intermittent colitis, (66) although many series have failed to find a relationship with severity of symptoms.

1.11.4 Age of onset.

There is some debate as to whether patients with onset of colitis early in life have an increased risk compared with older patients. Young patients have a longer potential lifespan and so higher risks reported in this age group could simply reflect duration of disease. The first study to report a higher risk in children followed-up 396 patients, all aged 14 years and below, who were first seen at the Mayo Clinic between 1919-1965. (53) They showed a 3% cancer incidence during the first decade of disease and a 20% incidence during each of the second and third decades after onset. This study probably included an element of referral bias of severely ill patients to a specialist centre, but these findings have now been confirmed by others. (56,61,67) The most recent study from Sweden (60) found that the cumulative colorectal cancer risk in patients with extensive colitis after 35 years follow-up from diagnosis was 40% in patients in whom the disease started before the age of 15 years and 25% in patients developing colitis between 15 and 39 years. This study also reported a higher cumulative incidence of colorectal cancer in patients with a later onset. In patients who were older than 40 years at the time of diagnosis of pancolitis, the cumulative incidence of colorectal cancer by 20 years was 16%, versus 5% for patients under 40 years of age at diagnosis. However, age of onset of disease as an independent risk factor has not been consistently reported. (56,68) Greenstein et al (56) calculated the age specific incidences per 1000 patient-years for both universal and left sided colitis. The authors thus estimated an incidence of 3.6 per 1000 patient-years in pancolitics who were 10-19 years of age at onset of disease compared with 12.7 per 1000 patient-years who were between 30 and 39 years of age at onset. In addition, the apparent increased risk of colorectal cancer for patients over age forty may reflect some contribution from the age-related risk of developing sporadic colorectal cancer. Some support for this view comes from reports

(62,66,69) that the interval between onset of disease and development of cancer is the same in young and older patients.

1.11.5 Geographical variation.

Studies of large populations in Britain, Israel and Sweden (60,61,70) have shown a similar excess cancer risk among patients with ulcerative colitis. A retrospective survey from Eastern Europe of 959 patients referred to a specialist hospital in Prague from all over Czechoslovakia between 1942 and 1981 revealed only six colorectal cancers. (71) Of 305 patients with total colitis, 138 were treated surgically, mostly by operations which spared the rectum. The relative risk for the whole series was 2.1 and for patients with total colitis it was 4.6 - lower values than for other countries. However, the cumulative incidence for all patients at 27 years was 2.9%, and for those with total colitis it was 11%, values similar to those from other studies in Europe, Israel and America. In Japan, the frequency of carcinoma in patients with ulcerative colitis has tended to increase in recent years and about sixty cases were reported up to 1989. (72,73)

Some studies from different geographical locations report similar cumulative cancer risks in ulcerative colitis but there are others that would suggest some variation between countries. Whether these variations are due to genetic or environmental factors remains to be determined. If the same environmental factors that are important in sporadic colorectal cancer play a major role in the development of cancer in colitis, one would expect a constant relative risk of cancer between patients with colitis and the general population but a varying cumulative risk from country to country.

1.11.6 Influence of treatment.

It is not fully known whether energetic medical treatment to reduce inflammation lowers cancer risk in ulcerative colitis. However, there is now a little evidence that treatment with sulphasalazine may do so, (74) despite a suggestion that folate malabsorption due to this drug could increase the risk. Drugs which liberate 5-aminosalicylic acid in the colon could reduce cancer risk by reducing inflammation or by an effect analogous to nonsteroidal anti-inflammatory drugs in normal subjects (75) and patients with adenomatous polyposis. (76)

Folate depletion in patients with ulcerative colitis (which is often but not always associated with sulphasalazine therapy) has been invoked as a possible risk factor for colonic neoplasia. (77) As folate deficiency predisposes to sporadic colon cancer and adenomas, (78) this is a worthwhile hypothesis that is being actively investigated in the colitis population. (79,80)

It has been postulated that azathioprine may increase the colorectal cancer risk in ulcerative colitis. The incidence of various cancers, especially non-Hodgkin lymphoma *is* higher in patients who receive azathioprine for immunosuppression after organ transplants than the general population. A study from the St. Marks group in 1994 (81) showed that among patients with extensive chronic ulcerative colitis there was no difference in cancer frequency between 86 patients who had received azathioprine and 180 matched pairs who had never received it. Therefore, Connell et al (81) concluded that the use of azathioprine did not appear to increase the cancer risk. However, the median period of treatment with azathioprine was only 12.5 months (range 2 days to 15 years).

The authors of the only large series to show no significant cancer risk in colitis adopted a policy of vigorous medical and surgical treatment. (54) All patients with colitis in

their community are treated by hospital based specialists. There is open access to the hospital clinic so that attacks of colitis can be treated early with topical or systemic steroids. Sulphasalazine or other 5-aminosalicylic acid derivatives are given for at least two years after the last symptoms, and most often continuously. Surgery is performed within days or weeks of failure of corticosteroid therapy. As a result of this policy, 9% of patients were operated on within the first year of illness and the cumulative colectomy rate was 23.7% within ten years and 32.4% within 25 years. For patients with total colitis at diagnosis, the rate was 35% within five years and about 40% within twenty years. It would seem that an aggressive approach contributed to the absence of any excess cancer risk. However, it needs to be remembered that the median follow-up in this study was only 11.7 (range 0-26) years.

1.11.7 Primary sclerosing cholangitis.

Several studies have indicated that the small subset (approximately 2% to 5%) of patients with primary sclerosing cholangitis (PSC) as well as ulcerative colitis may be at a higher risk of colorectal neoplasia. (82-86) In a case-control study the absolute cumulative risk of developing colon cancer or dysplasia for ulcerative colitis patients with sclerosing cholangitis was 9% after ten years of colitis, 31% after twenty years and 50% after twenty-five years compared with rates of 2%, 5% and 10% in ulcerative colitis controls matched for duration and disease extent ($p<0.001$). (87) This association has been supported by evidence from other centres. When 29 patients with long-standing ulcerative colitis and neoplasia were pair matched (88) with similar colitic patients without neoplasia, nine had pericholangitis and one had sclerosing cholangitis among the former but only two in the control group (odds ratio 9.0, 95% C.I 1.14 to 71.0). A population-based cohort of

patients with primary sclerosing cholangitis was identified in Sweden. For patients in this group who had ulcerative colitis at the time of diagnosis of cholangitis, the cumulative risk of colorectal cancer was 10% during the first decade and 33% during the first two decades of colitis. (89)

In contrast, Loftus et al's case-control study did not find a significantly increased relative risk for colon cancer in 178 patients with PSC and ulcerative colitis. (90) It has been postulated that alterations in bile acids secondary to liver disease may promote carcinogenesis in the colon, but colon cancer has developed even after liver transplantation for PSC in ulcerative colitis. (91) Ascertainment biases undoubtedly play a role in these studies; patients with PSC often have clinically quiescent colitis and may be followed up primarily by a hepatologist, whereas those patients whose colitis symptoms are more obvious may have subclinical PSC and be followed by a gastroenterologist. However, the suggestion of a link between PSC and colonic neoplasia in patients with ulcerative colitis remains.

An increased risk of colorectal cancer following orthotopic liver transplantation for PSC in patients with UC has also been documented with the incidence ranging from 5.6% to 11.1%. (91,92) or approximately 1% per person per year. (93)

1.11.8 Positive family history of sporadic colon cancer.

A positive family history of colon cancer is associated with a two to three fold risk for colon cancer in individuals with sporadic, non-colitic colorectal carcinoma. Little attention has been given, however, to the issue of whether a family history of colon cancer might also be a risk factor in patients with ulcerative colitis. A case-control study from the Mayo clinic of 297 patients found that a family history of colon cancer was twice as

common when ulcerative colitis was associated with colon cancer compared with UC controls matched for extent and duration of colitis. (94)

All of the above risk factors need further investigation to determine which are the most important parameters in influencing cancer risk. Of course the optimal study design for defining risk factors would be a prospective controlled study. However, given the long duration before enough cancers or dysplasias develop in a surveillance program, as well as ethical concerns about withholding surveillance colonoscopy or 5-ASA treatment from the control group, we must rely on case-control studies to offer the best approximation of colorectal cancer risk factors in ulcerative colitis. Chapter three reports the findings of a nationwide case-control study whose purpose was to elicit the most significant factors associated with a reduced cancer risk in patients with ulcerative colitis.

Section 3.

Patient education programs and how they may affect the cancer risk.

Another potential risk factor that may affect cancer risk in colitis is patient knowledge. It is feasible that patients who are unaware / unconcerned about the risk may be less motivated to attend colonoscopies and to comply with medication. Thus one approach that has not been investigated is the effect of a patient education program in reducing colorectal cancer risk. Patients may fail to attend surveillance colonoscopic examinations, usually because they do not like the test but possibly because they are unaware of the purpose of the program or of the cancer risk. Perhaps if patients fully realized the importance of surveillance and the reasons for its regularity, they would be more likely to attend.

1.12 The use of patient education in chronic diseases.

In the past a unilateral patronising style of health care was generally accepted, but patients are now becoming much more responsible for their own illness. Ulcerative colitis is a long term condition and the very nature of its chronicity requires a high level of patient responsibility for successful day-to-day management. Patient education has been widely accepted in many disciplines as a valid component of chronic disease management. (95) Such education teaches patients about their disease and its treatment. The patient who receives instruction is presumed to be in a better position to participate in his or her own health care and thus maximize therapeutic benefits.

Mazzuca reviewed the literature on patient education in a variety of chronic diseases in 1982 (96) and found patient education was most successful in improving compliance, clinical progress and overall health outcomes. Participation in a patient education program

for patients with inflammatory bowel disease has been shown to increase the patients' disease related knowledge and positively influence quality of life, depression and social activity. (97) Up to 75% (98,99) of patients with ulcerative colitis consider themselves insufficiently informed about their disease and when asked to prioritize their disease concerns they placed the risk of cancer at the top of their list, followed by new treatments, symptoms, psychological factors, diet and aetiology. (100) Thus being informed is not only a patient's right, but appears a necessity if we are to alleviate their fears and anxieties.

Patient education programs have been initiated in a variety of specialties (101-104) and have led to improved patient knowledge and satisfaction. Improving patient knowledge in type 1 diabetes mellitus is inversely correlated with glycosylated haemoglobin (105) and in the field of renal medicine an education program significantly improved calcium levels in patients on haemodialysis. (106) Thus it is reasonable to postulate that increasing knowledge and awareness of cancer risk among patients with ulcerative colitis may lead to a greater uptake of surveillance colonoscopy. Indeed it has already been shown that adequate health education increases the level of compliance with population screening programs for colorectal cancer in the general population. (107)

1.13 Measuring knowledge levels.

Health education issues are particularly relevant in ulcerative colitis because of the large amount of medical information that can be imparted to patients, the chronicity of the illness, the frequent contact with health care professionals and an increasing emphasis on self-care in some centres. Prior to the implementation of an effective education program it is critical to have the ability to assess an individual patient's level of knowledge concerning a disease and its management. There is, therefore, a need for a tool that can objectively

evaluate patient education programs in inflammatory bowel disease. Although there is growing interest in this area there are few published scales which measure such knowledge. An analysis of the existing knowledge scale by Jones et al (108) will be given in chapter four. Chapters four and five give an account of the development and validation of a self administered questionnaire that was devised as an index of patient knowledge - the Crohn's and Colitis Knowledge Score (CCKNOW Score).

1.14 Methods of improving patient knowledge.

Patients are keen to receive educational material in a variety of forms. (109) An Italian study (100) has reported that the media preferred by patients with inflammatory bowel disease were: specifically prepared books (73%), video cassettes (20%) and leaflets (25%). Ninety percent felt that specially prepared educational material could be very useful. A Leicester based study (99) demonstrated that of those patients who wanted more information, 60% wished to receive the advice from a trained advisor. Seventy-six percent wanted this person to be a hospital specialist but 50% would accept advice from a specialty trained nurse. Patient self-help groups are an alternative source of information. The National Association of Crohn's and Colitis is the main such group in Britain for patients with inflammatory bowel disease but many members are only transient, drawing from the group for a while and withdrawing once their need is met. (110)

Booklets and leaflets for patients with inflammatory bowel disease have been shown to be an effective means of imparting disease related information (111,112) and have become an important adjunct to the standard doctor-patient consultation. If we are to be certain that patients understand methods of diagnosis and the rationale behind treatment, the best teaching techniques should be employed. It is unfortunate that despite the routine use

of leaflets in outpatients, patients often feel that they need more information. (113,114) Technology has increased the options open to educators and videos are now frequently used in training. The potential of these techniques has led to their use in such diverse areas as consent for endoscopy (115) and reducing sexually transmitted disease rates in at risk groups. (116) The Internet is also becoming a widely available source of knowledge and is being used to disseminate information to a large audience. (117,118) In the USA there are many web pages devoted to patient education. (119) In addition to those provided by the National Institute of Health and various university departments of gastroenterology, there are a number of on-line magazines such as the "The Old Crohnie", "Keith's Crohn's Chronicle" and the "IBD Newsletter". However, at present many of the web pages that patients access are unstructured and are not subject to the usual peer review process afforded by medical journals. (120)

Videos can be used to inform most people about their disease and screening for complications without face-to-face consultations. They provide a consistent form of teaching, are a familiar medium to most patients and can communicate concepts in a realistic and visual manner. (121) Despite the changes such technology has brought to education and training there have been only limited attempts to evaluate them in the clinical context compared with traditional methods. An information leaflet and a video were produced for patients with ulcerative colitis that addresses their fears and anxieties. They do this by demonstrating and explaining the colonoscopy procedure. The leaflet and video also inform patients of the risk of colorectal cancer and how they may reduce their risk. Chapter six

details this project and reports the findings of a randomized controlled trial comparing the effectiveness of the video versus the leaflet on patient knowledge of colorectal cancer risk.

Section 4.

Cancer surveillance in ulcerative colitis.

Cancer surveillance is based on the hypothesis that repeated testing of a high-risk population will identify patients who either have or are likely to develop cancer and that an intervention (typically surgical) made at the time of a positive surveillance test will allow successful intervention at a premalignant stage or cure of an early cancer.

1.15 The rationale for and development of surveillance.

Twenty years ago patients who suffered an attack of ulcerative colitis that affected the whole colon were often invited to undergo total colectomy in order to protect them from developing cancer in the future. (122) Although some authorities still recommend early surgery, (60) the paper published by Morson and Pang (37) which drew attention to the predictive value of dysplastic mucosa in the rectum has had a profound influence on this practice. The initial observation that cancer in ulcerative colitis was often associated with a field change of dysplasia implied that *'at risk'* patients could be detected by rectal biopsy before the cancer became apparent. The introduction of effective and safe total colonoscopy in the early 1970's provided a more useful tool than sigmoidoscopy and barium enema, enabling much more of the colonic mucosa to be visualized and biopsied. It seemed logical that patients 'at risk', but whose quality of life was satisfactory, should not be advised to undergo a prophylactic total colectomy and ileostomy. Instead they should have regular colonoscopic examinations with multiple biopsies. (123-125) This policy, it was argued, (64,126) would detect cancer either before it became established or early in its evolution while still at a curative stage. This approach was so persuasive that for the past twenty years many specialized centres have adopted it without benefit of a prospective

randomized controlled trial. The success of a surveillance regimen depends on a clear understanding of lead time (the time from a positive surveillance test to a surgically incurable cancer) and sampling error. Unfortunately, there are few good data regarding either lead time (dysplasia to advanced colon cancer) or sampling error in the setting of cancer surveillance in ulcerative colitis. Despite this, current surveillance recommendations typically involve an initial screening colonoscopy at 7 to 10 years in patients with pancolitis with two to four random biopsies every 10 cm. Subsequent surveillance colonoscopies should be conducted at 1 to 2 year intervals to monitor for the development of dysplasia or early cancer. In left-sided colitis surveillance colonoscopies start after 15 to 20 years although there are few data supporting this extra delay. At colonoscopy it is recommended that multiple biopsies are taken from normal mucosa as well as from areas that look suspicious. All histologic specimens are examined for dysplastic change. Individuals whose biopsies show significant dysplasia and those found to have cancer are advised to undergo total colectomy.

Cancer surveillance in ulcerative colitis is not mandatory and a patient should only enter a program after a full explanation of its purpose and limitations. Entry entails acceptance by the patient of regular clinical assessment and endoscopy, even if symptoms are slight or absent, and includes an understanding that surgical treatment will be advised if definite dysplasia or carcinoma are detected. It must also be made clear that surveillance has not been proven to reduce cancer risk and cannot be guaranteed to do so. However, it does offer a reasonable chance of reducing cancer mortality through surgical treatment at a stage of either precancer or symptomless cancer. (65)

1.16 Strategy and methods of surveillance.

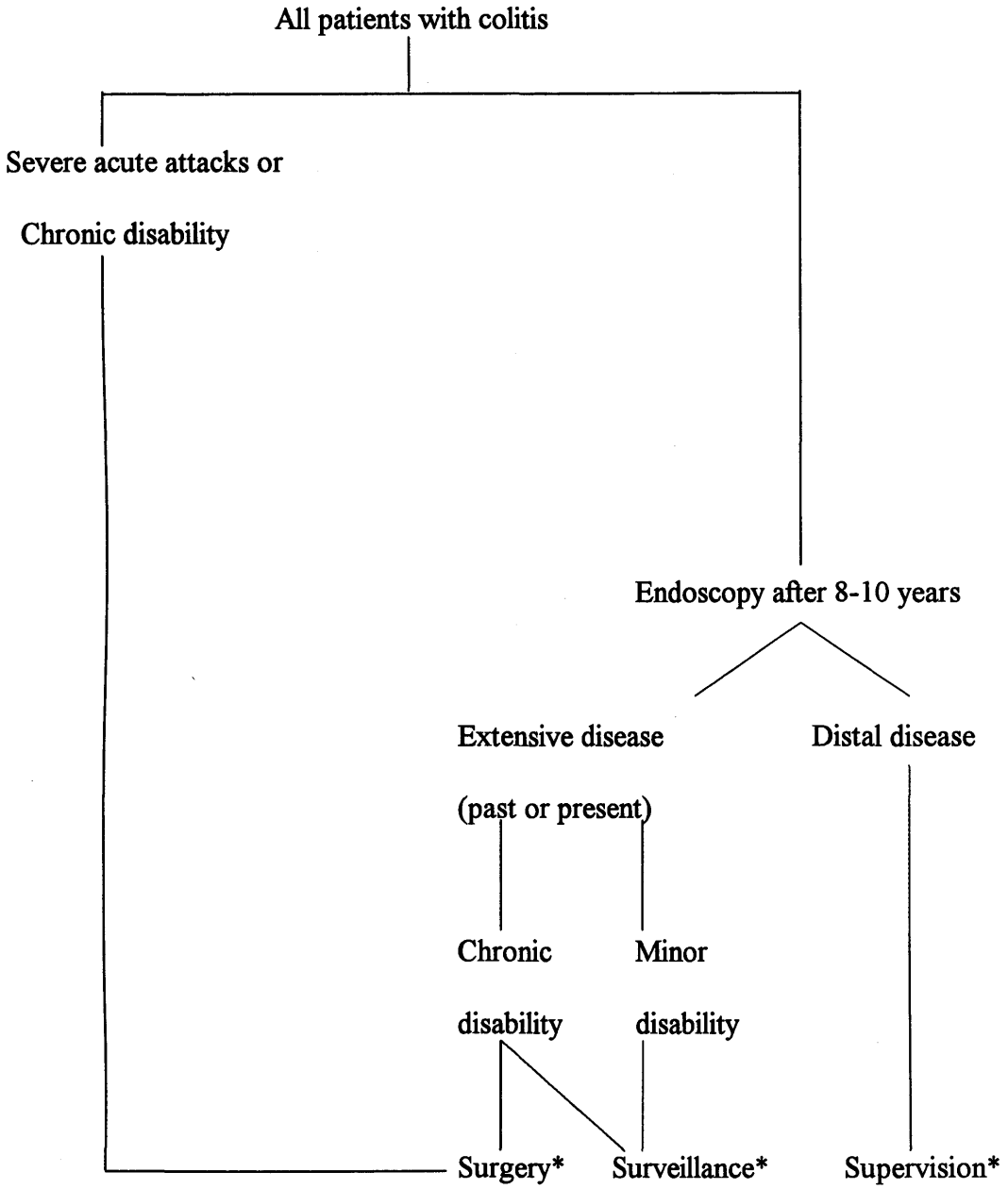
Surveillance is best performed during remission in order to eliminate the difficulty of differentiating reactive change from low-grade dysplasia. (127) At present all patients with UC should be advised to have a colonoscopy eight to ten years after diagnosis to check the extent of disease. Periodic colonoscopy should begin after 8 to 10 years of disease onset for extensive colitis and 15 to 20 years for left-sided disease. (125) Current recommendation is for regular screening at one to two year intervals. (125) Some have advocated an alternative schedule to account for the increase in cancer risk with longer duration of disease. (128-130) They suggest a gradual decrease in the screening interval from every 3 years for the second decade of disease to yearly by the fourth decade of disease. (128-130) The optimum frequency of examination is undecided. Cancers may be missed at colonoscopy and interval cancers have been reported if colonoscopy is performed once every two years. (131) Annual examination therefore appears desirable. If annual colonoscopy is difficult to arrange or is unacceptable to the patient, then a compromise in which annual flexible sigmoidoscopy is replaced by colonoscopy every second or third year appears a reasonable plan. (65) Such a program has not been tested in practice or published in a peer review journal.

During colonoscopy a full examination should be performed with a careful inspection of the entire colonic mucosa. Two to four random biopsies should be taken at 10 cm intervals throughout the entire length of the colon. (125) Some studies report that greater than 50% of all neoplasia associated with ulcerative colitis develops in the distal colon; presumably as a result of the invariable involvement of this region by the disease. (36,40,129,132-136) Therefore, they advocate additional sampling of the rectosigmoid with the goal of improving the diagnostic yield of random biopsy technique. (129,137)

Conversely, because cancer tends to develop less commonly in noninvolved bowel, biopsy sampling of the proximal colon is less sensitive in patients with well documented left-sided ulcerative colitis.

Particular attention should be paid to elevated mass like lesions (dysplasia associated lesions or masses - DALM's) because there is an increased likelihood that such areas may harbor dysplasia or carcinoma. (123,124,138) If such a lesion is present, additional biopsy specimens should be taken from the area. Extra biopsy specimens should also be taken from irregular plaques, villiform elevations, unusual ulcers, or strictures because these areas may also harbor neoplastic lesions. (123,124,139,140) Biopsy specimens from each segment of the colon should then be placed in separately labelled containers to facilitate rebiopsy of the area in question should the need arise at a later date. (141) Figure 1.3 is an algorithm illustrating the current suggested reassessment of patients with ulcerative colitis when under medical supervision.

Figure 1.3. Flow diagram illustrating the reassessment of patients with ulcerative colitis when under medical supervision 8-10 years after the onset of disease.



From Lennard-Jones JE. Prevention of cancer in inflammatory bowel disease. In Young GP, Rozen P, Levin B eds. Prevention and Early Detection of Colorectal Cancer. WB Saunders Company Limited. London 1996; 217-238

*See Figure 1.4. for management of dysplasia

1.17 Assessment of surveillance programs.

In the ten to twenty years since this policy was adopted the results from a number of large surveillance programs have been published. (42,64,123,136,142-149) Nearly all have confirmed the association between chronic ulcerative colitis and cancer and the authors have drawn attention to the life saving *potential* of this form of surveillance. Nevertheless, when these studies are reviewed critically it is apparent that the health gain from this approach is smaller than would have been predicted. (63,150-153) It is difficult to demonstrate a beneficial impact of a cancer surveillance program in patients with long-standing ulcerative colitis. One of the main difficulties in assessing its utility has been the large number of patients and long duration of study (15 to 20 years) required to demonstrate an effect on cancer stage and survival. (61,124,143-145,151) In addition, patient compliance can be a problem as multiple procedures can pose logistical problems, particularly for those who are young and mobile and tend to move several times through educational and employment change. Also, not all patients accept colectomy if dysplasia is detected. Finally, it has been difficult to conduct controlled studies because of the ethical issues involved in randomizing patients at high risk to a control arm.

Studies examining the impact of cancer surveillance in ulcerative colitis have produced conflicting results. (123,124,143,145-148,153) These studies suggested that cancer surveillance leads to the detection of early-stage cancer in only a minority of patients, resulting in a high cost-to-benefit ratio. (150-152) In fact, a significant number of patients present with cancer at an advanced stage despite surveillance. These studies, however, involved small numbers of patients with cancer (range one to seven cases) (123,124,143,145,146,148) and probably suffered from a sampling error. In addition, these

studies may have been less than optimal (152,154) because most consisted of small groups of patients followed for a relatively short duration.

When considering the success of surveillance programs, one has to consider how critical authors have been in their assessment of what constitutes success. Using quite stringent criteria the Leeds group have published two reviews (146,150) of 12 published studies in cancer surveillance in ulcerative colitis. Some were follow-up studies of earlier reports and all data, including some associated abstracts, were analyzed at the same time by two independent observers. (64,123,136,142-149,155) In all, 1916 patients were enrolled and 92 cancers discovered. Because all were descriptive as opposed to controlled studies, the Leeds group decided to look at each individual patient with cancer in order to audit whether surveillance had helped that individual or not.

The purpose of surveillance is to identify precancer or cancer at an early stage. However, the Leeds group (146,150) felt the inclusion of dysplasia alone as a measure of success was of debatable value. Therefore they limited their audit to those eventually found to have cancer. They defined success as the preoperative discovery of early cancer (graded Duke's A or B). However, in practice 40 of the cancers diagnosed in the series were Duke's C or more advanced. The authors took the view that because it was colonoscopic surveillance in which they were interested, cancers diagnosed by barium enema, rigid sigmoidoscopy, and those found incidentally at operation or autopsy should not count as successes. There were 28 that were diagnosed by these other methods. At the time they undertook the study low grade dysplasia was not generally regarded as being an indication for colectomy, unless associated with a lesion or mass (DALM). Indeed at that time patients with low grade dysplasia were seldom encouraged to undergo colectomy. For these reasons the two cancers found in patients who had been operated on solely for low

grade dysplasia were not included as successes. Three cancers were detected outside the criteria laid down for surveillance; that is to say they were discovered in patients who had limited colitis or alternatively developed earlier than 8 years after onset. Finally they drew a distinction between *screening* and *surveillance*. A patient who presents for the first time to a specialist colitis clinic is likely to undergo colonoscopy, either because they are symptomatic or to get a baseline assessment following transfer of care. This is not surveillance. It is a screening or assessment colonoscopy and does not in itself indicate an ongoing commitment by patient and doctor to regular examinations which are the hallmark of a surveillance regimen. At the time of the initial screening examination, up to 3% of patients with long-standing ulcerative colitis already have cancer, (40,136,147) and almost 12% manifest dysplasia. (40) They decided, therefore, to exclude patients in whom cancer was found at an *initial* colonoscopy undertaken at least 12 years after the onset of symptoms. There were eight such cases. If these audit criteria are applied, only 11 of the 92 patients (12%) could be counted surveillance successes. It should be remembered, however, that even 12% is an overestimate of the actual success rate. These 11 patients with early cancer are likely eventually to have presented with symptoms and they would have received treatment; they would not all have died. Indeed, some might have died from intercurrent disease before the Duke's A cancer caused symptoms. The five year survival rate of patients operated on for cancer in ulcerative colitis lies somewhere between 34% (156) and 62% (157) which is very similar to that of the general population. In conclusion the authors felt that only 5 or 6 of the 11 patients actually benefited from these 12 surveillance programs involving 1916 patients. The data summarizing all these surveillance programs can be seen in Appendix 2 as they have been included in the meta-analysis (chapter two).

Were the criteria too stringent? A smaller review of surveillance programs has been published by Lennard-Jones. (65) The results were divided into two groups depending on whether the program was conducted at a hospital with a regional catchment area or a tertiary referral centre. At four centres, Finland, (144) Sweden, (145,158) and Israel, (159) the majority of patients came from the hospital's catchment area. This was also likely to be the case in Leeds. (146) At these five centres, 583 patients were studied over 12-18 years and 2645 endoscopies (mostly colonoscopies) were performed. As a result, 13 patients underwent operation for dysplasia but no carcinoma was found. Nine carcinomas were treated surgically, eight at a stage of Duke's A or B. In addition three cancer deaths occurred; a patient whose caecal carcinoma presented after a nine year history of disease but before the first colonoscopy, (136) a patient who defaulted from surveillance, (146) and a patient whose operation was delayed when high grade dysplasia was discovered. (159) Two series from tertiary referral centres, in the USA (147) and the UK, (147) were characterized by a long history of disease at the start of surveillance, a relatively large number of cancers diagnosed and of patients treated surgically for dysplastic change. In one series only four of ten carcinomas (147) and in the other 11 of 20 carcinomas (147) were at Duke's stage A or B. Eleven cancer deaths occurred in the two series among 545 patients. One centre considered that 21 of 332 patients studied over 20 years benefited from the program. Twelve were operated on for dysplasia and this was confirmed in the operation specimen. Nine were treated surgically for symptomless cancer at Duke's stage A or B, all of whom survived. (147)

The study from St. Marks (64) which examined the impact of surveillance has been more promising. This was a study of surveillance over 22 years and cancer was detected at a favourable stage. Among 17 patients who developed carcinoma while under surveillance,

in 12 (71%) it was at an early stage (Dukes stage A or B). Data from Choi et al's 18 year surveillance program in the USA were collected prospectively and cancer was detected at an early stage in 15 of 19 patients (80%), compared with only 9 of 22 (41%) non surveyed cancer patients. (126) The overall 5 year survival rate was 77% for the surveillance group compared with only 36% for the control group ($p<0.03$).

Provenzale and co-workers (160) compared various strategies for managing a 30 year old patient with a 10 year history of pancolitis. The authors calculated that a colonoscopy every 3 years increased life expectancy by 7 months whereas one every year increased it by 1.2 years, as compared with no surveillance. Lashner and colleagues (161) in an uncontrolled study, examined outcome among patients with extensive ulcerative colitis of more than 8 years duration. Ninety-one screened patients had an average of 4.2 colonoscopies each and were compared with 95 individuals who had not been screened. In the screened group initial colonoscopy identified four patients with high grade dysplasia and six with low grade dysplasia. Eight of these ten patients came to surgery. Cancer was not found in any of the resected specimens. In total 8 colorectal cancers (of whom 4 died) were detected in the screened group compared with 6 (of whom 2 died) in the non-screened group. The total number of deaths was six in the screened group and 14 in the non-screened group. The benefit in detection of colorectal cancer in the screened group was marginal but the screened group in addition underwent regular clinical review and the overall mortality was lower than in the non-screened group. Other studies examining the outcome of patients under surveillance are also finding a similar benefit. (40,162)

The clinical effectiveness of a surveillance program has to be judged by its effect on cancer related mortality. Mortality is obviously least with prophylactic colectomy as the potential for malignant transformation has been removed. However, surveillance has

advantages over inaction or follow-up without investigation for patients who decline surgery or for whom it is inappropriate. At the five regional hospitals mentioned earlier it could be argued that the programs were clinically effective because there were no cancer deaths among 583 patients who remained under surveillance; 13 patients may have been prevented from developing cancer; and eight of nine cancers diagnosed as a result of surveillance colonoscopy were at a surgically curable stage.

At the two tertiary referral centres, 24 of 545 patients were saved from developing cancer, and 15 were operated on at a curable stage of cancer. However, there were 11 cancer deaths. It is possible that this mortality was less than expected among patients with long-standing extensive colitis seen at this type of hospital. The fact that mortality after surgical treatment for cancer was lower in patients treated within the surveillance program than among those who presented clinically outside it gives some support for this view. (40,126) However, these findings are no more than suggestive because cancers that developed outside the programs occurred in a population of unknown size and characteristics.

Much debate surrounds the efficacy of surveillance programs in UC. (151,152,163) These programs were widely introduced without benefit of randomized controlled trials to assess their efficacy and cost-effectiveness. It would now be unethical to randomize patients into a study of the benefits of screening and the only acceptable approach is to critically appraise current surveillance practices. Chapter seven gives an account of a national survey of the surveillance practices of consultant gastroenterologists across the United Kingdom and outlines areas where improvements could be made.

1.18 Safety and cost-effectiveness of surveillance.

The hazard rate of surveillance colonoscopy with multiple biopsies appears to be low. (164) In Koobatian and Choi's analysis, the overall complication rate associated with surveillance colonoscopy was 0.26%. There was a single complication of a silent perforation among 379 surveillance colonoscopies with a median of 18 biopsies per procedure. No other complication, including bleeding, infection, myocardial infarction or death resulted from the procedure. British experience has been similar with no incidence of complication recorded during 811 surveillance colonoscopies. (64) Thus the hazard rate for the procedure appears to be quite low and comparable to that associated with diagnostic colonoscopy. (164)

The cost of a surveillance program for patients includes time spent, travel expenses, loss of earnings, possible physical discomfort and anxiety and these may be met by the patient, insurance, or state healthcare systems. The financial costs of the actual program can be estimated. In the St Marks series, 1316 colonoscopies and 1568 rigid sigmoidoscopies were performed. (131) *Estimates* of hospital costs for flexible sigmoidoscopy and colonoscopy in the UK, published in 1991, were £29 and £106 respectively. (165) When the cost of histopathological examination of multiple biopsies was added, reasonable estimates for colonoscopy with assessment of biopsies was £150, and for each clinic visit with sigmoidoscopy and biopsy £50, giving a total cost over 20 years of £275,000. This figure includes clinical supervision of the patient with colitis, of which cancer surveillance was only a part. Applying the same arbitrary costs to the surveillance programs at the five regional hospitals, the total for the 583 patients who underwent 2645 endoscopies was about £400,000. These calculations are of course retrospective and subject to the inaccuracies of such an approach.

There have been three further published estimates of cost. One from England in 1988 estimated that to perform a single colonoscopy on all patients at 8 years, and thereafter to perform colonoscopy on each patient with extensive colitis every 2 years, would require 12 colonoscopies per 100,000 population annually. (155) These results suggested that one carcinoma would be diagnosed every 4 years in this population and the cost would be approximately £6,000 for each cancer (costed at £125 per colonoscopy). This estimate took no account of dysplastic lesions detected. An American calculation based on reports of surveillance programs up to 1984, and an annual colonoscopy priced at $1,000 for each examination, estimated that about $200,000 would be spent for each cancer found or prevented. (151) This calculation used double the frequency and approximately double the cost for each colonoscopy compared with the earlier report. It also used a value for cancer risk of 0.5% per year among patients with extensive colitis, which is half that derived from recent studies. The figures suggested by these two studies (£6,000 vs. $200,000) are widely separated but it should be remembered that they are based on different methods of calculating health care and certainly the UK estimate did not take into account dysplastic lesions detected. One came from an NHS hospital in the UK while the other is American based. In addition they were conducted at different times and this also limits any direct comparison of the costs.

These estimates compare favourably with that for the detection of colorectal cancer by occult blood screening in the general population which costs $35,000 per year of life saved, (166) and of £8,500 per cancer death prevented by a single flexible sigmoidoscopy. (167) Screening programs for other diseases in the general population are also expensive; it has been estimated that in cervical cancer and breast screening the estimated cost per death prevented is £30,000-£50,000. (168)

The third published estimate of the cost of colonoscopic screening in ulcerative colitis by Sonnenberg and El-Serag (Table 1.3) also compares it with other forms of endoscopic screening. (169) In their calculations the yearly incidence rate of colon cancer in ulcerative colitis is taken to be 0% in the first decade after initial diagnosis, 0.5% during the second decade and 1% and 1.5% during the third and fourth decades, respectively. For simplicity, an incidence rate of 1 per 100 was used throughout their analysis. If one screening endoscopy per 2 years was capable of detecting all cancers, 2 cancers per 100 endoscopies were detected during a 2 year period. Sonnenberg and El-Serag assumed that colonoscopy and biopsy had a sensitivity of 70% and thus this reduces that rate to 1.4 cancers per 100 endoscopies, equal to 1 cancer per 71 endoscopies. In calculating endoscopies per life year saved, it is assumed that death is prevented in only 50% of detected cancers, saving 10 life years per death prevented. In ulcerative colitis, 71 endoscopies per 10 life years times 50% equals 14 endoscopies per 1 life year. The costs of endoscopy and surgery were estimated as $1,000 and $25,000 respectively. A complication was estimated to result in 10 lost life years multiplied by the average annual US income of $26,000. In ulcerative colitis, a false positive rate of 10% per 71 endoscopies was assumed which yields seven false positive diagnoses. So, for every 71 endoscopies there are seven false positive diagnoses and one true positive diagnosis. If all eight patients with a positive diagnosis (false and true) undergo colectomy, surgery costs 8 x $25,000 = $200,000. The screening procedure costs 71 x $1,000 = $71,000 per cancer detected. Because therapy is only effective in only 50% of detected cancers, however, $142,000 (2 x $71,000) must be invested in screening to prevent one death. When compared with screening for precancerous lesions involving the oesophagus, stomach and colon the authors suggest that biannual colonoscopy in ulcerative colitis gave the highest yield per cost invested. The cost

of biannual surveillance in ulcerative colitis is comparable to annual screening for adenocarcinoma (in Barrett's oesophagus) and 1 per 5 years screening for colon cancer (in subjects without ulcerative colitis). The estimated costs of detecting one colorectal cancer in ulcerative colitis are summarized in table 1.4.

Table 1.3. Number of endoscopies performed per cancer case detected or life year saved.

Sensitivity of screening procedure	Incidence rate of cancer	Frequency of endoscopy per year	Endoscopies per cancer detected	Endoscopies per life year saved
70	0.01	0.5	71	14

Endoscopies per cancer detected = frequency of endoscopy / (sensitivity x incidence)

In calculating endoscopies per life year saved, it is assumed that death is prevented in 50% of the detected cancers, saving 10 life years per death prevented. For instance, 14 = 71 endoscopies / (10 yrs x 50%).

From Sonnenberg A, El-Serag HB: Economic aspects of endoscopic screening for intestinal precancerous conditions. Gastrointestinal Endoscopy Clinics of North America 1997; 7: 165-184

Table 1.4. Summary of the estimated costs of surveillance by author

Authors	Year of publication.	Cost of detecting one colorectal cancer in a patient with ulcerative colitis
Jones, Grogono and Hoare (155)	1988	£6,000
Collins, Feldman and Fordtran (151)	1987	$200,000
Sonnenberg and El-Serag (169)	1997	$71,000

Section 5.

The significance of dysplasia in ulcerative colitis.

Dysplasia is a precancerous marker which is defined as an unequivocal neoplastic transformation of the epithelium. It is often accompanied by genetic abnormalities on flow cytometric and molecular biologic analyses. Every paper on screening in ulcerative colitis has stressed the importance of dysplastic change in the colonic mucosa. Dysplasia is believed to represent one step in the histologic progression of a mucosa from normal to frank neoplasia. However, the histologic appearance of dysplastic change may vary from one epithelium to another. In the large intestine dysplastic epithelium is well recognized by histopathologists because it is found to some degree in all adenomatous polyps. The microscopic abnormalities include changes in size, shape, depth of staining and position of the nucleus within the cell. (170)

These changes are relatively easy to identify within adenomas, where there is a discreet area (usually raised) with a clearly defined edge between normal and dysplastic epithelium. The greater the degree of dysplasia the easier it is for the pathologist to make the diagnosis. Difficulties arise, however, when the changes are mild, where there is no clearly defined border between dysplastic and normal epithelium, and in the presence of an inflammatory change, where regenerative changes of the mucosa may mimic the appearances of mild dysplasia.

1.19 Sampling error.

Three problems have bedevilled the diagnosis of dysplasia in ulcerative colitis. The first is sampling error. When dysplasia was first introduced as a concept in ulcerative colitis it was believed to be a field change indicative of underlying cancer elsewhere in the bowel

and that it would usually be present in the rectum. (37) This was not an unreasonable assumption because the rectum bears the brunt of inflammation in most cases of ulcerative colitis. It is now recognized that dysplastic change is not necessarily a field change and indeed it is usually patchy. The consequences of this are that it is impossible to sample more than a tiny proportion of the colonic mucosa, even with multiple biopsies, and therefore it may be missed. A study in which multiple biopsies were taken at colonoscopy or from operation specimens has suggested that 33 biopsies are required to give a 95% chance of detecting dysplasia if it is present. (171) Similarly, if low grade dysplasia was found in 1 of 20 biopsies initially, 58 biopsies would be required at a second examination to be 95% confident of detecting it again. (171) At present dysplastic change cannot be identified macroscopically; it is a microscopic diagnosis and therefore suspicious areas cannot usually be targeted. However, it is possible that advances in colonoscopic techniques such as magnification, dye spraying and endoscopic fluorescence will improve pathological yield in the future. (172,173)

1.20 Dysplasia as a predictor of cancer.

The second problem is the significance of dysplastic change. It is generally recognized that dysplastic mucosa is premalignant. However, the likelihood of progression to cancer is difficult to predict. This applies not only to dysplasia in ulcerative colitis but is a well recognized problem in other situations. All tubular adenomas are dysplastic by definition. If left alone some remain benign (noninvasive) and represent no serious risk to an individual. Others will progress to an invasive cancer. Because polyps are readily identified colonoscopically and can be excised easily, the decision as to what to do is straightforward. Before colonoscopic polypectomy was available, surgical treatment was

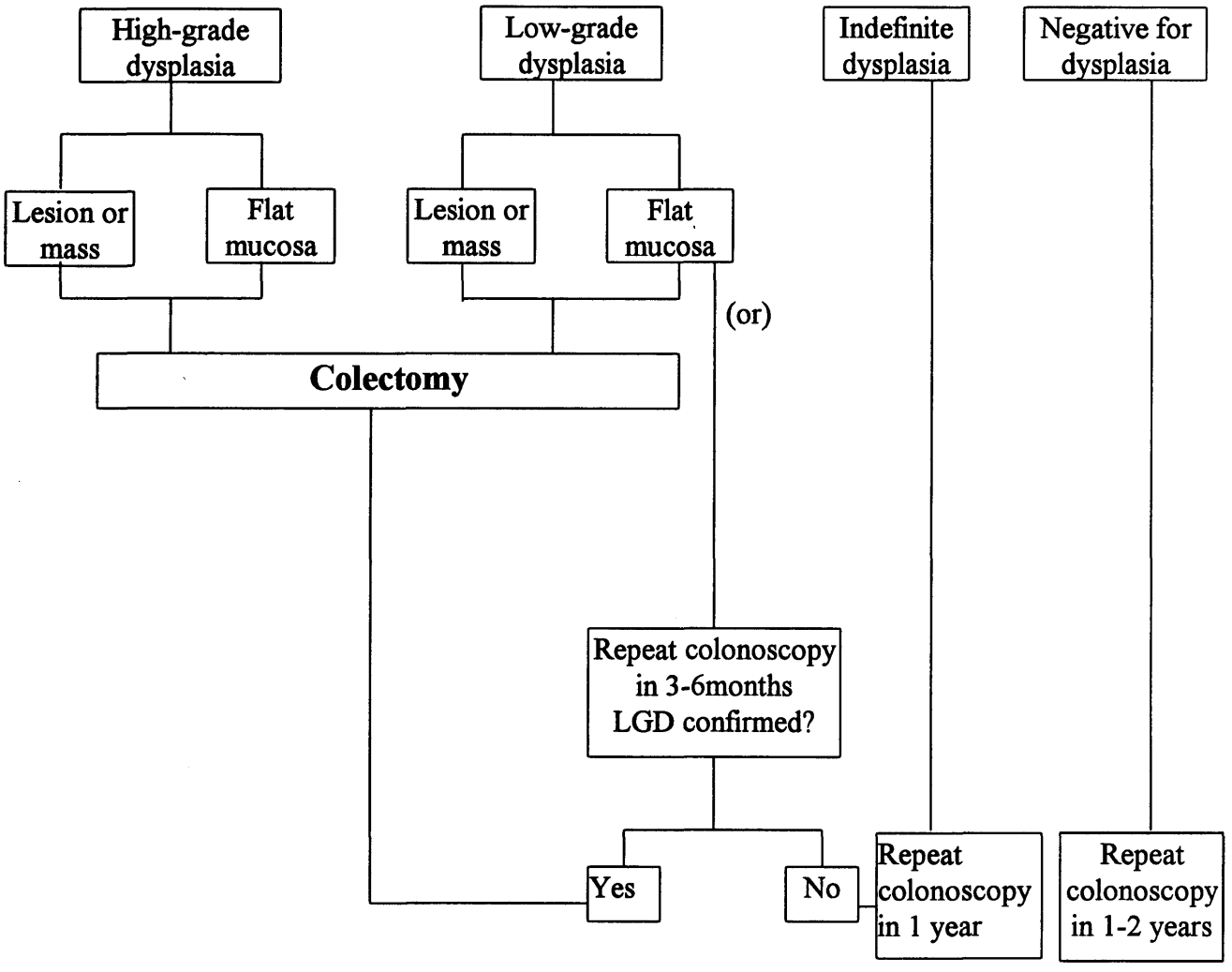
usually limited to those individuals where polyps were enlarging on barium enema or alternatively were greater than 1 cm in diameter at diagnosis. It is unclear in a given case of ulcerative colitis whether dysplastic mucosa develops into cancer. It may be that, as with polyps, the risk relates to the extent or degree of the dysplastic change, but it is difficult to assess the extent of dysplastic changes in a colitic colon because of sampling problems. Retrospective examination of excised colons has provided some information but the findings have not been particularly helpful. The majority of colectomy specimens which contain dysplastic mucosa did not turn out to have cancer (58,124,174) and conversely the majority of patients with cancer and ulcerative colitis do not have a field change of dysplasia. (175) The significance of dysplasia as a prognostic factor is made more difficult by the fact that the majority of patients with long-standing ulcerative colitis eventually develop some degree of dysplasia if followed for long enough. (143,146)

Bernstein et al (128) analyzed 1225 patients from the literature who had undergone colonoscopic surveillance. If a dysplasia associated lesion or mass (DALM) is found at colonoscopy, immediate colectomy reveals cancer in 43% of patients regardless of whether there was low grade dysplasia (LGD) or high grade dysplasia (HGD) in the DALM. When HGD in flat mucosa is the initial discovery, immediate surgery reveals carcinoma in 42% to 67% of the colectomy specimens. (128,131) If HGD is found at some time after the initial evaluation, 32% of patients prove to have carcinoma. Thus whenever a DALM or HGD is identified and confirmed by two expert gastrointestinal pathologists, this is a strong indication for colectomy.

If patients with DALM's are excluded, on the grounds that the biopsy may have been taken from a superficial part of a cancer, 69 of the 1225 patients were identified as having LGD on initial colonoscopy. Cancer was found in three of these patients (4.3%).

Overall 210 patients eventually developed LGD some time during their surveillance period and 17 of these developed cancer (8.1%). At first sight this may appear to be a useful predictor for the subsequent development of cancer. However, 95 patients in these studies were diagnosed as having indefinite changes of dysplasia, nine of whom (9.5%) eventually developed cancer. This analysis therefore suggests that definite LGD is no more predictive than indefinite LGD. Thus the management of LGD is problematic. In published series, when LGD was found on initial colonoscopy, 29% of patients showed progression at some time to HGD, DALM or cancer, and 19% of patients already had cancer at the time of immediate colectomy. (128) Although this latter figure may reflect referral bias which prompted a colectomy in these patients, 8% of patients who had a diagnosis of LGD at some time eventually progressed to cancer. Moreover, the St Mark's Hospital surveillance study indicates that the 5 year predictive value for HGD or cancer in patients with LGD is a troubling 54%. (131) After detecting LGD, the inability to find it on subsequent examinations offers little consolation because the progression to HGD or cancer still applies. (136) Therefore there is compelling evidence that the presence of LGD, even in flat mucosa, can be considered just as much an indication for colectomy as finding HGD or a DALM without waiting for a confirmatory colonoscopy. Figure 1.4 outlines a suggested colonoscopic surveillance strategy for dysplasia.

Figure 1.4. Suggested colonoscopic surveillance strategy based on findings at colonoscopy



From Itzkowitz SH: Inflammatory bowel disease and cancer. Gastroenterology Clinics of North America 1997; 26: 129-139.

1.21 Intra- and inter-observer variation.

The third problem associated with a diagnosis of dysplastic change in the bowel is related to the accuracy and reliability of the diagnosis. The ultimate authority in the diagnosis of most diseases is the pathologist. Clinicians accept as a rule that findings at post mortem or on histology are factual and can be relied on absolutely. A diagnosis of dysplasia in the context of ulcerative colitis, is anything but absolute. On the one hand, a biopsy taken from a mass lesion that is subsequently found to be a cancer may be reported as normal, (126) whereas in another patient a confident diagnosis of HGD sufficient to warrant advice for surgery may not in the event prove to be associated with cancer even after the passage of several years. (158) The most serious inaccuracies in this area relate to the interpretive differences between pathologists. It has long been recognized that there is a wide range of inter- and intra-observer variability in assessing whether a lesion is dysplastic or not (176) and greater problems arise when pathologists attempt to grade dysplastic change. Initially dysplasia was divided into three grades: (1) mild, (2) moderate and (3) severe. It became apparent that problems arose with the distinction between moderate and mild and mild and normal, and so a new classification was devised in 1983 (127) such that biopsies were classified as normal, indefinite, low grade or high grade. The result of this classification was that pathologists tended to overdiagnose low grade dysplasia to such an extent that it was no longer clinically helpful. Nearly all patients eventually develop LGD if followed for sufficient time and performing a colectomy on the grounds of LGD would have led to nearly everyone having this operation eventually. Indeed a recent mathematical model (160) to assess the cost-effectiveness of surveillance made this assumption and thereby drew the conclusion that there would be no saving in terms of surgical procedures by undertaking surveillance rather than by performing colectomy at an early stage.

Perhaps as a result of this "overkill" some pathologists decided to tighten their criteria for dysplasia. The St. Mark's group in 1994 (131) published a paper in which pathologists re-reported all the biopsies taken during their large surveillance study using a new more stringent system. Two experienced pathologists blindly reviewed 301 biopsies. Both observers agreed that 199 biopsies showed no dysplasia. The effect of this was to reduce the number of patients diagnosed as having definite dysplasia from 84 to 25. This had the advantage of making a diagnosis of dysplasia more relevant to the finding of cancer. Two of the 45 patients downgraded to no dysplasia did, however, develop cancer later, whereas of the 23 regarded as low grade or indeterminate for dysplasia three developed cancer, so the improvement in specificity was offset by a fall in sensitivity. Perhaps the most salutary observation to be made from this paper was the poor intra-observer agreement between the two experienced pathologists. The majority of the specimens examined were negative for dysplasia and as would be expected in these there was reasonable agreement. However, the two pathologists agreed in only 42% and 43% respectively where high grade and low grade dysplasias were concerned and in 19% for indefinite dysplasia. This shows that they disagreed more often than they agreed for each grade of dysplasia. Many clinicians would be unwilling to accept this as a gold standard on which to base an important clinical decision.

The value of indeterminate and low grade dysplasia as a diagnosis is therefore of limited value. Pathologists have difficulty in making a firm and consistent diagnosis. The lesion may be present at one time and absent at another, cancers often occur in the absence of low grade dysplasia, and the predictive value of low grade dysplasia in an individual patient is unsatisfactory. Two areas appear to have a good predictive value for cancer. The first is the presence of a DALM. (123) The presence of a DALM has a high predictive

value for cancer and as with other suspicious macroscopic lesions in the rest of the gastrointestinal tract they have to be taken seriously. In effect the finding of a DALM suggests that a superficial part of a neoplasm may have been biopsied. The second important dysplastic finding is high grade dysplasia. Although the finding of HGD does not necessarily imply that there is an underlying cancer, most studies have shown that this diagnosis is ignored at the patients' peril. Again, HGD may just represent a superficial part of an underlying malignancy rather than a field change in a premalignant colon, but around 50% of patients with high grade dysplasia have cancer at surgery.

A few observer variation studies concerning the grading of dysplasia in ulcerative colitis have been carried out with a general consensus that there is a significant degree of divergence. However, no study has compared the abilities of specialist gastrointestinal pathologists with generalists. Chapter eight details an inter-observer variation study directly comparing the ability of pathologists specializing in gastrointestinal pathology versus general pathologists to correctly grade dysplasia.

1.22 Markers to complement dysplasia.

There is a need to develop a better marker of malignancy in ulcerative colitis. To date full colonoscopy with multiple biopsies and a search for dysplastic change has been the only practical approach. However, dysplasia is not only insensitive, it is also nonspecific. The requirement is for a different measurement that provides a more accurate assessment of the likelihood of premalignancy within the colon.

1.22.1 Aneuploidy.

For this reason, new molecular markers to complement dysplasia have been sought. One such marker is aneuploidy which is the presence of excess DNA in a proportion of the cells. An abnormal quantity of DNA in the nucleus of colonic epithelial cells compared with the normal diploid amount in lymphocytes can be measured by flow cytometry (171,177) or microspectrophotometric analysis. (72) There is good correlation between the two methods of analysis but the latter is more time consuming.

The frequency of aneuploidy increases with the degree of histologic abnormality from non-neoplastic epithelium, through grades of dysplasia to carcinoma. (171) Different populations of aneuploid cells may be distinguished by the quantity of excess DNA in the cells at different sites in one colon. (171,177,178) Multiple populations of aneuploid cells tend to be associated with histologic dysplasia or carcinoma. (171) Each aneuploid type tends to remain constant with repeated sampling at the same site. (177) Aneuploidy may be found in the absence of dysplasia or carcinoma; less commonly dysplasia or carcinoma is found without aneuploidy. (171,177) There is evidence from follow-up studies that the area of aneuploidy tends to enlarge with time and an increasing number of different populations

appear. (177) Aneuploidy may precede dysplasia, (171,177) or be found simultaneously. (177)

The clinical importance of aneuploidy is that, when present without dysplasia, it is often an earlier marker of neoplastic change. When it occurs with indefinite or low grade dysplasia it adds a quantitative criterion which complements histologic assessment. Since dysplasia and aneuploidy do not always occur together, one type of observation does not replace the other. Aneuploidy can be detected in colonoscopic biopsies. Its usefulness as a clinical marker of precancerous change is being assessed and, though it cannot yet be regarded as a routine procedure, the data available are promising. (179-181)

1.22.2 Genetic abnormalities.

There is growing evidence that carcinoma in ulcerative colitis, like sporadic cancer, occurs in genetically unstable epithelium which accumulates gene mutations and / or deletions. It is possible that some patients have an inherited susceptibility to colorectal carcinoma and that this trait could be detected by examination of DNA obtained from a blood sample.

To be useful as a local clinical marker of premalignant potential in ulcerative colitis, gene structure or function must be identifiable in mucosal biopsies, brushings, or possibly lavage fluid or stool. Most of the experimental work to date has been done on colectomy specimens so as to yield sufficient material for analysis.

A promising marker of genetic change is the over expression of the protein p53 using immunohistochemistry techniques. Although less sensitive it correlates with molecular biologic techniques to detect allelic deletions, or point mutations of the p53 gene. Thus in colectomy specimens overexpression was observed in 16 of 20 dysplastic epithelia

adjacent to carcinomas and in 9 of 20 dysplastic masses remote from a carcinoma. (182) A recent study from Germany (183) looked at colonic lavage fluid and found that mutations in the p53 and Ki-*ras* genes were more frequent in patients with long standing ulcerative colitis (19%) than in control patients (3%) and concluded that the technique may be useful for screening for early malignancy in ulcerative colitis.

Two patients, one with high grade dysplasia and the other with indefinite dysplasia, have been studied at colonoscopy at which four large biopsies were taken at 10 cm intervals from around the circumference throughout the large bowel (36-90 per patient). After flow cytometry to separate aneuploid cells from diploid cells, the DNA was analyzed for loss of heterozygosity of the p53 gene, which was observed in 6 of 16 biopsies studied. (184) This technique is currently too complex for routine use.

Several other potential markers of malignancy are under active investigation. They include abnormal binding of lectin to the colonic epithelium (185,186) and specific antibodies directed against oncofetal and tumour associated antigens, such as CA 19-9, CA 50, CEA and TAG -72. (187-191) Studies also have examined mutational events associated with the neoplastic progression in ulcerative colitis. These investigations include analysis of mutation in oncogenes such as K-ras (192) and allelic deletion of tumour supressor genes, including APC, DCC and Rb. (184,193,194) Another promising marker is sialosyl-Tn antigen (STn), which can be identified immunohistochemically in archival specimens using monoclonal antibodies (McAb) TKH2. (195,196) McAb TKH2 reacts with the vast majority of sporadic colon cancers. This antibody does not react with normal colonic mucosa and binds only to approximately 11% of all surveillance colonoscopy biopsy specimens from patients with long-standing ulcerative colitis who have never manifested dysplasia. (197) In contrast, in ulcerative colitis patients who have developed cancer or

high grade dysplasia, more than 40% of all surveillance biopsy specimens reacted with McAb TKH2. (197) In addition, STn expression preceded dysplasia by several years (198) and often occurred in regions of the colon that subsequently developed cancer. Moreover, the interpretation of STn is not confounded by the presence of severe inflammation.

Further studies may help define the role of these and other promising markers in the management of ulcerative colitis patients undergoing surveillance. In future colonoscopic biopsies will increasingly be studied not only for dysplasia and aneuploidy, but also for genetic changes. A combination of markers, for example aneuploidy and loss of p53 heterozygosity, is likely to be more specific as a marker of precancer than either alone. (184)

An investigation into the potential of a further marker of dysplasia in ulcerative colitis - CYP1B1 was conducted. This is an iso-enzyme of cytochrome P450 and has been shown to be expressed in a range of human tumours (including colon) but not in normal tissue. (199) An account of its value as an additional marker of dysplasia is given in chapter nine.

Guide to the thesis.

In summary, there are many areas of controversy surrounding colorectal cancer in ulcerative colitis. The exact magnitude of the risk is uncertain, a single detailed study of all the risk factors thought to play a part in its development has not been conducted and the possible effect of patient knowledge on the cancer risk and early detection have not been assessed. There is no nationally accepted surveillance program and the current surveillance practices of gastroenterologists are unknown. The histological interpretation of dysplasia is fraught with inaccuracies and as yet there are no markers to complement dysplasia in routine use. The aims and justification for the studies carried out are described more fully in the course of the thesis, but briefly the aims were:-

- to determine as accurately as possible the risk of colorectal cancer in the ulcerative colitis population using new meta-analysis techniques (chapter 2)
- to study in further detail risk factors thought to play a part in the development of colorectal cancer in ulcerative colitis paying particular attention to pharmacotherapy (chapter 3).
- to establish the potential role of patient education on colorectal cancer risk (chapters 4 and 5).
- to investigate the most effective method of educating patients with ulcerative colitis about cancer risk and surveillance (chapter 6).
- to ascertain the current surveillance practice of gastroenterologists in the United Kingdom (chapter 7).
- to assess whether histological biopsies from surveillance colonoscopies should only be interpreted by histopathologists who specialise in gastrointestinal pathology (chapter 8).

- to investigate a new immunohistochemical marker for dysplasia in ulcerative colitis (chapter 9).

The final chapter (chapter 10) will summarise the main findings of the thesis and make recommendations for the future conduction of surveillance.

Chapter 2.

A meta-analysis determining the risk of colorectal cancer in ulcerative colitis.

2.1 Summary.

The risk of colorectal cancer (CRC) in patients with ulcerative colitis (UC) was estimated. A literature search using Medline together with the explosion of references identified 194 studies. Of these, 116 met the inclusion criteria from which a minimum amount of data (the number of patients and cancers detected) could be extracted. Overall pooled estimates, with 95% Confidence Intervals (CI), of cancer prevalence and incidence were obtained using a random effects model on either the log odds or log incidence scale as appropriate.

The overall prevalence of CRC in *any* UC patient, based on 116 studies, was estimated to be 3.7% (95% CI 3.2% to 4.2%). Of the 116 studies 41 reported the duration of colitis. From these the overall incidence rate was 3/1000 person-years duration (pyd), (95% CI 2/1000pyd to 4/1000pyd). The overall incidence rate for any child was 6/1000pyd (95%CI 3/1000pyd to 13/1000pyd). Of the 41 studies, 19 reported results stratified into 10 year intervals of disease duration. For the first ten years the incidence rate was 2/1000pyd (95% CI 1/1000pyd to 2/1000pyd), for the second decade the incidence rate was estimated to be 7/1000pyd (95% CI 4/1000pyd to 12/1000pyd), and in the third decade the incidence rate was 12/1000pyd (95% CI 7/1000pyd to 19/1000pyd). These incidence rates correspond to cumulative probabilities of developing CRC of 2% by ten years, 8% by twenty years and 18% by thirty years. The world-wide cancer incidence rates varied geographically being 5/1000pyd in the USA, 4/1000pyd in the UK and 2/1000pyd in Scandinavia and other countries. Over time the cancer risk has fallen since 1955, most markedly in Scandinavia.

Using new meta-analysis techniques the risk of CRC in UC was determined. The risk has been estimated by decade of disease and also defined in patients with pancolitis and in children. There has been a decrease in risk over time and the risk varied with geographical location.

2.2 Theoretical justification for this work.

Controversy surrounds the colorectal cancer risk in ulcerative colitis. Many studies have investigated this risk and reported disparate rates due to the different methodologies used in various studies. Although colorectal cancer in UC only accounts for 1% of all cases of CRC seen in the general population (137) it is a serious sequel of the disease and accounts for one sixth of all deaths in UC patients. (46) As a result it deserves our attention. Once the true cancer risk is known doctors will be in a better position to inform colitics and together with patients make evidence-based decisions on the need for surveillance and the screening interval.

2.3 Introduction.

Since colorectal cancer (CRC) was first recognised as a complication of ulcerative colitis (UC) by Crohn and Rosenberg in 1925 (48) a multitude of epidemiological studies have confirmed the increased risk. The exact magnitude of the risk remains controversial because of various biases and methodological errors in published studies. (151,152,154,200,201) To ascertain the size of the risk accurately would require a prospective cohort study based on all patients with ulcerative colitis in a defined geographic area. (65) However this is virtually impossible as in practice ascertainment of such cases is incomplete.

All studies, with the best of intentions, are susceptible to a number of biases. (200) Sackett and Whelan have outlined the methodological standards that should be met in order to define the real risk of colonic cancer in ulcerative colitis so that the data can be extrapolated to the individual patient and thus serve as a guide to their management. (154,202) They list six standards that should avoid eight of the most common biases. These include the correct formation of inception cohorts, an accurate description of the patients referral pattern, a high patient follow-up, a clear statement of the outcomes of the study, blind assessment and

adjustment for extraneous prognostic factors such as age, family history and treatment. When interpreting the observations from published studies one has to bear the following factors in mind: (151,203)

1 The number of years over which observations were recorded. Colorectal carcinoma in ulcerative colitis is unusual before patients have had the disease for ten years and consequently studies with shorter periods of follow-up are unlikely to detect high rates of colon cancer.

2 Series from referral centres are not representative of the general population. They are associated with an apparently increased risk of cancer as patients who are referred to a tertiary centre are often complicated, intractable or severe cases.

3 Some studies have included patients who were referred already having a diagnosis of cancer. In this situation one does not know the number of patients at risk from the referral base and therefore the incidence of cancer cannot be accurately estimated.

4 When patients have a colectomy, whether for cancer prophylaxis or medical reasons, they are no longer at risk of colonic carcinoma. Therefore if these patients are included in the analysis it will lead to an underestimate of the risk.

5 Obviously incomplete follow-up is far from ideal and if there is loss to follow-up of 10% of the original patient series the overall reliability of the data is a cause for concern.

6 It is desirable to have as many patients as possible in study groups. As patients are followed up for long periods their numbers naturally decline due to mortality from other causes and therefore when cumulative survival curves are based on small numbers rather than large populations, each cancer causes a disproportionate increase in probability, and, at the same time, the confidence limits of the curve widen to unacceptable levels. (204)

7 Life table analysis is believed to be the best method of assessing cancer risk in colitis (205) as it makes allowance for duration of follow up and the time at which a patient comes under observation. This is important in calculating at any point in time the 'effective number of patients at risk' of developing cancer. This method estimates the proportion of a population likely to develop carcinoma if that were the *only* factor leading to withdrawal during the period of follow up. It does not take into account patients who are withdrawn for other reasons, such as death from other causes and those who have a colectomy. Such patients never have the opportunity to develop cancer and so life table analysis can give the impression that the cancer risk is higher than it really is, especially in older age groups. In addition, different types of life table analysis can give different results. (57)

8 Many studies express cancer risk in terms of the ratio between observed and expected tumours. This relative risk is not an ideal method for young people as the number of expected colorectal carcinomas is very small and consequently any tumours reported in this age group would lead to an increased relative risk. Therefore it is preferable to compare patients with colitis of one age with that of another age, not with an external reference group (i.e. not with the general population).

9 The diagnostic methods for colorectal carcinoma have changed over the last thirty years. Prior to the 1960's single contrast barium enemas were the mainstay of diagnosis. During the early 1960's air contrast was introduced. Rigid sigmoidoscopy then became widely available and the 1970's saw the advent of fibreoptic endoscopy, including colonoscopy. It is important that published studies state the diagnostic method used to define the anatomic extent of disease as later techniques are much more sensitive. Several studies in the literature span this period and it is possible that patients initially assessed as having mild disease may actually have had more widespread involvement and therefore increased risk of cancer.

10 Lastly, several terms are used to express the extent of colitis. These include proctitis, left-sided colitis, substantial colitis, sub-total colitis and extensive colitis. Unfortunately authors interpret these terms differently and so there is obviously a need for standardisation of terminology.

Early estimates of CRC complicating UC were based on crude percentages and all were from major medical institutions, predominantly tertiary referral centres. These centres saw a greater proportion of patients who had more severe recalcitrant disease and also patients who had been referred *with* a diagnosis of cancer. These series were based on patients admitted to hospital and risks were related to the hospital population rather than the larger population of the host community. These and other factors led to an initial over reporting of cancer risk. Later population based studies covered defined geographical areas and aimed for complete case ascertainment. These studies are superior with respect to methodological standards and lean to more conservative risk estimates. However, population based centres probably include more patients with limited disease and therefore may under estimate the risk.

There is a general consensus from all studies that the CRC risk is highest in those with extensive disease of long duration. There is less certainty about how the risk may vary with geographical location. The reported world-wide variations may represent true differences relating to genetic or environmental factors. However, again the methodologies employed lacked uniformity and consequently it is not surprising that the CRC risk has been reported to be as low as 1.4% at 18 years (42) and as high as 34% after 25 years of disease.(206)

The aim of this meta-analysis is to give an overall estimate of the risk in all patients with UC by decade, define the risk for children and those with extensive colitis and give CRC incidence rates by country where possible. The meta-analysis accounts for variations in methodologies employed in different studies and considers the effects of high colectomy rates and inadequate follow-up.

2.4 Methods.

The meta-analysis was conducted according to the guidelines produced by the NHS Centre for Reviews and Dissemination at York University (207).

Identification of Primary Studies:

All published reports citing the risk of CRC in UC were collected by conducting a literature search on MEDLINE using the following keywords: colorectal cancer, ulcerative colitis, surveillance studies, dysplasia, risk factors and children. A comprehensive search of reference lists of all review articles and of the retrieved original studies was performed to find studies not identified by the MEDLINE search. This identified 194 independent studies dating back to 1925.

Inclusion and Exclusion Criteria:

English language articles were included where there was a clear definition of the population of patients being studied and where the criteria for diagnosing UC and CRC, along with their outcomes, were well described. Studies citing cancer mortality statistics (not cancer incidence) were excluded as this is not a true representation of cancer incidence. Also reports that obviously combined patients with UC and Crohn's disease in a common analysis were excluded. Where two or more publications from one institution appeared to include the same patients over a similar time period; only one was included in the analysis. (The publication covering the longest time period and containing the greatest amount of information was chosen).

Data Extraction:

Each paper was read, critically reviewed and examined for the quality of evidence presented. The following characteristics were extracted for each study using a predefined review form:-

1. Country of origin.
2. Type of centre conducting the study and study design.
3. Period over which the study was conducted.
4. Number of patients in the study.
5. Number of patients with total and left-sided colitis in the study.
6. Numbers who developed colorectal cancer (and whether they had total or left-sided colitis).
7. Whether referred cancers were included in the analysis.
8. The duration of follow-up of each study.
9. The ages of patients at time of onset of UC.
10. The ages of patients at the time of cancer diagnosis.

11. The duration of colitis at cancer diagnosis.

12. The number of patients in the study undergoing panproctocolectomy / partial colectomy.

13. The cumulative cancer incidence (if reported).

14. The relative cancer risk (if reported).

15. The number of patients followed up.

Studies that were suitable for inclusion (from which a minimum data set of number of patients and number of cancers detected could be extracted) were placed in one of three categories:

1. Crude cancer prevalence only reported.
2. Cancer incidence and duration of patient follow-up reported.
3. Cancer incidence stratified by decade and duration of patient follow-up reported.

Statistical Analysis:

All analyses were performed using Stata statistical software and macros for conducting meta-analyses. (208-210) Overall pooled estimates, together with 95% Confidence Intervals (CI), of the prevalence and incidence of CRC were obtained using a random effects model on either the log odds or log incidence scale as appropriate (211) (Appendix 1). Changes in the log incidence rate over time were assessed using mixed effects meta-regression techniques. (212) The size of the circles in figures 2.4, 2.5 and 2.6 are inversely proportional to the variance associated with the estimate of the log incidence rate in each study and the regression line was estimated using mixed effects meta-regression techniques. In addition to estimating the magnitude of the CRC risk in UC, and how that risk varies temporally, sub-group analyses were performed in order to explore between-study heterogeneity.

Where possible the actual observed number of cases of CRC and the person years duration (pyd) of follow-up were extracted from papers. When only the number of cases of CRC and cumulative probabilities were reported, pyd was calculated (Appendix 1). (213) If a study did not find any cases of cancer throughout its duration a small number (0.5) was used to allow a calculation to be performed.

2.5 Results.

194 studies were identified. Of the 194 studies, five reported cancer mortality data (46,214-217), ten did not give details concerning the background population (218-227), two included patients with Crohn's disease (174,228), four were reviews only, (229-232) 26 were updated by subsequent studies (7,42,45,50,58,124,126,142,147,149,233-248) and 31 overlapped with other studies or included the same patients (62,67,148,157,245,249-274). This left 116 studies suitable for inclusion in the analysis (36,52-57,59-61,64,66,69-71,73,123,131,133,136-138,143-146,155-159,206,275-358). The data extracted for each of these studies are listed in Appendix 2.

Overall Analysis.

Overall 54,478 patients were studied and a total of 1,698 colorectal cancers were detected. 9,846 patients had total colitis amongst whom 700 cancers were found. Fifty four studies (with 22,730 patients and 844 cancers) included data on age at cancer diagnosis with a mean of 43.2 years (95% CI 40.5yrs to 45.9yrs) and 61 studies reported the duration of colitis at cancer diagnosis with a mean of 16.3 years (95% CI 15.0yrs to 17.6yrs). There were 75 studies in category 1, 22 in category 2 and 19 in category 3 (page 94). Table 2.1 summarises the characteristics of the included trials by category. In the analyses that follow all studies were not given equal weighting, but were weighted proportionally to the number of cases of cancer that were included in the study.

Considering the overall prevalence of CRC in any patient with UC, based on the total 116 studies, a chi squared test for heterogeneity yielded $X^2=799.1$, $p<0.0001$ and therefore a random effects model produced an overall pooled estimate of the prevalence to be 3.7% with

95% CI 3.2% to 4.2%. Of the 116 studies, 35 included adequate data on patients with total colitis to calculate the prevalence in this group. In these 35 studies there were 8,351 patients with pancolitis and 451 cases of cancer. The X^2=127.5, p<0.0001 and a random effects model produced an overall pooled estimate of the prevalence to be 5.4% with 95% CI 4.4% to 6.5%.

Analysis of Studies Reporting Duration of Colitis (Categories two and three).

Of the 116 studies, 41 reported duration of colitis (Table 2.2). From these studies the overall incidence rate of CRC for any patient with colitis was 3 per 1000 person-years duration (pyd), with 95% CI 2/1000pyd to 4/1000pyd. The corresponding annual incidence rate of colorectal cancer in the general population given by the Office of National Statistics is 0.6 per 1000 population. (359) As 21 of the 41 studies did not report the cancer rates at ten year intervals (and simply gave an overall risk) it had to be assumed that the cancer risk, in terms of the log incidence rate, remained constant over time. The cumulative probabilities based on this unstratified data gave a risk of 3% (95%CI=2.2% to 3.8%) at 10 years, 5.9% (95%CI=4.3% to 7.4%) at 20 years and 8.7% (95%CI=6.4% to 10.9%) at 30 years (Figures 2.1 and 2.2).

Table 2.1. Characteristics of Studies Included

		♣Category 1 (n=75)*	♣ Category 2 (n=22) #	♣ Category 3 (n=19) ∝
Study design	Referral centre	55	11	8
	Surgical series	14	-	3
	Surveillance program	3	6	2
	Population / inception cohort	2	5	6
	Private practice	-	-	1
	Histology series	1	-	
Retrospective		70	11	12
Referred cancers included	Yes	10	1	1
	Missing data	41	3	5
Country	USA	41	7	4
	UK	8	4	7
	Scandinavia	12	6	3
	Other	14	5	5
Surgical intervention rate	(standard deviation)	22% (19.5) 38 studies	24.7% (15.0) 20 studies	25.1% (20.8) 12 studies
Pan-proctocolectomy rate	(standard deviation)	10.7% (20.0) 22 studies	9.1% (8.6) 7 studies	16.4% (19.0) 7 studies

*References(52,53,73,123,133,136-138,144,155-157,276-278,281,283-290,292-297,299,301,302,304,305,307-309,311-313,316,317,320-322,324,325,327,329-332,334,335,337-339,342-345,347-358)

#References(54,59,69,131,143,145,146,158,275,280,282,291,298,300,306,314,315,318,319,323,326,328,333)

∝ References (36,55-57,60,61,64,66,70,71,159,206,279,303,310,336,340,341,346)

♣Category 1 = Crude cancer prevalence only reported.
♣Category 2= Cancer incidence and duration of patient follow-up reported.
♣Category 3=Cancer incidence stratified by decade and duration of patient follow-up reported.

Table 2.2. 41 Studies Reporting Duration of Colitis (for key see page 100)

Ref.	First Author	# pts	#ca	Surgery (%)	Person Years Duration (pyd)	Point Estimate of Cancer Incidence/1000 pyd	95% Confidence Interval /1000 pyd	Follow up (%)
(300)	Gilat	504	3	7.1	3800.16	0.8	0.3 to 2.4	N/S
(54)	Langholz	1161	6	20.2	13583.7	0.4	0.2 to 0.98	99.9
(326)	Mellemkjaer	5,546	42	N/S	32721.4	1.3	0.9 to 1.7	N/S
(323)	MacDougall	637	15	37.2	5096	2.9	1.8 to 4.9	98.6
(158)	Jonnson	131	4	12.2	1152.8	3.5	1.3 to 9.2	90
(275)	Aktan	60	0	23.3	126	3.97	0.2 to 63.4	N/S
(69)	Kvist	759	17	39	7286.4	2.3	1.5 to 3.8	100
(306)	Hijmans	43	0	11.6	107.5	4.7	0.3 to 74.4	100
(131)	Connell	332	20	16.9	2490	8.0	5.2 to 12.4	96.3
(282)	Biasco	65	6	21.5	383.5	15.6	7.0 to 34.8	80
(333)	Radhaksrish	108	0	2.8	388.8	1.3	0.1 to 20.6	N/S
(145)	Lofberg	72	2	16.7	1483.2	1.3	0.3 to 5.4	97.2
(146)	Lynch	180	1	12.8	702	1.4	0.2 to 10.1	91.7
(280)	Banks	245	9	34.3	2964.5	3.0	1.6 to 5.8	99.7
(318)	Lanfranchi	122	1	15.5	353.8	2.8	0.4 to 20.1	N/S
(298)	Flood	148	1	N/S	429.2	2.3	0.3 to 16.5	88.5
(143)	Lashner	99	8	32.3	1683	4.8	2.4 to 9.5	91
(319)	Lashner	98	6	47	1685.6	3.6	1.6 to 7.9	100
(291)	Dennis	269	15	56.1	1102.9	13.6	8.2 to 22.6	N/S
(328)	Mirmadjlessi	112	1	8.9	492.8	2.0	0.3 to 14.4	N/S
(314,315)	Korelitz	121	9	47.1	2783	3.2	1.7 to 6.2	89.3

Ref.	First Author	# pts	#ca	Surgery (%)	Person Years Duration (pyd)	Point Estimate of Cancer Incidence/1000 pyd	95% Confidence Interval /1000 pyd	Follow up (%)
(59)	Mirmadjlessi	1160	82	30.5	16704	4.9	3.95 to 6.1	100
(56)	Greenstein	267	26	N / S	2189.4	11.9	8.1 to 17.4	97
(61)	Gyde	823	35	40	22632.5	1.5	1.1 to 2.2	97
(206)	Kewenter	234	15	66	1989	7.5	4.5 to 12.5	N / S
(66)	Edwards	624	22	N / S	7051.2	3.1	2.1 to 4.7	N / S
(55)	de Dombal	465	8	N / S	1395	5.7	2.9 to 11.5	100
(36)	Prior	676	35	64.8	10680.8	3.3	2.4	4.6 95.7
(341)	Stonnington	182	3	15.4	2548	1.2	0.4 to 3.7	96
(71)	Maratka	959	6	15.2	11124.4	0.5	0.3 to 1.2	N / S
(57)	Katzka	258	6	12.4	1986.6	3.0	1.4 to 6.7	95.7
(57)	Johnson	1,435	63	N / S	28700	2.2	1.7 to 2.8	100
(60)	Ekbom	3,117	91	12	93510	0.97	0.8 to 1.2	100
(64)	Lennard-Jones	401	22	24.7	4050.1	5.4	3.6 to 8.2	98
(70)	Gilat	1035	26	8.7	11902.5	2.2	1.5 to 3.2	100
(340)	Stewenius	462	9	N / S	6699	1.3	0.7 to 2.6	98%
(159)	Rozen	154	4	13.6	1617	2 .5	0.9 to 6.6	100
(346)	Thorlakson	182	12	N / A	1365	8.8	5.0 to 15.5	100
(336)	Russell	272	11	N / S	1768	6.2	3.4 to 11.2	N / S
(279)	Baker	374	22	7	6993.8	3.1	2.1 to 4.8	96.5
(303)	Grundfest	84	4	21.4	1327.2	3.0	1.1 to 8.0	94

N / S = Not Stated
N / A = Not Applicable
#pts = Number of patients in the study
#ca = Number of cancers detected

Figure 2.1. Overall Incidence Of Colorectal Cancer (with 95% Confidence Intervals) For Any Patient With Ulcerative Colitis.

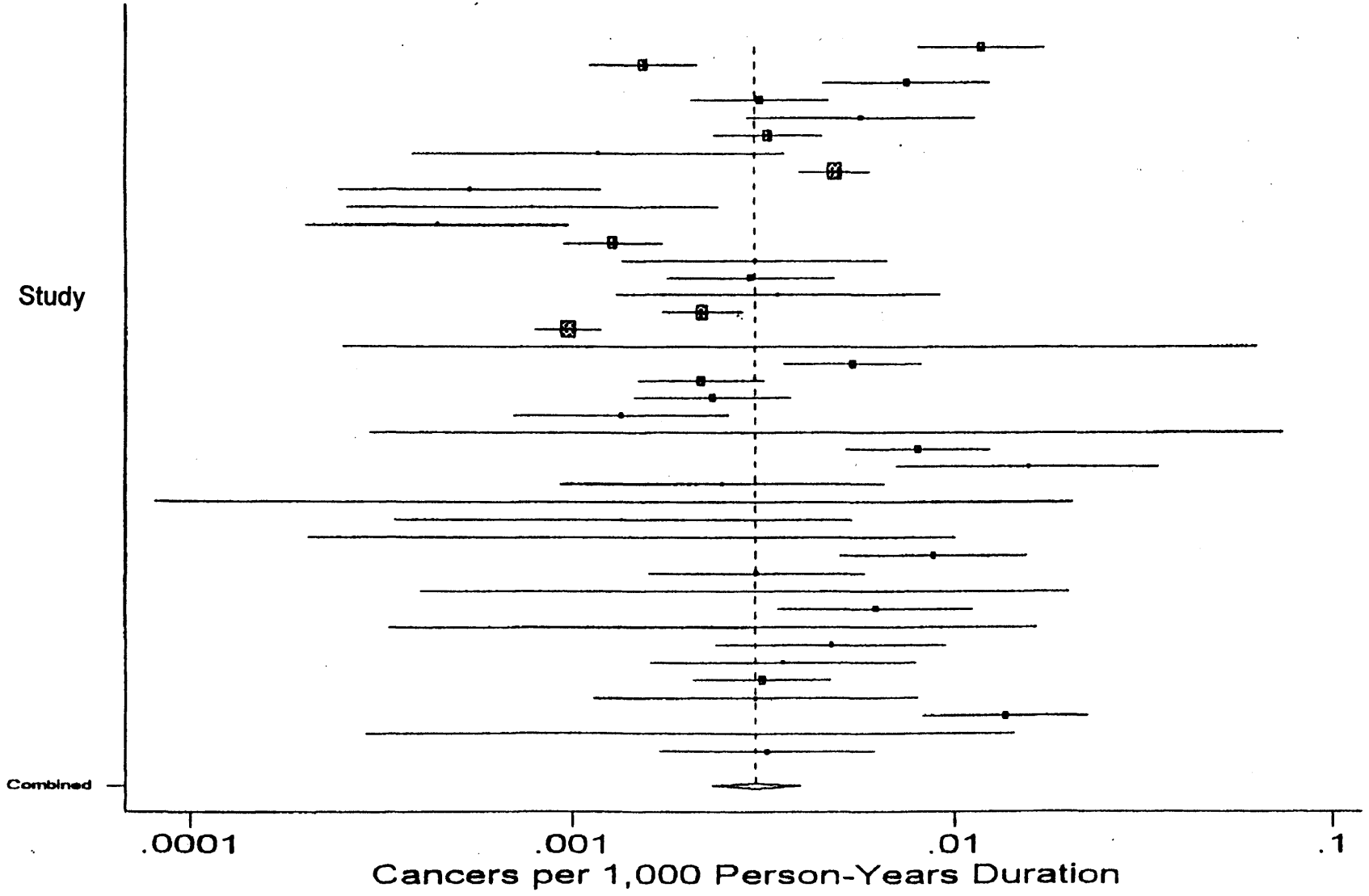
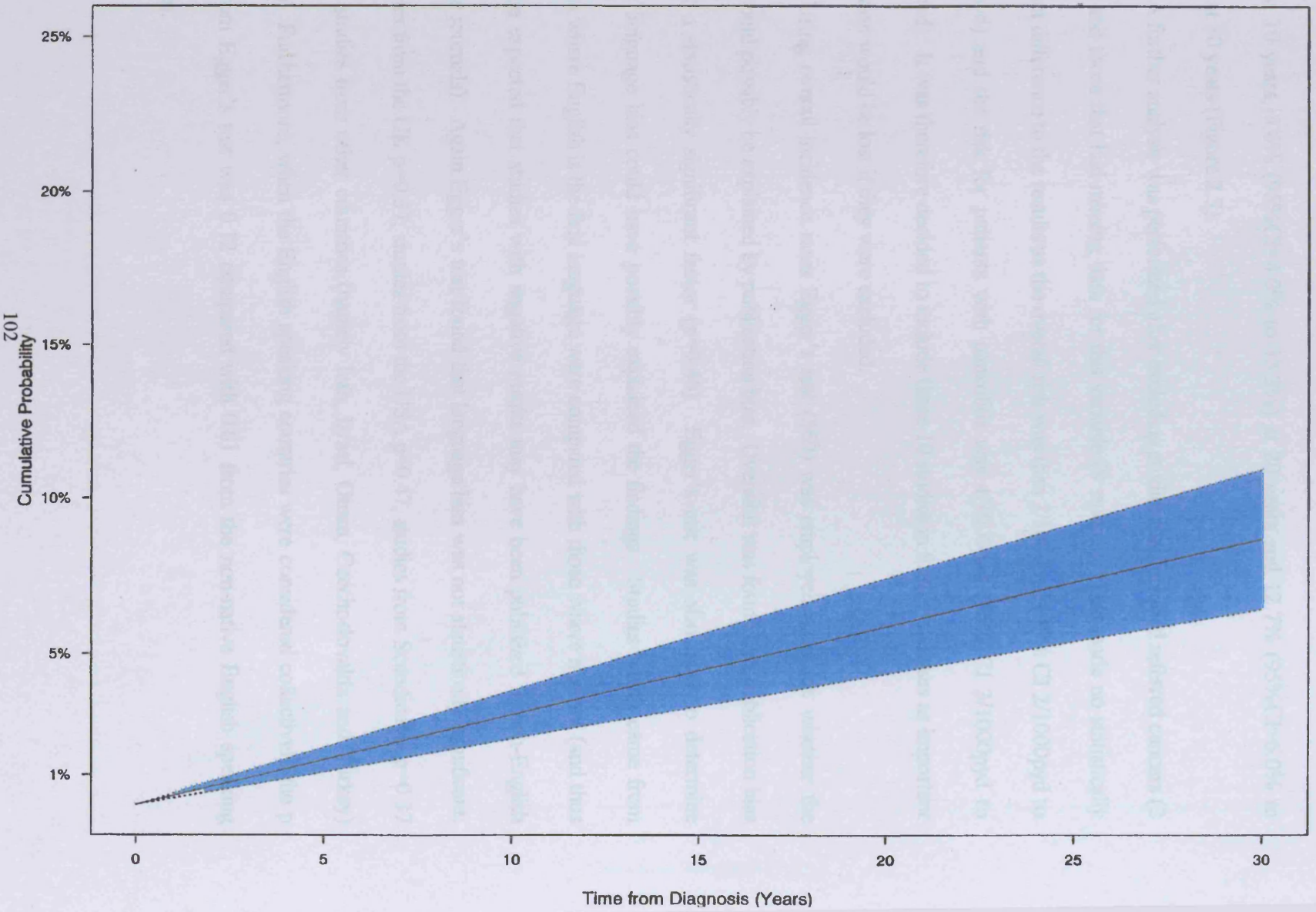


Figure 2.2. Cumulative Risk Of Developing Colorectal Cancer (With 95% Confidence Intervals) For Any Patient With Ulcerative Colitis Based on Unstratified Data (n=41).

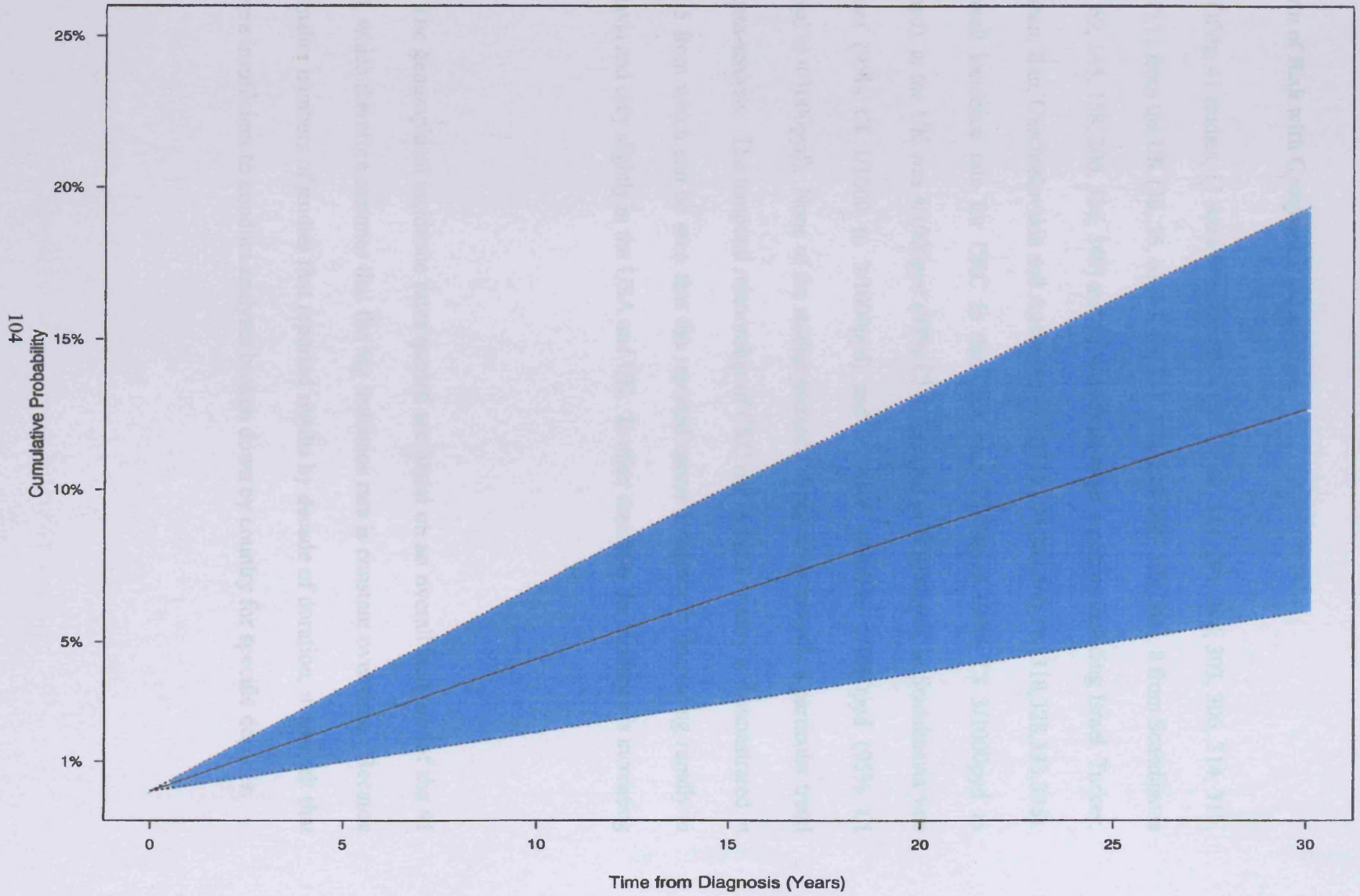


Twenty six studies in categories two and three reported data for patients with total colitis and in this group the incidence rate of CRC was 4 per 1000pyd, with 95% CI 3/1000pyd to 6/1000pyd. The unstratified cumulative probabilities give a risk of 4.4% (95%CI=2.0% to 6.8%) at 10 years, 8.6% (95%CI=4.0% to 13.3%) at 20 years and 12.7% (95%CI=6.0% to 19.3%) at 30 years (Figure 2.3).

A further analysis was performed after excluding studies that included referred cancers (2 studies) and those that had missing data for this variable (8 studies). This made no statistically significant difference to the results as the overall risk was then 2/1000pyd (95% CI 2/1000pyd to 3/1000pyd) and the risk for patients with pancolitis was 4/1000pyd (95% CI 3/1000pyd to 5/1000pyd). It was therefore decided to include these 10 studies in further analyses as important information would be lost if they were excluded.

Using overall incidence rates Egger's test (360) was employed to check whether the results could possibly be explained by publication bias. Overall it was found that publication bias was not a statistically significant factor (p=0.46). Egger's test was also used to determine whether language bias could have possibly explained the findings. Studies which came from countries where English is the first language were compared with those where it is not (and thus it may be expected that studies with negative results may have been published in non-English language journals). Again Egger's test found that language bias was not statistically significant: for studies from the UK p=0.37, studies from the USA p=0.47, studies from Scandinavia p=0.37 and for studies from other countries (namely Iran, Israel, Oman, Czechoslovakia and Turkey) p=0.90). Furthermore, when the English speaking countries were considered collectively the p value from Egger's test was 0.72 compared with 0.61 from the non-native English speaking countries.

Figure 2.3. Cumulative Risk Of Developing Colorectal Cancer (With 95% Confidence Intervals) In Pancolitis Based on Unstratified Data (n=26).



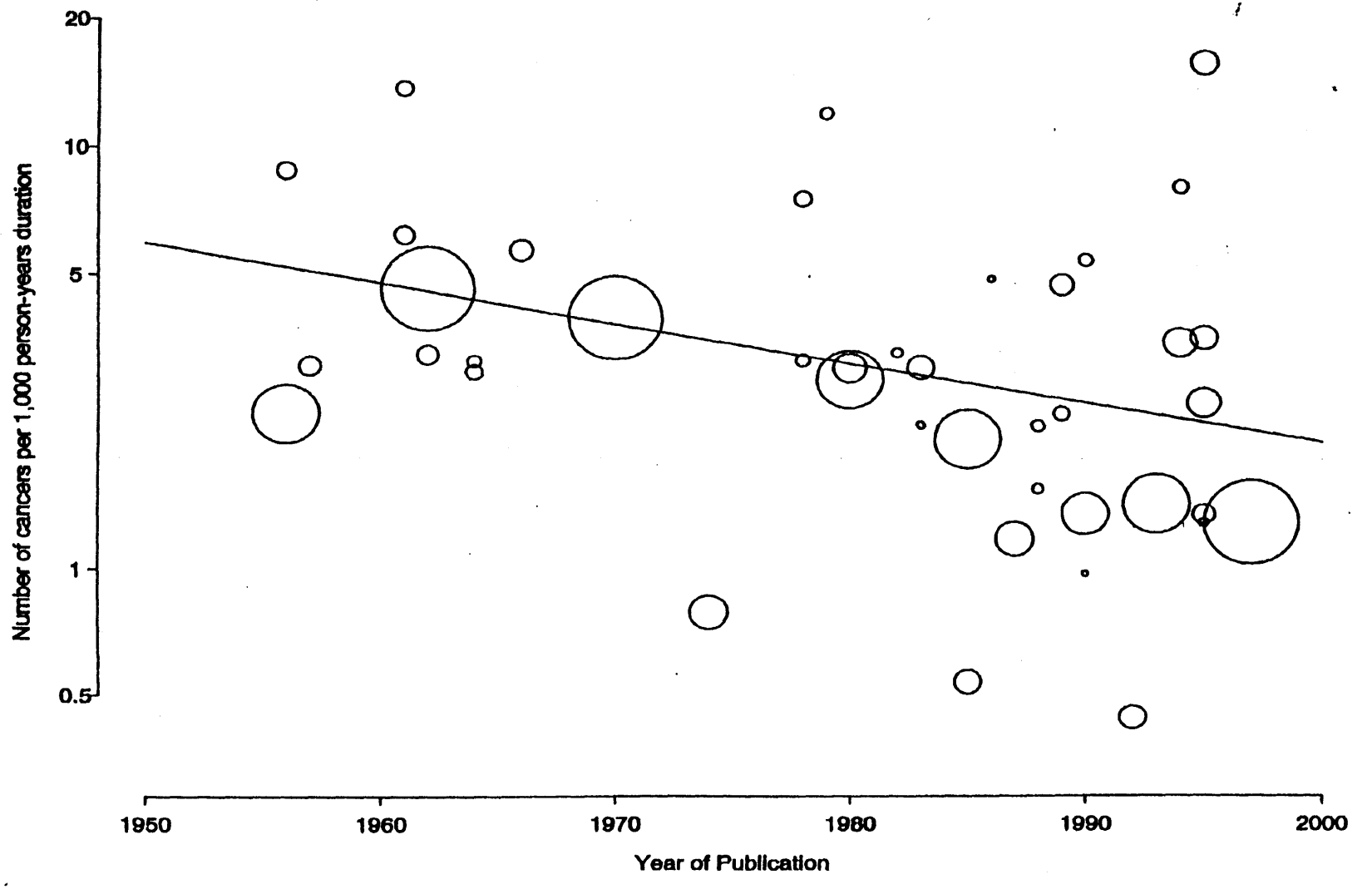
When the cancer risk for all 41 studies was plotted against the year of publication (Figure 2.4) it was seen that the reported cancer incidence has fallen from 1955 to the present day.

Variation of Risk with Geographical Location.

Of the 41 studies, 11 were from the USA (56, 57,59, 143, 291, 298, 303, 306, 314, 315, 319, 341),11 from the UK (36, 55, 61, 64, 66, 131, 146, 279, 280, 323,346), 8 from Scandinavia (54, 60, 69, 145, 158, 206, 326, 340) and 11 were from other countries including Israel, Turkey, Italy, Oman, Iran, Czechoslovakia and Australia (70,71,159,275,282,300,310,318,328,333,336). The overall incidence rate for CRC in the USA was 5/1000pyd (95% CI 3/1000pyd to 7/1000pyd), in the UK was 4/1000pyd (95% CI 3/1000pyd to 5/1000pyd), in Scandinavia was 2/1000pyd (95% CI 1/1000 to 3/1000pyd) and in other countries 2/1000pyd (95% CI 1/1000pyd to 4/1000pyd). None of the studies exerted a strong drive towards a particular trend in the meta-analysis. The temporal relationship of CRC risk in each country is demonstrated in figure 2.5 from which can be seen that the reported cancer incidence is decreasing rapidly in Scandinavia and only slightly in the USA and UK. In other countries the incidence is increasing slowly.

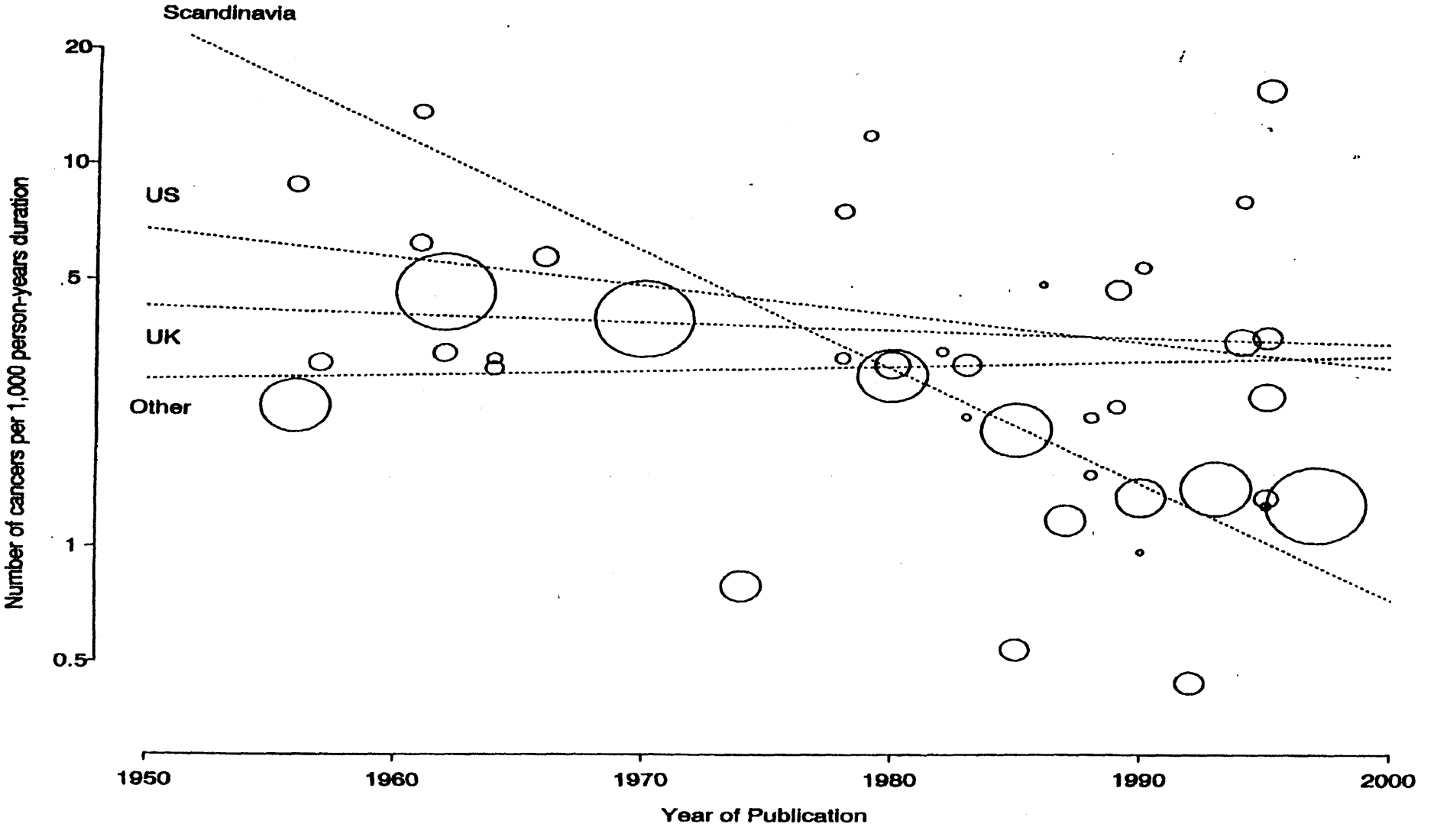
The geographical incidence rates quoted are based on an overall analysis (of the 41 studies), which therefore assumes that the log incidence rate is constant over time. Because of the smaller numbers of studies that reported results by decade of duration, it was felt that these were insufficient to conduct analyses broken down by country for specific decades.

Figure 2.4. Temporal Variation In Overall Cancer Incidence.



The circles represent an individual study; the sizes of which are directly proportional to the number of patients in the study.

Figure 2.5. Temporal Variation in Cancer Incidence by Geographical Location.

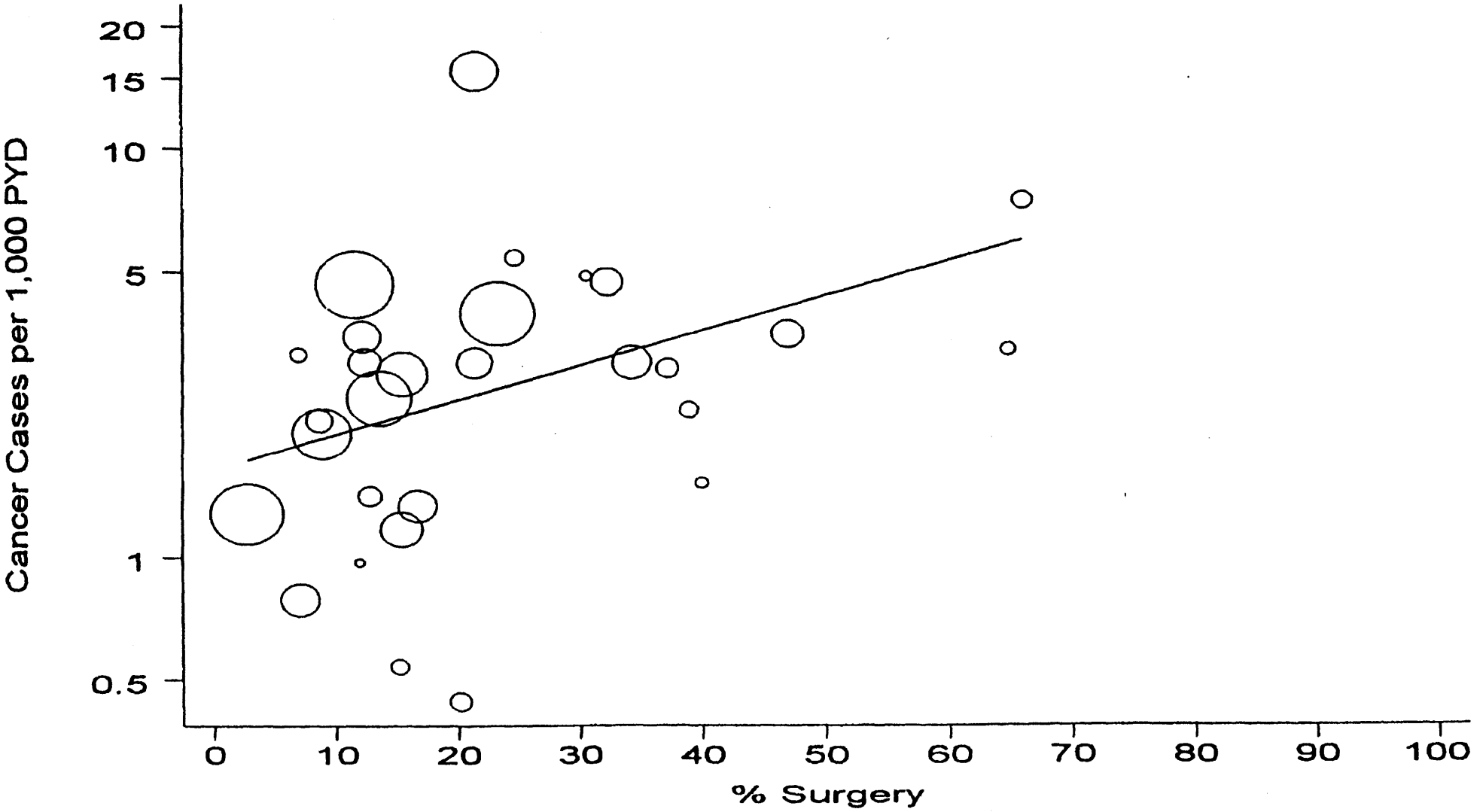


The circles represent an individual study; the sizes of which are directly proportional to the number of patients in the study.

Variation of Risk with Colorectal Surgery.

Panproctocolectomy (PPC) rate alone did not exert a statistically significant effect on the CRC risk ($Z=0.4$, $p=0.7$). When all forms of surgery were considered (PPC + resections of varying degree) it can be seen from figure 2.6 that reported CRC incidence rate increases with higher rates of surgical intervention.

Figure 2.6. Colorectal Cancer Incidence Increases With Higher Rates Of Surgical Intervention.



The circles represent an individual study; the sizes of which are directly proportional to the number of patients in the study.

Analysis of Studies Reporting Risk Stratified Into Ten Year Intervals (Category three).

Of the 41 studies, 19 reported results at ten yearly intervals of disease duration (Table 2.3). From these studies it was possible to estimate how the CRC risk increased with increasing duration of disease and thus stratify the results at ten year intervals. For the first ten years duration the overall incidence rate was 2/1000pyd (95% CI 1/1000pyd to 2/1000pyd), whilst for the second decade of disease the overall incidence rate was estimated to be 7/1000pyd (95% CI 4/1000pyd to 12/1000pyd) and in the third decade of disease the incidence rate was estimated to be 12/1000pyd (95% CI 7/1000pyd to 19/1000pyd). See figures 2.7-2.9. These decade specific incidence rates correspond to a cumulative risk of 1.6% (95%CI=1.2% to 2%) by ten years, 8.3% (95%CI=4.8% to 11.7%) by twenty years and 18.4% (95%CI=15.3% to 21.5%) by thirty years (Figure 2.10).

Table 2.3. 20 Studies Reporting Cancer Incidence at 10 Year Intervals (for key see page112)

Ref.	First Author	# pts	#ca	Cumulative cancer incidence at 10 years				Cumulative cancer incidence at 20 years				Cumulative cancer incidence at30 years			
				#ca	pyd	incid	95%CI	#ca	pyd	incid	95%CI	#ca	pyd	incid	95%CI
(56)	Greenstein	267	26	1	1335	0.8	0.1 to 5.3	8	540	14.8	7.4 to 29.6	7	220	31.9	15.2 to 66.8
(61)	Gyde	823	35	8(t)	3980	2.0	1.0 to 4.0	12(t)	2295	5.2	3 to 19.2	9(t)	725	12.4	6.5 to 23.9
(206)	Kewenter	234	15	3(t)	1398	2.2	0.7 to 6.7	9(t)	429	21.0	10.9 to 40.4	2(t)	73	27.5	6.9 to 109.7
(66)	Edwards	624	22	5	1046	4.8	2.0 to 11.5	11	498	22.1	12.2 to 39.9	6	109	55.1	24.8 to 122.6
(55)	deDombal	465	8	1	1027	0.98	0.14 to 6.9	3	211	14.3	4.6 to 44.1	4	138	29.1	10.9 to 77.3
				1(t)	282	3.5	0.5 to 25.2	2(t)	101	19.8(t)	5 to 79.2	4(t)	69	58 (t)*	21.8 to 154.5
(36)	Prior	676	35	2	1043	1.9	0.5 to 7.7	18	5910	3.0	1.9 to 4.8	12	688	17.5	9.9 to 30.7
(341)	Stonnington	182	3					3	2500	1.2	0.4 to 3.7				
(71)	Maratka	959	6	0	6731	0	-	3	2900	1	0.3 to 3.2	2	1105	1.8	0.5 to 7.2
				0(t)	2151	0.2	0.01 to 3.7	2(t)	925	2.2 (t)	0.5 to 8.6	2(t)	396	5.1 (t)	1.3 to 20.2
(57)	Katzka	258	6	1	393	2.6	0.4 to 18.0	3	1758	1.7	0.6 to 5.3	3	1499	2.0	0.6 to 6.2
				0(t)	145	3.4	0.2 to 55.1	2(t)	717	2.8	0.7 to 11.2	2(t)	980	2.0	0.5 to 8.2
(310)	Johnson	1,435	63	12	11939	1.0	0.6 to 1.8	34	6629	5.1	3.7 to 7.2	15	1590	9.4	5.7 to 15.7
(60)	Ekbom	3,117	91	34	21685	1.6	1.1 to 2.2	20	9335	2.1	1.4 to 3.3	27	3184	8.5	5.8 to 12.4
(64)	Lennard-Jones	401	22	0	1406	0	-	11	1512	7.3	4.0 to 13.1	11	1130	9 7	5.4 to 17.6
(70)	Gilat	1035	26	2	3895	0.5	0.1 to 2.1	11	198	55.6	30.8 to 100.4	7	100	70.1	33.4 to 147
(340)	Stewenius	462	9	3	877	3.4	1.1 to 10.6	5	1070	4.7	2 to 11.2	1	164	6.2	0.9 to 43.3
				2(t)	648	3.1	0.8 to 12.3	4(t)	791	21(t)	10.9 to 40.3	1(t)	247	27.4(t)	6.9 to 110
(159)	Rozen	154	4	1	1232	0.8	0.1 to 5.8	2	605	3.3	0.8 to 13.2	1	210	4.8	0.7 to 33.8
(346)	Thorlakson	182	12	3	1140	2.6	0.9 to 8.2	9	230	39.2	20.4 to 75.3				

Ref.	First Author	# pts	#ca	Cumulative cancer incidence at 10 years				Cumulative cancer incidence at 20 years				Cumulative cancer incidence at30 years			
				#ca	pyd	incid	95%CI	#ca	pyd	incid	95%CI	#ca	pyd	incid	95%CI
(336)	Russell	272	11	1	1160	0.9	0.1 to 6.1	10	200	50.1	26.9 to 93				
(279)	Baker	374	22	0	3534	0	-	13	2400	5.4	3.1 to 9.3	7	803	8.7	4.2 to 18.3
(303)	Grundfest	84	4	0	769	0	-	2	412	4.9	1.2 to 19.4	1	116	8.7	1.2 to 61.2

N / S = Not Stated
N / A = Not Applicable
#pts = Number of patients in the study
#ca = Number of cancers detected
pyd = Person years duration
incid = Cumulative cancer incidence/1000pyd
95%CI = 95% Confidence Interval/1000pyd
(t) = Total colitis

Figure 2.7. Overall Incidence Of Colorectal Cancer (With 95% Confidence Intervals) For Any Patient With Ulcerative Colitis After Ten Years Of Disease.

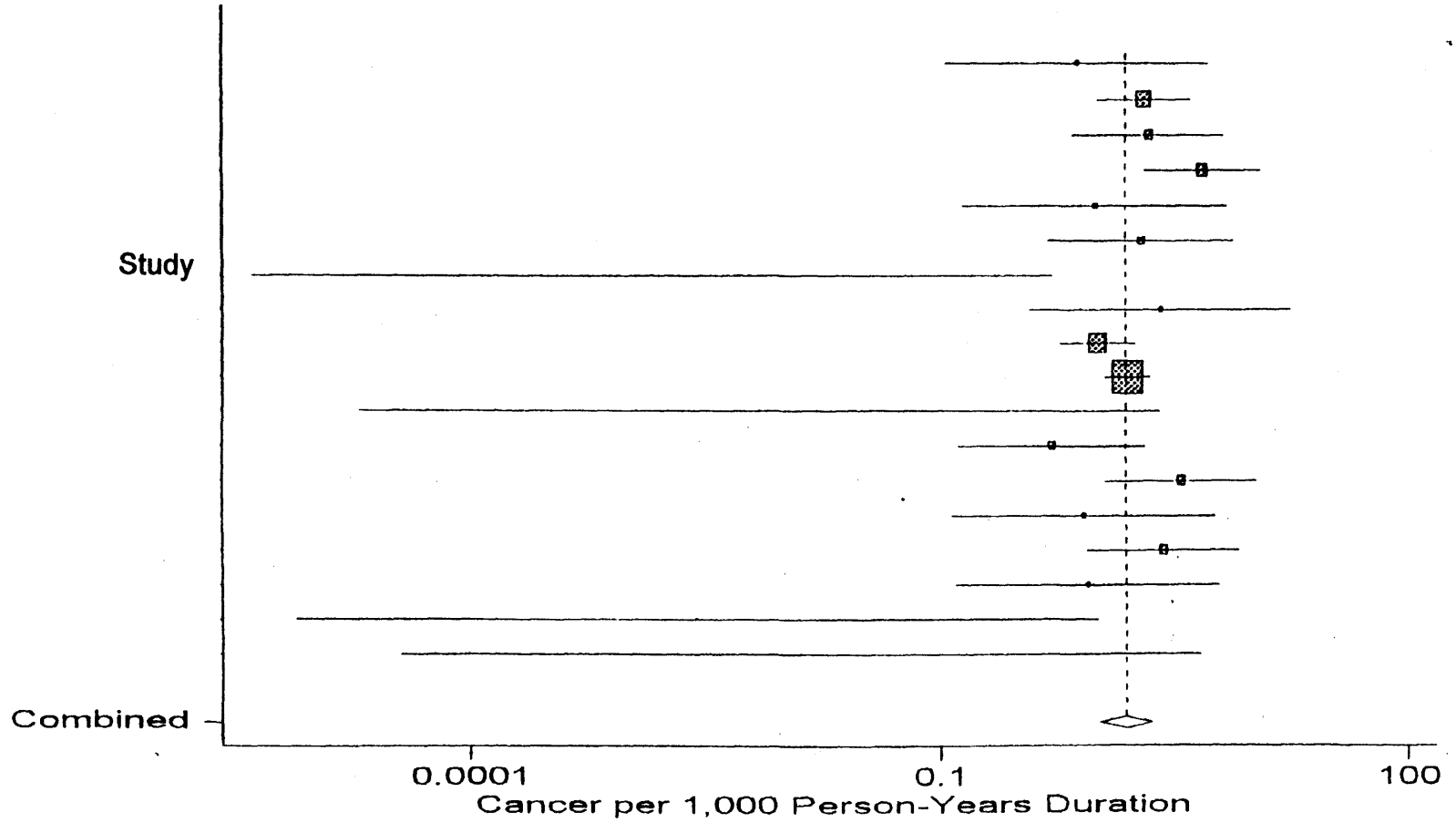


Figure 2.8. Overall Incidence Of Colorectal Cancer (With 95% Confidence Intervals) For Any Patient With Ulcerative Colitis After Twenty Years Of Disease.

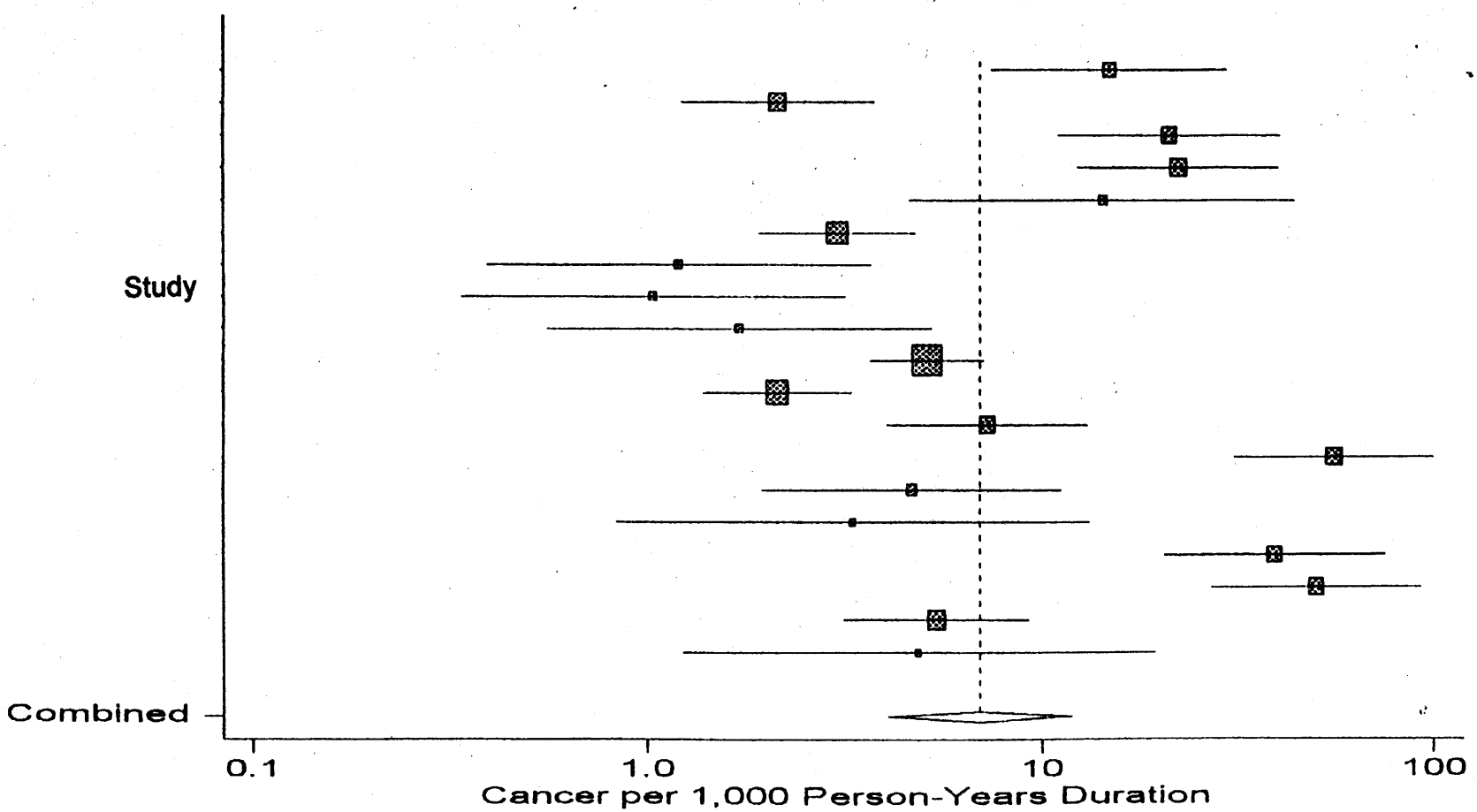


Figure 2.9. Overall Incidence Of Colorectal Cancer (With 95% Confidence Intervals) For Any Patient With Ulcerative Colitis After Thirty Years Of Disease.

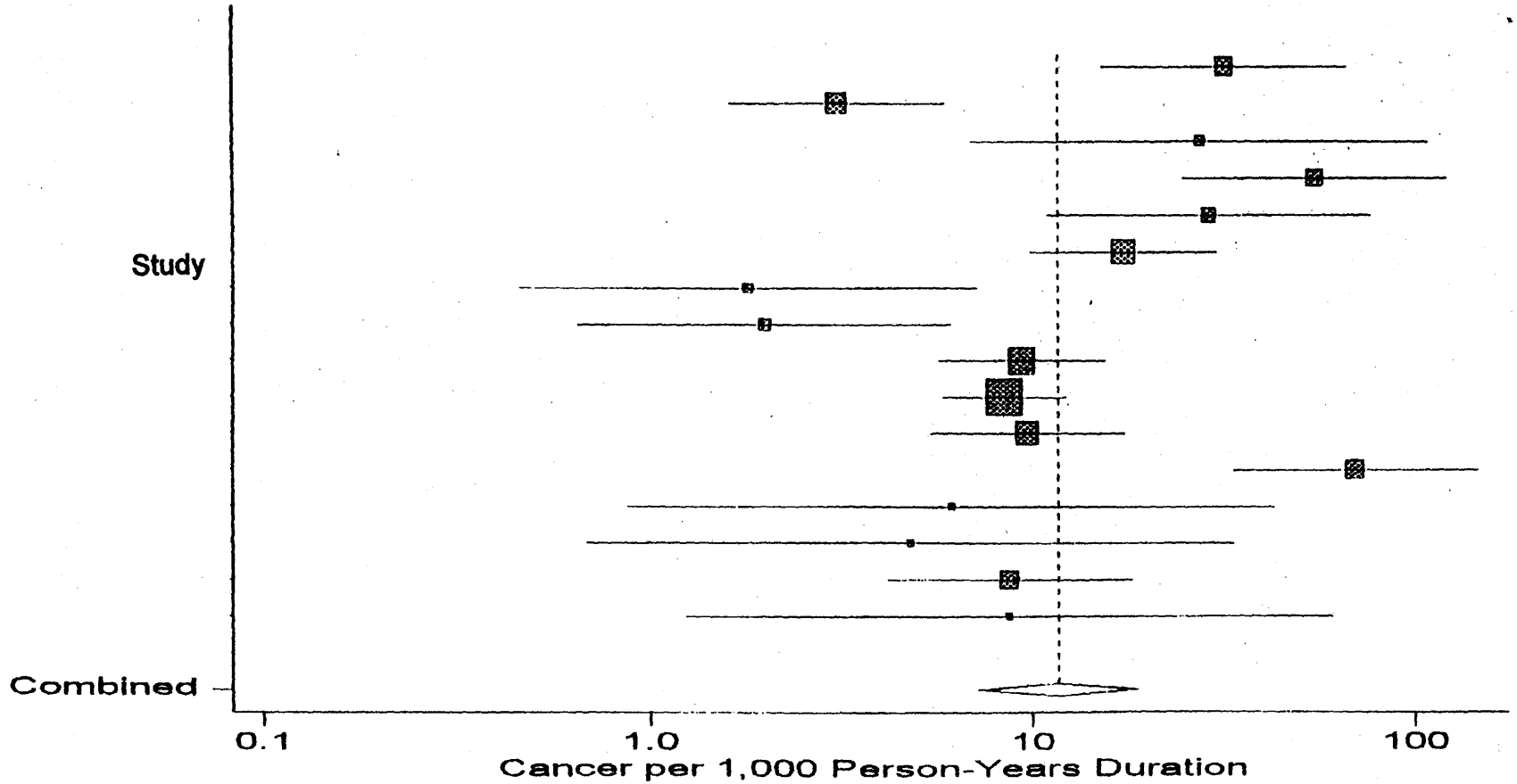
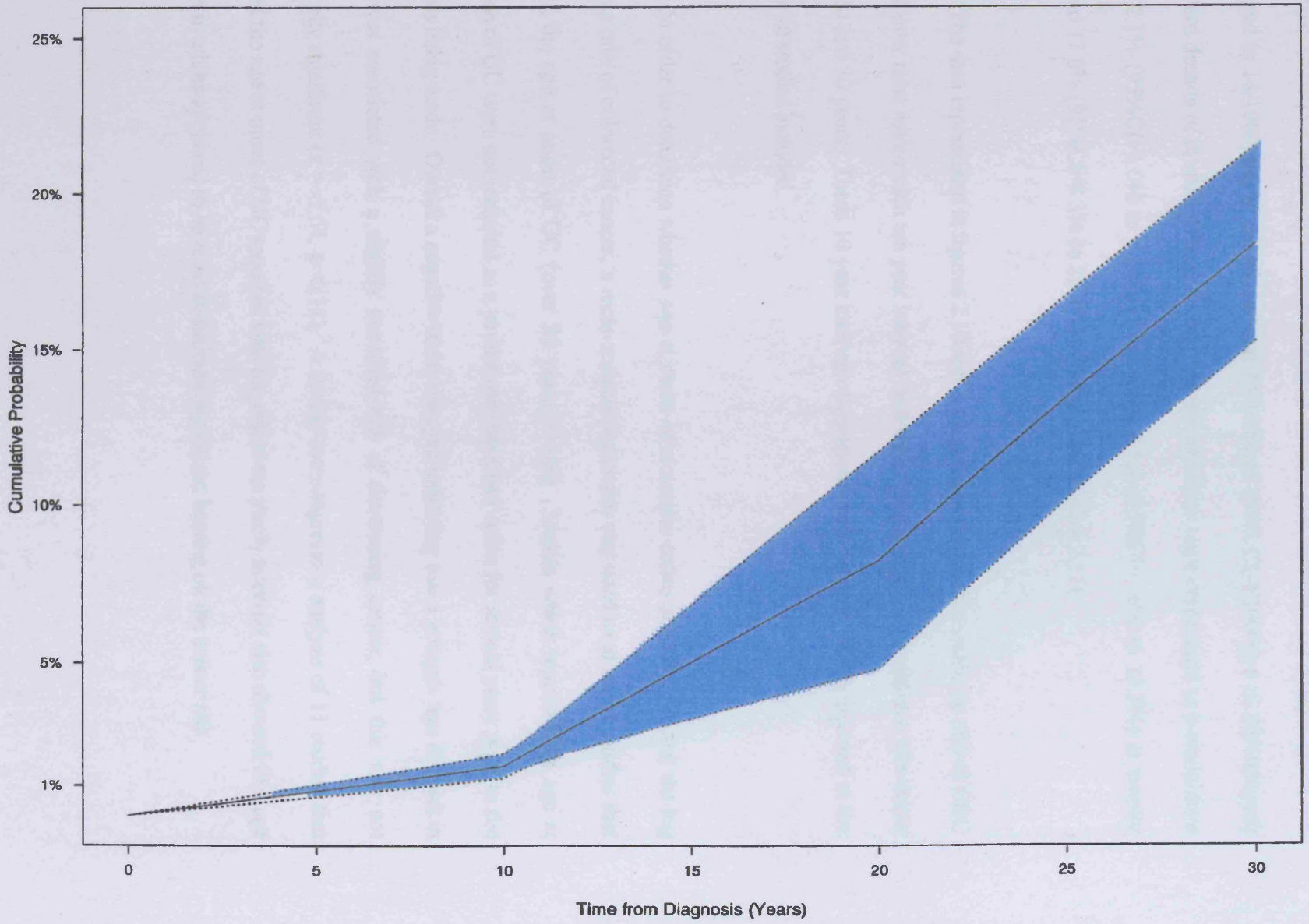


Figure 2.10. Cumulative Risk Of Developing Colorectal Cancer (With 95% Confidence Intervals) For Any Patient With Ulcerative Colitis Based on Stratified Data (n=19).

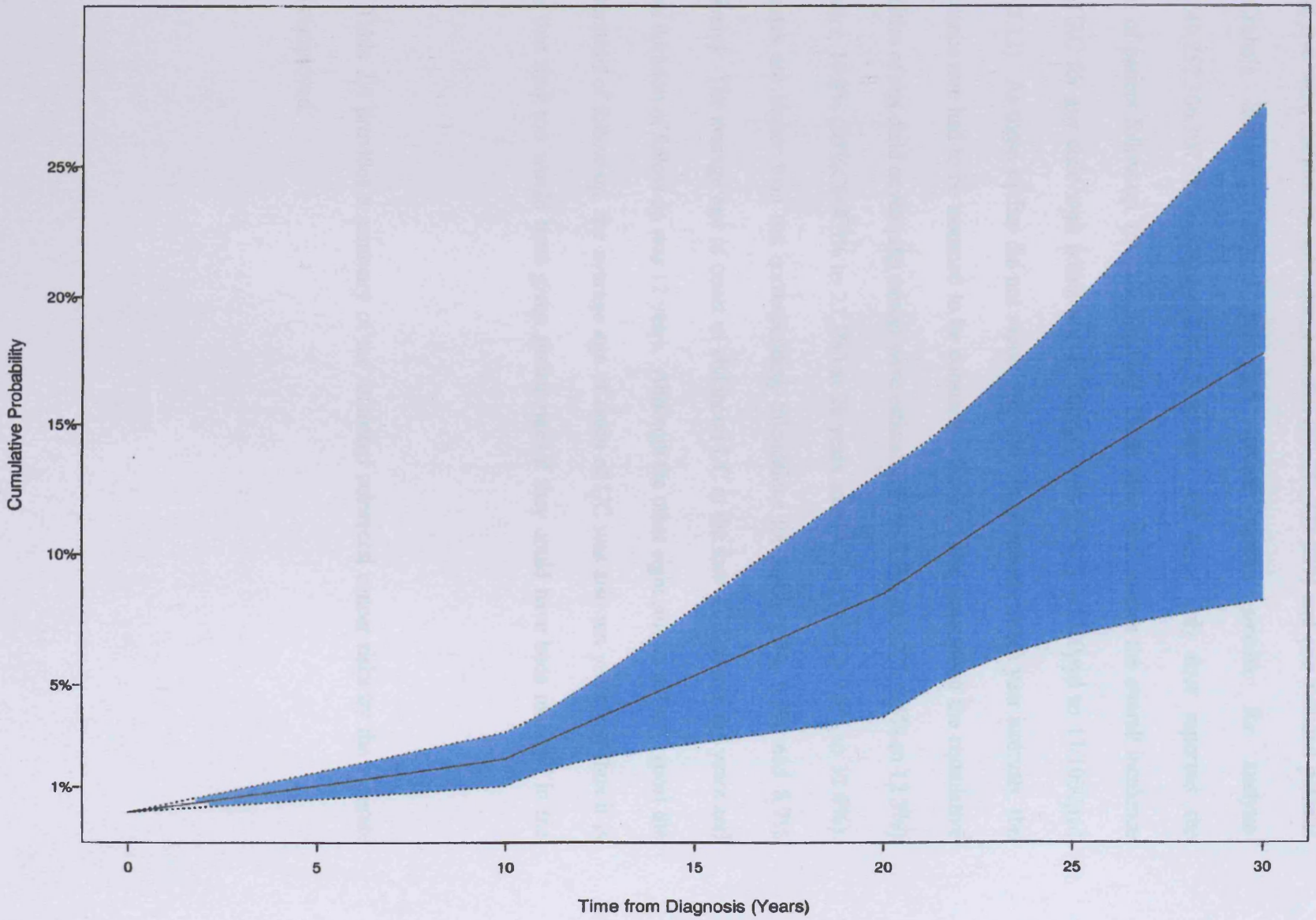


Of the 19 studies in category three, six studies reported data for patients with total colitis. The stratified decade specific incidence rates for this group were estimated to be 2/1000pyd (95% CI 1/1000pyd to 4/1000pyd) in the first decade, 7/1000pyd (95% CI 3/1000pyd to 14/1000pyd) in the second and 11/1000pyd (95% CI 4/1000pyd to 28/1000pyd) in the third decade of disease. These decade specific incidence rates correspond to a cumulative risk of 2.1% (95%CI=1.0% to 3.2%) at ten years, 8.5% (95%CI=3.8% to 13.3%) at twenty years and 17.8% (95%CI=8.3% to 27.4%) at thirty years (Figure 2.11).

The data represented in figures 2.10 and 2.11 assumes that the log incidence rate of CRC is linear over time *within* each ten year interval, and that changes in the log incidence rate occur at 10, 20 and 30 years. These 10 year intervals correspond with the time points reported in the majority of studies included.

In order to determine whether age at onset of ulcerative colitis in adults affected the log incidence rate of colorectal cancer, a meta-analysis regression was conducted on 21 studies that reported the age at onset of UC (over 20 years of age). Studies which reported the age at diagnosis of UC were not included as a patient may have had colitis for several years prior to the diagnosis being made. Overall a negative trend emerged indicating that a younger age at onset in adults was associated with a slightly increased risk of developing cancer, but this was not statistically significant ($z = -1.61$, $p=0.11$). A further meta-regression analysis of 11 studies that reported the age at onset of UC together with the risk at ten yearly intervals also showed that age at onset in adults appeared to have no statistically significant bearing on the cancer risk.

Figure 2.11. Cumulative Risk Of Developing Colorectal Cancer (With 95% Confidence Intervals) For Pancolitics Based on Stratified Data (n=6).



Analysis of Studies Reporting Data on Children Only.

Eighteen studies in the literature estimated the incidence of CRC in children with UC. Of these, five were updated by subsequent studies (50,233,237-239) and one included patients with Crohn's disease. (268) This left twelve studies suitable for analysis. (53,67,249,252,306,307,314,315,317,332,337,338,356) Of these only four reported the duration of patient follow-up. (50,249,306,314) From these four studies the overall incidence rate of CRC for any child with colitis was 6/1000pyd with 95%CI 3/1000pyd to 13/1000pyd (Figure 2.12). As these studies did not report the numbers of cancers at ten year intervals, the log incidence rate had to be assumed to be constant. Based on this assumption the cumulative probabilities of any child developing cancer were estimated to be 5.5% (95%CI=2.5% to 12.3%) at 10 years, 10.8% (95%CI=4.8% to 23.1%) at 20 years and 15.7% (95%CI=7.2% to 32.6%). These rates are higher than the corresponding calculations for adults (3%, 5.9% and 8.7% respectively). The average age of onset of childhood UC in the four studies was ten years and the mean duration of follow up was 12 years. Although the other eight studies did not report the mean duration of follow up, the average age of onset of UC was also ten years and thus it is possible that they too would have given similar rates if they could have been included in the analysis.

Table 2.4 provides a summary of the estimated colorectal cancer risks by the separate methods employed.

Figure 2.12. Overall Incidence Of Colorectal Cancer (With 95% Confidence Intervals) For Children With Ulcerative Colitis.

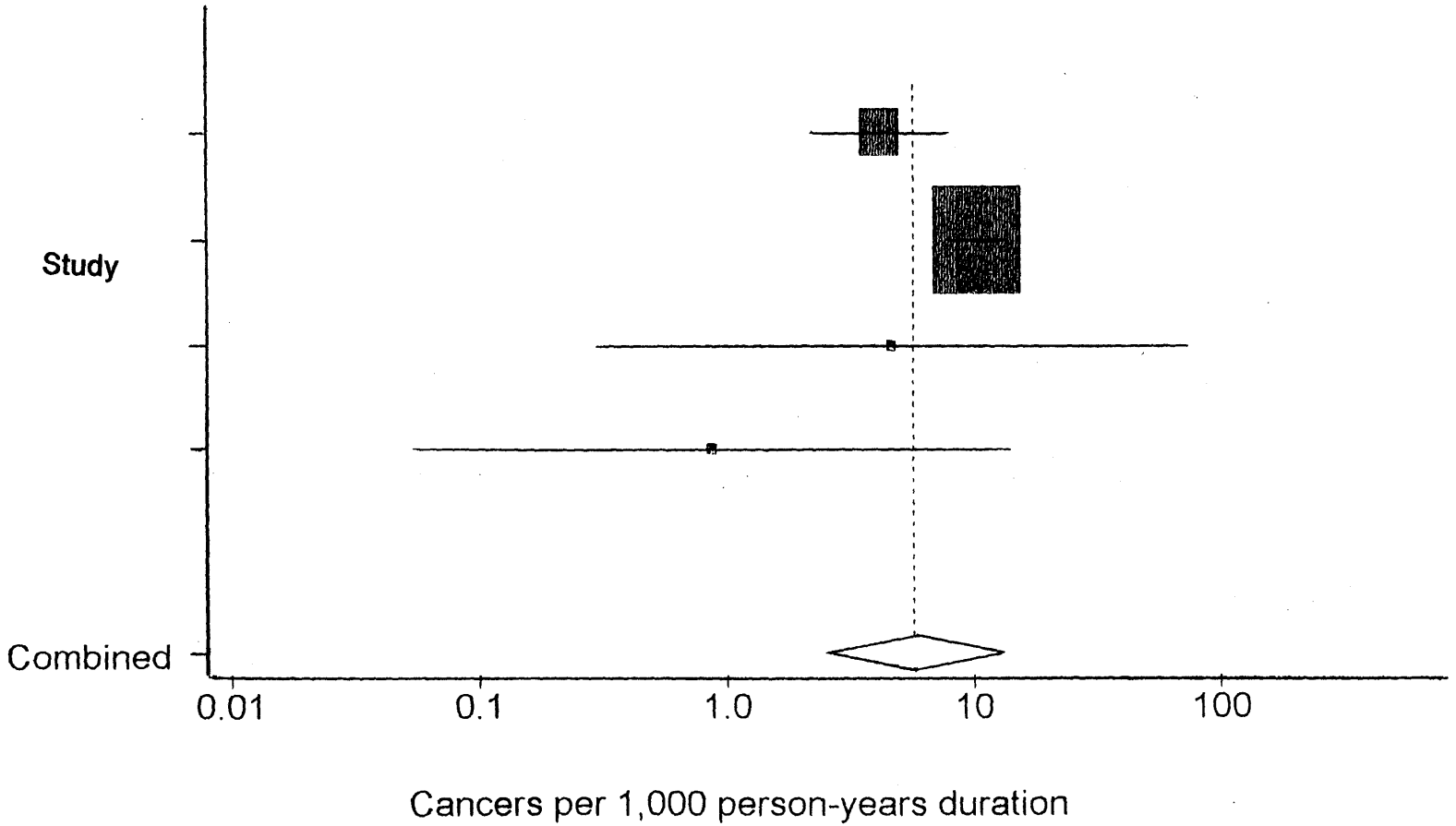


Table 2.4. Summary of Estimated Cancer Risks:

			Unstratified Data			Stratified Data	
	All Patients (116 studies)	Total UC (35 studies)	All Patients (41 studies)	Total UC (26 studies)	Children (4 studies)	All Patients (19 studies)	Total UC (6 studies)
Overall Cancer Prevalence (%) (95% CI)	3.7% (3.2% to 4.2%)	5.4% (4.4% to 6.5%)					
Cancer Incidence Rate at 10 years / 1000 pyd (95% CI)			3/1000 (2 to 4/1000)	4/1000 (3 to 6/1000)	6/1000 (3 to 13/1000)	2/1000 (1 to 2 /1000)	2/1000 (1 to 4/1000)
Cumulative Cancer Risk (%) at 10 years (95% CI)			3% (2.2 to 3.8%)	4.4% (2.0 to 6.8%)	5.5% (2.5 to 12.3%)	1.6% (1.2 to 2%)	2.1% (1.0 to 3.2%)
Cancer Incidence Rate at 20 years / 1000 pyd (95% CI)			3/1000 (2 to 4/1000)	4/1000 (3 to 6/1000)	6/1000 (3 to 13/1000)	7/1000 (4 to12 /1000)	7/1000 (3 to 14/1000)
Cumulative Cancer Risk (%) at 20 years (95% CI)			5.9% (4.3 to 7.4%)	8.6% (4.0 to 13.3%)	10.8% (4.8 to 23.1%)	8.3% (4.8 to 11.7%)	8.5% (3.8 to 13.3%)
Cancer Incidence Rate at 30 years / 1000 pyd (95% CI)			3/1000 (2 to 4/1000)	4/1000 (3 to 6/1000)	6/1000 (3 to 13/1000)	12/1000 (7 to19 /1000)	11/1000 (4 to 28/1000)
Cumulative Cancer Risk (%) at 30 years (95% CI)			8.7% (6.4 to 10.9%)	12.7% (6.0 to 19.3%)	15.7% (7.2 to 32.6%)	18.4% 15.3 to 21.5%)	17.8% (8.3 to 27.4%)

pyd = Person years duration

2.6 Discussion.

This is the first comprehensive systematic review and meta-analysis assessing the risk of colorectal cancer in ulcerative colitis although several reviews have been published addressing this issue. (201-203,230,262) It is also the first meta-analysis of stratified (by duration of disease) cancer incidence rates. The precision of the pooled estimates, both overall and stratified, is due to the relatively large numbers of observations, but the pooled estimates also take into account the between-study heterogeneity, as they are based on random effects meta-analysis models. The shortcomings of this meta-analysis are accepted. The methods used have made a number of assumptions and must be applied with caution. Consequently the results must be interpreted warily. However, in the absence of any large multicentre studies or individual patient data analysis they provide the most accurate method of determining the CRC risk in the current climate.

Most meta-analyses are subject to publication bias as studies with "negative" conclusions are less likely to result in a publication. As there is much debate concerning the risk of CRC in UC this meta-analysis avoids this bias as authors reporting low rates of CRC in UC are just as likely to have their work published as those reporting very high cancer incidences. This was demonstrated using Egger's test which also showed that language bias does not appear to explain the findings. Although desirable, it was impossible to include unpublished studies in the meta-analysis. There are no registers of observational studies (as there are for clinical trials) and so it is exceedingly difficult to identify unpublished data.

Other possible biases have been considered. It may be argued that the meta-analysis was subject to selection bias in that there may have been a greater chance of inclusion of cases treated by gastroenterologists with the exclusion of cases not treated by gastroenterologists. This is

unlikely as many of the studies in the meta-analysis were population-based and their inclusion did not rely on contact with a gastroenterologist. Another possible source of bias is ascertainment bias with a greater likelihood that cancers were detected among those having active follow-up. It is accepted that this may have played a role as the majority of the cases came from surveillance programs or tertiary referral centres and very few studies included in the meta-analysis used national cancer registry data.

From 116 published studies it was found that the overall prevalence of CRC in any patient with ulcerative colitis was 3.7% which increased to 5.4% for those with pancolitis. Of the 41 studies that reported duration of disease the overall incidence of CRC in any patient with UC was estimated at 3/1000pyd. There is dispute in the literature as to whether young age at onset of colitis is an independent risk factor for CRC. It was found that for any child with UC (irrespective of disease extent) the incidence of CRC was estimated to be 6/1000pyd which is higher than that calculated for adults. However, this estimate is based on only four studies compared to 41 in the adult analysis and is thus less accurate as can be seen by the width of corresponding confidence intervals.

The studies that reported duration of colitis allowed a calculation of the incidence rates of CRC for all patients and for those with total colitis. In the initial analysis these incidence rates were assumed to be constant over time, and from these the unstratified cumulative cancer probabilities were calculated. For any patient with colitis the risk was 3% at ten years, 6% at twenty years and 9% at thirty years. Pancolitics had higher risks of 4% at ten years, 9% at twenty years and 13% at thirty years.

From the studies that reported the number of cancers at ten year intervals it was possible to stratify the risk. That is to say it was possible to calculate the increase in CRC risk with

increasing duration of disease. Such studies led to an estimation of the cumulative risk for any patient with UC to be 2% at ten years, 8% at twenty years and 18% at thirty years. Only six studies reported the results by decade for patients with pancolitis and these gave similar cumulative cancer estimates. One expects that the risk for pancolitics would be higher than for any patient with less extensive disease but it is likely that the small number of studies in the pancolitis group (n=6) accounts for the similarity in the results as evidenced by the wide confidence intervals in the calculations. Another factor may have contributed to this apparent similarity in risk. It is unusual that in the articles selected around 20% had total colitis, a figure that has been found to pertain to clinical series, when it is known that publications must tend towards inclusion of more extensive cases. In this respect, it is noted that only 35 studies in the whole meta-analysis included data on total colitis with other studies not providing sufficient information on disease extent. As over half the cancers developed in people not stated to have extensive colitis, it suggests that many of these cases did in fact have extensive disease. In this context the similarity of risks between the total colitics and all colitics is understandable.

Overall the incidence of CRC in UC is falling (Figure 2.4). This finding is at odds with those of Lashner et al who stated that there was a dramatic increase in the risk of developing CRC in patients with long-standing UC whose disease onset was after 1972 compared with those having their disease onset during or before 1972. (319) This decrease in the reported cancer incidence has occurred despite the virtual abolition of prophylactic colectomy after approximately ten years of disease. So why has the cancer risk fallen? The period of the meta-analysis saw the introduction of aminosalicylates. These agents are known to modify disease activity and there is some evidence that they exert some protection against CRC. (74,329,361,362) Their protective effect is thought to be mediated in a similar way to aspirin in the general population i.e. by inhibiting mucosal prostaglandin synthesis. (75) The period

covered by the meta-analysis also includes the introduction of surveillance programs for CRC in UC. It was hoped that vigorous surveillance strategies would lead to increased cancer detection. Although the number of cancers being detected has fallen this does not necessarily mean that surveillance has failed. If the beneficial influence of 5-ASA compounds is real and the true incidence of CRC in UC is decreasing, although we may be better at finding cancers (with colonoscopy), detection rates are not increasing because in real terms there are fewer cancers to be found.

The incidence of CRC does vary with geographical location. In the USA and UK the rate was higher than in Scandinavia and other countries. There are several possible explanations for this finding. It could represent true genetic or environmental population differences relating to the severity or course of the illness although there is little evidence to suggest that the clinical course of UC varies with country. It is possible that the Western diet plays a role exerting an influence in patients with colitis in a similar way to CRC in the general population. Alternatively it may reflect more active medical therapy strategies for severe disease, particularly in Scandinavia. Indeed a study from Copenhagen which took such an approach found a very low CRC risk and is the only large published study to report no excess cancer risk (54). Another possible explanation may be a variation between countries in approach to surveillance for CRC. Obviously centres with a comprehensive program having high rates of patient follow-up (64) are likely to detect a significantly higher proportion of cancers than centres with less aggressive policies. Finally, studies that come from hospitals serving a defined catchment area provide a good estimate of cancer risk as it is assumed that cases of all grades of severity are seen. Most of the good data of this type comes from Scandinavia (60,61) and this fact may be part of the reason why the incidence appears lower than in the USA or Britain.

It has been suggested that high colectomy rates in patients with UC will reduce the incidence of cancer. This would appear logical as resected bowel obviously no longer has malignant potential. When this relationship was analysed (Figure 2.6) the opposite was found to be true i.e. when more colectomies / resections are performed the cancer incidence is also higher. This is at odds with what one would initially expect but perhaps centres having a low threshold for surgery are also more aggressive in their surveillance strategies and are consequently detecting more cancers by regular colonoscopy. The studies with the highest operation rates (69,206,291) were reviewed as it was not entirely clear whether colectomies had been carried out for cancer prophylaxis or because a cancer had already been identified on barium examination / colonoscopy. However, when these studies were excluded from the analysis the relationship remained unchanged. It is possible that the inclusion of surgical series in this analysis biases the results as some cancers would have been found in operation specimens where surgery was not being carried out for cancer prophylaxis.

A long term prospective study of patients with colitis, with complete follow-up, would be the most accurate method of assessing the cancer risk in these patients. However, this is an enormous undertaking and is unlikely to be achieved. The risk has therefore been determined from the next best method available; a meta-analysis. However, a meta-analysis relies heavily on the quality of data that is reported in published studies. Another option to further refine the estimation of the cancer risk would be a meta-analysis of individual patient data from the published literature. However, this assumes that the raw data from studies is still accessible and would require international collaboration between large centres of excellence.

In summary this meta-analysis has estimated as accurately as possible the risk of colorectal cancer in ulcerative colitis having found it to be 2% at ten years, 8% at twenty years

and 18% at thirty years (irrespective of disease extent). Estimates for patients with total colitis are less reliable due to the smaller number of studies in the analysis. The incidence of CRC in children is higher than for adults. Incidence rates for CRC are higher in the USA and UK compared to Scandinavia and other countries. Since 1955 the overall number of cases of CRC in UC has fallen but the decrease is most marked in Scandinavia.

Now that the cancer risk has been determined it is possible to give patients an evidence based estimate of their personal risk and allow them to make an informed decision regarding surveillance. In the next chapter, the risk factors for CRC complicating UC are investigated so that the individual risk for patients could be quantified further.

Chapter 3.

A case-control study investigating the risk factors for colorectal cancer in ulcerative colitis.

3.1 Summary.

The risk factors thought to play a part in the development of colorectal cancer in patients with ulcerative colitis were investigated. A case-control study was conducted comparing 102 cases of CRC in UC with controls matching for age, sex, duration and extent of disease. Hospital records were used to extract data and the odds ratios (OR) for cancer risk were estimated by conditional logistic regression. A multivariate model assessed the contribution of individual variables in a forward selection procedure.

Independent of other variables regular 5-ASA therapy reduces cancer risk by 75% (OR 0.25, 95% C.I 0.13 to 0.48, $p<0.00001$). After adjusting for other variables it was found that taking mesalazine regularly reduces risk by 81% (OR 0.19, 95% C.I 0.06 to 0.61, $p=0.006$). Visiting a hospital doctor more than twice a year also reduces risk (OR 0.16, 95% C.I 0.04 to 0.60, $p=0.007$) although this may be a marker of compliance. Considering variables independently, having one to two colonoscopies during the history of colitis confers a protective effect (OR 0.22, 95% CI 0.09 to 0.55, $p<0.001$) and a family history of sporadic CRC in any relative increases risk five fold (OR 5.0, 95% C.I 1.10 to 22.82, $p<0.04$).

Colorectal cancer risk among patients with ulcerative colitis can be reduced through regular therapy with 5-ASA medication in particular mesalazine. Colonoscopic surveillance may be best targeted on those unable to take 5-ASA's (e.g. due to allergy) and those with a positive family history of CRC.

3.2 Theoretical justification for this work.

It is widely accepted that the risk of colorectal cancer in ulcerative colitis increases with extent and duration of disease. However, the contribution of other possible risk factors has not been rigorously explored. Of course the optimal study design for defining risk factors would be a prospective, controlled study. There is a long period before cancers or dysplasias develop in a surveillance program and there are ethical concerns about withholding surveillance colonoscopy or 5-ASA medication from the control group. Thus we must still rely on case-control studies to offer the best approximation of colorectal cancer risk factors in ulcerative colitis. Identifying risk factors would allow better targeting of subgroups at greatest risk, thus enabling more cost-effective surveillance.

3.3 Introduction.

The risk of CRC in UC becomes significant after 8 to 10 years of colitis and increases at a rate of 0.5% to 1% between the second and fourth decades of disease. (63) After forty years of pancolitis approximately 25% to 30% of patients will have developed colorectal cancer. (60) The risk of colorectal cancer is not related to duration of disease alone but also to its extent. (61,281) However, the severity and frequency of attacks do not confer an increased risk. (57,58) There is some evidence that if the onset of UC is at a young age the risk of malignant transformation is increased independent of either disease duration or anatomic extent although this is disputed. (56,60,62,70)

Several studies have suggested that if patients with UC also have primary sclerosing cholangitis they may be at a higher risk of developing colorectal cancer. (83-85) The evidence for other potential risk factors is scarce. A positive family history of colon cancer, (77,94) smoking (74) and folate depletion (77,363) may affect the occurrence of colorectal cancer.

Aspirin is thought to have an anti-neoplastic effect in the large bowel (364) and regular consumption of low dose aspirin reduces the risk of adenomatous polyps and fatal colon cancer in the general population. (365,366) There is growing evidence that the chronic consumption of aminosalicylates, in particular sulphasalazine, may also provide some protection against colorectal cancer in patients with ulcerative colitis through a similar mechanism of action. (74,329,361,367) As these studies are few in number the aim of this study was to investigate this hypothesis further whilst also studying the effect of other 5-ASA compounds that have previously been neglected.

The aim of this investigation was to assess the risk factors thought to play a part in the development of colorectal cancer in UC and to build a statistical model which would identify the combination of factors which is most hazardous.

3.4 Methods.

The investigation was designed as a retrospective matched case-control study. In order to identify cases 164 consultant gastroenterologists across England and Wales were contacted and asked permission to review the medical records of their patients with known colorectal cancer complicating UC. Nineteen gastroenterologists (eight from teaching hospitals and eleven from district general hospitals) who were interested in the study agreed to a search of their patient records and / or pathology databases. Once potential cases had been identified a visit was made to each hospital and various details from each patient's record were systematically recorded on a structured proforma (Appendix 3).

Cases and Controls:

For subjects to be included in the study, the diagnosis of UC needed to be confirmed clinically, histologically and radiologically. The criteria used were those established by Lennard-Jones. (3) Cases who were deceased at the time of the study were included provided the medical notes had not been destroyed. Cases were excluded if they had been referred with a diagnosis of colorectal cancer where UC was an incidental finding and if full case note documentation was not available.

From 133 cases collected, 102 met the inclusion criteria and these were matched with controls from the Leicestershire inflammatory bowel disease patient database which was first rigorously assembled during the late 1980's using established international diagnostic criteria. (368) The matching criteria were:

1. sex
2. age within ten years
3. extent of disease at the time of diagnosis of UC and
4. duration of disease within a five year window.

In addition controls had to have an intact colon and not have a colorectal cancer at the time of diagnosis of the case. It was not possible to match cases with a control from the same hospital as most hospitals do not have a database of their IBD patients.

Data Collection:

The following information was extracted from all inpatient and outpatient medical records for each subject from the date of diagnosis of UC until the date of the patient's cancer diagnosis. The data for cases were extracted and recorded in the same manner by myself. Data from control notes were independently extracted by myself and one other investigator (Dr E

Jackson) as a quality control check that data retrieval was uniform and accurate. All medical notes (whether or not they pertained to UC) were reviewed so that a comprehensive history, in particular family history, could be obtained. Data extracted included:

1. Age at diagnosis of UC.
2. Pharmacotherapy: Treatment for the five to ten years prior to the development of cancer including 5-ASA preparations, corticosteroids (systemic and local) and aspirin. If there was a significant period of time (>/= one year) during which a subject was not taking medication, either because it had been stopped by a doctor or if a subject was documented as being a poor complier with medication, they were recorded as not taking regular medication.
3. Average frequency of contacts with a hospital physician or surgeon per year over the course of their disease.
4. Number of barium enemas and colonoscopic examinations during follow-up of their UC.
5. Activity of UC: Each subject was placed into one of six categories as follows; a) silent disease, b) one exacerbation every ten years, c) one exacerbation per 1-10 years, d) one exacerbation per month to one year, e) one exacerbation per month and f) continuous symptoms. In the final calculations this variable was reduced to three categories (see Table 3.2) to prevent small sample sizes in the statistical analysis.
6. Smoking history at the time of diagnosis of UC.
7. Presence of primary sclerosing cholangitis (PSC) confirmed at endoscopic retrograde cholangio-pancreatography / percutaneous transhepatic cholangiography / liver biopsy. Serological values of raised liver function tests for more than one year (in the absence of PSC) were also recorded.
8. Positive family history of IBD and colorectal cancer.

For cases, the age at cancer diagnosis and its site and stage were also recorded. It was not possible to investigate the effect of folate on colorectal cancer risk. After examining twenty sets of notes it was obvious that folate levels were not routinely measured or recorded in the subjects' medical notes and therefore this variable was not studied further.

Statistical analysis:

The study was designed to have a power of 80% to detect an odds ratio of 2.5 at the level of 5% significance assuming a prevalence of 65% for each risk factor in the control group. Conditional logistic regression was used to compute estimates of odds ratio (OR) as a measure of association between various exposures and colorectal cancer, together with 95% confidence intervals. Risk parameters 2-6 were analysed as categorical variables in the final analysis. Model development used changes in minus twice the log-likelihood (which is a relative measure of model fit) to assess the contribution of individual variables in a forward selection procedure, with variables being added to the model if the change was statistically significant at the 5% level.

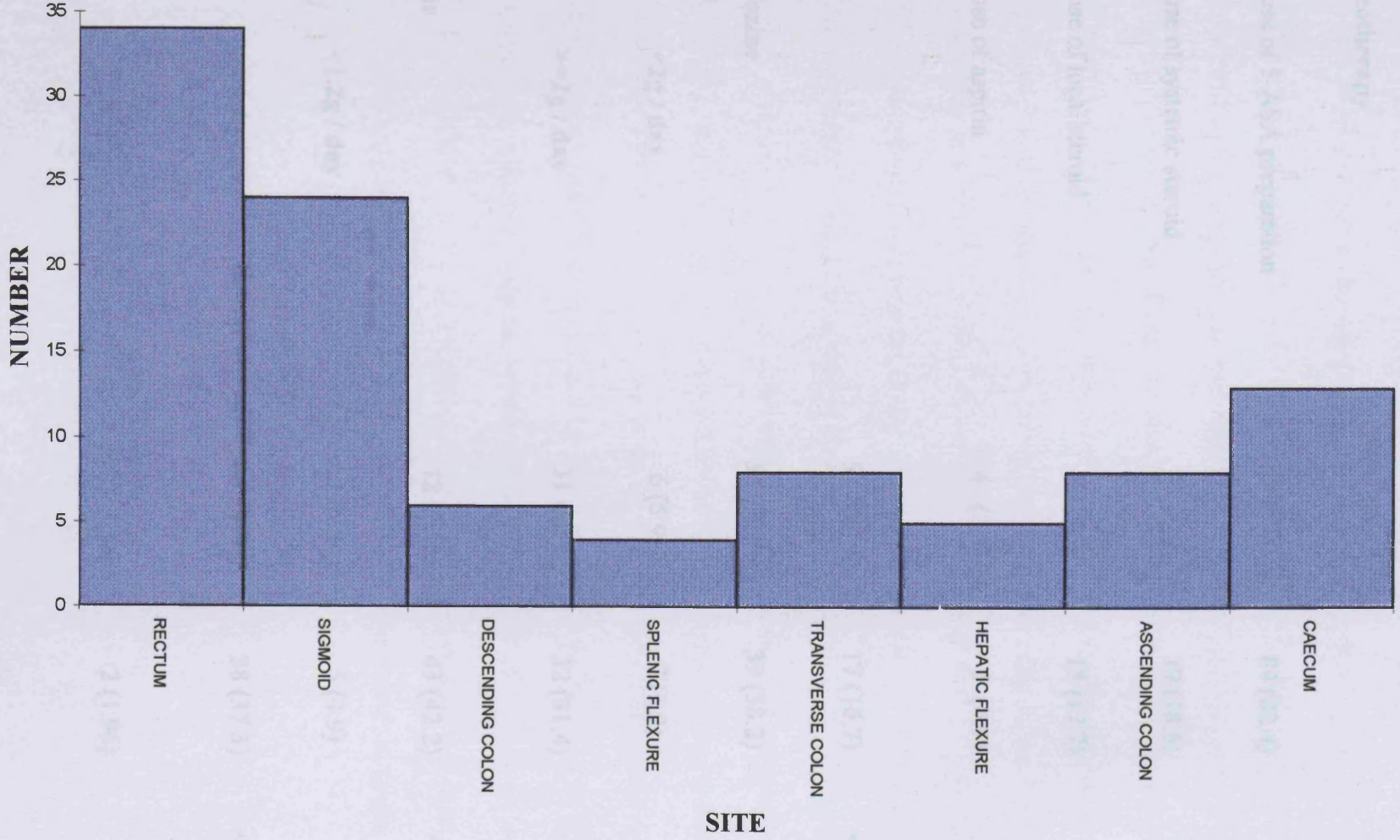
3.5 Results.

The characteristics of cases and controls are summarised in table 3.1. The mean age at the time of diagnosis of colorectal cancer was 57.4 years (standard deviation +/-12.9) and the mean interval between diagnosis of UC and colorectal cancer was 16.1 years (standard deviation +/-9.7). For controls the mean duration of disease was 16 years (standard deviation +/- 9.4). Fifty seven percent of cancers were located in the rectosigmoid area with the remainder evenly distributed around the rest of the colon (Figure 3.1). Typically, over the course of their disease, cases were much less likely to take medication on a regular basis (Table 3.2.), had fewer contacts with their hospital physician and had fewer colonoscopic examinations. Subjects with cancer had more family members with a history of sporadic colorectal cancer but the activity of disease, number of barium enemas and family history of IBD did not differ significantly between cases and controls. The number of subjects with primary sclerosing cholangitis and raised serological liver function tests were small and therefore could not be investigated further. Table 3.2 shows the distribution of patients taking individual 5-ASA drugs. Of the 51 cases who took a 5-ASA compound on a regular basis; 37 were taking sulphasalazine, 12 took mesalazine and 2 had other drugs. In comparison, of the 84 controls receiving a 5-ASA compound, 39 took sulphasalazine, 43 took mesalazine and 2 had others.

Table 3.1. Characteristics of cases and controls.

		CASES [n (%)]	CONTROLS [n (%)]	P-VALUE
SEX	MALES	64 (62.7)	64 (62.7)	1.0
	FEMALES	38 (37.3)	38 (37.3)	1.0
ETHNIC ORIGIN	CAUCASIAN	96 (94.1)	58 (56.9)	<0.0001
	ASIAN	6 (5.9)	44 (43.1)	<0.0001
AGE AT DIAGNOSIS OF UC	<15	3 (2.9)	1 (0.98)	0.31
	15-29	27 (26.5)	22 (21.6)	0.41
	30-49	36 (35.3)	42 (41.2)	0.39
	50+	36 (35.3)	37 (36.3)	0.88
MEAN AGE AT DIAGNOSIS OF UC (SD)		41.33 years (+/-16.8)	43.59 years (+/-16.1)	
MEAN DURATION OF DISEASE (SD)		16.1 years (+/-9.7)	16 years (+/-9.4)	
EXTENT AT DIAGNOSIS	PROCTITIS	6 (5.9)	5 (4.9)	0.76
	LEFT SIDED	34 (33.3)	33 (32.4)	0.88
	SUBTOTAL / TOTAL	62 (60.8)	64 (62.8)	0.77
PHYSICIAN / SURGEON CONTACTS PER YEAR				
<1		32 (31.4)	9 (8.8)	<0.0001
1-2		59 (57.8)	58 (56.9)	0.89
2+		11 (10.8)	35 (34.3)	<0.0001
NUMBER OF COLONOSCOPIES (over U.C history)				
<1		26 (25.5)	8 (7.8)	0.0007
1-2		42 (41.2)	64 (62.8)	0.002
2+		34 (33.3)	30 (29.4)	0.55
NUMBER OF BARIUM ENEMAS (over UC history)				
<1		19 (18.6)	26 (25.5)	0.24
1-2		57 (55.9)	56 (54.9)	0.89
2+		26 (25.5)	20 (19.6)	0.31
ACTIVITY OF UC				
SILENT DISEASE		22 (21.6)	20 (19.6)	0.73
1 EXACERBATION / 10 YRS		38 (37.3)	41 (40.2)	0.67
1 EXACERBATION / 1-10 YRS		31 (30.4)	30 (29.4)	0.88
MORE FREQUENT		11 (10.8)	11 (10.8)	1.0
SMOKING HISTORY AT DIAGNOSIS OF UC				
NEVER SMOKED		76 (74.5)	68 (66.7)	0.22
CURRENT SMOKER		11 (10.8)	12 (11.8)	0.82
EX-SMOKER		15 (14.7)	22 (21.6)	0.20
PRIMARY SCLEROSING CHOLANGITIS		1 (0.98)	0	0.32
RAISED LIVER FUNCTION TESTS (NO PSC)		12 (11.8)	11 (10.8)	0.82
FAMILY HISTORY OF COLORECTAL CANCER		10 (9.80)	2 (1.96)	0.02
FAMILY HISTORY OF IBD		5 (4.9)	5 (4.9)	1.0

FIGURE 3.1. ANATOMICAL DISTRIBUTION OF CANCERS THROUGHOUT THE COLON



Most cancers were located in the rectosigmoid region (total =102 patients).

Table 3.2. Distribution of patients taking 5-ASA medication.

	CASES [n (%)]	CONTROLS [n (%)]	P-VALUE
Pharmacotherapy			
Regular use of 5-ASA preparation	51 (50.0)	84 (82.4)	<0.0001
Regular use of systemic steroid	5 (4.9)	19 (18.6)	0.002
Regular use of local steroid	8 (7.8)	18 (17.7)	0.04
Regular use of aspirin	4 (3.9)	5 (4.9)	0.73
No Drug	51 (50)	17 (16.7)	<0.0001
Sulphasalazine	37 (36.3)	39 (38.2)	0.77
<2g / day	6 (5.9)	7 (6.9)	0.77
>=2g / day	31 (30.4)	32 (31.4)	0.88
Mesalazine	12 (11.8)	43 (42.2)	<0.0001
<1.2g / day	1 (0.98)	5 (4.9)	0.1
>= 1.2g / day	11 (10.8)	38 (37.3)	<0.0001
Other	2 (1.96)	2 (1.96)	1.0

The independent effect of each variable on the odds ratio of developing colonic cancer is seen in table 3.3. The most striking finding was the strong protective association of regular 5-ASA therapy, reducing cancer risk by 75% (OR 0.25, 95% C.I 0.13 to 0.48, $p<0.00001$). When individual 5-ASA drugs and their doses were analysed, mesalazine at a dose of 1.2g per day or greater, reduced colorectal cancer risk by 91% compared to no treatment (OR 0.09, 95% C.I 0.03 to 0.28, $p<0.00001$) and was also protective when taken at lower doses (OR 0.08, 95% C.I 0.08 to 0.85, $p=0.04$). The benefits of sulphasalazine were less pronounced and an effect was only evident for a dose of 2g per day or greater (OR 0.41, 95% C.I 0.18 to 0.92, $p=0.03$). Other 5-ASA medications had a non-significant protective effect. Frequent visits to see a hospital doctor was also highly protective (OR 0.098, 95% C.I 0.03 to 0.29, $p<0.00001$), as was having between one and two colonoscopies over the history of their colitis (OR 0.22, 95% C.I 0.09 to 0.55, $p<0.001$). Systemic and local steroid therapy also have a statistically significant protective role but a dose response effect was not demonstrated for either route of administration. Smoking history, particularly being an ex-smoker at the time UC was diagnosed, was associated with a non-significant protective effect. A positive family history of colorectal cancer in any family member increased cancer risk by a factor of five (OR 5.00, 95% C.I=1.10 to 22.82, $p<0.04$), but when only first degree relatives were considered this fell to 3.5 and was no longer significant (OR 3.50, 95% C.I 0.73 to 16.85, $p=0.11$). Aspirin use had a minimal protective role which was not statistically significant, but this may be due to the small numbers taking this therapy in the study.

TABLE 3.3. Independent effect of characteristics on colorectal cancer risk.

VARIABLE		OR	95% C.I	P-VALUE
SMOKING	Smoked at time UC diagnosed (compared to non-smoker)	0.71	0.28 to 1.8	0.47
	Ex-smoker when UC diagnosed (compared to non-smoker)	0.53	0.23 to 1.22	0.14
5-ASA	No	---	---	---
	Yes	0.25	0.13 to 0.48	<0.00001
	Mesalazine (<1.2 g/day)	0.08	0.08 to 0.85	0.04
	Mesalazine (>=1.2 g/day)	0.09	0.03 to 0.28	<0.00001
	Sulphasalazine (<2 g/day)	0.56	0.17 to 1.84	0.34
	Sulphasalazine (>=2 g/day)	0.41	0.18 to 0.92	0.03
	Other (e.g. olsalazide,balsalazide)	0.40	0.04 to 3.58	0.41
SYSTEMIC STEROID	Yes (compared to none)	0.26	0.01 to 0.70	0.008
LOCAL STEROID	Yes (compared to none)	0.44	0.19 to 1.02	0.06
ASPIRIN	Yes (compared to none)	0.80	0.21 to 2.98	0.74
CONTACT WITH HOSPITAL DOCTOR	1 to 2 visits per year (compared to none)	0.32	0.14 to 0.76	0.009
	More than 2 visits per year (compared to none)	0.098	0.03 to 0.29	<0.00001
BARIUM ENEMA	Any (compared to none)	1.07	0.88 to 1.29	0.50
COLONOSCOPY	1 to 2 over course of disease (compared to none)	0.22	0.09 to 0.55	0.001
	More than 2 over course of disease (compared to none)	0.42	0.16 to 1.10	0.08
RAISED ALK PHOS (WITHOUT PSC)		1.14	0.41 to 3.15	0.80
FAMILY HISTORY OF COLORECTAL CANCER	Any relative	5.00	1.10 to 22.82	0.04
	1st degree relative	3.50	0.73 to 16.85	0.11
ACTIVITY OF DISEASE	1 exacerbation / 10 years	0.85	0.40 to 1.82	0.67
	1 exacerbation / 1-10 years	0.95	0.35 to 2.60	0.92
	1 exacerbation / month-1 year (or more frequent)	0.93	0.34 to 2.60	0.90

The development of a suitable model and the contribution of variables to the various stages of the model development can be seen in table 3.4. The final model included regular 5-ASA therapy, frequent contacts with a hospital doctor, a positive family history of sporadic colonic cancer in any relative and one to two colonoscopies over the course of UC history. Table 3.5 shows the effect of these variables, in terms of Odds Ratios, adjusted for the other variables in the model. Regular consumption of mesalazine at a dose of 1.2g / day or greater (OR 0.19, 95% C.I 0.06 to 0.61, p=0.006) and frequent visits to a hospital physician (OR 0.16, 95% C.I 0.04 to 0.60, p=0.007) confer the greatest benefit after adjusting for the other variables. The possibility of all interactions between the variables in the final model were investigated and none were statistically significant at the 5% level.

Table 3.4. Model development.

VARIABLE / MODEL	-2 LOG LIKELIHOOD	CHANGE	P-VALUE
NULL MODEL			
SMOKING	136.28	2.35	0.31
5-ASA	120.00	21.10	**<0.000001**
SYSTEMIC STEROID	132.69	8.71	0.003
LOCAL STEROID	137.46	3.95	0.05
ASPIRIN	139.90	0.11	0.74
CONTACT WITH HOSPITAL DOCTOR	117.09	24.32	<0.00001
BARIUM ENEMA	140.95	0.45	0.50
1 TO 2 COLONOSCOPIES	127.62	13.78	0.01
RAISED ALKALINE PHOSPHATASE	139.95	0.07	0.80
CRC IN ANY RELATIVE	135.58	5.82	0.02
CRC IN 1ST DEGREE RELATIVE	138.46	2.94	0.09
ACTIVITY OF DISEASE	141.18	0.22	0.97
5-ASA + CONTACT WITH HOSPITAL DOCTOR	110.67	9.33	**0.01**
5-ASA + SYSTEMIC STEROID USE	116.5	3.5	0.06
5-ASA + LOCAL STEROID USE	119.7	0.3	0.58
5-ASA + CRC IN ANY RELATIVE	115.2	4.98	0.03
5-ASA + 1-2 COLONOSCOPIES	113.2	6.5	0.04
5-ASA + CONTACT WITH HOSPITAL DOCTOR + CRC IN ANY RELATIVE	106.76	3.9	0.05
5-ASA + CONTACT WITH HOSPITAL DOCTOR + 1-2 COLONOSCOPIES	104.34	6.3	**0.04**
5-ASA + CONTACT WITH HOSPITAL DOCTOR + CRC IN ANY RELATIVE + 1-2 COLONOSCOPIES	99.4	4.94	**0.03**

The p values highlighted in bold represent the most influential factors at each stage of the analysis

Table 3.5. Adjusted odds ratios for the most influential variables.

VARIABLE		ODDS RATIO	95% C.I	P-VALUE
5-ASA	None	---	---	---
	Yes	0.47	0.22 to 1.00	0.05
CONTACT WITH HOSPITAL DOCTOR	<1	---	---	---
	1 to 2 per year over the course of disease	0.43	0.16 to 1.15	0.09
	>2 per year over the course of disease	0.19	0.06 to 0.65	0.008
CRC IN ANY RELATIVE	No	---	---	---
	Yes	6.38	0.97 to 41.96	0.05
COLONOSCOPIES AFTER DIAGNOSIS	<1	---	---	---
	1 to 2 over the course of disease	0.27	0.09 to 0.77	0.02
	>2 over the course of disease	0.52	0.17 to 1.56	0.24
AFTER ADJUSTMENT FOR INDIVIDUAL 5-ASA DRUGS:-				
	None	---	---	---
MESALAZINE	<1.2 g / day	0.18	0.02 to 1.92	0.16
	>=1.2 g / day	0.19	0.06 to 0.61	0.006
SULPHASALAZINE	<2 g / day	0.93	0.22 to 3.91	0.92
	>=2 g / day	0.85	0.32 to 2.26	0.75
OTHER	variable doses	1.21	0.08 to 18.97	0.89
CONTACT WITH HOSPITAL DOCTOR	<1	---	---	---
	1 to 2 per year over the course of disease	0.42	0.15 to 1.18	0.10
	>2 per year over the course of disease	0.16	0.04 to 0.60	0.007
CRC IN ANY RELATIVE	No	---	---	---
	Yes	6.84	0.80 to 58.60	0.08
COLONOSCOPIES AFTER DIAGNOSIS	<1	---	---	---
	1 to 2 over the course of disease	0.33	0.11 to 1.01	0.05
	>2 over the course of disease	0.55	0.18 to 1.71	0.30

As all the controls in this study came from one area (Leicester) a further analysis stratified by case was conducted to assess whether this may have biased the results (Table 3.6). There were 12 case-control pairs in which both the case and control were from Leicester. These data were compared with the other 90 pairs where the control came from Leicester but the case came from elsewhere. Regarding 5-ASA medication the independent odds ratio (OR) for non-Leicester pairs was 0.25 (95% CI=0.13 to 0.51, p=0.0001) and for Leicester pairs was 0.2 (95% CI=0.02 to 1.71, P=0.14). It is interesting to note that the point estimate is therefore lower for the Leicester pairs with the analysis only losing its statistical significance due to a small numbers effect. Looking specifically at mesalazine >=1.2g / day, the OR for non-Leicester pairs was 0.14 (95% CI=0.05 to 0.41, p=0.0003) and for Leicester pairs was 0.25 (95% CI=0.03 to 2.24, p=0.2). The effect is not as marked in the Leicester pairs but mesalazine is still protective (again the statistical significance is lost due to a small numbers effect). The analysis for hospital visits and colonoscopies can also be seen in table 3.6. As there were a smaller number of pairs from Leicester (12 vs 90) the data from this analysis can only be interpreted qualitatively but the general trend is maintained.

Table 3.6. Stratified analysis comparing Leicester with non-Leicester pairs.

VARIABLE	ODDS RATIO	95% C.I	P-VALUE
5-ASA Medication			
Leicester	0.2	0.02 to 1.71	0.14
Non-Leicester	0.25	0.13 to 0.51	0.0001
Mesalazine (>=1.2g / day)			
Leicester	0.25	0.03 to 2.24	0.2
Non-Leicester	0.14	0.05 to 0.41	0.0003
Visits to hospital doctor (1-2 / year)			
Leicester	0.5	0.07 to 3.73	0.5
Non-Leicester	0.27	0.10 to 0.73	0.01
Visits to hospital doctor (>2 / year)			
Leicester	1.0	0.12 to 8.56	0.9
Non-Leicester	0.10	0.01 to 0.2	<0.0001
Colonoscopies (1-2 over the disease)			
Leicester	0.17	0.02 to 1.69	0.13
Non-Leicester	0.24	0.09 to 0.63	0.004
Colonoscopies (>2 over the disease)			
Leicester	0.41	0.02 to 10.71	0.6
Non-Leicester	0.44	0.16 to 1.22	0.1

There were 44 Asian control patients compared to 6 Asian cases. Therefore a stratified analysis based on ethnicity was carried out to assess if this may have biased the results (Table 3.7). There were 57 pairs where both the case and control were Caucasian and an analysis of the independent effect of 5-ASA medication on these pairs gave an OR of 0.30 (95% CI=0.13 to 0.65, p=0.003). Regular consumption of mesalazine at a dose of >=1.2g / day was also still highly protective with an OR of 0.1 (95% CI=0.02 to 0.39, p=0.001). Having 1-2 colonoscopies over the course of their disease was protective (OR=0.16, 95% CI=0.05 to 0.55, p=0.003) as were frequent visits to a hospital doctor (OR=0.17, 95% CI=0.04 to 0.65, p=0.01).

Table 3.7. Stratified analysis of 57 non-Asian pairs.

VARIABLE	ODDS RATIO	95% C.I	P-VALUE
5-ASA Medication	0.30	0.13 to 0.65	0.003
Mesalazine (>=1.2g / day)	0.1	0.02 to 0.39	0.001
Visits to hospital doctor (1-2 / year)	0.5	0.17 to 1.47	0.2
Visits to hospital doctor (>2 / year)	0.17	0.04 to 0.65	0.01
Colonoscopies (1-2 over the disease)	0.16	0.05 to 0.55	0.003
Colonoscopies (>2 over the disease)	0.38	0.11 to 1.27	0.1

Finally a stratified analysis was performed to assess if there was any difference in the results from teaching vs district hospitals (Table 3.8). There were 29 pairs where the case and control came from teaching hospitals and 73 pairs where the case alone was from a district hospital. 5-ASA's were protective in both groups with identical odds ratios of 0.25. The effect of mesalazine (>=1.2g / day) also gave similar results with an OR of 0.1 in teaching hospitals (95% CI=0.01 to 0.78, p=0.03) and 0.18 in district hospitals (95% CI=0.06 to 0.53, p=0.02). Of the teaching hospital pairs, 8 did not visit their hospital doctor, 16 visited once or twice a year and 5 visited more than twice a year. From the district hospital pairs, 24 never visited, 43 saw their hospital doctor once or twice a year and 6 saw them more frequently. Considering colonoscopies, of the teaching hospital pairs 12 had never had a colonoscopy after diagnosis, 8 had one to two and 9 had more than two. In district hospital pairs, 14 had never had a colonoscopy after diagnosis, 34 had one to two and 25 had more than two. Examining visits to a hospital doctor and colonoscopies, again qualitatively the general trend is unchanged. Both the numbers and the distribution of patients in the analysis led to the results being non-significant.

Table 3.8. Stratified analysis comparing teaching with district hospital pairs.

VARIABLE	ODDS RATIO	95% C.I	P-VALUE
5-ASA Medication			
Teaching hospital	0.25	0.07 to 0.86	0.03
District hospital	0.25	0.12 to 0.54	0.001
Mesalazine (>=1.2g / day)			
Teaching hospital	0.1	0.01 to 0.78	0.03
District hospital	0.18	0.06 to 0.53	0.02
Visits to hospital doctor (1-2 / year)			
Teaching hospital	0.55	0.13 to 2.26	0.4
District hospital	0.26	0.09 to 0.78	0.02
Visits to hospital doctor (>2 / year)			
Teaching hospital	0.35	0.06 to 1.94	0.2
District hospital	0.05	0.01 to 0.22	0.0001
Colonoscopies (1-2 over the disease)			
Teaching hospital	0.26	0.07 to 0.96	0.04
District hospital	0.19	0.05 to 0.65	0.01
Colonoscopies (>2 over the disease)			
Teaching hospital	0.34	0.06 to 1.81	0.2
District hospital	0.43	0.13 to 1.44	0.2

3.6 Discussion.

Colorectal cancer (CRC) risk in patients with UC can be substantially reduced by taking 5-ASA therapy on a regular basis. After adjusting for other variables, mesalazine is particularly effective, reducing the cancer risk by 81%. This protective effect is independent of dose but becomes statistically significant for 1.2 grams per day or greater. The benefits of sulphasalazine are not as pronounced and a significant effect is only seen at higher doses (2 grams per day or greater). A family history of sporadic colorectal cancer in any relative is associated with a five fold increased risk although this did not reach statistical significance after adjustment for other variables in the analysis. Systemic and local steroid use also have an inverse relationship with the development of colorectal cancer although their effects were not as influential in the model analysis.

Previous studies (74,329,361) have suggested a protective role for sulphasalazine against the development of colorectal cancer and recent research has shown that mesalazine selectively induces apoptosis of tumour cells in sporadic colorectal cancer. (367) Pinczowski et al's study (74) examined a large population-based cohort of 3,112 patients and compared 102 cases with 196 matched controls. The authors only looked at the use of pharmacological therapy for 3 months but found a protective effect for sulphasalazine with an odds ratio of 0.38 (95% CI=0.20 to 0.69) independent of disease activity. Bansal and Sonnenberg's case-control study (361) looked at patients with both Crohn's disease and UC. They too used logistical regression analysis but only examined non steroidal anti-inflammatory drug (NSAID) consumption and did not investigate the effect of 5-ASA's in particular. This withstanding, they demonstrated a trend for NSAIDs to exert a protective influence against CRC in patients with inflammatory bowel disease with an odds ratio of 0.84 (95% CI=0.65 to 1.09). Moody and colleagues (329)

compared the risk of developing CRC in UC patients who were compliant with sulphasalazine with non-compliers. She demonstrated that out of 168 patients who were diagnosed between 1972 and 1981, 3% of those who were compliant with sulphasalazine developed CRC compared with 31% of the non-compliers ($X^2 = 20.2$, df=1.0, $p<0.001$).

This study not only agrees with the findings of these reports, but has also allowed an analysis of the effects of other 5-ASA compounds, and has demonstrated that mesalazine exerts an even greater protective influence than sulphasalazine. It is postulated that NSAIDs and 5-ASA compounds work in a similar way and may reduce CRC risk by inhibiting mucosal prostaglandin synthesis. (75) This is supported by four lines of research. Firstly, there is a reduced risk of large bowel adenomas among aspirin and NSAID users. (364,365,369) Secondly, NSAIDs decrease the number and size of colorectal adenomas in patients with familial adenomatous polyposis (76) and thirdly the morbidity and mortality rates for CRC are low in patients on chronic NSAIDs. (75,365,370) Finally, NSAIDs have been shown to decrease the number and size of chemically induced colon adenomas and carcinomas in experimental animal studies. (371,372) In this study only 3.9% of cases and 4.9% of controls were taking aspirin. These small numbers limit any interpretation of its role. However, it does mean that the beneficial effects of 5-ASA compounds are not due to the co-incidental use of aspirin.

Patients who see a hospital doctor of any grade frequently and have at least one colonoscopy are less likely to develop bowel cancer. However, these actions do not necessarily reduce the risk for malignancy per se and probably represent markers for compliance. This compliance is also likely to be associated with a high compliance of taking prescribed medication. Thus, the protective effect found for pharmacological agents may be an

underestimate as controls are more likely to be compliant even in this respect when compared with cases.

A higher colonoscopy rate among the controls strengthens the results as it makes it unlikely that this group will have a high frequency of undetected cancers. Although colonoscopy has not been proven to be of beneficial effect with regards to reducing the colorectal morbidity in this patient group, it is a consistent finding in most studies that being subjected to a surveillance program upgrades the Duke stage when the cancers are diagnosed. (126,162) In some reported studies of surveillance cancers are still missed even with six monthly examinations and patients should understand that a colonoscopy is not an absolute guarantee against malignant transformation. (205,373)

A positive family history of CRC is an established risk factor for colorectal cancer in the general population (374) and in the present study having any family member with a sporadic colonic cancer increased the risk for patients with UC by a factor of five. The relationship was not maintained during the development of a model, and became non-significant when only first degree relatives analysed, but this may be a small numbers effect. Indeed research from the Mayo clinic has shown that a family history of colorectal cancer in over 2,000 first degree relatives was twice as common in 147 UC patients with CRC than in 150 UC controls matched for age, sex, extent and duration of colitis. (94)

The strengths of this study include a uniform approach to data retrieval and the retrieval of all medical notes for both cases and controls. A second investigator independently extracted data from control notes using the same proforma as a quality control check that the information had been retrieved accurately. A national database of IBD patients does not exist in the United Kingdom, and thus case identification could not have been carried out by any other method than

the one chosen. Controls were identified from the Leicestershire database and thus in some instances differed in geographical location from the cases. Although cases and controls were not always of the same ethnic group, they were all Europeans or South Asians. The analysis shows this is unlikely to have had a bearing on the results. It has been shown that the odds ratio for 5-ASA medication is actually lower in the 12 pairs from Leicester compared with the other 90 pairs, the analysis only losing its statistical significance due to a small numbers effect. Furthermore when the data was analysed after removing South Asian cases and controls from the investigation, it was found that 5-ASA medication (including mesalazine), frequent visits to a hospital doctor and 1-2 colonoscopies were all still highly protective against colorectal cancer in the colitis population. In addition, there have been no documented studies stating the colorectal cancer risk differs in South Asian populations or vary with geographical location across the U.K. Indeed Kochhar's study (313) from India stated that the crude incidence of CRC in South Asian patients with UC was comparable to the 3-4% incidence reported from Anglo-Saxon countries.

A factor that is crucial in studies of cancer risk in UC is the colectomy rate in the population studied. If the colectomy rate was higher in Leicester compared to other geographic areas, that would eliminate patients from the pool at risk for developing CRC and leave behind only very low risk individuals as controls. Probert's study (375) demonstrated a similar colectomy rate for patients in Leicestershire (in particular Asians) compared with reported rates for St Marks (45) and north-east Scotland (376) and thus this should not be a source of bias in the present study.

Criticisms could be levelled at ways of determining the length and dosage of pharmacological therapy continuously over long periods of time. This is a valid criticism since doses differ with duration of disease and therefore an average dose was estimated for each

subject over the course of their colitis. If there was any doubt whatsoever as to whether a subject was taking medication (or if they had their treatment discontinued for longer than one year) they were classed as non compliers and so the findings are based on subjects clearly identified as taking medication on a regular and virtually continuous basis. Patients who had their medication temporarily interrupted (e.g. a pregnant woman who feared adverse drug effects on the foetus) were recorded as being compliant. All retrospective studies that rely on retrieving information from medical records are subject to some inaccuracies (e.g. in medication usage) and it may be suggested that direct patient interview would be more suitable. However, this is not possible in this study as some cases and controls are deceased and in addition patient recall of facts is also fraught with inaccuracies and would introduce another source of bias. The medical record is the most legitimate source of data as it provides a contemporary record made at the time of consultation.

The strong associations that have been found for regular 5-ASA therapy and frequent visits to a hospital physician and the risk of developing colorectal cancer are likely to have an important impact on care programmes and screening for colorectal cancer in patients suffering from ulcerative colitis. The cost effectiveness of a colonoscopic surveillance program in ulcerative colitis has been questioned by many authors. (150-152) Physicians may choose to better target colonoscopic surveillance on those who are at greatest risk i.e. those unable to take regular 5-ASAs (for example due to allergy), have a positive family history of CRC and perhaps have primary sclerosing cholangitis. Likewise it should be possible to reduce the frequency of examinations in those at lower risk. This effort and expense may be better directed at educating and encouraging them to take their medication regularly. Such an approach should be supported by hospital based follow-up for all patients although patients have to take a modicum of responsibility for their illness. The combination of seeing a hospital doctor on a regular basis,

compliance with medication and attendance at colonoscopy offers the greatest degree of protection against colorectal cancer that patients can control themselves.

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Chapter 4.

The development and validation of a tool to measure patient knowledge in inflammatory bowel disease.

4.1 Summary.

A tool measuring patient knowledge about inflammatory bowel disease and its treatment was developed - the Crohn's and Colitis Knowledge Score (CCKNOW score). Thirty multiple choice questions were constructed into a draft questionnaire. This was piloted on a random selection of participants with differing inflammatory bowel disease (IBD) knowledge levels; junior doctors, nurses and ward clerks. Factor analysis eliminated questions with poor discriminant ability. The resulting 24 item questionnaire was re-tested on the three groups and a Kruskal-Wallis test determined the questionnaires ability to discriminate between the groups. Reliability and readability were tested using Cronbach's alpha and the Flesch Kincaid reading score respectively. The validated CCKNOW score was then tested on patients from the Leicestershire IBD database.

CCKNOW scores differed significantly across the groups of doctors, nurses and ward clerks (median 22, 16 and 5 respectively) $T = 40.35$, $p<0.0001$. The reliability was very good with a Cronbach's alpha of 0.95 and the readability was also high. The median score on the CCKNOW for IBD patients was 10 with no significant difference between ulcerative colitis and Crohn's disease. Patients who are members of NACC (National Association of Crohn's and Colitis) achieve statistically significantly higher scores than non-members (difference in medians 4, 95% Confidence Interval = 4 to 6, $p<0.0001$).

The CCKNOW score provides an index of overall knowledge. It is self-administered and tests (Crohnbach's alpha and Kruskal-Wallis) show it to be valid, reliable and readable. It may be used in the future as a tool to evaluate patient education programs.

4.2 Theoretical justification for this work.

Patient education should be an integral part of comprehensive IBD care. If a patient has good knowledge of their disease and manages their condition appropriately one would hope that they would have fewer disease complications. However, objectives such as complications of disease (e.g. colorectal cancer) provide very late and imprecise guides of knowledge deficits. Prior to the general introduction of individual or group based education programs (whether for newly diagnosed or established IBD patients) there should be an index that can evaluate them objectively. Consequently there is a need for an efficient and reliable tool which can assess deficiencies in knowledge so that patient education programs can be designed and evaluated comprehensively.

4.3 Introduction.

Patient knowledge and understanding varies widely in inflammatory bowel disease. Some patients show evidence of advanced reading about IBD and its treatment options. Others do not possess even a basic understanding of their condition and have virtually no recall of previous discussions with their physician. A working knowledge of their disease and its management is essential for patients with chronic disorders such as IBD. Such knowledge can positively influence quality of life, social activity and ability to cope and comply with treatment. (96,97,377) Various studies from Europe have demonstrated that patients with IBD want detailed information on both social and medical aspects of their disease. (98-100,113,114,378) In addition there is evidence that providing patients with such information can reduce consultation rates and decrease anxiety levels. (379)

Although there is growing interest in patient education in IBD there are few published scales which measure such knowledge. (108) In contrast much research has been conducted on

the development of assessment tools in other areas of medicine; most notably diabetes mellitus and end stage renal failure. (380-385) In type 1 diabetes mellitus glycosylated haemoglobin concentration was inversely correlated with patient scores for overall knowledge (105) and it seems reasonable to predict that increased knowledge of IBD may lead to fewer complications and better self management.

The aim of this investigation was to develop a valid and reliable self-administered questionnaire to assess patient knowledge of IBD and its treatment. Additional aims were that the test be easy to administer and score and that it require only basic reading skills. This chapter initially presents an analysis and discussion of the development, discriminant validity and internal reliability of the instrument developed for that purpose; the Crohn's and Colitis Knowledge Score (CCKNOW score). It goes on to report the findings when the questionnaire was posted to patients with IBD from the Leicestershire IBD patient database.

4.4 Methods.

The procedure used to develop the questionnaire was divided into four stages:-

1. The development of knowledge areas to be assessed.

The areas to be covered by the test were based on key elements in the educational materials used in our clinics. The effects of these educational booklets have already been assessed in previous studies (112,386) and they were initially developed after consultation with several clinicians with an interest in IBD. The booklets deal with symptoms, investigations, theories of aetiology and medical and surgical treatment.

2. Preparation of multiple choice questions.

Forty multiple choice questions were developed each defining specific knowledge to be evaluated in the following areas of IBD management; (a) general IBD understanding, (b) medication, (c) diet and (d) complications of IBD. All MCQ's were reviewed by physicians to consider their relevance to patient education. A number of questions were revised resulting in a total of thirty questions being included for evaluation in the assessment of patient knowledge levels (Appendix 4). The revised set of thirty questions consisted of general knowledge, including anatomy and investigation (16), medication (6), diet (2) and complications of IBD (6). Only two questions were specific to either Crohn's disease or ulcerative colitis and thus the majority of the questions should have been answerable by all respondents.

3. Pilot study of draft multiple choice questions.

Participants were randomly selected from three groups that were expected to differ in IBD-relevant knowledge and included (a) 17 junior doctors (most knowledgeable), (b) 16 state registered nurses (moderately knowledgeable) and (c) 20 ward clerks (least knowledgeable). Each participant was sent a questionnaire with a covering letter explaining the purpose of the study and stressing the confidentiality of the answers. The questionnaires were self-administered and returned anonymously.

4. Analysis of returned questionnaires and MCQ selection and revision.

Scoring of the CCKNOW was one point for each correct answer with no negative marking. Questions were analysed by factor analysis to maximise valid discrimination. (387) Factors with an eigenvalue greater than one were chosen. An eigenvalue is the standardized variance associated with a particular factor. The sum of the eigenvalues cannot exceed the

number of variables in the analysis, since each variable contributes 1 to the sum of variances. The interpretation of the factorial structure was based on factor loadings (coefficients) which were equal to or greater than 0.5. The revised CCKNOW score was then re-tested on doctors, nurses and ward clerks so that new summary scores for the groups could be determined.

Criterion related validity was assessed using the Kruskal-Wallis test, a non parametric one -way analysis of variance, as the data from the three groups were not normally distributed (as demonstrated by the Shapiro-Wilk test). This test was used to assess the statistical significance of the difference in scores between the three groups. The reliability of the CCKNOW Score was tested by calculating the internal consistency using Cronbach's alpha - an index of inter-item consistency that can vary between 0 and 1; higher values reflecting higher levels of internal consistency. (388) Readability of the test questionnaire was determined using the Flesch Kincaid reading score. (389)

Once the CCKNOW Score was validated it was posted to 647 IBD patients who were randomly selected from the Leicestershire IBD patient database and are of mixed social class and ethnic background. The IBD patients in Leicestershire are cared for by one of seven gastroenterologists and so no single consultant (and his practice) could have influenced the results. Correlation between knowledge score and membership of the National Association of Crohn's and Colitis patient self help group (NACC) was performed. The data were assessed for non-normality using the Shapiro-Wilk test, the level of statistical significance between the groups subsequently assessed using the Mann-Whitney U-test and ninety five percent confidence intervals were calculated. (390)

4.5 Results.

The mean and median scores, 95% confidence intervals along with standard deviations of the participants in the pilot study are shown in table 4.1. Junior doctors had higher scores than staff nurses who in turn did better than ward clerks. The factor analysis resulted in five factors with an eigenvalue greater than one. For each of these factors, questions with a factor loading greater than 0.5 were regarded as acceptable for inclusion in the final questionnaire. Questions with a factor loading of less than 0.5 were rejected. From this analysis six items were deemed to be unsuitable for inclusion (questions one, five, eight, fourteen, nineteen and twenty one). The redrafted questionnaire consisted of twenty four multiple choice questions (MCQ's) covering five objectives (Table 4.2). Eight questions related to general IBD knowledge, five to medication, four to anatomy, five to disease complications and two related to diet. The revised 24 item CCKNOW score was re-tested on doctors, nurses and ward clerks. The junior doctors obtained a median score of 22, nurses 16 and ward clerks 5 (Table 4.1).

Internal consistency was assessed in two ways. Firstly a Kruskal-Wallis test indicated that the 24 item CCKNOW scores differed significantly across the three groups, $T = 40.35$ (adjusted for ties), $p<0.0001$. Secondly Cronbach's alpha was very high; 0.95. The readability (assessed using the Flesch Kincaid reading score) of the CCKNOW score was also very good. The test questionnaire scored favourably in that it was classed as being easy to read (score of 77.9/100), only thirteen percent of its sentences were passive and it had a reading grade level of 4.4 (meaning that an American schoolchild of fourth-fifth grade would understand the questionnaire).

Table 4.1 Results of the pilot CCKNOW Score for junior doctors, staff nurses and ward clerks (thirty and twenty four MCQ's – revised questionnaire).

		Mean (95% C.I.)	Median (95% C.I.)	Standard deviation
Junior Doctors (n=17)	30 items	27.3 (26.4 to 28.2)	28 0 (27.0 to 28.0)	1.8
	24 items (revised questionnaire)	21.9 (21.1 to 22.7)	22.0 (21.0 to 23.0)	1.6
Staff Nurses (n=16)	30 items	20.6 (19.0 to 22.2)	20.5 (19.0 to 23.0)	3.3
	24 items (revised questionnaire)	15.9 (14.2 to 17.6)	16.0 (14.0 to 18.0)	3.4
Ward Clerks (n=20)	30 items	9.5 (6.9 to 12.1)	8.0 (7.0 to 12.0)	5.9
	24 items (revised questionnaire)	6.1 (3.9 to 8.3)	5.0 (3.0 to 8.0)	5.1

Doctors score more highly than nurses who in turn do better than ward clerks.

Table 4.2. Number of questions by section for revised 24 item questionnaire (see Appendix 4).

Section	
General knowledge	8
Anatomy	4
Medication	5
Diet	2
Complications	5

Questions covered most aspects of inflammatory bowel disease.

Omits questions 1, 5, 8, 14, 19 and 21 in Appendix 4.

The validated CCKNOW score was then further tested on the patient group described previously. Overall 354 questionnaires were returned (response rate = 55%). Two hundred patients had ulcerative colitis and one hundred and fifty four had Crohn's disease. 182/290 respondents were members of NACC (response rate = 63%) and 172/357 were non-members (response rate = 48%).

The median score for IBD patients was 10 (95% C.I = 9 to 10) with no significant difference in the scores for patients with U.C. and Crohn's disease (median 9; 95% C.I = 9 to 10 and median 10; 95% C.I = 9 to 11 respectively). The CCKNOW scores for patients by disease and membership of NACC are shown in table 4.3. Using the Shapiro-Wilk W test the data from these groups were found to be from a non-normal distribution and so non parametric tests were utilised (Mann-Whitney U test).

Patients who are members of NACC, whether they have U.C. or Crohn's disease, achieve significantly better scores than non members with a difference in median scores of 4.0, $p<0.0001$ (95% C.I = 4 to 6). Patients with IBD who do not belong to NACC have only slightly higher knowledge levels than ward clerks (lay people) with median scores of 8 and 5 respectively. Members of NACC score more highly with knowledge levels approaching those of nurses (12 and 16 respectively). As questionnaires were posted anonymously it was not possible to trace which subjects returned their questionnaire. However, eighty respondents added their names and addresses to the questionnaire and with their permission their medical notes were reviewed to determine whether duration of disease affected the CCKNOW score. Duration of disease bore no correlation to the CCKNOW score with respondents having IBD for a couple of years being just as likely to have a low/high score as someone who had had IBD for twenty years.

Table 4.3. CCKNOW Scores for IBD patients by disease and membership of NACC (twenty four MCQ's).

	Mean(95% C.I.)	Median (95% C.I.)	Standard Deviation
Ulcerative colitis NACC (n = 96)	12.4 (11.4 to 13.4)	12.5 (10.0 to 14.0)	5.0
Crohn's disease NACC (n = 86)	12.6 (11.5 to 13.7)	12.0 (11.0 to 14.0)	5.3
Ulcerative colitis Non member (n=104)	7.9 (7.2 to 8.6)	8.0 (7.0 to 9.0)	3.8
Crohn's disease Non member (n = 68)	7.8 (6.8 to 8.8)	7.5 (6.0 to 9.0)	4.0

Members of NACC score more highly than non-members irrespective of having ulcerative colitis or Crohn's disease.

Considering the group as a whole, mixed levels of understanding were ascertained from the general knowledge section of the questionnaire. Most patients (78%) realised that just because they may have been symptom free for three years they were not cured of their condition and the vast majority (96%) knew that they could not pass on their disease to family members if they were not careful about personal hygiene. However 72% of patients were unaware that IBD runs in families, 47% did not understand that IBD can affect parts of the body other than the bowel and 77% did not know that smoking was associated with Crohn's disease. (391) Fifty eight percent were not aware that a child with IBD may be shorter than his/her friends, these responders actually believing that they may be either less intelligent or may not live beyond the age of forty five.

Regarding medication there was some confusion between the different types of drug used to treat IBD. Sixty percent understood the role of immunosuppressive drugs but 76% thought that sulphasalazine and mesalazine were examples of such drugs. Sixty eight percent knew that sulphasalazine was used to reduce the frequency of relapse but only 26% were aware that it can reversibly reduce male fertility. (392) Concerning steroids, 49% did not know that they can be administered rectally and intravenously as well as orally, and 56% thought that side effects from steroids started immediately (even after small doses) and that all side effects disappeared after they were discontinued.

As far as complications of IBD are concerned 78% were unaware which patients were at increased risk of bowel cancer and therefore who should be under surveillance with 7% believing that if they passed blood in their stools they definitely had bowel cancer. Fifty eight percent did not understand what a fistula was and 79% did not realise that a woman with Crohn's disease may find difficulty in becoming pregnant. (393)

4.6 Discussion.

In developing the CCKNOW score four criteria were chosen as goals. These included a) reliability, b) validity, c) ease of administration and d) readability. The 24 item CCKNOW score displays high levels of reliability as estimated by the coefficient alpha and validity is also high with the Kruskal-Wallis test demonstrating its ability to significantly discriminate doctors from nurses and could separate both of these groups from ward clerks. Discrimination was further improved by removing questions with factor loadings less than 0.5. The CCKNOW score has a good readability score which makes it ideal as a self-administered tool for assessing patient knowledge levels. The 55% response rate for the CCKNOW score was lower than was hoped but this is not unexpected for a postal survey after a single mailing. (394)

The CCKNOW score provides a robust index of overall knowledge and could be utilised in the future to evaluate patient education programs. It allows a comparatively inexpensive assessment of knowledge status for entire IBD populations thereby freeing specialist IBD educators for more individual and goal orientated teaching tasks. Those who wish to assess IBD knowledge on a single occasion may use the 24 item version and if users wish to conduct repeated assessments (for example before and after an education program) two parallel 12 item versions may be developed for this purpose. It will help individual clinicians identify those topics to which they should give added attention during their general discussions with patients under their care. An additional use for the CCKNOW score may be to initiate discussions in self help groups and in seminar-based teaching sessions. Most knowledge assessment tools in other specialities have been used to evaluate education programs and through feedback correct patient's knowledge deficits. The CCKNOW score may be used to assess the knowledge not only of patients but also family members. Educating spouses could result in greater

understanding and an increase in the practical support given to patients in their home environment.

The CCKNOW was developed along similar lines to tests of knowledge in other areas of medicine (380-385) in that crucial knowledge content was defined, questions of poor discriminatory ability were excluded and various psychometric tests showed the CCKNOW questionnaire to have very promising properties. In the field of diabetic medicine the CCQ-1 (105,383) has been used to discriminate between performance in home monitoring, general management and overall scores stratified on a basis of patients' HbA1c levels. In nephrology the KDQ and CKKT (380,381) have been used to establish the knowledge base of established dialysis patients for whom concordance with dietary, fluid, medication or treatment regimens remains an ongoing challenge. It is understandable that good diabetic control can be achieved by education as such patients have direct control of their own treatment. The treatment of IBD may be regarded as less complicated for the patient but many self medicate during exacerbations and a significant proportion turn to alternative medicines. (395) Increasing knowledge in IBD may not have the same impact as in diabetes although it should help improve compliance with medication and colonic cancer screening programs.

All patients with IBD need to have a comprehensive knowledge base although it could be argued that it is unnecessary to burden a patient with too much information. For example, a patient with distal colitis may not need to know about fibrostenotic Crohn's disease or the risk of colorectal cancer. However, the CCKNOW only has five questions which are specific to either Crohn's disease or ulcerative colitis with most being appropriate to both conditions. In addition, limiting patient knowledge and protecting patients against any anxiety provoking issues may be seen as paternalistic. American gastroenterologists inform their patients of the CCFA (Crohn's

and Colitis Foundation of America) which is a patient self-help organisation similar to NACC in Britain. Their official publication, written specifically for people with IBD, (396) is a 213 page book which comprehensively covers many aspects of IBD and is readily available to patients and their families. With the increasing recognition of the role patients must play in therapy and the need for concordance rather than simple compliance it is important to supply patients with accurate and detailed information about a range of aspects of their disease.

The CCKNOW score compares favourably with the IBD Knowledge Questionnaire (KQ) developed by Jones et al (108) with both questionnaires having high levels of reliability (Cronbach's alpha 0.95 and 0.84 respectively). Unlike the KQ, in the development of the CCKNOW, questions that the majority of people got wrong as well as those on which most participants scored correctly were excluded as both were regarded as poor discriminators of knowledge between groups. Some may feel that even if questions are well understood by the majority of patients (and thus have little discriminatory value) they should still be included as it may be dangerous not to detect patients whose knowledge is deficient in crucial areas. However, the questions excluded by factor analysis, with the exception of questions five and fourteen are not "crucial areas of knowledge" and question fourteen was phrased in an ambiguous way and could be modified in any future version of the CCKNOW. Thus the CCKNOW does not miss patients whose knowledge is inadequate in important areas.

The KQ found that patients with Crohn's disease were more knowledgeable than those with ulcerative colitis whereas the present study found no difference between the groups. The results from the CCKNOW may be more representative as it was tested on a larger patient group. Both questionnaires identified similar misconceptions amongst the IBD population; namely that there was general confusion concerning medication and a widespread belief that IBD

does not run in families. Hawkey's study of information leaflets also found confusion about the familial occurrence of IBD. (111)

The lack of knowledge displayed by patients in the second part of this study gives no reason to be complacent about their current understanding of IBD. The higher scores achieved by NACC members are not unexpected as they have greater access to information, and membership in itself suggests they may be more motivated to learn. It may be argued that NACC members scored more highly because they may have suffered more disease complications and may have had their disease for a longer period of time compared with non members. This would appear not to be the case as many NACC members enrol as new patients i.e. early after diagnosis and have not had IBD for a sufficient time to develop complications. Indeed 19% of patients from a study in Leicester did not attend NACC meetings as they felt they were too ill. (397) In addition many members are only transient, drawing from the group for a while and withdrawing once their need is met. (110)

Further support of the questionnaires' validity and reliability will be largely based on its continued use in the clinical setting. Even so it is obvious that there are large deficits in patients' knowledge and this must be addressed if we hope to achieve better self-management of IBD. Although the CCKNOW score tests knowledge it is not a direct measure of medical outcomes (e.g. reduced frequency of complications such as colorectal cancer). In the next chapter an investigation of the potential role for the CCKNOW score in these issues is reported.

Chapter 5.

Assessment of whether patient knowledge affects the colorectal cancer risk in ulcerative colitis.

5.1 Summary.

The possible relationship between knowledge about ulcerative colitis (UC), its cancer risk and the development of colorectal cancer (CRC) was investigated using the previously developed and validated instrument - the CCKNOW score - described in chapter 4.

The 24 item CCKNOW score was mailed to patients known to have developed colorectal cancer as a complication of ulcerative colitis (cases) and to people with UC from the Leicestershire inflammatory bowel disease patient database who had not developed cancer (controls).

The mean CCKNOW scores for cases was 8.21 (SD 3.02) and for controls was 8.27 (SD 4.3). These scores did not differ significantly between cases and controls (Difference=0.06, 95% CI = -1.7 to 1.5, p=0.9). There were four times as many NACC members (National Association of Crohn's and Colitis) in the control group compared to the cancer group and patients who are members of NACC achieve statistically significantly higher scores than non-members (11.6 vs. 7.8, 95% CI = -0.1 to 7.6, p=0.05). However, after adjusting for NACC membership, the CCKNOW score did not appear to be associated with having developed cancer (OR=1.04, 95% CI = 0.92 to 1.18, p=0.5).

The CCKNOW scores were comparable in cases and controls. Thus, in a retrospective study, no evidence has been demonstrated an association between patient knowledge and the risk of developing colorectal cancer in patients with ulcerative colitis (UC). However, knowledge may have been increased in cases as a direct result of having had CRC as a complication of UC.

5.2 Theoretical justification for this work.

Formal efforts to improve patient education are associated with fewer disease complications in a number of conditions. However, this theory has not been investigated in ulcerative colitis. Comparing knowledge levels in patients with uncomplicated UC with colitis patients who *have* developed colorectal cancer would allow an assessment of whether knowledge may be an important and modifiable risk factor for CRC in UC.

5.3 Introduction.

The effectiveness of patient education on improving patient self-management has been well documented in a variety of diseases. A beneficial effect has been demonstrated in asthmatics. Patients who underwent an education program and consequently improved their asthma knowledge had fewer hospitalizations, fewer visits to family physicians and reduced attendances at accident and emergency departments. (398) Patient education has also been shown to be key in the outpatient management of thromboembolic disease. (399) A well organized, structured education program enabled patients to learn the necessary skills that permit complex and valuable therapies to be managed on an outpatient basis.

Improving knowledge in chronic disorders such as diabetes (105,400) and asthma appears to reduce the frequency of complications. It was thus postulated that firstly, good knowledge levels may be associated with fewer complications in patients with ulcerative colitis. Secondly, it seems reasonable to expect that patients who understand colitis and its cancer risk are more likely to manage their disease appropriately by attending surveillance colonoscopies and complying with medication. In this way such patients may have a lower mortality from colorectal cancer as a complication of ulcerative colitis through earlier detection. The purpose of

this study was to examine the relationship between knowledge about IBD and the development of colorectal cancer using the CCKNOW score.

5.4 Methods.

The development of the tool used to evaluate knowledge, the CCKNOW score, has previously been described in chapter 4. It is a 24 item multiple choice questionnaire that assesses knowledge in the following areas of IBD management; (a) general IBD understanding, (b) medication, (c) diet and (d) complications of IBD.

Cases of colorectal cancer complicating ulcerative colitis nation-wide were identified in the previous study conducted in chapter 3. Hospital records were checked to ensure that cases were alive and approval of consultants in charge of patient care was sought before mailing the CCKNOW score to them. Seventy questionnaires were posted to cases. One hundred controls (matched for age and sex) identified from the Leicestershire IBD patient database were also mailed a CCKNOW score. These controls were not the same patients as those used in developing the CCKNOW score described in the previous chapter.

The level of statistical significance between the mean scores of cases and controls was estimated using an independent two sample t-test and ninety five percent confidence intervals were calculated. (390) Assessment of the statistical significance of an association between being a case and a variety of potentially important characteristics was undertaken using logistic regression in SPSS. The study has a power of 70% to detect an odds ratio of 3.0 at the 5% significance level assuming an *average* exposure in the control group of 30%.

5.5 Results.

After one mailing forty two questionnaires were returned by the cases having CRC complicating UC (response rate = 60%) and forty four were returned from the UC controls (response rate = 44%). The characteristics of cases and controls are shown in table 5.1. There was no significant difference in the two groups in terms of age, gender and the length of time spent in full time education. However, there were four times as many members of NACC in the control group compared to the cases.

The mean score of the patients who had developed colorectal cancer complicating UC was 8.21 with a standard deviation in their score of 3.02 (range 0-13). Controls had similar scores with a mean of 8.27 (standard deviation 4.3, range 0-22). An independent two sample t-test showed that there was no statistically significant difference between the mean scores of the two groups controls (Difference=0.06, 95% CI = -1.7 to 1.5, p=0.9).

Scores were analysed according to membership of the National Association of Crohn's and Colitis (NACC). The mean score for patients who are members, irrespective of being a case or a control, was 11.6 (standard deviation 5.3) whereas the mean scores for non-members was 7.8 (standard deviation 3.2). This difference was statistically significant (Diff=3.8, 95% CI = -0.1 to 7.6, p=0.05). The possibility of NACC membership biasing the results was investigated by repeating the analysis after excluding the self-help groups members. This reduced the mean scores in both groups but to a greater extent in the control group. The new mean scores were 8.13 for cases and 7.44 for controls respectively; i.e. patients who had had colorectal cancer now achieved higher knowledge scores than those who had not. However, this difference was still not statistically significant (Diff=0.69, 95% CI= -0.8 to 2.2, p=0.4). Therefore, NACC members were included in the rest of the analyses.

Table 5.1. Characteristics of Cases and Controls.

	Cases (n=42)	Controls (n=44)
Gender: Male	28 (67%)	31 (70%)
Female	14 (33%)	13 (30%)
Mean Age (SD)	59.9 years (12.1)	59.8 years (10.2)
Mean years spent in full time education (SD)	12.9 years (2.9)	12.4 years (3.9)
NACC membership	2 (5%)	8 (18%)
Mean score on 24 item CCKNOW (SD)	8.2 (3.0)	8.3 (4.3)
Number with good score (>11) on the CCKNOW	5 (12%)	8 (18%)

SD = Standard Deviation

Cases and controls were comparable except for membership of NACC

Logistic regression analysis found no statistically significant associations between scores on the CCKNOW, gender, age and years spent in full time education (Table 5.2). Being a member of NACC was associated with a reduction in the risk of developing colorectal cancer by 78% and scoring more than 11 on the CCKNOW reduced risk by 39% but these findings did not reach statistical significance ($p=0.07$ and $p=0.42$ respectively) possibly due to the relatively small numbers. After adjusting for NACC membership, the CCKNOW score did not appear to be associated with having developed cancer (OR=1.04, 95% CI = 0.92 to 1.18, $p=0.5$).

Table 5.2. Relationship Between Characteristics and the Risk of Developing Colorectal Cancer.

Variable	Odds Ratio	95% Confidence Interval	P - Value
Gender (Female/Male)	1.19	0.48 to 2.98	0.71
Age (years)	1.00	0.96 to 1.04	0.95
Years in full time education	1.04	0.91 to 1.19	0.57
Membership of NACC	0.22	0.04 to 1.13	0.07
"Good" score (>11) on CCKNOW	0.61	0.18 to 2.04	0.42
"Good" score on CCKNOW adjusting for NACC membership	1.04	0.92 to 1.18	0.5

Statistical significance was assessed using logistic regression.

The response rate amongst cases and controls was 60% and 44% respectively. The CCKNOW was mailed only once. Hospital records were used to identify whether cases were deceased. These were not as accurate as was hoped and in two instances the questionnaire was returned by a relative stating that the patient had died. Concern was raised that this may have been the reason why other questionnaires amongst cases had not been returned. In order to avoid any possible anxiety to relatives the non-responders were not sent any further questionnaires. Consequently, so that both groups were treated uniformly, the CCKNOW was not posted to non-responding controls.

The medical records of the cases had already been reviewed in chapter 3. This data was reviewed to investigate whether there were any differences in the responding and non-responding cases. From table 5.3 it can be seen that there were no statistically significant differences between responders and non-responders in terms of gender, extent of disease and stage of cancer when diagnosed.

Table 5.3. Characteristics of Cases Who Returned the CCKNOW vs. Non-Responders.

		Responders (n=42)	Non-Responders (n=28)	P-Value
Gender: Male		30 (71%)	14 (50%)	0.07
Female		12 (29%)	14 (50%)	0.07
Mean age at diagnosis of UC (SD)		40 yrs (15.5 yrs)	35 yrs (16.9 yrs)	-
Mean Age at Diagnosis of Cancer (SD)		57.6 yrs (12.3 yrs)	52.3 yrs (12.1 yrs)	-
Mean duration of disease before developing cancer (SD)		17.6 yrs (8.4 yrs)	17.2 yrs (12.9 yrs)	-
Extent of UC:	Proctitis	1 (2%)	2 (7%)	0.34
	Left-sided	15 (36%)	8 (29%)	0.53
	Total	26 (62%)	18 (64%)	0.84
Stage of cancer at diagnosis:	Dukes A	12 (29%)	4 (14%)	0.16
	Dukes B	14 (33%)	11 (39%)	0.61
	Dukes C	15 (36%)	10 (36%)	1.0
	Dukes D	1 (2%)	3 (11%)	0.14

SD = Standard Deviation

Responders and non-responders were comparable.

Considering questions from the general knowledge section of the questionnaire individually, both cases and controls (74% and 68% respectively) knew that just because they may have been symptom free for three years they were not cured of their condition but only a fifth (21% and 23%) knew that IBD runs in families. A similar number in each group (only 14% and 16%) realised that a child with IBD may not grow to be as tall as his or her friends with the remaining responders actually believing that they may be either less intelligent or may not live beyond the age of forty five. A difference between the two groups was noted in the question concerning whether IBD can affect parts of the body other than the bowel. Only 26% of cases answered this correctly compared to 46% of the controls.

When examining the questions concerning medication some confusion was demonstrated. A similar number (57% and 55%) understood the role of immunosuppressive drugs but more controls knew that azathioprine was an example of such a drug (18% vs. 5%). Many more controls (73% vs. 55%) knew that sulphasalazine was used to reduce the frequency of relapse and were aware that it can reversibly reduce male fertility (27% vs. 5%). Regarding steroids an equivalent number (50% of cases and 55% of controls) knew that they can be administered rectally and intravenously as well as orally.

Perhaps not surprisingly more cases (29% vs. 18%) were aware which patients were at increased risk of bowel cancer and therefore who should be under surveillance. However, even with a personal history of cancer complicating colitis this is still a surprisingly small number. Fourteen percent of cases thought that if they passed blood in their stool it meant that they definitely had bowel cancer compared with 9% of controls. Again more cases understood what a fistula was (43% vs. 25%) and had a better knowledge of bowel anatomy with 41% knowing the location of the terminal ileum compared to 30% of controls.

5.6 Discussion.

The level of knowledge in patients with ulcerative colitis is the same irrespective of whether they had developed colorectal cancer or not. Thus patient knowledge does not appear to affect the risk in patients with UC. It was expected that cases would have significantly lower knowledge levels than controls as it was anticipated that poor knowledge could be a risk factor. This was based on the assumption that patients with poor knowledge would be less likely to attend surveillance colonoscopies and comply with medication. Both of these factors have been shown to have a protective effect against cancer in colitis. (74,329,362)

However, the study could be biased. There is a strong possibility that the knowledge level of cases has been significantly modified by the process of having colorectal cancer. It is likely that cases would have learnt more about their condition as a direct result of having cancer and the need to undergo surgery. The data would support this view in that cases had notably better scores on anatomy questions and more knew who was at risk of bowel cancer compared to the control group. Controls achieved the same or better scores in other sections, knowing more about 5-ASA medications and IBD affecting other parts of the body. It may be of significance that controls were more knowledgeable about sulphasalazine and mesalazine as these medications may be protective against colorectal cancer in UC.

It was not possible to investigate differences between the cancer survivors who responded to the study and patients who had died from cancer complicating colitis. However, it is worth considering the possibility that patients who died may be those who were diagnosed at a later stage and these may also be the cases who were less knowledgeable. The study could be improved by obtaining further data from the medical records of the cases. Data such as missed colonoscopy and outpatient clinic appointments could be extracted and a comparison made between responding and non-responding cases.

This would investigate the hypothesis that non-responders were those who were less compliant. However, obviously no data could be obtained concerning non-responding patients' knowledge levels.

The findings are based on a small sample size and one should bear in mind that all the controls came from the Leicestershire IBD database. This limits any interpretation of the results. However, it is interesting to note that there were more members of the National Association of Crohn's and Colitis (NACC) in the control group. NACC members achieved significantly higher scores on the questionnaire which agrees with the findings in chapter four. A positive but non-significant association between membership of NACC and a reduction in the risk of developing colonic cancer has been demonstrated. If this hypothesis is correct, could that protection be mediated through better knowledge or is it simply because they are a highly motivated group who attend surveillance and comply with medication? This is an interesting concept which merits further investigation through the continued use of the CCKNOW score in clinical practice.

It is possible that patients with a history of colorectal cancer become more knowledgeable about ulcerative colitis and its complications because of their personal experience. They might therefore be expected to score more highly on the questions about cancer. While cases did score more highly than controls only 29% of cases answered the question on who was at risk of cancer correctly and 14% thought that the presence of blood in the stools meant they definitely had bowel cancer. Similar findings have been reported in breast cancer where Vaeth (385) found that following treatment, patients continued to have significant deficiencies in their understanding of cancer risk factors.

Ideally this study should be conducted prospectively with all patients completing the CCKNOW score at regular intervals, such as outpatient consultations. The CCKNOW could be

used in its 12 item form (giving patients the two different versions alternately and periodically adding new questions) to prevent patients from learning answers. In this way one could obtain a true indication of the knowledge level of cases prior to developing cancer and be able to assess whether poor knowledge is a significant risk factor. However, such an approach would take at least ten years and possibly as long as thirty to complete as the vast majority of colorectal cancers in UC occur after the first decade of disease. (60,63,65) Easier outcomes to assess (instead of waiting for CRC to develop) would be frequency of flare ups or the number of missed outpatient and colonoscopy appointments. These measures of compliance could be surrogate markers for the likelihood of developing cancer but this has not yet been assessed. This concept could be investigated in the future to determine whether knowledge can be used as a measure of such behaviours as adherence to therapeutic regimens or medical outcomes including reduced frequency of complications.

Although a direct relationship between patient knowledge and the development of cancer has not been demonstrated there is evidence suggesting that increasing knowledge in the general population improves uptake of screening for colorectal cancer in the general population. (107) The same may be true for patients with ulcerative colitis. Many modalities are used to improve patient's understanding of their disease and the next chapter investigates the effects of a video and information leaflet on patient knowledge in a randomized controlled trial.

Chapter 6.

A randomized controlled trial comparing the efficacy of a video and information leaflet vs information leaflet alone on patient knowledge about surveillance and cancer risk in ulcerative colitis.

6.1 Summary.

The effect of a video and information leaflet vs. information leaflet alone on improving patient knowledge in ulcerative colitis was investigated in a randomized controlled trial.

One hundred and twenty four patients were recruited from the gastroenterology outpatient departments of two Leicester hospitals. Participants completed a questionnaire prior to receiving the leaflet / viewing the video, immediately afterwards and one month later.

One hundred and fifteen questionnaires were returned (response rate = 93%). Both videos and leaflets increased knowledge with mean percentage improvements in scores of 71% (95% CI=40.2 to 100) and 49% (95% CI=32.1 to 66) respectively. However the difference between the two interventions was not statistically significant (Difference=22%, 95% CI= -56.3 to 13.2, p=0.2). After one month knowledge levels fell in both groups to 55% (95% CI=33.2 to 75.8)(video plus leaflet) and 36% (95% CI=23.7 to 48.6) (leaflet alone).

Leaflets and videos have an important role in reinforcing information provided by clinicians. However, there appears to be no immediate or prolonged advantage of a video over and above that of a simple information leaflet. The cost implications of producing a video such as extra staff time need to be weighed against the minor benefit that this medium has to offer.

6.2 Theoretical justification for this work.

Adequate health education is known to increase the level of compliance with population screening programs for colorectal cancer (107) and so could be important in the uptake of surveillance in ulcerative colitis. Many patients want information about their disease and its complications, (378,401) indeed recent work shows that 77% of UC patients in Leicester were keen to receive more information on screening for colorectal cancer. (49) A study from Italy has shown the majority of patients with UC placed risk of colorectal cancer as first on their list of priorities concerning areas where further information is needed. (100) Thus the supply of better information to patients with UC is important and may increase uptake and compliance with surveillance programs. How this is best achieved is investigated in this chapter.

6.3 Introduction.

To improve the chances of detecting dysplasia or cancer at a surgically curable stage, patients should be advised to comply with treatment and attend regular surveillance colonoscopies. (402) A problem with existing colonoscopic screening programs has been patient recruitment and compliance with some patients defaulting from surveillance. This may be because many patients are unaware of the risk of bowel cancer and they are anxious about the test. Therefore, a lack of knowledge may be an important factor contributing to both poor recruitment and subsequent attendance.

The most effective vehicles for imparting information to patients in addition to the standard doctor-patient consultation have not yet been clearly identified. Patients will accept educational material in a variety of forms (109) and a significant improvement in understanding can be achieved by use of both videos and information leaflets. (101-

104,111) Written and video educational materials can be used without face to face consultations to inform most people about their disease and screening for complications. They provide a consistent form of teaching, are a familiar medium to most patients and videos can communicate concepts in a realistic and visual manner. (121) Video tapes are increasingly used to inform and educate patients but their benefits, compared to more traditional methods, are not yet established.

Both an information leaflet and a video (403) for patients with ulcerative colitis were produced. Their purpose was to educate patients about colorectal cancer risk and address fears experienced by patients. This was done through demonstrating and explaining the colonoscopy procedure. The aim of this study was to improve cancer knowledge in patients with UC and assess whether this is best achieved by the use of a patient information leaflet alone or by watching the video *and* reading the information leaflet.

6.4 Methods.

Patients with ulcerative colitis were recruited from the gastroenterology outpatient departments of the Leicester General Hospital and Leicester Royal Infirmary after routine appointments. All patients were over 18 years of age with an established diagnosis of UC based on clinical, histological and radiological criteria. They had sufficient disease to be at an increased risk of bowel cancer i.e. at least with disease to the splenic flexure but preferably total or subtotal colitis. Written informed consent to participation in the study was obtained. Patients were excluded if they had a past history of colorectal cancer as a complication of ulcerative colitis, if they had previously had a prophylactic colectomy and if they did not read or could not understand English.

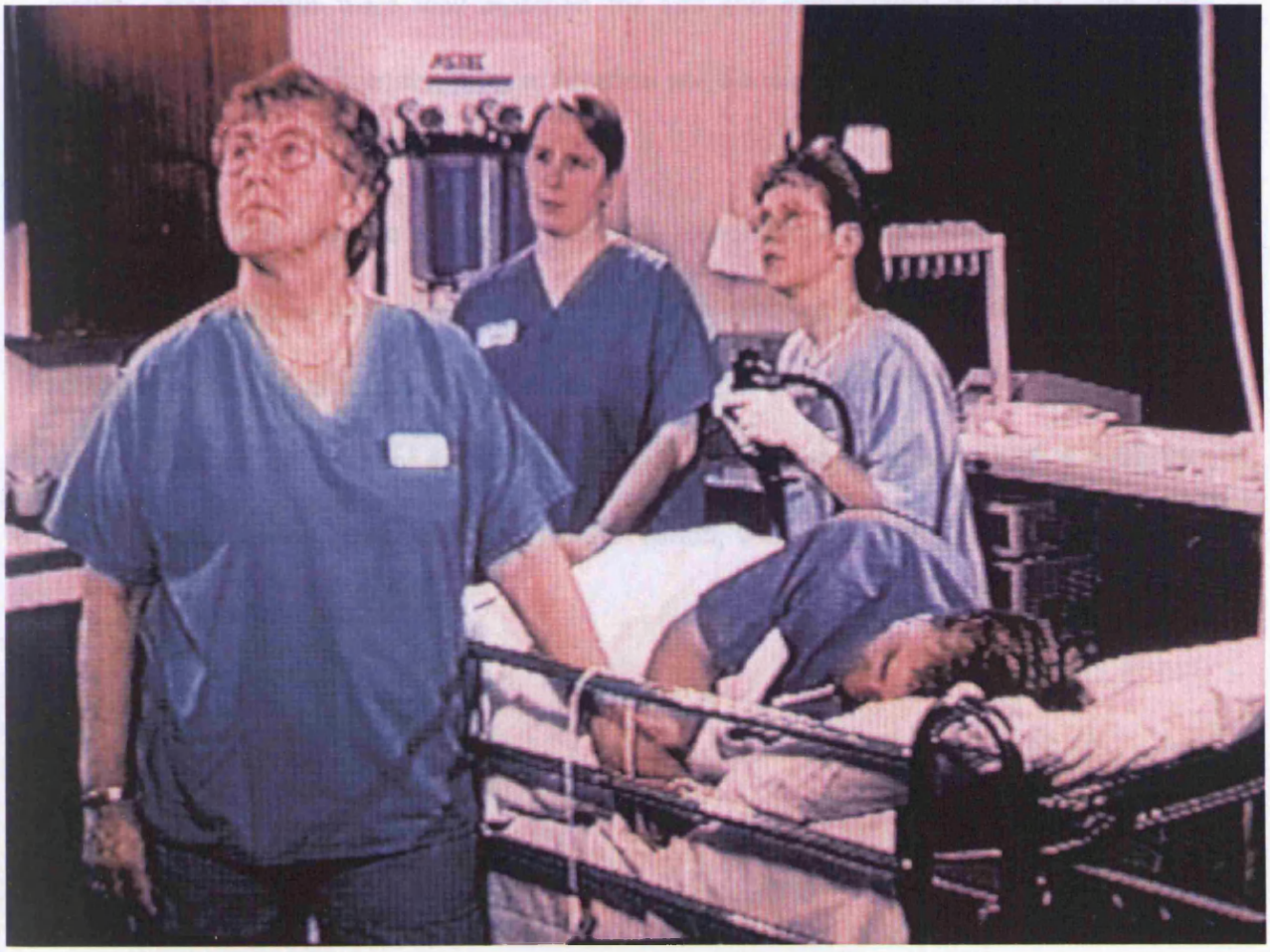
All subjects completed a 12 item questionnaire investigating their knowledge about having a colonoscopy and cancer risk in UC (Appendix 5). Eight questions pertained specifically to colorectal cancer (questions 1-7 and 11). The CCKNOW questionnaire was not used as the aim of the study was to investigate cancer knowledge and only two questions on the CCKNOW relate to cancer risk. The questionnaire was self administered and no help was given by the investigator in its completion. Patients were then randomly allocated to one of two groups stratified by age >= 60 years and membership of the National Association of Crohn's and Colitis (NACC). Members of group 1 were asked to read a patient information leaflet in a separate room (Appendix 6). This leaflet was prepared by two authors (myself and Dr J.F.Mayberry) and was previously piloted (along with the 12 item questionnaire) on 10 patients. It has a Flesch reading ease of 64.3 and only 27% of its sentences are passive. Members of group 2 were asked to watch the video (403) that was produced by myself and the Leicester University Audio-Visual Department (Appendix 7) *and* were also given the information leaflet. The text of the leaflet and the

script of the video mirrored each other so that an equivalent amount of factual information were imparted in both media. A still from the video is shown in figure 6.1. Immediately after either intervention each patient completed the 12 item questionnaire again. One month later the questionnaire was posted to each participant (with a reply paid envelope) to assess whether knowledge levels had been maintained or decreased.

Statistical analysis:

A pilot study of ten patients was used to estimate the mean and standard deviation of the percentage improvement on the questionnaire for patients receiving the leaflet. A difference of 40% in the mean percentage improvement between the two groups was considered to be the minimum clinically worthwhile difference. It was estimated that a randomised controlled trial with 53 patients in each group would be able to detect a 40% difference in mean improvement between the groups at the 5% significance level with 80% power, assuming the standard deviation was 73%. A two sample t-test was used to compare the mean difference in the improvement (compared to baseline) of the scores between the two groups. Further analysis allowing for potential confounding factors made use of multiple regression techniques.

Figure 6.1. A still from the video showing the colonoscopy procedure.



6.5 Results.

One hundred and twenty four patients were recruited from outpatients and 115 subjects returned the third questionnaire (response rate = 93%). Fifty nine patients were randomly allocated to reading the leaflet and 56 patients watched the video *and* received the leaflet. Each group were well matched for age and membership of NACC and were comparable in terms of gender, disease duration and disease extent (Table 6.1).

After analyzing the scores of the 115 responders it was evident that educating patients, by whatever method, results in a mean improvement of 60% (95% CI=42 to 77) in scores immediately after the intervention. This fell to 45% (95% CI=33 to 57) after one month. For the eight cancer questions the increase was more impressive with a mean 85% (95% CI=63 to 106) improvement post intervention, with a mean 67% (95% CI=49 to 85) improvement at one month.

Table 6.1 Characteristics of patients recruited to the study.

		LEAFLET ALONE	VIDEO + LEAFLET.
		(n=59)	(n=56)
Gender:	Male	27 (46%)	29 (52%)
	Female	32 (54%)	27 (48%)
NACC membership		13 (22%)	11 (20%)
Disease extent:	<splenic flexure	8 (14%)	9 (16%)
	>=splenic flexure	49 (83%)	46 (82%)
	Unknown	2 (3%)	1 (2%)
Mean age		47.9 years (95% CI=43.8 to 52.0)	47.2years(95% CI=43.3 to 51.1)
Mean duration of disease		11.1 years (95% CI=8.6 to 13.7)	11.0 years(95% CI=8.0 to 14.0)

The two groups are comparable for all parameters.

The absolute scores for the two groups along with the mean percentage difference in scores immediately after the intervention and at one month are summarized in table 6.2. Overall there was no statistically significant difference in the baseline scores between the two groups with a mean score in the leaflet alone group of 7.10 (95% CI=6.5 to 7.7) and in the video group of 7.05 (95% CI=6.4 to 7.7); p=0.4. Directly after the intervention they improved to 9.7 (95% CI=9.1 to 10.2) and 10.2 (95% CI=9.8 to 10.6). At one month these figures had dropped to 8.9 (95% CI=8.3 to 9.5) and 9.5 (95% CI=9 to 10) respectively. Concentrating on the eight cancer questions the corresponding scores were 4.2 (95% CI=3.7 to 4.6) and 4.3 (95% CI=3.9 to 4.7) at recruitment, 6.3 (95% CI=5.9 to 6.7) and 6.8 (95% CI=6.5 to 7) immediately post intervention and 5.7 (95% CI=5.2 to 6.1) and 6.3 (95% CI=5.9 to 6.7) one month later. The mean improvement in the scores for the cancer questions at one month compared to recruitment was 1.5 for the leaflet group and 2.0 for the video group (Diff=0.5, 95% CI= -1.2 to 0.14, p=0.13).

The mean percentage difference in the scores were calculated for the first and second, and second and third questionnaires (Table 6.2). Considering all twelve questions; the mean percentage improvement in score in the leaflet alone group was 49% (95% CI=32.1 to 66) immediately after reading the leaflet and in the video group was 71% (95% CI=40.2 to 100) The difference was not statistically significant (Difference=22%, 95% CI= -56.9 to 13.8, p=0.2) due in part to the large standard deviations. After one month the mean percentage improvement had fallen to 36% (95% CI=23.7 to 48.6) in the leaflet alone group and to 55% (95% CI=33.2 to 75.8) in the video group (Difference=19%, 95% CI= -43.3 to 6.6, p=0.15).

Table 6.2. Mean scores and mean percentage difference in scores at recruitment, post intervention and at one month.

	At recruitment	Immediately after intervention	At one month
Mean score (SD)			
12 questions			
Leaflet alone	7.10 (2.4)	9.7 (2.3)	8.9 (2.3)
Video and leaflet	7.05(2.4)	10.2 (1.6)	9.5 (2.0)
8 cancer questions			
Leaflet alone	4.2 (1.6)	6.3 (1.5)	5.7 (1.7)
Video and leaflet	4.3 (1.6)	6.8 (1.1)	6.3 (1.4)
Difference in mean percentage change (SD, p value)			
12 questions			
Leaflet alone		49.1% (66.6)	36.2% (48.7)
Video and Leaflet		70.5% (116.0)	54.5% (81.2)
		p=0.22	p=0.15
8 cancer questions			
Leaflet alone		76.2% (100.9)	57.0% (91.4)
Video and leaflet		94.1% (130.3)	77.3% (106.2%)
		p=0.4	p=0.3

SD = Standard Deviation

Both forms of education increase patient knowledge levels although the improvement falls after one month.

For the eight questions related to colorectal cancer in colitis, again both media improved the scores, but the difference between the two interventions was not statistically significant. Immediately after the intervention the leaflet group's mean percentage difference in score increased by 76% (95% CI=50.5 to 102) and the video group's increased by 94% (95% CI=60 to 128.2) (Difference=18%, 95% CI= -60.8 to 25.1, p=0.4). At one month this had fallen to 57% (95% CI=33.5 to 80.1) for those reading the leaflet and 77% (95% CI=49.5 to 105.1) for those who watched the video (Difference=20%, 95% CI= -57.2 to 16.2, p=0.3).

Multiple regression analysis of the scores was performed to identify factors, in addition to the education provided, that might have affected the test scores, i.e. confounders. There was no statistically significant change in the mean percentage difference of the scores after adjusting for either gender, duration or extent of disease.

6.6 Discussion.

Both reading a leaflet and watching a video increase knowledge in patients with ulcerative colitis. There was no statistically significant difference between the two groups with patients receiving the leaflet benefiting just as much as patients who were allocated to watch the video *and* receive the leaflet. Although the improvement in scores is considerable immediately after the intervention, both groups had a reduction in knowledge after one month.

Over the past decade, videos have become an increasingly common vehicle for providing patients with basic information about their disease and its treatment. They have been used to educate patients about upcoming procedures and to promote compliance with drug therapies. (115,404,405) Due to their growing appeal to health providers, patients and their families, many units have jumped on the 'bandwagon' of producing videos, but without adequately assessing their advantages over more established methods. Very little is made in the literature of the potential disadvantages of producing patient oriented education videotapes such as cost, time and the collaboration required amongst various specialists for a successful outcome. Consideration should be given to the initial production cost, which is substantial. The video in this study cost £5,300 to produce and lasts 9 minutes. This included filming over three days, tape stock, editing, music and graphics. However, not included in this calculation is the time spent writing and redrafting the script. It has been estimated (406) that the project co-ordinator / clinical editor devotes a minimum of 200 hours to the completion of a 20 minute video. In addition actors were not used and the good will of clinical staff and a patient was relied upon. Once a video has been made it also costs more to duplicate further copies compared to a booklet. The booklet used in the study was a simple in-house leaflet without any colour illustrations. This can be produced

for only a few pence and is much cheaper to duplicate. Although the videotape increased knowledge to a greater extent than the leaflet, the difference was not statistically significant. Thus, as only a marginal benefit was shown in the video group, one has to question whether it is cost-effective to allocate resources to producing videos as opposed to simple education leaflets. In this study the aim was to specifically increase the cancer risk knowledge of patients with UC. It may be that resources would have been better directed at improving the efficacy of the surveillance program.

Similar findings have previously been reported. Meade et al (407) randomized 1,100 patients from a primary care setting to either receiving a booklet, viewing a video tape or receive no intervention on colon cancer information in the general population. The authors found that knowledge was enhanced in the two intervention groups compared to receiving no information at all. However, there was no difference in knowledge gained by reading the booklet or watching the video tape (23% vs 26%). One possible explanation for these findings was that they had tailored the booklet and video to their target group. They gave special attention to developing the content relevant to their patients learning needs, designing the instruments to reflect ethnic diversity, organizing content in a clear manner, using the active voice, writing or narrating in a conversational style, using short words and sentences, incorporating headers and cues and summarizing points. Printed materials are commonly used to communicate information but they are often produced at reading levels above that of the intended reader. For those with low reading skills, videotapes may offer a significant advantage over booklets because of their visual appeal. Like Meade et al (407) the leaflet used in the current study was specifically produced with special attention given to developing the content relevant to patients learning needs. It has an easy reading level, with

few of its sentences being passive and this may explain why patients in this study benefited equally from reading the leaflet as they did from watching the video.

It is well accepted that videos consistently increase short-term knowledge among audiences of disparate interests. Stalonas and colleagues (408) contrasted video, live lecture, and written material in instructing alcoholics on the problems of alcoholism. Although randomization was unclear and the sample size small, this study showed that videotape instruction proved more effective in increasing *short-term* knowledge than did the other methods. However, knowledge of alcoholism returned to baseline after one month. The follow-up group had a 50% dropout rate signifying that only the most motivated patients had returned for follow-up. Kim et al (103) examined the effect of a brief education program on glaucoma patients. They randomized 72 patients to either receiving a simple education program of a video and brochures or no intervention at all. Perhaps not surprisingly the 'exposed' group performed significantly better when tested at two weeks than did the 'unexposed' group. However, the effect of education was lost at retesting six months later. These studies suggest that video education is no better and no worse than other methods in promoting *long-term* knowledge retention and that patient education must be repeated to maintain a useful effect.

It is hoped that increasing knowledge in patients with UC will encourage them to attend surveillance and the effect of educational interventions on attendance at colonoscopy appointments could be examined in the future. Whether education will modify the disease behaviour of these patients is uncertain. Pace et al (409) found that a group receiving diet instruction by video adhered better than a control group to a low cholesterol diet one week after the instruction. At two months, however, the drop out rate for the video group exceeded 40%. Even among those remaining in the trial, dietary compliance had returned

to baseline. The attempt of Vogler and colleagues (410) to curb alcoholism had a 40% drop out rate with the remaining participants being equally compliant at six and twelve month follow-up; independent of the type of initial instruction they received (instruction alone, instruction plus counselling, or the latter two plus films of the participants while drunk). These studies by Pace (409) and Vogler (410) suggest that long term compliance operates independently of initial educational intervention and make it doubtful that patients will significantly change behaviour.

The study may be criticized for not having a control group with no intervention. However, it is common practice to give all patients with ulcerative colitis leaflets covering many aspects of their disease including cancer risk and the need for surveillance. The aim was to simulate everyday practice and compare it with a new intervention. Thus, it was not appropriate to have a third group receiving no information at all. Indeed it may have been regarded unethical had this been done. Likewise the study did not compare the leaflet vs. video alone rather than the leaflet vs. video *and* leaflet. Again because it is usual practice to supply patients with leaflets this approach would have been a departure from the norm. It is possible that knowledge gain after watching the video would have differed significantly from the leaflet group had participants been allowed to take a copy of the video home to be viewed in their own surroundings at leisure. It has been shown that the setting in which a video is seen affects short-term knowledge retention. (411) In order to ensure that conditions were uniform for all participants it was felt necessary to conduct this study in a controlled environment, that is in the hospital setting, and thus not allow patients to take a copy of the video home.

Information materials are no substitute for good verbal discussions, but consultations are usually short and evidence exists that patients do not receive the

information they want and need. (412) Leaflets and videos can therefore play an important part in supplementing and reinforcing information provided by clinicians. However, there appears to be no advantage of a video over and above a simple leaflet written at an appropriate reading level for its target audience. Whatever method is adopted, patient education needs to be repeated to ensure that any initial benefit is maintained. Specialist inflammatory bowel disease (IBD) nurses could provide the ideal link between the physician and information packages, being able to answer any patient queries and reinforce important take home messages. This is a technique that has already been utilized in other specialties (106,413) but is in its infancy in IBD. Another element is that videos are passive with patients being unable to interrogate them. Advances in multi-media will enable patients to do just this either via a CD-ROM (414,415) which they could take home or via a world wide web page, the latter having the advantage of being easy to update and link with other material.

Chapter 7.

An analysis of the performance of gastroenterologists when screening for colorectal cancer in ulcerative colitis.

7.1 Summary.

An assessment of the colorectal cancer screening practices of British gastroenterologists for patients with ulcerative colitis was conducted. After a pilot study of consultants in the Trent region, a postal questionnaire was mailed to all consultant gastroenterologists in the United Kingdom identified through the British Society of Gastroenterology (n=412). The questionnaire investigated aspects of surveillance in UC patients.

After three mailings 341 questionnaires were returned (response rate 83%). 94% of consultants state they practice cancer surveillance in UC with 35% maintaining a register of patients in such programs. All doctors screen patients with total colitis, 24% with left sided colitis and 2% screen in proctitis. The mean duration of disease before surveillance is commenced is 9.2 years (range 1-15 years) for pancolitis and 12.4 years (range 7-20 years) for left sided colitis ($P<0.0001$). Only 4% of doctors routinely offer patients with disease of more than 10 years duration a prophylactic colectomy and 46% routinely perform a colonoscopy on all patients after 10 years of disease to check extent of disease. Colonoscopies are conducted by an accredited gastroenterologist in 65% of cases with the remainder being carried out by a trainee or a colorectal surgeon. Biopsies are reviewed by general pathologists in 55% of hospitals and by specialists in gastrointestinal pathology in 45% of cases. When histology reveals low grade dysplasia only 4% recommend an immediate colectomy but for high grade dysplasia this rises to 53%. Sixteen percent of gastroenterologists were unaware of the significance of a Dysplasia Associated Lesion or Mass (DALM).

The majority of gastroenterologists practice surveillance on a disorganized basis. There is inconsistency in the management of dysplasia and education of gastroenterologists concerning the pitfalls of surveillance is needed.

7.2 Theoretical justification for this work.

Many clinicians practice colonoscopic surveillance in patients with UC in the hope of detecting an early cancer at a surgically curable stage. However, much debate surrounds the efficacy of such surveillance programs (151,152,163) which were widely introduced without benefit of the randomized controlled trials needed to assess both efficacy and cost-effectiveness. It would now be unethical to randomize patients into a study of the benefits of screening and the only acceptable approach is to critically appraise current practices in surveillance.

7.3 Introduction.

The recognized drawbacks of screening programs in UC include poor patient compliance, difficulties of detecting and interpreting dysplasia and the magnitude of the false negative problem i.e. some cancers will be missed. However, colonoscopies are relatively safe procedures with few complications occurring during surveillance programs. (164) In addition, there is some evidence that surveillance can detect cancers at an earlier stage. (64,126) More recently a case control study by Karlen et al has found that surveillance may reduce colorectal cancer mortality, (162) although the results were not statistically significant. These recent studies give impetus to efforts to identify the reasons for the general failure of screening programs in UC.

Surveillance is best performed during remission so eliminating the difficulty of differentiating reactive change from low-grade dysplasia. (127) Periodic colonoscopy should begin at 8 to 10 years of disease for extensive colitis and 15 to 20 years for left-sided disease. (125) Current recommendation is to perform regular screening at one to two year intervals. (125) Some have advocated an alternative schedule to account for the increase in cancer risk with longer duration of disease. (128-130) They suggest a gradual decrease in the screening interval from every 3 years for the second decade of disease to yearly by the fourth decade of disease. (128-130) During a colonoscopy a full examination should be performed with a careful inspection of the entire colonic mucosa. Two to four random biopsies at 10 cm intervals from the entire length of the colon are currently recommended. (125) Particular attention should be paid to elevated lesions (DALM's) because there is an increased likelihood that such areas may harbor dysplasia or carcinoma. (123,124) If such a lesion is present, additional biopsy specimens should be taken from the area. Any ambiguity in histological interpretation should be confirmed by a second experienced pathologist. If severe dysplasia, or a DALM, is discovered at any time then colectomy is indicated. (58,123) Patients need to be aware that surveillance cannot guarantee a reduced cancer risk, but rather that it offers a reasonable chance of detecting precancer or symptomless cancer. (65)

The aims of this study were to determine the screening practices of British gastroenterologists for patients with ulcerative colitis. National data were collected using a postal questionnaire. In addition to the overall analysis of data, differences in practice between consultants in teaching and district hospitals were investigated. The information

from respondents at the same institutions was examined for consistency and agreement within the workplace.

7.4 Methods.

A questionnaire to assess the screening practices of gastroenterologists for colorectal cancer in patients with ulcerative colitis was developed and piloted on thirty consultant gastroenterologists in the Trent region. In the light of their comments the questionnaire was modified and new questions added (Appendix 8). This included the introduction of short case scenarios. Colour photographs of typical appearances found at colonoscopy in ulcerative colitis were included with the questionnaire and consultants were asked to identify which lesions they would biopsy.

The questionnaire sought information about the administration of colonic surveillance including the existence of registers and whether these were computerized. Information on who was responsible for updating such lists and for contacting defaulters was recorded. The types of patients included in a screening program according to extent of disease, age at diagnosis and the time interval at which screening was initiated were noted. In addition consultants were asked their views on routine colonoscopy or prophylactic colectomy after ten years of disease. The questionnaire also aimed to establish who performs most of the screening colonoscopies, how many histological biopsies are routinely taken and who interprets these biopsies (general vs. gastrointestinal pathologist).

Five case scenarios followed these questions. Their purpose was to confirm the validity of earlier questions and to elicit the management practice of gastroenterologists in various situations such as the finding of low grade dysplasia, dysplasia with a DALM and

high grade dysplasia at colonoscopy. Lastly, six colour photographs of appearances that may be seen at a screening colonoscopy were shown (Figure 7.1). Three of these photographs were from an endoscopy unit library (taken with patient's consent) and the others were scanned from a reference guide for endoscopists (based on an expert round table) with the publisher's permission. (416) Respondents were asked which appearances would lead them to take a ***further*** biopsy in addition to routine random biopsies from the colon.

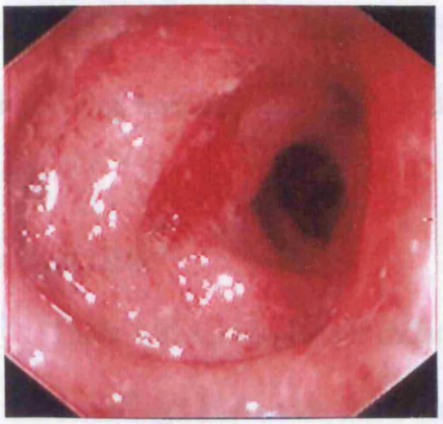
The modified questionnaire was mailed to all consultant gastroenterologists in the United Kingdom (a list for this purpose having been obtained from the British Society of Gastroenterology). Altogether three mailings were posted at intervals of approximately six weeks. The overall data were analyzed and the questionnaires reviewed to ascertain whether there was a difference in practice of gastroenterologists at teaching and district hospitals. In addition, information from respondents at the same institutions were compared.

Statistical Analysis.

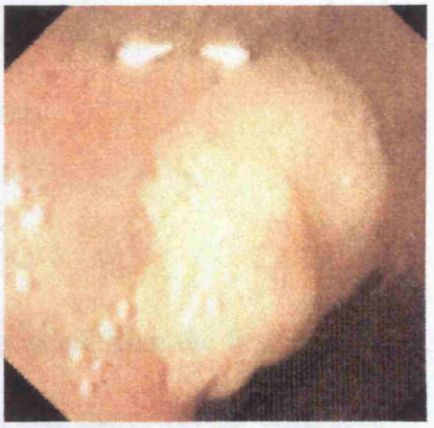
Comparison of proportions were assessed by the X^2 test. Differences in time intervals at which screening is commenced were analyzed using a Mann-Whitney test. The probability values quoted are two tailed.

Figure 7.1. Colour photographs used in the questionnaire.

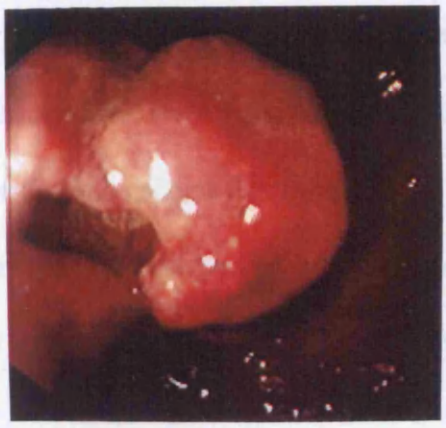
You are colonoscoping a patient whose colitis is endoscopically quiescent. In addition to taking random biopsies, would you take a biopsy if you saw the following appearances? (please circle as appropriate)



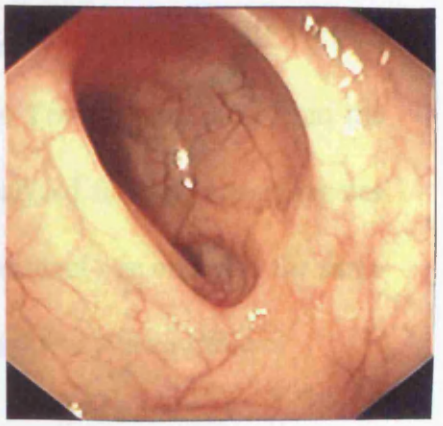
Yes / No



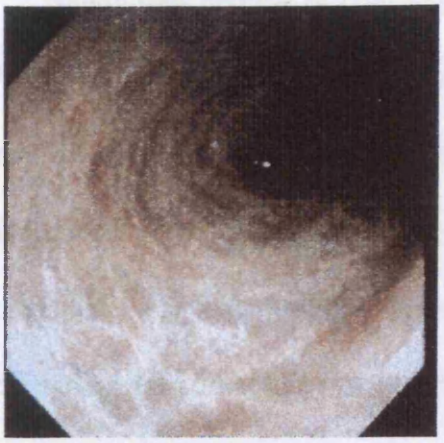
Yes / No



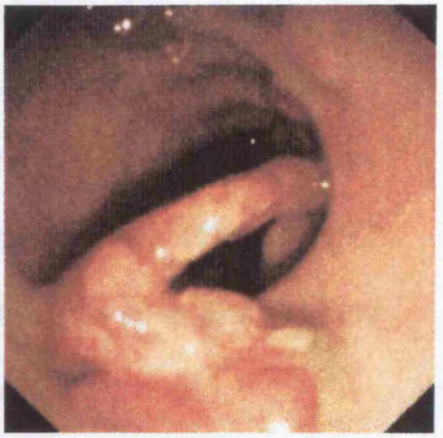
Yes / No



Yes / No



Yes / No



Yes / No

7.5 Results.

After three mailings 340 questionnaires were returned (response rate 83%). In 42 cases the questionnaires were not completed because the consultant did not see patients with inflammatory bowel disease. This left 298 questionnaires which were analyzed: 90 from teaching hospital consultants and 208 from district hospitals.

Quality of Data.

There was no significant difference in answers by responders from the first, second and third mailings and hence the overall results are reported. As there was no difference between replies from each mailing it is reasonable to assume, from market survey techniques (394) that non-responders (17%) would have been likely to answer in a similar way and therefore these data are representative of gastroenterologists across the UK. Two questionnaires were received from thirteen consultants in the Trent region (one from the pilot and the second from the current study). These were analyzed for any inconsistencies in answers. There was no intra-observer variation as each consultant responded in the same way in both questionnaires. Hence the data presented are robust and reproducible.

Overall Surveillance Practice.

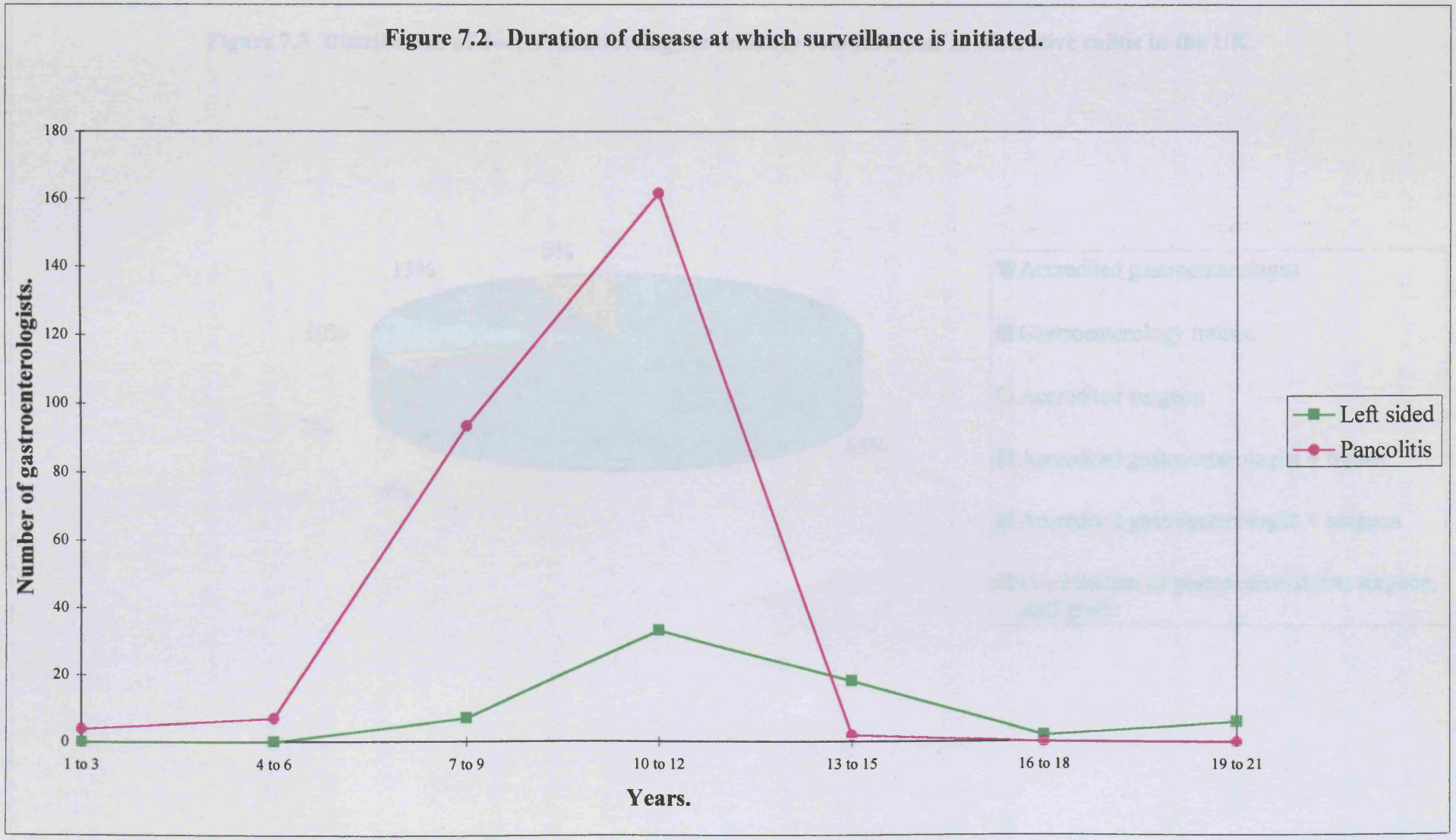
Ninety four percent of consultant gastroenterologists (physicians) state they practice colorectal cancer surveillance for patients with ulcerative colitis with 35% maintaining a register of patients in surveillance programs. Of those who have a register 49% are computerized with the rest probably being held on card index format. Only 17% of hospitals have a specific doctor / nurse who keeps the surveillance list up to date and 61% have a system for contacting people who default from follow-up.

All doctors who practice surveillance screen patients with total colitis, 24% enter people into a program who have left sided disease and 2% screen patients with proctitis. The mean duration of disease before surveillance is commenced is 9.2 years (range 1-15 years) for total colitis and 12.4 years, (range 7-20 years) for left sided colitis (Figure 7.2). Mann-Whitney test normalized statistic (adjusted for ties) = 7.8, $p<0.0001$: median difference = 2 (95% CI = 1-3). Age at diagnosis of colitis seems to have limited bearing on a clinician's decision to screen as 96% of gastroenterologists enter people into a program when colitis is diagnosed at the age of fifty and above (all consultants screening patients who developed colitis before the age of fifty years).

When asked if they routinely offered patients with disease of more than ten years duration a prophylactic colectomy, only 4% of doctors gave a positive response. Many more doctors (46%) stated that they routinely perform a colonoscopy on all patients with UC after ten years of disease to reassess the extent of their colitis.

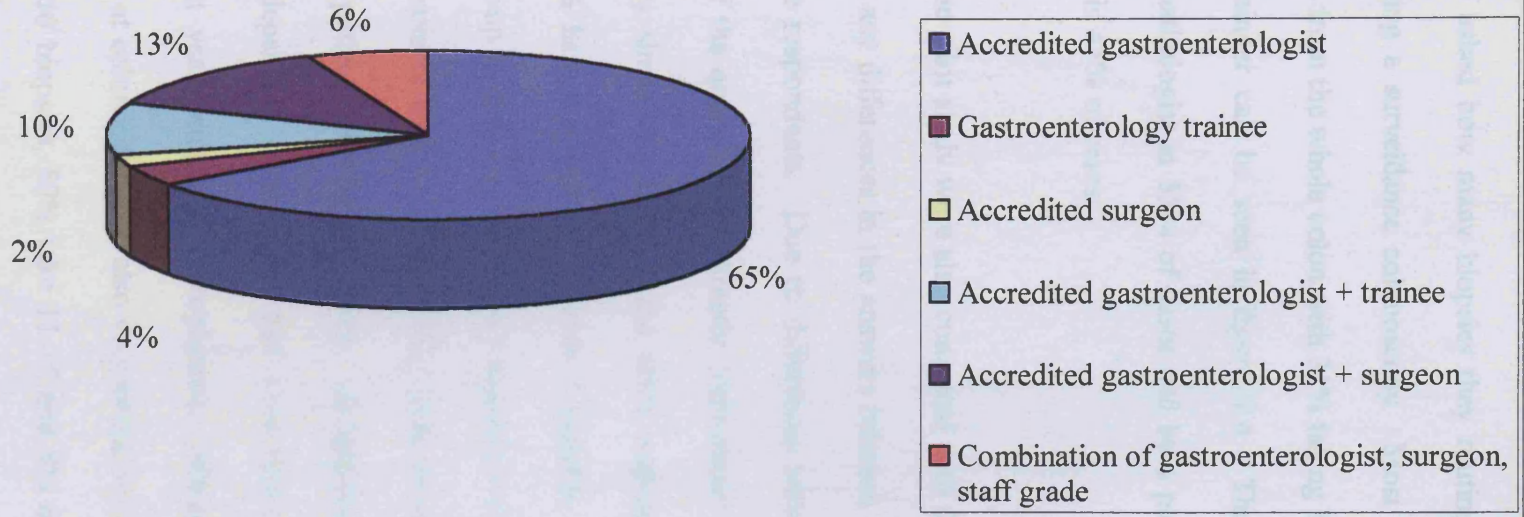
Each gastroenterologist completing a questionnaire was asked to indicate (by ticking one of four boxes) which *single* group *mainly* conducted routine screening in the department. Despite these instructions, 2 categories or more were chosen by 29% of respondents. Screening is mainly conducted by an accredited gastroenterologist in 65% of programs. Four percent are conducted mainly by a trainee and 10% by a trainee and consultant together. In 13% of hospitals colonoscopies are performed by a mixture of accredited gastroenterologists and consultant surgeons. The remainder are carried out by a combination of consultant surgeons, surgical trainees and staff grade doctors (Figure 7.3).

Figure 7.2. Duration of disease at which surveillance is initiated.



Mean duration of disease at which surveillance is commenced is 9.2 yrs (range 1-15 yrs) for pancolitis and 12.4 yrs (range 7-20 yrs) for left sided disease. Mann Whitney normalised statistic = 7.8, P<0.0001. Median difference = 2 (CI = 1-3).

Figure 7.3 Distribution of doctors conducting surveillance colonoscopies in ulcerative colitis in the UK.

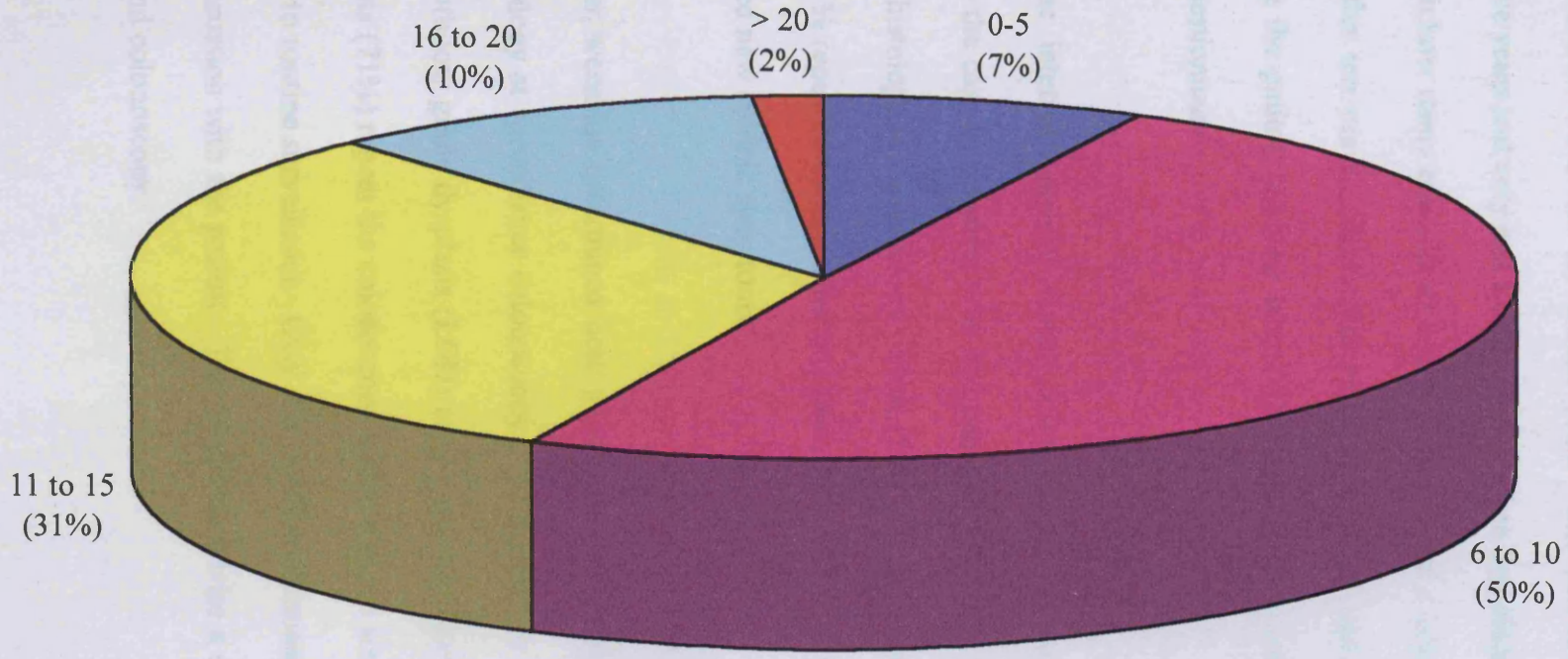


Most colonoscopies are conducted by an accredited gastroenterologist.

Respondents were asked how many biopsies they routinely take for histological assessment when performing a surveillance colonoscopy. Most (50%) stated they take between 6 and 10 biopsies from the whole colon with 31% taking between 11 and 15. The pattern amongst the remainder can be seen in figure 7.4. The histological slides are interpreted by a general pathologist in 55% of cases and by a pathologist specializing in gastrointestinal pathology in 45% of cases.

The results from the pilot study were also compared with the results from the main study to see if there were any differences in the answers between consultants in the Trent region and the rest of the respondents. Due to differences between the pilot and main questionnaire only nine of the questions are directly comparable. The answers from the Trent consultants are very similar to those of the other respondents: 92% stated they practice surveillance, 33% have a register of surveyed patients, 17% have a dedicated person to keep the register up to date and 75% have a system for contacting defaulters. All Trent consultants screen patients with pancolitis, 25% screen those with left-sided disease and none routinely screen patients who have proctitis. All gastroenterologists in the Trent region screen patients independent of their age and none routinely offer patients with disease of more than ten years duration a prophylactic colectomy. The number of histological biopsies taken at colonoscopy are also very similar to other respondents across the country: 42% take 6-10 biopsies, 50% take 11-15 and 8% take between 16 and 20 biopsies. Finally, half the biopsies are reviewed by a general pathologist with the other 50% being reviewed by a pathologist who specializes in gastrointestinal disease.

Figure 7.4. Number of histological biopsies taken at colonoscopy.



Most colonoscopists take between six and ten biopsies.

Clinical Scenarios.

The first clinical scenario posed the problem of what to do with a 45 year old woman who had suffered from UC for fifteen years. She had total colitis, had been symptom free for five years and only had a colonoscopy when first diagnosed. This vignette provided a check on how many consultants routinely performed a colonoscopy to reassess extent of disease after ten years. Sixty eight percent would arrange a colonoscopy with 17% also reviewing the patient one year later. This result agreed favourably with earlier responses on the questionnaire.

To elicit the interval between repeat colonoscopies in surveillance programs, scenario two posed the case of a patient who had pancolitis for thirty years with quiescent disease and normal histology at colonoscopy. Most (55%) would repeat the examination in three years time, 27% repeated the test after one year, 10% after five years and 8% only if the patient developed new colonic symptoms.

Three further scenarios determined how gastroenterologists manage patients who have abnormal histology at surveillance colonoscopy. The results are summarized in table 7.1. When faced with low grade dysplasia (LGD) after a normal colonoscopy the majority of gastroenterologists (71%) repeat the colonoscopy within three to six months and if LGD is not found, return to routine surveillance. Only 4% would recommend a colectomy in the near future after discussion with the patient. The remainder advise a colectomy if LGD is confirmed at a second colonoscopy.

If LGD is found at colonoscopy along with the endoscopic appearance of a dysplasia associated lesion or mass (DALM); the response differs widely. In this situation 30% of doctors recommend a colectomy, 37% advise a colectomy only if LGD is confirmed at a second examination and 33% stated they would return to surveillance if LGD was not found at a repeat test. The fact that 16% (49/298) of consultant gastroenterologists conceded they were not aware of the meaning of the term DALM or of its implication contributes to the concern generated by these responses. With the finding of high grade dysplasia (HGD) on biopsy 53% of consultants advise their patients to have a colectomy, 42% only advise colectomy if HGD is established at a repeat colonoscopy and 5% would return to surveillance if HGD was not confirmed at a repeat test.

Targeted Biopsies.

In addition to random biopsies taken from around the colon, participants were asked to indicate which appearances at colonoscopy would lead them to take ***extra*** biopsies. Six colour photographs depicted different pathologies: acute inflammation, a DALM, a carcinoma, normal tissue, a scarred colon and a pseudopolyp. All gastroenterologists would biopsy the carcinoma, and the vast majority (98%) biopsied the DALM. Ninety two percent also took a sample from the pseudopolyp. Most doctors (86%) biopsied the inflamed colon and 48% took a sample from the scarred colon. Fifteen percent of consultants also biopsied normal tissue and eleven percent of respondents indicated that they would take a biopsy from every picture.

Table 7.1. The management of patients with abnormal histology following a surveillance colonoscopy in the UK

	Management:		
	Colectomy (%)	Colectomy if histology confirmed at second colonoscopy (%)	Return to surveillance if histology not confirmed (%)
Histology:			
Low Grade Dysplasia	4	25	71
Low Grade Dysplasia + DALM*	30	37	33
High Grade Dysplasia	53	42	5

* = Dysplasia Associated Lesion or Mass

Teaching vs. District Hospital Gastroenterologists.

There was little variation between responses from gastroenterologists in teaching and district hospitals. Only three aspects of screening were significantly different between the groups. A greater number of trainees (10%) carry out colonoscopies in teaching hospitals than in district hospitals (2%). (Yates corrected $X^2 = 7.83$, $p<0.0005$). Correspondingly, more colonoscopies are conducted by accredited gastroenterologists in district hospitals: 70% in district compared with 54% in teaching hospitals (Yates corrected $X^2 = 5.9$, $p<0.02$). Pathologists specializing in gastrointestinal disease are more likely to review biopsies in teaching hospitals (80%) than district general hospitals (40%). (Yates corrected $X^2 = 57$, $p<0.00001$). The remaining difference lay in the management of patients with low grade dysplasia. There is a trend for gastroenterologists in district hospitals to return patients to surveillance much more readily than consultants in teaching hospitals who are likely to advise a colectomy if repeat histology confirms LGD (X^2 for trend = 8.1, p = 0.04 with 3 degrees of freedom).

Many institutions have more than one gastroenterologist and as such replies from consultants within the same hospitals were compared. There were twenty three teaching and thirty five district hospitals with more than one respondent. A third of consultants in both categories disagreed about the facilities available in their departments. They failed to agree on whether a register of people in surveillance programs existed, whether that register was computerized, if anyone kept the list up to date and whether a system was in place for contacting defaulters.

7.6 Discussion.

This study is the first to investigate the screening practices of British gastroenterologists for colorectal cancer in patients with ulcerative colitis. Ninety-four percent of gastroenterologists say they practice surveillance, but it is carried out in an ad-hoc and disorganized fashion. Although the increased risk of colorectal cancer in UC is universally recognized there is no unanimity between gastroenterologists on the surveillance process (61) and thus it is not surprising that a wide variation in the surveillance practices of UK gastroenterologists has been found. Indeed with the current emphasis on evidence-based practice it is salutary to observe that not a single randomized controlled study has been undertaken to test the hypothesis that "colonoscopic surveillance in ulcerative colitis works". (128,151,152) However, this is unlikely to ever be achieved for ethical and cost reasons.

Not only is there uncertainty about the facilities available within units but also about how screening should be conducted and abnormalities dealt with. Despite only a slightly increased risk of colonic cancer in left sided disease, a quarter of gastroenterologists enter such patients into a full colonoscopic surveillance program even though regular flexible sigmoidoscopy is likely to be adequate once the maximum extent of the disease has been defined. (65) Nevertheless, only half the respondents in this study routinely determine extent of disease after ten years duration. The majority of doctors who practice surveillance rightly commence screening in total colitis three to four years earlier than when the disease is left-sided. However, there is again a wide variation in practice with some initiating screening immediately after diagnosis and others waiting for fifteen years after the onset of UC.

Since the hazard rate for cancer increases with duration of disease, intervals between screening tests should not be uniform. (130) The ideal interval has yet to be established but it has been suggested that a colonoscopy every 3 years during the second decade of disease, every 2 years in the third and every year thereafter would be reasonable. (417) The present study has shown that 10% of doctors wait five years between examinations and 8% wait until a patient develops new symptoms. This is far too long as interval cancers can occur within two years of an examination. (54,131) It is reasonable to expect that cancer / dysplasia detection rates could be improved by screening patients every six to twelve months. However, there is currently no evidence to support this and the cost-effectiveness of such a protocol has not been assessed.

Colectomy rate is one of the main determinants of cancer risk in a population of patients with ulcerative colitis. However, only 4% of British gastroenterologists routinely offer patients a prophylactic colectomy after ten years of disease. Although some may consider this proposal "ridiculous", it is worth bearing in mind that countries with an aggressive policy towards the disease, such as Denmark, have some of the lowest rates of colonic cancer in UC. (42,54) With improved surgical techniques quality of life for patients is improved after surgery and is high irrespective of the surgical procedure. (418)

It is not known to what extent dysplastic changes are unequivocally detectable at colonoscopy. Failure of a biopsy from one wall to show dysplasia does not guarantee its absence from the opposite wall. Therefore, the number of biopsies taken at each colonoscopy is a factor in the detection of dysplasia or carcinoma. The majority of respondents only took between six and ten samples at colonoscopy. Previous studies have suggested that as many as 33 biopsies are required to give 90% confidence in detecting dysplasia, if present. (131) Even if multiple biopsies are taken at 10cm intervals, only

0.05% of the entire area of the colon is sampled. (148) Obviously it is wise to take as many biopsies as possible, but the number is limited by feasibility and cost. The interpretation of histology in ulcerative colitis is critical to the success of screening programs. It is not known whether pathologists who specialize in gastrointestinal disease achieve a greater degree of accuracy when assessing colonic biopsies compared with general pathologists. This will be evaluated in the next chapter as the implication would be for an increased workload in specialist units.

The skills of endoscopists in recognizing pathology at colonoscopy appears reasonably good. On the whole appropriate biopsies were taken in this study, although 11% of endoscopists biopsied all lesions in the assessment and 92% biopsied the pseudopolyp. Colour quality of the sample photographs could have influenced choice, or respondents may have mis-interpreted the question, but these answers need to be viewed in the context of a general surveillance practice of taking only six to ten biopsies in total. Although colonoscopists appear to be reasonable at interpreting pathology, the ability of endoscopists to *detect* pathology during a colonoscopy is outside the realms of this study. However, dysplasia is notoriously difficult to identify with flat dysplasia most often occurring in apparently "healthy" mucosa. Significant miss rates for adenomas less than 1cm in diameter have been reported and so smaller, more subtle lesions may be easily overlooked. (419)

The management of dysplasia is not straight forward. Ideally the finding should be discussed with the patient and a joint decision taken about management. (128) It is widely accepted that HGD is an indication for colectomy as the probability of concurrent cancer is high. (63,420) It is therefore disturbing that only 53% of doctors in this study advised immediate colectomy when a patient had HGD. No one wishes to suggest unnecessary

surgery but dysplastic areas detected during one colonoscopy may not be found during a follow-up examination. If there is doubt about the diagnosis a second pathologist should review the histology before a decision is taken. (421)

Equally perturbing is the management of DALM's. These lesions take on a number of appearances and have a high propensity for malignancy. (123) Sixteen percent of gastroenterologists were unaware of their significance with many managing the lesion in an unacceptable way by pursuing surveillance and not colectomy when it is detected. The finding of low grade dysplasia in flat mucosa may also be an indication for colectomy as the five year predictive value of LGD for either cancer or HGD is as high as 54%. (131,136) Despite this, 71% of respondents advocated continued surveillance with only 4% recommending a colectomy. These findings are similar to those of Bernstein (422) who also discovered a lack of understanding of dysplasia and its management amongst American gastroenterologists. One of the main limitations of this study is that the responses of gastroenterologists were not checked by an independent assessment of a sample of their practices. Some concerns around this area are raised by the lack of uniformity in responses from consultants working in the same hospital.

For primary screening to be effective the W.H.O list five criteria:

1. The disease should be a significant health problem.
2. The natural history is compatible with early detection at a premalignant or early cancer stage.
3. Screening tests must be sensitive, safe and specific.
4. High compliance with the screening test.
5. Screening must be cost effective.

Many authors argue that UC, despite being a premalignant condition, does not meet all of the above criteria. (151,152,163,423) However, as a surveillance program of sorts exists, it is the duty of the clinician to conduct screening comprehensively and consistently. To ensure success there needs to be mandatory external accreditation of screening and quality assurance.

It would appear that continued education of gastroenterologists concerning the many aspects and pitfalls of surveillance is needed. At present there is no uniformity in the screening practices of British gastroenterologists for colonic cancer in patients with UC. If screening continues in this disorganized fashion cancers will continue to be missed and the process and its practitioners will be discredited. One could argue that screening programs fail because of poor patient compliance as non attendees are much more likely to develop cancer. (155) This is a legitimate concern and is one of the problems that needs to be addressed when deciding how to improve the whole process. Nevertheless, it would be a disservice to our patients if we use this excuse to allow surveillance to continue to be conducted in a poorly standardized manner.

In the next chapter attention is turned from the physician to the pathologist. The findings of an inter-observer variation study when grading dysplasia in UC amongst two groups of pathologists (general pathologists and those specializing in gastrointestinal pathology) are reported. This addresses the question raised earlier in this chapter as to the possible need for specialist histology services.

Chapter 8.

Inter-observer variation between general versus specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis.

8.1 Summary.

The degree of inter-observer variation between two groups of pathologists (one specialising in gastrointestinal pathology and the other being general pathologists) when grading dysplasia in ulcerative colitis was investigated.

Fifty one coded slides showing varying degrees of dysplasia were mailed to seven histopathologists with expertise in gastrointestinal disease and six general histopathologists. Pathologists allocated each biopsy into one of four categories without the benefit of a clinical history or an opportunity to use the 'indefinite' category that is included in the Riddell classification. (127) The observers responses were analysed using Kappa statistics.

The overall Kappa statistic for gastrointestinal pathologists was 0.30 (95% CI=0.26 to 0.34) and for general pathologists was 0.28 (95% CI=0.23 to 0.32). Agreement was best for high grade dysplasia (Kappa of 0.54 and 0.61 for GI pathologists and generalists respectively). Of the 51 slides there was total concordance of the 13 pathologists in only four slides (7.8%). (95% CI=0.4% to 15.2%).

Gastrointestinal pathologists are no better than generalists when grading dysplasia in UC and agreement is poor in both groups. There is therefore no evidence that there would be any benefit in having specialist histopathology centres concentrating specifically on the interpretation of all surveillance colonoscopy biopsies from around the country. It must be made clear to the public that surveillance and screening programs carry a significant rate of histological variability and perfection cannot be expected or achieved with present methods.

8.2 Theoretical justification for this work.

Histological dysplasia is the cornerstone of colorectal cancer surveillance in ulcerative colitis. Inter-observer variation in the grading of dysplasia in biopsies from patients with ulcerative colitis has been documented, but there has been no work comparing the abilities of general pathologists with gastrointestinal pathologists. If rates of inter-observer variation differ significantly between the two groups the implication might be that all colonoscopic biopsies should be reviewed in a centre of excellence by experts in their field. The logistical and economic ramifications of such a policy would be enormous. This study was therefore conducted to directly compare the performance of specialists with general pathologists.

8.3 Introduction.

Warren and Sommers (350) recognized as early as 1949 the presence of a dysplastic lesion in the colon of patients with chronic UC. The presence of this lesion was confirmed by Dawson and Pryse-Davies in 1959. (256) However, it remained for Morson and Pang in 1967 to recommend that a search for dysplasia in rectal biopsies might help in the early detection of colorectal carcinoma. (37) Dysplasia in the context of UC is defined as an unequivocal neoplastic change of the enteric epithelium confined within the basement membrane in which it arose. (127) The histological features along with a standard classification scheme were described in 1983 in a seminal paper by Riddell et al. (127) A pathologist's decision concerning the degree of dysplasia in ulcerative colitis plays a crucial role in patient management. For example a histological diagnosis of high grade dysplasia is an indication for panproctocolectomy as a patient is very likely to have a synchronous carcinoma or is liable to develop one in the near future. (128,424,425)

Inter-observer studies regarding dysplasia in ulcerative colitis have produced varying results. The studies conducted by Riddell et al (127) and Dundas et al (426) suggested that agreement between observers is good. However these authors placed dysplasia on a linear scale by calculating an average grading of dysplasia and comparing individual observers with that average. This averaging tends to minimise any discrepancy between observers and thus produces an artificially higher rate of agreement. Work carried out by Dixon et al (176) and Melville et al (427) both found that inter-observer agreement was poor. Dixon et al's study (176) was conducted amongst histopathologists with an interest in gastrointestinal pathology and it is therefore disturbing that they found a low level of agreement even for high grade dysplasia ranging from 100% down to 33%. The rates of agreement were better over the two categories of 'dysplasia' versus 'no dysplasia' ranging from 68% to 84% but there were difficulties distinguishing reactive changes from dysplasia. Melville et al (427) noted that the overall agreement between pathologists grading specimens was poor with each pair agreeing on between 42% and 65% of slides. Again the best agreement was for slides that were said to show no dysplasia.

Recently pathologists have received unfavourable media attention concerning other cancer screening programs with some being accused of diagnostic or professional incompetence. As agreement between pathologists with an interest in gastrointestinal pathology for grading dysplasia in UC was low in their study, Dixon et al (176) postulated that it would be likely that non-specialists would fare even worse in such an exercise. The aim of this study was therefore to compare the ability of histopathologists who specialise in gastrointestinal pathology with general pathologists in the grading of dysplasia in patients with ulcerative colitis.

8.4 Methods.

All local surveillance colonoscopy pathology reports on rectal and colonic biopsy specimens from patients known to have developed colorectal cancer as a consequence of ulcerative colitis between 1985 and 1999 were reviewed to identify cases in which the presence of dysplasia had been mentioned. The slides from these cases were examined by two consultant pathologists and fifty one slides were selected as suitable for inclusion in the study. They showed a spectrum of disease and each fell into one of four categories: (1) high grade dysplasia, (2) low grade dysplasia, (3) reactive hyperplasia / cellular atypia or (4) none of these (inactive colitis). Typical microscopic appearances of high and low grade dysplasia can be seen in figures 8.1 and 8.2.

The slides were then coded and posted to histopathologists who had previously agreed to take part in the study after contact by letter. Of these there were nine pathologists with an acknowledged specialist expertise in gastrointestinal disease and nine general pathologists. The pathologists who agreed to participate were ensured of their anonymity and for this reason their names have not been divulged. The response rate was 78% (7/9) among gastrointestinal histopathologists and 67% (6/9) among general histopathologists. The thirteen observers were given a period of two weeks to read the slides and were unaware of each other's results. Each observer read the slides only once. By deliberately not heightening awareness to diagnostic standards it was hoped to assess the every day practice of pathologists. Therefore no diagnostic criteria were circulated and no clinical history was provided with the slides.

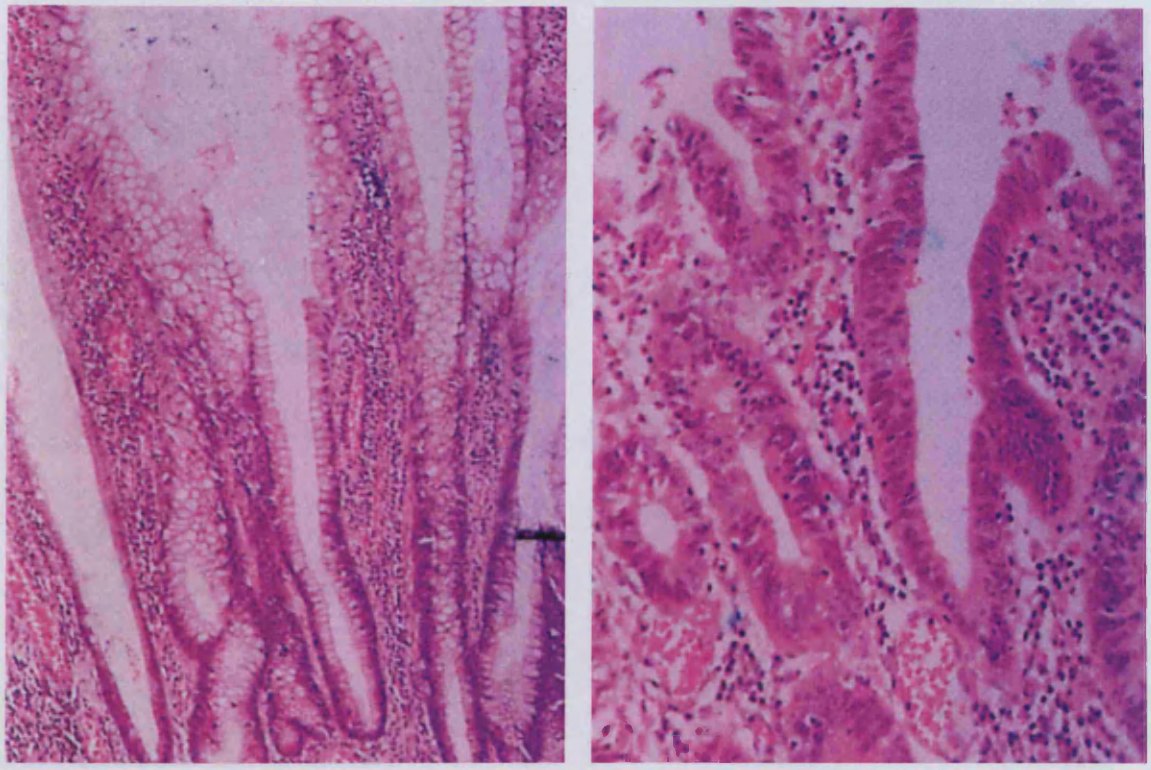
Statistical Analysis.

The sample size of 51 slides was chosen so that the study would be able to estimate the probability of disagreement between any two pathologists using a 95% Confidence Interval (CI) to within +/- 10%, assuming that the underlying probability of disagreement was 15%. (428)

The observers responses were analysed using Kappa statistics. Kappa is an index of observer agreement which indicates how much greater it is than would be expected by chance. (390) The value of Kappa can range from -1.0 to +1.0. A value of 0 indicates chance agreement only, while a value of +1.0 indicates perfect agreement. It is generally accepted that a value of +0.75 or above reflects excellent agreement, a value of 0.4 to 0.75 suggests fair to good agreement and a value of less than 0.4 means agreement is poor. Pairwise, overall and category specific Kappa statistics were calculated. (429)

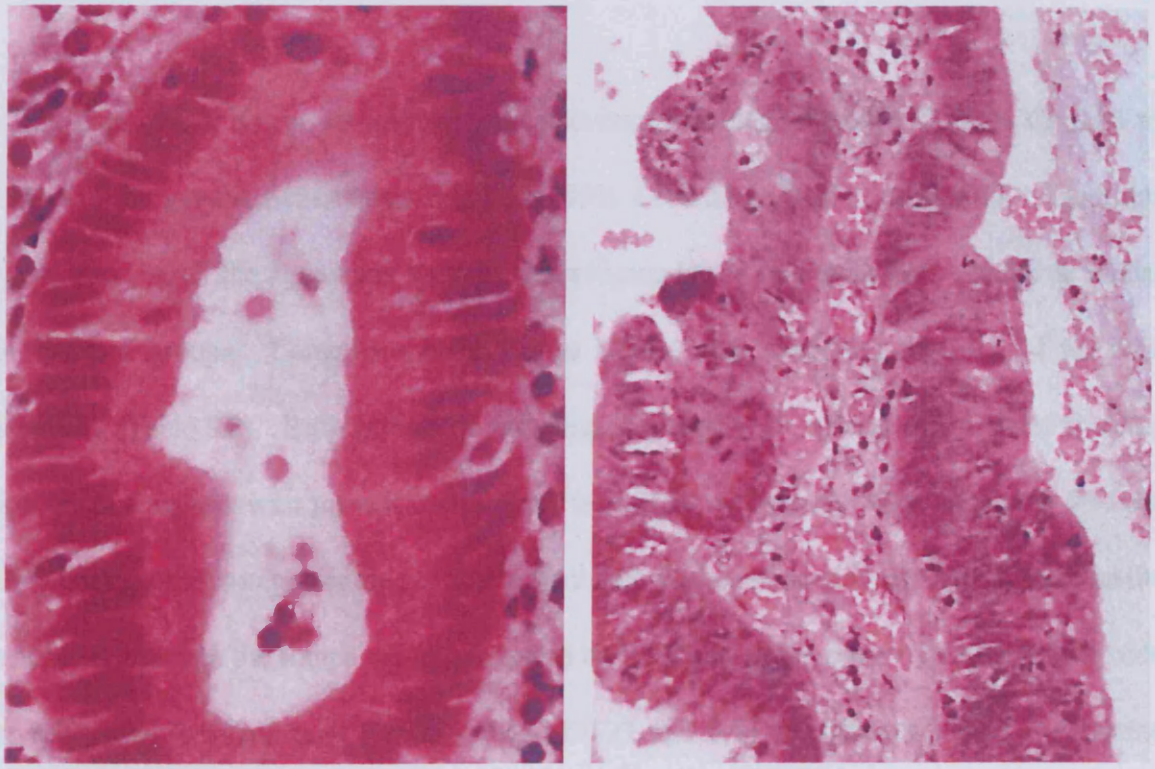
The number of slides allocated to each category was recorded. The gradings of the thirteen observers were also examined, searching for slides on which there was total agreement and disagreement, slides where all gastrointestinal pathologists agreed / disagreed and slides where all general pathologists agreed / disagreed.

Figure 8.1. Dysplasia in ulcerative colitis (low power).



Histological appearance of low grade dysplasia in the lower crypts (left) and high grade (severe) dysplasia in the colonic mucosa (right). In the high grade, the markedly abnormal nuclei show pleomorphism and pseudostratification. H&E stain, x 120.

Figure 8.2. High power views comparing mild (low grade) dysplasia with severe (high grade) dysplasia.



In mild dysplasia (left), the cells are hyperchromatic with mucin loss, but nuclear polarity is regular. Polarity is completely lost in severe dysplasia (right). H&E stain, x 480.

8.5 Results.

For each pair of observers an unweighted Kappa statistic was calculated (Table 8.1). Pathologists 1-7 were those who have a special interest in gastrointestinal pathology and pathologists 8-13 were general pathologists. The Kappa value varied between 0.12 and 0.51 for gastrointestinal histopathologists and 0.11 and 0.48 for general histopathologists. This indicates that agreement between pairs of observers was generally poor (430) irrespective of whether they had any interest in gastrointestinal disease.

The overall Kappa statistic for gastrointestinal pathologists was 0.30 (95% CI=0.26 to 0.34) and for general pathologists was 0.28 (95% CI=0.23 to 0.32) (Table 8.2). Again this shows that overall the agreement between pathologists is not only poor but remarkably similar for the two groups. Category-specific Kappa values were calculated for each of the four categories (Table 8.2). Both groups of pathologists had greatest agreement for slides showing high grade dysplasia with general pathologists tending to agree more often (Kappa = 0.61 vs. 0.54). In the other categories the gastrointestinal pathologists showed closer agreement than the generalists although the Kappa values are low in both groups. Inter-observer variation was wide for low grade dysplasia with Kappa values of 0.23 and 0.18 for gastrointestinal and general pathologists respectively. Reactive hyperplasia / cellular atypia produced similar Kappa statistics of 0.25 and 0.16 and the fourth category of inactive colitis also gave low Kappa values of 0.16 and 0.14.

Table 8.1. Unweighted Kappa Statistics (with 95% confidence intervals) for paired comparisons.

	Path 1	Path 2	Path 3	Path 4	Path 5	Path 6	Path 7	Path 8	Path 9	Path 10	Path 11	Path 12	Path 13
Path 1	-	0.43 0.2 to 0.65	0.25 0.09 to 0.41	0.12 0.02 to 0.23	0.15 0.02 to 0.27	0.59 0.32 to 0.87	0.48 0.24 to 0.72	0.2 0.05 to 0.34	0.22 0.05 to 0.38	0.37 0.17 to 0.57	0.19 0.05 to 0.33	0.23 0.07 to 0.39	0.33 0.14 to 0.53
Path 2		-	0.12 0.01 to 0.23	0.16 0.03 to 0.28	0.24 0.08 to 0.39	0.40 0.18 to 0.62	0.36 0.16 to 0.57	0.24 0.09 to 0.40	0.15 0.02 to 0.28	0.28 0.09 to 0.41	0.19 0.05 to 0.33	0.27 0.10 to 0.44	0.26 0.09 to 0.43
Path 3			-	0.44 0.23 to 0.65	0.38 0.19 to 0.58	0.27 0.10 to 0.44	0.39 0.18 to 0.59	0.18 0.05 to 0.32	0.24 0.08 to 0.40	0.47 0.25 to 0.69	0.33 0.15 to 0.52	0.52 0.29 to 0.75	0.35 0.16 to 0.54
Path 4				-	0.44 0.23 to 0.65	0.18 0.05 to 0.31	0.17 0.04 to 0.30	0.25 0.09 to 0.41	0.17 0.04 to 0.3	0.20 0.06 to 0.34	0.27 0.11 to 0.44	0.31 0.14 to 0.49	0.17 0.05 to 0.3
Path 5					-	0.27 0.11 to 0.44	0.26 0.1 to 0.43	0.29 0.11 to 0.46	0.14 0.02 to 0.25	0.29 0.11 to 0.44	0.2 0.06 to 0.34	0.48 0.26 to 0.71	0.12 0.01 to 0.23
Path 6						-	0.51 0.25 to 0.76	0.14 0.02 to 0.26	0.35 0.14 to 0.57	0.36 0.16 to 0.57	0.24 0.08 to 0.39	0.38 0.18 to 0.59	0.43 0.21 to 0.66
Path 7							-	0.13 0.02 to 0.25	0.32 0.12 to 0.52	0.39 0.18 to 0.6	0.34 0.15 to 0.54	0.43 0.21 to 0.65	0.40 0.19 to 0.62
Path 8								-	0.13 0.01 to 0.24	0.21 0.06 to 0.36	0.13 0.02 to 0.24	0.33 0.14 to 0.51	0.11 0.01 to 0.21
Path 9									-	0.32 0.13 to 0.51	0.28 0.19 to 0.45	0.25 0.09 to 0.42	0.26 0.09 to 0.43
Path 10										-	0.21 0.06 to 0.36	0.48 0.26 to 0.71	0.3 0.12 to 0.48
Path 11											-	0.39 0.19 to 0.59	0.43 0.22 to 0.65
Path 12												-	0.29 0.12 to 0.47
Path 13													-

Path = Pathologist. Very few Kappa values over 0.5 are seen indicating poor inter-observer variation.

Table 8.2. Unweighted Kappa values for the two groups of pathologists.

	G.I. Pathologists (n=7)	General pathologists (n=6)
Overall Kappa (95% CI)	0.30 (0.26 to 0.34)	0.28 (0.23 to 0.32)
Kappa for High Grade Dysplasia (95% CI)	0.54 (0.48 to 0.6)	0.61 (0.53 to 0.69)
Kappa for Low Grade Dysplasia (95% CI)	0.23 (0.17 to 0.29)	0.18 (0.10 to 0.26)
Kappa for Reactive Hyperplasia / Cellular Atypia (95% CI)	0.25 (0.19 to 0.31)	0.16 (0.08 to 0.24)
Kappa for "none of these" category (95% CI)	0.16 (0.10 to 0.22)	0.14 (0.06 to 0.22)

The kappa values show poor inter-observer agreement especially for low-grade dysplasia and reactive changes.

Concordance between all thirteen pathologists, between the seven gastrointestinal pathologists and between the six general pathologists is shown in table 8.3. Of the 51 slides there was total concordance in only four (7.8%; 95% CI=0.4% to 15.2%). Gastrointestinal pathologists agreed fully on six slides (11.8%; 95% CI=3.0% to 20.6%) and general pathologists agreed totally on eight (15.7%; 95% CI=5.7% to 25.7%). Concordance was greatest for slides graded as showing high grade dysplasia.

Table 8.3. Concordance Between Pathologists in Grading Dysplasia.

	All Pathologists Agree (n=13)	All G.I. Pathologists Agree (n=7)	All General pathologists Agree (n=6)
High Grade Dysplasia	4 (7.8%)	4 (7.8%)	5 (9.8%)
Low Grade Dysplasia	0	0	2 (3.9%)
Reactive Hyperplasia / Cellular Atypia	0	2 (3.9%)	1 (2%)
"None of These" Category	0	0	0

There was total agreement in only 7.8% of slides.

8.6 Discussion.

This study has shown that inter-observer agreement in the classification of biopsies in ulcerative colitis is poor in both general pathologists and those who are experts in the field of gastrointestinal pathology with overall Kappa statistics of 0.28 and 0.30 respectively. There is no support for the contention that specialist histopathology centres concentrating specifically on the interpretation of all surveillance colonoscopy biopsies from around the country would be of any benefit. Other studies have also found that specialists are just as likely to disagree as generalists in other fields of pathology. McCluggage et al noted that inter-observer agreement was no better between two observers with an interest in gynaecological pathology than other pairs of observers when grading cervical intra epithelial neoplasia. (431) Similarly, O'Sullivan et al (432) found that although specialist cytopathologists brought a different viewpoint to the reporting of cervical smears than histopathologists, they lacked standardization in the reporting of smears despite guidelines issued by the British Society for Clinical Cytology. The automation of slide reading for colonic dysplasia is in an early phase and at present offers no more an effective solution to the problem of inter-observer variation. (433)

The results show that agreement was fair for high grade dysplasia but there was haphazard disagreement in all other categories. In other words observers disagreed about low grade dysplasia just as much as reactive hyperplasia / cellular atypia. This underlines the difficulties involved in distinguishing reactive and dysplastic changes with any consistency. When a clinician sees low grade dysplasia on a pathology report from a surveillance colonoscopy, current recommendations state he should at least repeat the procedure with further biopsies to confirm the diagnosis. However, the endoscopist may have difficulty obtaining biopsies from the initial area especially if the dysplastic biopsies came from an area of

flat dysplasia which could be macroscopically indistinguishable from normal mucosa. (170) In addition, the pathologist may not interpret the biopsy as dysplastic even if it came from the same region as previously. Some authors suggest that if *low or high* grade dysplasia has been found the clinician should recommend immediate colectomy. (420,434,435) Is it therefore worthwhile repeating colonoscopies once dysplasia has been identified? This is a dilemma faced by gastroenterologists as dysplasia in flat mucosa detected during one colonoscopy may not be found or confirmed during a follow-up colonoscopy. The audit reported in chapter seven showed that 96% of gastroenterologists would repeat the colonoscopy in this situation with only 4% discussing immediate colectomy with their patient. If immediate surgery was carried out there may be an excess of colectomy specimens without any semblance of dysplasia. However, if low grade dysplasia is found in the presence of a dysplasia associated lesion / mass (DALM) there is a much stronger case for immediate surgery as the predictive value for high grade dysplasia or cancer is much higher. (123,128)

Inter-observer variation studies are artificial and may not give an accurate representation of a clinical situation for several reasons. Technical differences may arise. The archive material in this study came from two centres and the choice and quality of the haematoxylin and eosin stains may not have suited individual pathologists. Clinical details were not provided with the slides. In reality a pathologist will receive some information with the biopsies even though they may only be cursory remarks such as "U.C for fifteen years, surveillance colonoscopy". Pathologists often review previous specimens from the same patient and will be more impressed by the changes between specimens than by the particular features of a single specimen. In a difficult case more time will be given to a biopsy than in an inter-observer variation study. Pathologists give a discursive description in their reports rather than committing themselves exclusively to a definite diagnosis and often review the biopsies in multidisciplinary meetings

where an appropriate management plan emerges. Thus inter-observer variation studies are contrived and may explain to some extent the wide variations observed between participants.

This study has a number of limitations. As the slides were posted to each participant, they were not reviewed by pathologists in a controlled environment. Although most doctors appreciate research is important, it inevitably takes second place to every day work commitments. Therefore it is unlikely that the slides would have been examined under optimum conditions i.e. in a leisurely manner at the beginning of the day. More likely they would have been reviewed a few at a time between other commitments or at the end of a busy day. Also it cannot be guaranteed that participants did not consult a textbook or the opinion of a colleague whilst reviewing the slides. It could be argued that the results would have been improved if diagnostic criteria had been circulated as studies in other fields of pathology such as the grading of cervical intra-epithelial neoplasia, (431) cutaneous malignant melanomas (436) and chronic gastritis (437) demonstrate that an awareness of a grading system improves Kappa statistics. However, this is unlikely in this study as one would expect gastrointestinal pathologists to be familiar with a grading system and their Kappa statistics were no better than those of general pathologists.

The results might have been improved by including an "indefinite" category (as there is in the Riddell classification) as some pathologists may have called a number of cases reactive because they were forced to select a single diagnosis whereas in reality there is no clear cut answer. The results may also be improved by inviting pathologists to examine the slides in one location simultaneously under examination type conditions. This would also have the added benefit of providing an opportunity for discussion and perhaps developing new guidelines after the exercise had been completed.

There are many other examples in pathology where a significant degree of inter-observer variation has been recorded especially where a grading system is used. (438-445) The public and health service administrators have an unreasonable expectation of zero error concerning cancer screening programs. They are largely unaware that errors are unavoidable even in the hands of experts and the fear of litigation following a false negative diagnosis is beginning to threaten various programs. (446) In 1996 the College of American Pathologists developed guidelines after a conference on liability and quality issues in cervical cytology. (447) They stated that even with the use of automated re-screening devices errors still occur and that skilled cytologists have an irreducible false negative rate of at least 5%. Other objective tests have been investigated for diagnosing pre-malignancy in ulcerative colitis. They include mucin and lectin histochemistry, (186) flow cytometry with DNA aneuploidy, (175,448) immunohistochemistry, (449) morphometry (450) and more recently digital image analysis. (451) Despite these techniques, the histological identification of dysplasia remains the gold standard in cancer surveillance in ulcerative colitis and will do so for the foreseeable future. It must therefore be made clear to patients participating in surveillance that such programs carry a certain rate of variability which does not mean the pathologist is incompetent and that zero error cannot be expected.

Routine double reporting of some specimens has been practised in some areas with a resulting increase in workload. The present study indicates that the extra effort involved is not effective in avoiding grading errors at the borderline between reactive and low grade dysplasia or between low and high grade dysplasia. In practice it is likely that a general histopathologist would discuss a borderline biopsy with a colleague before making a diagnosis of dysplasia. However, these results suggest that two heads are not better than one for light microscopy and reinforce the need for a molecular biology or immunocytochemical technique to identify early

neoplastic change in tissue samples from a variety of sites. The following chapter reports an investigation into CYP1B1 (an isoenzyme of cytochrome P450) and its potential role as a new marker of dysplasia in ulcerative colitis.

Acknowledgement.

I would like to thank all the pathologists who took part in this study and appreciate the difficult and tedious analysis that they undertook.

Chapter 9.

An investigation to determine the potential of cytochrome P450 isoenzyme CYP1B1 as a possible marker of dysplasia in the colon of patients with ulcerative colitis.

9.1 Summary.

Cytochrome P450 CYP1B1 has been demonstrated at the protein level in 122/127 human tumour samples (including colon, breast, lung, oesophagus and skin) and in 0/128 corresponding controls. (199) On the basis of this finding it was suggested that CYP1B1 would be an ideal marker for the diagnosis of cancer.

In order to test this hypothesis, monoclonal antibodies were raised against CYP1B1 and these antibodies were used for immunohistochemical staining of paraffin-embedded routine biopsies from patients with normal colon, active ulcerative colitis, Crohn's disease, dysplastic ulcerative colitis and frank adenocarcinoma of the colon. Antibodies LDS 100 and LDS 101 were used and N-acetyltransferase Type I, which is strongly expressed in normal colonic mucosa and tumours, was used as the positive control. (452) Slides were evaluated blind.

Low intensity staining was detected in dysplastic and malignant colonic mucosa from patients with colitis. It was also seen in morphologically abnormal cells in two cases of active ulcerative colitis. No staining was detected in normal tissue or in the samples from patients with Crohn's disease.

The results are encouraging in that they indicate the potential usefulness of CYP1B1 in the early detection of colorectal cancer in patients with ulcerative colitis. However, the staining detected was weak and inconsistent and a significant amount of further development is necessary before CYP1B1 can be used as a reliable marker of dysplasia or malignancy.

9.2 Theoretical justification for this work.

The previous chapter and other studies (176,427) have shown that there is a large degree of inter-observer variation amongst pathologists when grading dysplasia in surveillance colonoscopy biopsies from patients with ulcerative colitis. A marker of precancerous tissue would help in the grading of dysplasia and could improve the predictive value of surveillance. CYP1B1 is an isoenzyme of cytochrome P450 that is expressed in a wide range of human tumours. (199) If CYP1B1 is expressed in dysplastic tissue in addition to frankly malignant tumours it will have significant benefits in identifying precancerous tissue when screening for colorectal cancer in patients with ulcerative colitis.

9.3 Introduction.

The cytochromes P450 are a large family of haemoproteins which have a major role in the oxidative metabolism of a wide range of xenobiotics and some endogenous compounds. Members of the cytochrome P450 family of drug metabolising enzymes play an important role in cancer because they have the capacity to both activate and to detoxify drugs and carcinogens. Most P450s are found in normal tissue, although their expression may be altered in tumours. However, cytochrome P450 1B1 (CYP1B1) is unique in that it appears to be expressed only in malignant cells. In addition, it seems that many, if not all types of malignant cells express this P450 isozyme, suggesting CYP1B1 could be of value as a general tumour marker. (199,453,454) Previous studies on CYP1B1 have concentrated on purification, characterisation and cloning of this enzyme from human and mouse cells, with little attention paid to its expression and regulation at the protein level. (455-457) Recently, CYP1B1 expression has been found in advanced breast and colonic tumours. (199,454) These findings suggest it could be a marker for malignant cells in these tissues. These studies were limited by use of a

polyclonal antibody which could have recognised proteins other than CYP1B1 and, in addition, only advanced tumours were studied. To date no studies on the colon have looked at early cancers or precancers (dysplasia).

Any molecular medical technique for the early diagnosis of carcinoma must, in order to be clinically and economically viable, be able to distinguish between inflammation, dysplasia and early carcinoma. The aim of this investigation was to extend the published work on CYP1B1 in advanced tumours by using highly specific monoclonal antibodies to ensure that it is not expressed in normal and inflamed tissue in ulcerative colitis and consequently investigate whether it is present in dysplastic tissue.

9.4 Methods.

The investigation was conducted with Professor D. Burke and Dr L. Stanley at the Department of Pharmaceutical Sciences of the De Montfort University in Leicester. Studies from Professor Burke's laboratory in Aberdeen (199) capitalized on the fact that polyclonal antisera raised against CYP1A1 also recognize CYP1B1. However cross reacting antisera were not appropriate for detailed studies of CYP1B1 and so Professor Burke and Dr Stanley undertook the production of monoclonal antibodies (McAbs) against CYP1B1:

An antipeptide strategy was adopted for the McAb production. This part of the project was undertaken as part of a collaboration with Dr Roger James (Leicester University). The published deoxyribonucleic acid (DNA) sequence of CYP1B1 was used to synthesize three peptides corresponding to the N- and C- termini of CYP1B1:

1. PB1	CGTSLSPNDPW	N-terminus.
2. PB2	AVQNLQAKETC	C-terminus.
3. PB3	CAVQNLQAKET	C-terminus.

The difference between peptides PB2 and PB3 is that in PB2 the C (cysteine) residue is present naturally whereas in PB3 the natural C residue is omitted and one has been added at the N-terminal end for conjugation. Their purities were assessed by high performance liquid chromatography and mass spectrometry. Each peptide was conjugated to the carrier protein, keyhole limpet haemocyanin (KLH), and the resulting conjugates were used to immunize mice (two mice per peptide) for McAb production. Preliminary antibody (from blood samples) was screened by enzyme-linked immunosorbent assay (ELISA) using

CYP1B1 in two forms: (a) microsomes from human lymphoblastoid cells constitutively expressing recombinant CYP1B1 (Gentest - a commercially available antiserum) and (b) inclusion bodies from *E.coli* expressing the C-terminal portion of human CYP1B1 (kindly provided by Dr. W.T. Melvin, University of Aberdeen). Hybridomas were made using the spleen from this mouse and secreted monoclonal antibodies were screened. Individual clones were selected and their binding characteristics determined. Cell culture supernatants were screened in order to expedite the characterization of the McAbs. Two antibodies, now named LDS 100 and LDS 101, were obtained.

Validation of the McAbs took place in two stages. Initially, ELISA's and Western immunoblots were used to identify the best McAbs for detection of CYP1B1 in the pure state and in microsomes. Secondly, Western immunoblots were carried out using a range of different P450 isozymes in order to ensure that McAbs selected are monospecific for CYP1B1. Once these experiments were completed the McAbs could be used with confidence for immunohistochemistry.

Once the antibody validation had been completed by Professor Burke, Dr Stanley and their collaborators, a study was conducted to investigate the expression of CYP1B1 in inflamed, quiescent, dysplastic and carcinomatous tissue in patients with inflammatory bowel disease (IBD). Archival colon samples from seventeen patients with IBD (some of the same samples from patients identified in chapter 8) were provided by Dr Hugh MacKay at the Department of Pathology, Leicester General Hospital. Three patients had adenocarcinomas, three dysplasia, four active ulcerative colitis, three Crohn's disease, two quiescent Crohn's colitis and two came from normal colons. The samples were randomized, fixed in neutral buffered formalin, embedded in paraffin wax, sectioned and placed on aminopropyl triethoxysilane (APES)- treated microscope slides.

The immunohistochemical staining of tissue was carried out according to the following unpublished protocol which had been developed by Dr Stanley. Each experiment was run with a positive control (NAT 177 - N-acetyltransferase). This is a polyclonal rabbit antiserum raised against human N-acetlytransferase and is present in all epithelial cell types.(452) Two negative controls were used (one without any second antibody to ensure that the peroxidase block had been successful and the other with LDS 56 (an irrelevant McAb) to ensure there was no non-specific binding of the primary antibody).

1. The sections were dewaxed in xylene for 4x15 minutes at room temperature.
2. Slides were then rehydrated in 2x100% isopropyl alcohol, 1x70% isopropyl alcohol, 1x water and 2x 0.05M Tris-HCl (pH 7.6) containing 0.15M sodium chloride (TBS). (5 minutes each).
3. Endogenous peroxidase was inhibited with freshly prepared 1% hydrogen peroxide in TBS for 30 minutes
4. Non-specific binding was inhibited with 1% normal horse serum in TBS for 30 minutes. The primary CYP1B1 monoclonal antibody was diluted with TBS containing 1% normal horse serum and 50-200 microlitres layered on to each slide. Titration experiments were conducted to determine which concentration of antibodies gave the clearest staining without significant background staining. The concentrations tested were 1:5, 1:50, 1:100, 1:200, 1:500, 1:1000 and 1:2000. A dilution factor of 1:100 was subsequently used in the study. The slides were then incubated overnight at 4°C.
5. On day 2 of the experiment the sections were firstly washed with TBS for three successive ten minute periods to remove unbound antibody.
6. The second antibody was then diluted with normal horse serum and TBS and applied to each slide and incubated for 30 minutes.

7. After three further washes in TBS (10 minutes each), ABC (Avidin-Biotin Complex) staining reagent was added to each slide and incubated for 30 minutes.
8. After a 10 minute TBS wash the sections were colourimetrically stained with filtered diaminobenzidine / hydrogen peroxide using Sigma Fast tablets and then lightly counterstained with haematoxylin for approximately 1 minute. The sections were then washed with tap water until the nuclei turned blue.
9. Finally the sections were dehydrated (with five minutes each of 1x water, 1x 70% isopropyl alcohol and 2x 100% isopropyl alcohol), air dried and mounted in glycerine jelly (DPX).

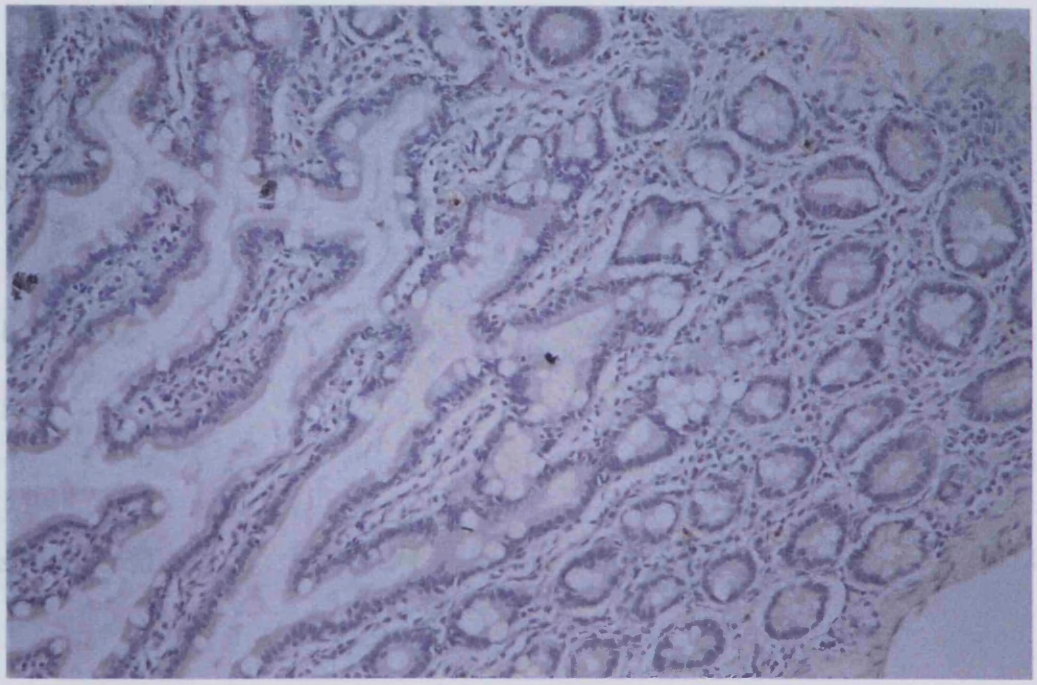
The sections were examined by light microscopy by Dr Stanley and colleagues to establish the presence or absence of immunostaining and its distribution.

9.5 Results.

Immunohistochemistry for the P450 isoenzyme CYP1B1 showed that small areas of immunoreactivity could be detected in dysplastic and frankly neoplastic tissue. There was no detectable immunoreactivity for CYP1B1 in any of the normal colorectal tissue (Figure 9.1). In addition, no staining was seen in quiescent or active Crohn's disease. However, there was a small amount of staining in inflamed colonic tissue from two patients with ulcerative colitis. CYP1B1 immunoreactivity was not detected in one of the tumour slides (Table 9.1).

Although staining for CYP1B1 was definitely present in some of the tissues, its intensity was low. This is demonstrated in figure 9.2. In addition the pattern of staining was dissimilar in different sections with the distribution of CYP1B1 expression varying. Sometimes CYP1B1 was detected in the nucleus of cells whereas in other slides staining was seen within the cytoplasm.

Figure 9.1. Normal colorectal tissue after staining for CYP1B1.



There is no detectable immunoreactivity for CYP1B1 in normal colorectal tissue.

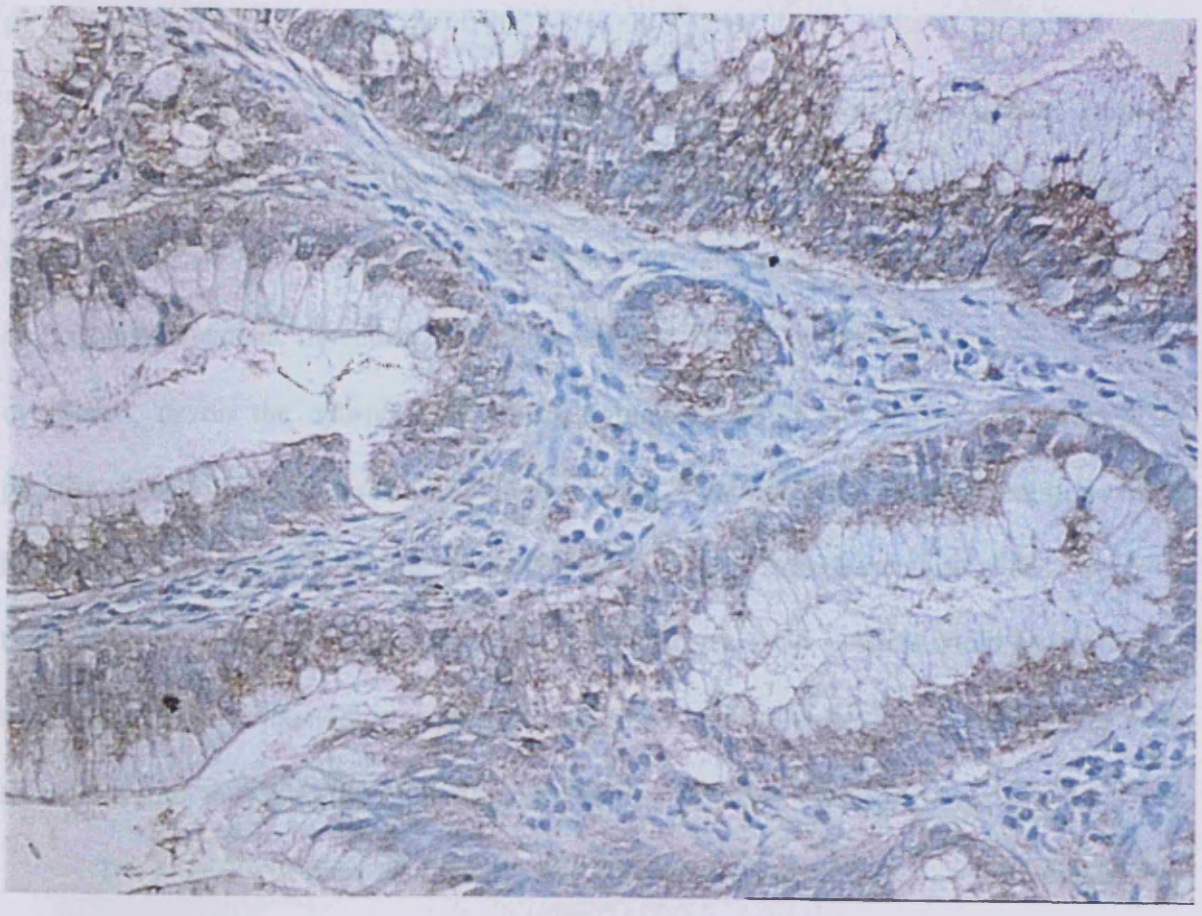
Table 9.1. Results indicating the expression of CYP1B1.

DIAGNOSIS	LDS 100 / 101 (CYP1B1)	LDS 56 (negative control)	NAT 177 (positive control)
Normal	0/2	0/3	N.D
Crohn's colitis (quiescent)	0/3	N.D	2/2
Crohn's colitis (active)	0/2	0/1	1/1
Ulcerative colitis	2/4	0/1	2/2
Dysplasia	2/2	N.D	2/2
Neoplasia	5/6	1/2	2/2

N.D = Not done

The results indicate that small areas of staining for CYP1B1 could be detected in dysplastic and neoplastic colonic tissue in ulcerative colitis.

Figure 9.2. High power view showing staining for CYP1B1 in mildly dysplastic tissue.



This is a typical section demonstrating the low intensity of staining. In this slide the weak staining is mainly seen in the cytoplasm.

9.6 Discussion.

CYP1B1 has been detected by immunostaining in dysplastic tissue from patients with chronic ulcerative colitis. However, the staining was very faint in most of the specimens and was not a consistent finding. Some staining was also seen in a small number of biopsies from inflamed tissue. Not all the tumours tested were positive for CYP1B1. For these reasons CYP1B1 cannot be used as a marker of malignancy in ulcerative colitis at its present stage of development.

There may be a number of reasons why the experiments have failed to produce dependable results. Firstly, it may have been unwise to use archival material for immunohistochemical staining. Bertheau et al (458) demonstrated that the immunohistochemical detection of some antigens located either in the nucleus, in the cytoplasm, or on the cytoplasmic basement membrane can be impaired by storage of paraffin slides for periods as short as three months. Therefore one should be cautious when interpreting retrospective immunohistochemical studies on stored unstained slides. Some of the paraffin slides used in this study were up to four years old and this could have affected the results. An obvious solution to this problem would be to repeat the study using fresh tissue and stain the slides the same day (or certainly within one week).

The intensity of the staining may have been weak as monoclonal antibodies (McAbs) were used in the study as opposed to polyclonal antibodies (PcAbs). The reason for using McAbs was they react with only a single epitope on a molecule whereas PcAbs frequently recognise a number of antigenic sites on a target molecule. (459) In consequence it might be predicted that PcAbs will always allow a greater accumulation of immunoglobulin molecules on an individual target molecule in the tissue sample, and will hence inevitably lead to a greater intensity of immunocytochemical labelling than can be achieved using

McAbs. However, although staining with McAbs may be faint they are much cleaner reactions than the staining seen with PcAbs. Polyclonal antisera contain a mixture of antibodies specific for the immunising antigen together with an excess of non-specific antibodies directed against unrelated antigens. This, along with cross linking between PcAbs amplifying the degree of staining, constitutes a major potential cause of unwanted staining. Monoclonal antibodies in contrast are largely free from this problem of background staining due to non-specific immunoglobulin. Despite the weak staining often elicited with McAbs it was decided that a McAb should be used in the study conducted as they are inherently more discriminative reagents.

The results from this investigation are encouraging in that staining was present in some slides. However, a significant amount of further development is necessary and work should be undertaken to optimize the staining by means of antigen retrieval. This could be carried out in a number of ways. Firstly, more concentrated stocks of antibody could be generated and optimised using Integra flasks. These special cell culture flasks have recently become available and allow the production of much more concentrated supernatants (in the order of 100-1000 times more concentrated than previously). Secondly, the histological slides could be pre-incubated with a protease (e.g. trypsin) to break the formaldehyde bonds thus releasing more antigen. Thirdly, it may be beneficial to use the technique of microwave ablation to retrieve more antigen. Finally it may be possible to achieve sharper tissue staining if the slides were incubated with fresh, dry isopropanol prior to mounting in DPX or the final colour reaction could be intensified using metal ions such as nickel and copper.

Some of the staining for CYP1B1 was seen in the nucleus and in other areas in the cytoplasm. It is therefore possible that CYP1B1 migrates from one part of the cell to another according to different stages of the cell cycle. Further experiments with Western

blotting conducted by Dr Stanley have also detected CYP1B1 in both the nucleus and microsomes. Only one 52 kiloDalton (kD) band of CYP1B1 was seen in the microsome lanes whereas three bands of 30kD, 52kD and 60kD were seen in the nucleus lane (Figure 9.3). It is thus possible that CYP1B1 is processed in different portions of the cell or it may have a role transporting steroids between different cell compartments. Work is currently being undertaken by staff at De Montfort University to validate this observation.

From the work conducted, although small areas of staining for CYP1B1 were detected in dysplastic tissue, at present this cannot be related directly to the subsequent development of a tumour. However, if the technique can be perfected, and CYP1B1 is shown to be expressed consistently in dysplastic and malignant tissue, this immunohistochemical test would be much more objective than the existing morphological criteria used to detect early neoplastic changes. Ideally a prospective study where the expression of CYP1B1 is determined in repeated biopsies from a large number of patients undergoing surveillance colonoscopies should be conducted. In this way CYP1B1 could be related to the disease state as well as to the subsequent development of tumours. Further work (at De Montfort University) is planned to address the question of whether CYP1B1 can be detected in samples obtained by non-invasive methods (blood samples, or better still urine). If detection of CYP1B1 in body fluids is possible, then the opportunity exists to develop a blood or urine test for screening purposes. This would potentially have much wider applicability than a purely immunohistochemical screening approach.

Figure 9.3. Immunodetection of CYP1B1 in subcellular fractions.

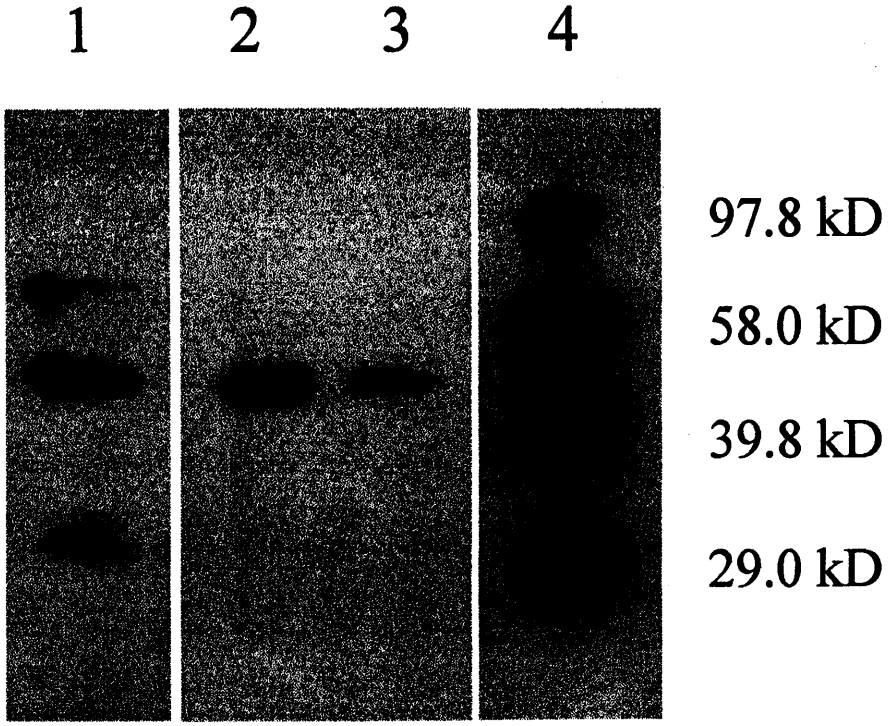
1. Nuclear fraction.

2. Microsomal fraction.

3. Microsomal fraction.

4. Markers

Antibody LDS101



Western blot demonstrating the presence of CYP1B1 in both the nucleus and cytoplasm.

Chapter 10.

Conclusions, discussion and recommendations.

The hypothesis that underlies this thesis is that screening for colorectal cancer in ulcerative colitis is ineffective. The reasons are unclear but may include uncertainty as to the exact magnitude of risk, poor targeting through an incomplete understanding of risk factors leading to cancer, inadequate patient knowledge concerning the risk, poorly organised surveillance programs and limited skills amongst endoscopists and histopathologists, with difficulties identifying areas of dysplasia and disagreement about its grading.

The discussion which follows summarises the main conclusions of this thesis and relates them to the original hypothesis. The discussion will not repeat what has already been stated in previous chapters but will emphasise the major conclusions. The limitations of the studies will be considered and areas for future research identified. Although some authors feel the colorectal cancer risk in young patients with colonic Crohn's disease is similar, (460-462) only patients with UC have been studied and so the conclusions of this thesis should be limited to this group.

Magnitude of the risk.

The meta-analysis reported in chapter 2 used new statistical techniques and estimated ***the colorectal cancer risk for any patient with ulcerative colitis to be 2% at ten years, 8% at twenty years and 18% after thirty years of disease.*** This is a little lower than was previously thought but does not differ from the general consensus that there is an exponential rise with increasing duration of disease. (61,63,64)

Although this meta-analysis has some limitations it is the first and largest attempt to define the risk of cancer in ulcerative colitis across the board. The power of any meta-analysis is highly dependent on the quality of data collected and reported in the selected studies. For example, in many publications the indications for proctocolectomy were far from clear. Ideally all cases where an operation was performed for a diagnosis of colorectal cancer should have

been excluded and only procedures for uncontrolled disease or for cancer prophylaxis included. However, if all studies where this was not apparent had been excluded, too few reports would have been left in each category to allow any meaningful analysis. This is particularly so when one bears in mind that this is only one of several criteria under consideration.

It could be argued that the analysis was incomplete as only publications in the English language were included. The reason for excluding foreign language studies was the difficulty of extracting information accurately from such studies. If papers in foreign languages had been translated, one would have been dependent on the accuracy of those translations and their not having missed out or misinterpreted data. Furthermore, a Medline search for non-English language articles from the period 1966 to 1999 using colorectal cancer, dysplasia, surveillance and ulcerative colitis as keywords resulted in only 3 foreign language studies. One of these was in Japanese (463) and two were in Portuguese. (464,465) If this search over the last 33 years is representative of the whole time span since colorectal cancer in UC was first reported in 1925, very few studies will have been missed in the meta-analysis and therefore the results are likely to be representative. They are certainly representative of the English speaking world.

Other limitations in the analysis come from the problem of comparing referral centres with population-based studies. There was a clear tendency for more recent studies to be population-based and this could be the underlying reason why ***the analysis demonstrated a decrease in colorectal cancer incidence in more recent times.*** In addition, many of the population-based studies and studies from hospitals serving a defined catchment area came from Scandinavia and this may be part of the reason why ***the incidence appears lower in Scandinavia than in Britain or the USA***. If the meta-analysis were to be repeated it may be improved by dividing these groups of studies and performing separate analyses to determine whether this is the case. However, the problem of having a small number of studies in each

category of the meta-analysis would arise again and this is why such an approach was not chosen originally.

Evaluation of risk factors.

A possible reduction in colorectal cancer risk through the use of aminosalicylates has been previously reported (74,329,361) and is supported by the findings in chapter three of this thesis. Having recorded the drug history for 5-10 years preceding the development of cancer in 204 patients the data showed that ***regular consumption of 5-ASA compounds, in particular mesalazine, reduces colorectal cancer risk by 81%.*** The possible reasons for a decrease in cancer risk through the use of 5-ASA medication have previously been described (75,76,364,365,369-372) and now that the evidence for regular consumption of such compounds as a means of preventing cancer is more compelling, studies concentrating on how to increase compliance with medication merit further investigation.

Visiting a hospital doctor frequently and having at least 1-2 colonoscopies over the course of the disease were also protective although these factors are likely to be markers for compliance. People attending outpatients and having colonoscopies are also more likely to take their medication regularly. ***Patients who developed colorectal cancer were five times more likely to have a family history of sporadic colorectal cancer than controls.*** Although this finding lost its significance during the model development (possibly due to a small numbers effect) it seems likely that it could still be an important risk factor which should be taken into consideration in any attempts to better target screening. Indeed similar results were published from work conducted at the Mayo Clinic which showed that a family history of colorectal cancer in first degree relatives was twice as common in UC patients with colorectal cancer. (94)

The matching criteria used in the study could be improved if the study were to be repeated. The actual age of the cases and controls was used as matching criteria rather than age of onset of colitis. The latter would have been more valid especially if one factors together disease duration within a five year window. For example, it was possible to have a case who was 25 years old at onset of colitis, and after 15 years of disease developed cancer at age 40. The matched control however, could be 15 years old at colitis onset and only followed for 10 years, so that he or she would only be age 25 at the study endpoint and might not even be old enough to have "shown" a cancer.

No published evidence exists that a surveillance program has any effect on cancer risk in ulcerative colitis. Any future study should record the number of colonoscopies which were carried out specifically for surveillance purposes rather than other reasons such as disease exacerbation. In this way a direct estimate of the value of regular surveillance in terms of reducing colorectal cancer mortality could be made. In addition, the use of immunosuppressive agents should have been noted as these may have contributed to the beneficial effects demonstrated for aminosalicylates.

Patient knowledge of cancer risk.

Chapter four of this thesis reported the development and validation of a tool to measure inflammatory bowel disease knowledge (the CCKNOW score). It is only the second index to be developed in this area and was tested on a significantly larger number of patients than the previous questionnaire. (108) It showed that ***patients who are members of the National Association of Crohn's and Colitis are significantly more knowledgeable than non-members.*** The subsequent use of the CCKNOW score in chapter five on some of the patients identified in the case-control study ***failed to demonstrate any evidence of an***

association between patient knowledge and risk of developing colorectal cancer. Nevertheless poor patient knowledge may still be an important cause for non-attendance at colonoscopies and therefore a possible risk factor for cancer. The design of the study in chapter five has an underlying weakness which precludes it having any power to show a significant association between cancer risk and knowledge. It was retrospective with a small number of participants. Cases who received a CCKNOW score questionnaire may have scored more highly *because* they had developed cancer. It is likely such patients became more knowledgeable about their disease because of extensive investigations and treatment, which is likely to have included counselling. Thus the results of chapter five need to be interpreted with caution. Indeed, there were four times as many members of NACC in the control group compared to the cancer group and in view of the finding in chapter four that NACC members are more knowledgeable, one is surprised by the comparable levels of knowledge in the two groups. This suggests that counselling and disease management are likely to have increased knowledge levels in the cancer group. In a future study data should be collected prospectively so that knowledge levels can be assessed prior to any development of colorectal cancer. The CCKNOW could be completed yearly when patients attend outpatients or at a surveillance colonoscopy. This is obviously beyond the time span of a two year M.D. project but would allow a determination of whether poor knowledge is, indeed, a prognostic indicator of cancer development. An alternative way of examining the data would have been to stratify the CCKNOW score according to colon cancer stage at diagnosis to determine whether those who were diagnosed at a later stage had poorer knowledge.

Patient education programs are costly and the study in chapter six comparing use of a video plus information leaflet versus information leaflet alone showed that ***knowledge***

levels fall after only one month following any educational intervention. Thus any form of patient education has to be repeated on a regular basis. The study also demonstrated that ***videos are no more effective at educating patients about cancer risk than a simple information leaflet.*** These results support the findings of other studies on patient education. (103,407,408) In general, patient education does not modify disease behaviour. (409,410) Although it would be reassuring to think informing patients of cancer risk would encourage them to attend surveillance colonoscopies this assumption would only be justified if appropriate studies were conducted. This could be easily investigated but would take several years before valid results could be obtained.

Surveillance programs.

Despite clinicians' awareness of cancer risk, there is no consistent approach to surveillance and no national cancer surveillance program for patients with ulcerative colitis. Results of the audit presented in chapter seven show that ***where cancer surveillance is practiced, it is inconsistent and disorganized.*** In addition, ***there were also discrepancies regarding the management of dysplasia found at colonoscopy.*** Surveillance was originally introduced without having been proved of value in a randomized controlled trial. This, along with the belief that surveillance is not cost-effective, (152,163) has presumably contributed to the lack of a standardized program. It is now too late to randomize patients to either a surveillance or no intervention group to assess any advantages or disadvantages. Indeed power calculations have suggested that it would be necessary to randomize over 4,000 patients to obtain a useful answer. (160) However, if surveillance is to be practiced, clinicians may benefit from guidelines issued by an authoritative body such as the British

Society of Gastroenterology with the aim of educating doctors and introducing some uniformity.

The histopathological grading of dysplasia in ulcerative colitis is fraught with inaccuracies. Some authors have reported significant inter-observer variation (176,427) although no published work has investigated the abilities of general versus specialist pathologists. The results from chapter eight demonstrate that ***experts in gastrointestinal pathology are just as likely to disagree as general pathologists when grading dysplasia with a significant degree of inter-observer variation.*** Therefore, it would appear there is no advantage to the examination of surveillance colonoscopy biopsies by specialist histopathologists.

In view of the degree of inter-observer variation most hopes of improving identification and grading of dysplasia are pinned on discovery of a new marker of dysplasia. One such marker, CYP1B1, was investigated in chapter nine. Unfortunately, ***although CYP1B1 showed some degree of staining in dysplastic tissues, it was very faint and not a consistent finding.*** Unless the marker can be optimized it will not have a role in identifying dysplasia. Thus alternative immunocytochemical or molecular biology techniques need to be investigated. A genetic predisposition to ulcerative colitis is well established, (17) although the genes responsible are yet to be comprehensively identified. Another avenue to explore therefore is the contribution of cancer susceptibility genes to the development of colorectal carcinoma complicating ulcerative colitis. This could be carried out on the patients identified in the case-control study (chapter three) by analyzing germ-line DNA (extracted from venous blood). Any consistent abnormalities in the genes encoding p53, mismatch repair genes and APC could be sought. Any abnormalities could then be further investigated by analysis of the tumours themselves, using histochemical and

molecular techniques to look for specific alterations of protein expression, or loss of heterozygosity studies for specific tumour suppressor genes.

Conclusions.

The results contained in this thesis highlight the problems faced by clinicians when considering surveillance for colorectal cancer in patients with ulcerative colitis. Clinicians should be aware that 1 in 5 patients will develop cancer within thirty years of disease irrespective of disease extent. This risk may be modified through regular consumption of aminosalicylates, in particular mesalazine. The results from the case-control study should compel doctors to encourage patients to attend surveillance colonoscopies and hospital outpatient clinics. The findings suggest that surveillance should be especially targeted at patients with ulcerative colitis who have a family history of sporadic colorectal cancer and those who are unable to take 5-ASA compounds.

Although poor patient understanding of cancer risk appears not to be a risk factor for colorectal cancer, clinicians need to inform patients about the rationale behind disease management. This will need to be repeated at regular intervals and a good but transient effect can be achieved with simple leaflets.

Thus the issue of colorectal cancer in ulcerative colitis remains a dilemma for most doctors as surveillance is of unproven value. However, the regular consumption of aminosalicylates can lead to a reduction in cancer risk and it may be better to allocate resources to improving compliance with such medication. A randomized control trial of surveillance versus ensured regular therapy with aminosalicylates may be considered in the future. It should *not* be unethical as would be the case if one patient group were

randomized to a no intervention arm. However, the patients in the surveillance group would be excluded from mesalazine use and the practicalities of such a trial make it a somewhat unrealistic study. In the meanwhile, if clinicians are to continue surveillance in the ulcerative colitis population, there is urgent need for standardization with national guidelines which define the frequency of endoscopy and training standards for endoscopists and histopathologists. This urgent priority will not be a fail-safe mechanism but is a responsibility which we owe to patients with ulcerative colitis who are at risk of colorectal cancer.

Recommendations.

Based on the review of the literature and the findings of this thesis the following approach to surveillance in the ulcerative colitis population is suggested:-

1. All patients should have a screening colonoscopy after 8-10 years to check disease extent.
2. The meta-analysis confirmed that cancer risk is minimal in the first decade of disease and therefore regular surveillance should begin 8-10 years after disease onset (not date of diagnosis) for pancolitis and after 15-20 years for left-sided disease.
3. As the risk of cancer increases exponentially with time, there should be a decrease in the screening interval with increasing disease duration. For patients with pancolitis, in the second decade of disease a colonoscopy should be conducted every three years, every two years in the third decade and yearly by the fourth decade of disease.

4. It may be argued that colonoscopy is not necessary in a patient with left-sided disease. However, chapter three demonstrated that 33% of cancers were diagnosed in patients who had left-sided colitis at disease onset. In addition, disease can extend and if such patients only have a flexible sigmoidoscopy any extension of disease may be missed. Therefore, although there is no evidence as yet, it is recommended that such patients should have a colonoscopy every five years with a flexible sigmoidoscopy in the interim years (following the same time schedule suggested for pancolitics).
5. Patients who do not wish to have a full colonoscopic examination should be encouraged to have a flexible sigmoidoscopy instead as chapter three showed that over half of the cancers complicating ulcerative colitis are found in the recto-sigmoid region.
6. Patients with primary sclerosing cholangitis (including those with an orthotopic liver transplant) represent a sub-group of patients at higher risk of cancer (82-89,91-93) and they should have annual colonoscopy. Likewise, chapter three suggests patients who have a positive family history of sporadic colorectal cancer are also at an increased risk and the timing of colonoscopy should be at least biannual.
7. Surveillance should be performed during remission in order to eliminate the difficulty of differentiating reactive change from dysplasia on histological biopsies.
8. During colonoscopy a full examination should be performed with careful inspection of the entire mucosa. Thereafter, two to four random biopsies should be taken at 10 cm intervals throughout the entire colon with additional biopsies of suspicious areas. Additional sampling of the recto-sigmoid area with the goal of improving the diagnostic yield from random biopsies is advocated. (129,137)

9. Whenever a DALM or high grade dysplasia is identified this is a strong indication for colectomy. (58,123)
10. When low grade dysplasia is found, the findings should be discussed with the patient and a joint decision taken about whether to return to surveillance or to opt for colectomy. The patient must be made aware that firstly, even if he has surgery a cancer will not necessarily be found, and secondly that a repeat colonoscopy will not necessarily confirm the presence of abnormal histology even if it is present. Any ambiguity in histological biopsy interpretation should be confirmed by a second experienced pathologist although chapter eight demonstrated that this may have limited value.

Cost of surveillance.

The guidelines suggested will require adequate allocation of resources. As such, an estimate has been made of the cost of such a program. In a community of 300,000 one would expect the incidence of UC to be approximately 30 cases per year. With a prevalence of twelve times that figure, there would be approximately 360 patients with the disease. A previous study conducted in Leicestershire (368) estimated that 40% of patients with UC will have total / subtotal colitis and 20% will have left-sided disease. This correlates with 144 patients having pancolitis and 72 having left-sided disease in a population of 300,000. In Probert et al's study (368) 61% of the population had disease for more than eight years and 14% had disease for more than 15 years. This would mean that there would be approximately 88 patients with pancolitis of greater than eight years duration and 10 patients with left-sided disease of more than 15 years duration i.e. the period when regular surveillance in

these two groups should begin. The cost of a colonoscopy is estimated as £880 in the private sector (including histological examination of biopsies). For the purpose of these calculations the upper limit of the cost of a colonoscopy was taken (hence using the cost in the private sector). Therefore the calculations are generous and in the NHS the cost of surveillance may well be less than this. If an average of one colonoscopy every two years is assumed for each group, a gastroenterologist would perform 44 colonoscopies for pancolitis and 5 for left-sided disease. The cost of surveillance would therefore be (44x£880) +(5x£880) = £43,120 per year in a community of 300,000.

The simplest way to monitor the implementation of the suggested guidelines would be to record the attendance of patients at colonoscopy. This is most easily performed with a computerized system that automatically sends defaulters a further appointment. It is known that it is those patients who default from surveillance who are more likely to develop colorectal cancer and for it to be identified at a later stage. (155) Thus follow-up of such patients is critical to the success of any surveillance program. The attendance of patients at colonoscopy would need to be audited in approximately five years time. This would allow time for implementation of surveillance programs across the country and would give some indication of whether patients are complying with the surveillance regimen.

Ulcerative colitis patients should be encouraged to attend hospital outpatient departments at least once per year even if they are asymptomatic. This opportunity should be taken to educate and remind patients of their cancer risk, reinforce the

importance of surveillance and ensure they are continuing to take maintenance aminosalicylate therapy.

Patients must be aware that surveillance cannot guarantee a reduced cancer risk but rather offers a reasonable chance of detecting precancer or symptomless cancer. This should be made clear to patients along with an estimate of their individual risk so that those who are unenthusiastic about surveillance can make an informed decision.

Appendices.

Appendix 1.

Calculation of Person-Years

Binary Outcome

If the probability of developing CRC at some point is denoted by p, i.e. r cancers observed in n patients, then the outcome used for each study is the log odds of developing CRC, i.e. $\log[p/(1-p)]$, which it is assumed is normally distributed with approximate variance $1/r + 1/(n-r)$. (466) Either a fixed or random effects meta-analysis model, as determined by a χ^2 test for heterogeneity, is then used to produce an overall pooled estimate of the log odds and its associated standard error. (211) For interpretation, the pooled log odds are transformed back onto a probability scale, with the following approximation for the variance being used, where y is the log odds,

$$\mathrm{Var}[p] = [\exp(y)/(1+\exp(y)) - \exp(y)^2/(1+\exp(y))^2]^2 \mathrm{Var}[y]$$

Incidence

For studies which report the number of cancer observed out of a total person-years from diagnosis, then the meta-analysis is performed on the log incidence scale, i.e. if d cancer are observed in k person-years, the log incidence is $\log(d/k)$, and its approximate variance is $1/d$. (466) Either a fixed or random effects meta-analysis model, as determined by a χ^2 test for heterogeneity, is then used to produce an overall pooled estimate of the log incidence and its associated standard error. (211) For interpretation purposes, the pooled log incidence is transformed onto a cumulative probability scale. Assuming h is the pooled log incidence, then the cumulative probability, P, of

developing CRC at t years after diagnosis is exp(-exp(h) t), and the approximate variance of P is given by

$$\mathrm{Var}[P] = [\exp(h)\, t \exp(-\exp(h)\, t)]^2 \mathrm{Var}[h]$$

Stratified Incidence

For studies which reported the number of cancers and person-years from diagnosis stratified by length of follow-up, a further analysis could be performed in which the incidence was assumed to be constant *within* each time interval, rather than over the whole time period as above. Because of heterogeneity of the reporting of stratified results only three time intervals were used, 0-10, 11-20 and 21-30 years from diagnosis. For each interval a separate meta-analysis was performed using the methods outlined above, producing three estimates, h_1, h_2 and h_3, for the log incidence in each interval and their associated standard errors. The cumulative probability of developing CRC at time t_2 years say into the second interval, i.e. $10 + t_2$ years since diagnosis, $P(10+t_2)$, is then given by

$$P(10+t_2) = \exp(-\exp(h_1)\, 10) \exp(-\exp(h_2)\, t_2)$$

All analyses were performed using Stata and macros for conducting meta-analyses. (208-210) Mixed effect models were used in order to explore whether the between-study heterogeneity that existed could be explained by the study characteristics collected. (212,467)

Appendix 2. Data extracted from papers in the meta-analysis.

(N / S = Not Stated, N / A = Not Applicable, Freq = Frequency)

Appendix 2. (N/S = Not Stated, N/A = Not Applicable, Freq = Frequency)

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(56)	USA	Referral centre Retrospective	1960-76	N/A	267	158	109	26	21
(61)	UK & Sweden	Referral centre Retrospective	1945-65	N/A	823	486	337	35	29
(206)	Sweden	Inception Cohort Retrospective	1951-75	N/A	234	234	0	15	15
(66)	UK	Inception Cohort Retrospective	1938-62	N/A	624	236	388	22	17
(339)	UK	Surgical series Retrospective	Up To 1959	N/A	222	N/S		15	—
(55)	UK	Referral centre Retrospective	1952-63	N/A	465	210	218	8	8
(53)	USA	Referral centre Retrospective	1919-65	N/A	396	303	93	52	—
(42)	Denmark	Population	1960-78	573,237 in 1978	783	124	637	7	2
(36)	UK	Referral centre Retrospective	1940-76	N/A	676	462	214	35	35
(341)	USA	Population Inception cohort	1935-79	53,000	182 (84 probable UC)	60	119	3	1

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(59)	USA	Referral centre Retrospective	1973-84	N / A	1160	668	492	82	63
(71)	Czech	Referral centre Retrospective	1942-1981	N / A	959	305	654	6	4
(214)	Sweden	Population	1955-84	Unknown	1547	545	1002	15	—
(300)	Israel	Population	1961-70	Unknown	504 (90 probable UC)	69	—	3	1
(54)	Denmark	Population Inception cohort	1962-1987	550,000	1161	207	954	6	2
(326)	Denmark	Population Inception cohort	1977-89	Unknown	5,546	N/S		42	—
(57)	USA	Private practice	1955-80	Unknown	258	106	152	6	4
(133)	USA	Referral centre Retrospective	1958-76	N / A	1,142	N/S		29	27
(50)	USA	Referral centre Retrospective	1918-59	Unknown	427	N / S		46	—
(323)	UK	Referral centre Retrospective	1947-63	Unknown	637	196		15	9
(158)	Sweden	Population	1977-91	65,000	131	76	55	4	4

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(310)	Australia	Referral centre Retrospective	1950-80	Unknown	1,435	425	1010	63	44
(60)	Sweden	Population	1922-84	1,300,000	3117	1045	2072	91	65
(283)	Sweden	Population	1945-79	1,520,000	1339	1274	—	25	24
(275)	Turkey	Referral centre Retrospective	1960-69	N/A	60	19	41	0	—
(249)	Sweden	Population (+ Surv. prog)	1961-90	65,000	32	24	8	0	—
(64)	UK	Referral centre + Surv. prog	1966-87	Unknown	401	307	94	22	—
(45)	UK	Referral centre Inception cohort	1966-75	Unknown	269	60 *	—	0	—
(70)	Israel	Population	1970-80	1,300,000	1035	147	—	26	13
(240)	UK	Referral centre Retrospective	1966-76	N/A	229	229	—	5	5
(149)	Sweden	Population + Surv. prog	1961-83	70,000	127	77	50(proctitis excl)	3	3
(69)	Denmark	Referral centre Retrospective	1964-83	N/A	759	312	447	17	10

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(330)	USA	Inception cohort	1944-60	Unknown	525	68	—	17	9
(281)	USA	Referral centre Retrospective	1913-58	N/A	7000	N/S		178	—
(260)	USA	Referral centre Retrospective	1938-68	N/A	1200	N/S		35	29
(7)	USA	Referral centre Population Retrospective	1935-64	Unknown	108	31	—	5	5
(295)	USA	Referral centre Retrospective	1955-70	N/A	613	36	—	37	36
(340)	Sweden	Population	1958-82	Unknown	462	134	236	9	7
(313)	India	Referral centre Retrospective	1977-88	N/A	436	129	307	8	6
(335)	Sweden	Referral centre Retrospective	1941-59	N/A	500	N/S		26	N/S
(284)	USA	Surgical series Retrospective	1946-61	N/A	57	N/S		3	N/S
(243)	Czech	Referral centre Retrospective	1940-66	N/A	645	174	471	3	N/S
(306)	USA	Referral centre Retrospective	1932-60	N/A	43	18	25	0	—

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(256)	UK	Referral centre Retrospective	1946-58	N/A	663	264	399	19	13
(241)	UK	Referral centre	1966-73	N/A	171	N/S		3	N/S
(131)	UK	Surveillance program	1972-92	N/A	332	N/S	N/S	20	N/S
(124)	Sweden	Surveillance program	1974-82	N/A	71	41	30	1	1
(156)	USA	Referral centre Retrospective	1959-88	N/A	1156	N/S		102	86
(235)	Denmark	Referral centre Retrospective	1960-71	540,000	332	N/S		0	—
(144)	Finland	Surveillance program	1976-89	N/A	66	30	36	0	—
(282)	Italy	Surveillance program	1980-86	N/A	65	49	16	6	—
(274)	Sweden	Surveillance program	1977-85	70,000	93	52	41	1	1
(159)	Israel	Surveillance program	1976-94	N/A	154	26	—	4	1
(148)	USA	Referral centre Retrospective	1972-83	N/A	248	N/S		7	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(333)	Oman	Prospective cohort	1987-94	2,000,000	108	20	88	0	—
(58)	UK	Surveillance program	1966-80	N/A	303	N/S		13	N/S
(147)	USA	Surveillance program	1974-86	N/A	213	151	62	9	N/S
(137)	USA	Referral centre Retrospective	1957-91	N/A	3093	34	11	52	41
(142)	USA	Referral centre Retrospective	1972-77	N/A	75	75	0	11	11
(136)	USA	Referral centre Retrospective	1977-87	N/A	121	63	58	7	5
(351)	USA	Referral centre Retrospective	1975-79	N/A	188	N/S		9	N/S
(145)	Sweden	Surveillance program	1973-88	N/A	72	72	0	2	2
(146)	UK	Surveillance program	1978-90	N/A	180	180	0	1	1
(250)	UK	Referral centre Retrospective	1952-68	N/A	368	N/S		6	N/S
(304)	USA	Referral centre Retrospective	1937-49	N/A	451	N/S		3	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(343)	Sweden	Referral centre Retrospective	1940-55	N/A	439	N/S		17	16
(257)	UK	Surgical series Retrospective	?	N/A	153	N/S		8	N/S
(350)	USA	Surgical series Retrospective	1927-46	N/A	180	N/S		9	N/S
(346)	UK	Surgical series Retrospective	1949-55	N/A	182	N/S		12	N/S
(278)	USA	Referral centre Retrospective	1940-56	N/A	402	N/S		12	N/S
(253)	USA	Referral centre Retrospective	1925-49	N/A	147	N/S		7	N/S
(468)	USA	Referral centre Retrospective	?	N/A	1564	N/S		98	N/S
(297)	USA	Referral centre Retrospective	?	N/A	855	N/S		0	—
(469)	USA	Referral centre Retrospective	?	N/A	792	N/S		22	N/S
(320)	USA	Referral centre Retrospective	1947-56	N/A	391	160	—	8	7
(252)	Denmark	Referral centre Retrospective	1961-71	N/A	62	7	—	0	—
(246)	Denmark	Referral centre Retrospective	1964-76	N/A	412	N/S		4	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(261)	USA	Referral centre Retrospective	N/S	N/A	1200	N/S		33	N/S
(272)	UK	Referral centre Retrospective	1947-51	N/A	126	N/S		5	N/S
(280)	UK	Referral centre Retrospective	1931-50	N/A	245	69	—	9	N/S
(318)	Italy	Referral centre Retrospective	1969-76	N/A	122	41	81	1	N/S
(244)	UK	Referral centre Retrospective	1938-48	N/A	129	N/S		4	N/S
(348)	USA	Surgical series Retrospective	1961-75	N/A	726	N/S		70	N/S
(267)	USA	Referral centre Retrospective	Up to 1950	N/A	684	N/S		19	N/S
(470)	USA	Referral centre Retrospective	1918-37	N/A	2000	893	1107	109	N/S
(301)	USA	Referral centre Retrospective	1945-50	N/A	316	N/S		12	N/S
(254)	USA	Surgical series Retrospective	1939-47	N/A	450	N/S		9	N/S
(334)	USA	Referral centre Retrospective	1927-45	N/A	206	N/S		3	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(321)	UK / USA	Surgical series Retrospective	1955-58	N/A	152	N/S		6	N/S
(322)	USA	Surgical series Retrospective	N/S	N/A	226	N/S		9	N/S
(354)	USA	Referral centre Retrospective	1915-49	N/A	483	N/S		31	N/S
(336)	Australia	Referral centre Retrospective	1954-59	N/A	272	N/S		11	N/S
(305)	USA	Referral centre Retrospective	1935-55	N/A	326	N/S		19	N/S
(352)	USA	Referral centre Retrospective	1932-50	N/A	118	N/S		4	3
(338)	Australia	Referral centre Retrospective	1950-62	N/A	80	51	29	2	2
(332)	USA	Referral centre Retrospective	1953-66	N/A	43	30	13	1	N/S
(298)	USA	Referral centre Retrospective	1948-55	N/A	148	62	86	1	1
(270)	USA	Surgical series Retrospective	Up to 1949	N/A	263	N/S		18	N/S
(269)	USA	Referral centre Retrospective	Up to 1947	N/A	100	35	65	2	N/S
(312)	USA	Referral centre Retrospective	N/S	N/A	143	N/S		7	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(289)	USA	Surgical series Retrospective	1946-54	N/A	307	N/S		11	N/S
(357)	Hungary	Referral centre Retrospective	1956-70	N/A	157	N/S		0	—
(358)	Hungary	Referral centre Retrospective	1961-70	N/A	141	14	127	3	N/S
(355)	USA	Referral centre Retrospective	12 yrs	N/A	66	11	55	0	—
(329)	UK	Referral centre Retrospective	1972-1992	N/A	175	143	32	10	6
(155)	UK	Referral centre Retrospective	1974-85	N/A	313	N/S		7	6
(143)	USA	Surveillance program	1977-85	N/A	99	99	0	8	8
(319)	USA	Surveillance program	1986-92	N/A	98	98	0	6	6
(157)	UK	Referral centre Retrospective	1944-76	N/A	676	N/S		35	N/S
(266)	USA	Referral centre Retrospective	1960-76	N/A	267	N/S		26	21
(471)	UK	Referral centre Retrospective	1945-75	N/A	486	486	0	29	29
(264)	UK	Referral centre Retrospective	N/S	N/A	465	210	218	8	8

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(271)	UK	Referral centre Retrospective	1960-75	N/A	269	N/S		0	—
(286)	USA	Surgical series Retrospective	1927-46	N/A	166	N/S		12	N/S
(290)	UK	Surgical series Retrospective	1941-51	N/A	63	N/S		7	N/S
(174)	UK	Surveillance program	1978-84	N/A	189	112	77	4	4
(138)	UK	Surveillance program	N/S	N/A	43	34	9	2	2
(302)	Sweden	Referral centre Retrospective	N/S	N/A	150	113	37	1	N/S
(349)	Denmark	Referral centre Retrospective	2 yrs	N/A	100	N/S		1	0
(126)	USA	Surveillance program	1974-91	N/A	2050	N/S		41	27
(62)	USA	Referral centre Retrospective	1959-88	N/A	1156 *	N/S		100	85
(279)	UK	Surgical series Retrospective	1952-76	N/A	374	362	22	22	21
(303)	USA	Surgical series Retrospective	1957-77	N/A	84	83	1	4	N/S
(344)	India	Referral centre Retrospective	2.5 yrs	N/A	69	15	36	2	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	Number with:- others	Number of cancers whole series	Number of cancers Total UC
(288)	India	Referral centre Retrospective	1956-60	N/A	46	2	44	0	—
(331)	Israel	Referral centre Retrospective	1961-85	N/A	169	N/S		1	N/S
(309)	USA	Referral centre Retrospective	1930-46	N/A	164	N/S		2	N/S
(325)	USA	Referral centre Retrospective	approx 30 yrs	N/A	362	N/S		10	9
(291)	USA	Referral centre Retrospective	?-1957	N/A	269	N/S		15	N/S
(230)	USA	Cumulative Series	1927-44	N/A	1467	N/S		28	N/S
(296)	USA	Referral centre Retrospective	1922-37	N/A	88	N/S		0	—
(276)	Kuwait	Referral centre Retrospective	6 yrs	N/A	43	6	37	0	—
(347)	Finland	Surgical Series Retrospective	1969-84	N/A	235	N/S		16	16
(258)	Sweden	Radiol Series Retrospective	1940-46	N/A	204	86	118	22	18
(328)	Iran	Referral centre Retrospective	1973-82	N/A	112	31	81	1	N/S
(316)	Turkey	Referral centre Retrospective	1969-77	N/A	204	21	180	2	N/S

Ref	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(277)	Norway	Surgical Series Retrospective	1969-78	N/A	158	127	31	10	N/S
(353)	USA	Referral centre Retrospective	1943-62	N/A	750	N/S		25	N/S
(123)	USA	Surveillance Program	1975-78	N/A	112	N/S		7	6
(52)	USA	Surgical Series Retrospective	1962-73	N/A	41	N/S		8	N/S
(52)	USA	Histol Series Retrospective	1962-73	N/A	204	N/S		3	N/S
(307)	USA	Referral centre Retrospective	1934-53	N/A	18	N/S		1	N/S
(327)	Puerto Rico	Referral centre Retrospective	1974-80	N/A	102	N/S		2	N/S
(73)	Japan	Referral centre Retrospective	1954-75	N/A	159	60	99	0	—
(299)	Singapore	Referral centre Retospective	1956-70	N/A	10	4	6	1	1
(293)	USA	Referral centre Retospective	1950-63	N/A	1258	N/S		24	N/S
(247)	Sweden	Referral centre Retospective	1938-48	N/A	290	N/S		9	8
(356)	Sweden	Referral centre Retospective	1920-54	N/A	137	N/S		6	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(268)	USA	Referral centre Retospective	1947-56	N/A	52	30	22	4	4
(233)	USA	Referral centre Retospective	1944-53	N/A	139	96	43	2	N/S
(314, 315)	USA	Referral centre Retospective	1929-58	N/A	121	N/S		9	N/S
(285)	Sweden	Referral centre Retospective	1939-58	N/A	98	10	78	2	N/S
(242)	Czech	Referral centre Retospective	1940-60	N/A	414	N/S		1	N/S
(308)	USA	Surgical series Retrospective	N/S	N/A	18	N/S		2	N/S
(337)	UK	Referral centre Retospective	1938-56	N/A	60	N/S		2	N/S
(255)	UK	Med+Surg Retospective	1947-55	N/A	346	133	213	6	6
(251)	USA	Referral centre Retospective	1923-28	N/A	693	N/S		15	N/S
(273)	USA	Referral centre Retospective	1934-43	N/A	336	N/S		2	N/S
(342)	? Sweden	Referral centre Retrospective	1940-47	N/A	54	N/S		1	N/S
(238)	USA	Referral centre Retrospective	1925-31	N/A	95	N/S		6	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(234)	USA	Referral centre Retrospective	1925-31	N/A	871	N/S		28	N/S
(236)	USA	Surgical series	1936-46	N/A	101	N/S		4	N/S
(292)	USA	Referral centre Retrospective	1934-51	N/A	269	N/S		11	N/S
(245)	USA	Referral centre Retrospective	1918-37	N/A	2000	893	1107	109	N/S
(237)	USA	Referral centre Retrospective	1919-23	N/A	5	N/S		0	—
(248)	USA	Referral centre Retrospective	N/S	N/A	145	N/S		6	N/S
(311)	Denmark	Referral centre Retrospective	1933-48	N/A	143	N/S		2	N/S
(345)	USA	Referral centre Retrospective	1934-59	N/A	440	N/S		15	N/S
(324)	Canada	Referral centre Retrospective	1930-50	N/A	205	N/S		5	N/S
(67)	USA	Referral centre Retrospective	1955-74	N/A	336	188	113	9	N/S
(287)	Romania	Surgical series Retrospective	1988-97	N/A	14	N/S		2	N/S
(294)	Argentina	Referral centre Retrospective	1946-65	N/A	100	36	64	4	N/S

Ref.	Country	Centre & study design	Period	Population	Number of patients	Number with:- total colitis	others	Number of cancers whole series	Total UC
(259)	Sweden	Population	1922-84	1,300,000	3121	1045	2072	91	65
(317)	USA	Referral centre Retrospective	?	N/A	26	N/S		1	N/S
(239)	Sweden	Referral centre Retrospective	1920-48	N/A	134	73	* 33	1	N/S

Appendix 2 continued. Further data extracted from papers in the meta-analysis:-

(N/S = Not Stated, N/A = Not Applicable, Freq = Frequency)

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(56)	Yes	N/S	N/S	23.4yrs	31.6yrs	N/S	N/S
(61)	No	(17-38 yrs)	48yrs	17.5yrs (1.3-34 yrs)		17.3	40
(206)	N/S	8.5	N/S	17yrs (7 - 44 yrs)		N/S	66
(66)	N/S	N/S	41yrs (20-72 yrs)	N/S		N/S	N/S
(339)	Yes	N/S	42yrs	14yrs		N/A	N/A
(55)	No	N/S	N/S	N/S		N/S	N/S
(53)	No	Up to 43yrs	N/S	N/S		10.1	N/S
(42)	No	6.7yrs (1-18 yrs)	N/S	N/S		N/S	19.2
(36)	No	15.8 yrs	47 yrs (32-74yrs)	20 yrs (8-49 yrs)		58	64.8
(341)	No	14 (median)	49yrs	N/S		13.7	15.4
(59)	No	14.4yrs(1mo-44yrs)	43 yrs (21-76 yrs)	18 yrs (5-38 yrs)		N/S	30.5
(71)	No	N/S	58 yrs	22.3 yrs (16-35 yrs)		3.3	15.2
(214)	No	N/S	N/S	N/S		N/S	N/S
(300)	No	7.54 yrs (1-46 yrs)	N/S	16.3 yrs (3-29 yrs)		N/S	7.1
(54)	No	11.7 yrs(0-26yrs) (median)	58.5 yrs (15-86yrs)	14.3 yrs (9-24 yrs)		N/S	20.2
(326)	No	5.9 yrs (1-13)	N/S	N/S		N/S *	N/S *

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(57)	No	N/S	49 yrs (22-73 yrs)	21 yrs (10-35 yrs)		9.3	12.4
(133)	N/S	N/S	36.5 yrs(20-70 yrs)	19.6 yrs (20-70 yrs)		N/S	N/S
(50)	N/S	(6 months-19 yrs)	18 yrs	15 yrs		11.2	19.9
(323)	No	(1-16 yrs)	N/S	N/S		N/S	37.2
(158)	No	N/S	N/S	N/S		N/S	12.2
(310)	N/S	(3 months-40 yrs)	45.1 yrs (total) 70.2 yrs (left sided)	19 yrs	13 yrs	N/S	N/S
(60)	No	(1-60 yrs)	Varies with age at onset	N/S		7.8	12
(283)	No	N/S	N/S	17.5 (males)	11.9 (females)	N/S	21at 15yrs
(275)	N/A	(only 9 patients FU>5 yrs)	N/A	N/A		N/S *	23.3
(249)	N/A	18 yrs (0-30 yrs)	N/A	N/A		15.6	21.9
(64)	No	N/S	50 yrs (25-76 yrs)	20.3 yrs (11-42)		N/S	24.7
(45)	N/A	(maximum 11 yrs)	N/A	N/A		N/S	9.3
(70)	No	11.5 yrs (1-52 yrs)	N/S	N/S		5.2	8.7
(240)	No	N/S	47.8 yrs(42-55 yrs)	20.8 yrs (13-28 yrs)		N/S	17
(149)	No	N/S	N/S	12.6 yrs (2-27 yrs)		N/S	26
(69)	No	N/S	N/S	14 yrs		26	39

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(330)	N/S	N/S	N/S	N/S		7.0	12.4
(281)	N/S	N/S	N/S	N/S		N/S	N/S
(260)	N/S	N/S	37.7 yrs	16.9 yrs (6 months-38 yrs)		N/S	N/S
(7)	No	N/S	N/S	N/S		N/S	N/S
(295)	Yes	N/S	40 yrs (16-67 yrs)	18 yrs (1-39 yrs)		N/S	23.8
(340)	No	14.5 yrs	N/S	12.2 yrs (1-21 yrs)		N/S	N/S
(313)	Yes	N/S	49.9yrs (38-67 yrs)	12.1 yrs (7-25 yrs)		N/S	3.7
(335)	Yes	N/S	32.3 yrs	15.4 yrs		N/S	N/S
(284)	Yes	N/S	48.3 yrs(32-62 yrs)	14.6 yrs (12-20 yrs)		N/A	N/A
(243)	No	76%FU for> 5 yrs 21.1%FUfor>20yr	N/S	N/S		N/S	14.4
(306)	N/A	2.5yrs(1mo-14 yrs)	N/A	N/A		7.0	11.6
(256)	N/S	N/S	43.9 yrs(24-63 yrs)	17.7 yrs (2-28 yrs)		N/S	>28
(241)	N/S	3.3 yrs (1-7 yrs)	N/S	N/S		N/S	17
(131)	No	7.5 yrs (0.2-20 yrs)	51 yrs (32-80 yrs)	21 yrs (12-42 yrs)		2.1 *	16.9
(124)	No	N/S	60 yrs	30 yrs		1.4 *	12.7
(156)	N/S	N/S	48 yrs (19-77 yrs)	21 yrs (5-46 yrs)		N/S	N/S
(235)	N/A	N/ S	N/A	N/A		8.73	16.9

Ref	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(144)	No	N/S	N/A	N/A		9.1	18.2
(282)	No	5.9 yrs (+-3.4 yrs)	N/S	N/S		13.8	21.5
(274)	No	N/S	N/S	9 yrs		11.8	11.8
(159)	No	10.5 yrs	N/S	N/S		N/S	13.6
(148)	No	N/S	N/S	N/S		N/S	16.5
(333)	N/A	3.6 yrs(9mo-7 yrs)	N/A	N/A		1.5	2.8
(58)	No	6.87	48.8 yrs(26-71 yrs)	18.5 yrs (11-30 yrs)		N/S	21.1
(147)	No	4 yrs (1-26 yrs)	N/S	N/S		N/S	23.5
(137)	No	N/S	43 yrs (17-75 yrs)	18 yrs		N/S	N/S
(142)	Yes	N/A	45.6 yrs(28-80 yrs)	12.9 yrs (10-20 yrs)		N/S	37.3
(136)	No	N/S	N/S	18.4yrs(11-25) 29yrs(20-38)		4.13	10.7
(351)	N/S	N/S	N/S	N/S		N/S	N/S
(145)	No	N/S	45 yrs (32-58 yrs)	23.5 yrs (15-32 yrs)		N/S	16.7
(146)	No	N/S	45	21		3.9	12.8
(250)	No	N/S	46 yrs (23-62 yrs)	17.58 yrs (12.5-22 yrs)		N/A	N/S
(304)	N/S	N/S	40.3 yrs	7.3 yrs		N/S	N/S
(343)	N/S	N/S	N/S	N/S		N/S	N/S

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(257)	N/S	N/A	42 yrs	N/S		N/A	N/A
(350)	N/S	N/S	41 yrs	(3-13 yrs)		N/A	N/A
(346)	N/S	N/S	50.1 yrs(30-73 yrs)	16.9 yrs		N/A	N/A
(278)	N/S	N/S	36.4 yrs(24-47 yrs)	8.75 yrs (7 months-22 yrs)		16.2	20.9
(253)	N/S	N/S	N/S	(12-18 yr;based on 5 patients)		N/S	N/S
(468)	No	N/S	N/S	N/S		N/S	N/S
(297)	N/A	N/S	N/A	N/A		N/S	N/S
(469)	N/S	N/S	N/S	17.1 yrs (4-32 yrs)		N/S	N/S
(320)	N/S	N/S	33.7 yrs(21-48 yrs)	18.6 yrs (8-28 yrs)		15.1	31.2
(252)	N/A	N/S	N/A	N/A		3.2	21
(246)	Yes	4 yrs (1-12 yrs)	N/S	N/S		N/S	41
(261)	N/S	N/S	41 yrs	20.5 yrs (7 months - 32yrs)		N/S	N/S
(272)	No	N/S	43 yrs	19.6 yrs		N/S	19
(280)	No	12 1 yrs	N/S	N/S		9.4	34.3
(318)	N/S	2.9 yrs	N/S	N/S		N/S	15.5
(244)	N/S	N/S	37 yrs	7 yrs		N/S	N/S
(348)	N/S	(3-17 yrs)	N/S	17.1 yrs (0.5-41 yrs)		N/A	N/A

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(267)	N/S	N/S	N/S	N/S		28.8	33
(470)	N/S	N/S	42 yrs	18 yrs (1 month-49 yrs)		N/S	N/S
(301)	N/S	N/S	44.3 yrs(25-57 yrs)	16 yrs (6-31 yrs)		N/S	N/S
(254)	N/S	N/S	36.6 yrs	9 yrs		N/A	N/A
(334)	N/S	N/S	N/S	N/S		N/S	N/S
(321)	N/S	N/S	40.8 yrs(29-52 yrs)	16.58 yrs (2.5-27 yrs)		N/A	N/A
(322)	N/S	N/S	39.3 yrs(21-59 yrs)	17 yrs (13-25 yrs)		N/A	N/A
(354)	N/S	N/S	(14-64 yrs)	10.7 yrs (3-45 yrs)		N/S	48
(336)	N/S	N/S	N/S	N/S		N/S	N/S
(305)	N/S	N/S	36 yrs	18 yrs		N/S	N/S
(352)	Yes	N/S	30 yrs (22-35 yrs)	10.2 yrs (3-19 yrs)		N/S	N/S
(338)	No	N/S	17 yrs (14-20 yrs)	N/S		N/S	23.8
(332)	No	N/S	27 yrs	11 yrs		23.3	25.6
(298)	No	2.9 yrs	N/S	N/S		N/S	N/S
(270)	N/S	N/S	N/S	N/S		N/A	N/A
(269)	N/S	N/S	N/S	N/S		1	19
(312)	Yes	N/S	43 yrs (22-65 yrs)	11.6 yrs (2-18 yrs)		N/S	N/S

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(289)	No	N/S	N/S	N/S		N/A	N/A
(357)	N/A	N/S	N/A	N/A		1.3	1.3
(358)	N/S	N/S	N/S	N/S		N/S	2.8
(355)	N/A	N/S	N/A	N/A		1.5	22.7
(329)	No	N/S	67 yrs (37-87yrs)	7.9 yrs (5-12 yrs)		N/S	28
(155)	No	N/S	55 8 yrs (35-74yrs)	13.7 yrs (8-20 yrs)		8 *	9.9
(143)	No	N/S	N/S	N/S		N/S	32.3
(319)	No	N/S	N/S	N/S		N/S	47
(157)	Yes	N/S	47 5 yrs(33-70 yrs)	N/S		N/S	N/S
(266)	N/S	N/S	N/S	N/S		N/S	N/S
(471)	No	N/S	N/S	N/S		N/S	N/S
(264)	No	N/S	N/S	N/S		N/S	N/S
(271)	N/S	N/S	N/A	N/A		N/S	15 at 10yrs
(286)	N/S	N/S	N/S	9 yrs		N/A	N/A
(290)	Yes	N/S	49 7 yrs	18.3 yrs		N/A	N/A
(174)	N/S	N/S	N/S	N/S		N/S	10.6
(138)	No	N/S	N/S	N/S		N/S	4.7
(302)	No	N/S	N/S	N/S		N/S	16.7

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(349)	No	N/S	69 yrs	37 yrs		N/A	N/A
(126)	No	N/S	43 yrs	20.2 yrs (2-33 yrs)		N/S	N/S
(62)	N/S	N/S	47.7 yrs(19-77 yrs)	20.7 yrs (5-46 yrs)		N/S	N/S
(279)	No	N/S	47.8 yrs(24-73 yrs)	20.4 yrs (11-42 yrs)		N/A	7
(303)	No	N/S	N/S	N/S		N/A	21.4
(344)	N/S	N/S	N/S	N/S		N/S	N/S
(288)	N/A	N/S	N/A	N/A		N/S	N/S
(331)	N/S	N/S	N/S	N/S		N/S	2.7
(309)	No	N/S	39 yrs(32-43 yrs)	15 yrs (14-16 yrs)		N/S	N/S
(325)	N/S	N/S	N/S	18 yrs (11-37 yrs)		N/S	6.4
(291)	Yes	N/S	35 yrs	16 yrs		N/S	56.1
(230)	N/S	N/A	N/A	N/A		N/A	N/A
(296)	N/A	N/S	N/A	N/A		0	3.4
(276)	N/A	N/S	N/A	N/A		2.3	2.3
(347)	N/S	N/S	35 yrs(19-86 yrs)	14.4 yrs (5-26 yrs)		N/A	N/A
(258)	N/S	N/S	N/S	N/S		N/A	N/A
(328)	N/S	4.4 yrs (1-10 yrs)	N/S	N/S		N/S	8.9
(316)	N/S	N/S	N/S	N/S		4.4	4.9

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(277)	N/A	N/S	39.9 yrs(23-73 yrs)	17.8 yrs (9-28 yrs)		95.6	95.6
(353)	N/S	N/S	48 yrs	9 yrs		N/S	N/S
(123)	N/S	N/S	47.7 yrs(32-74 yrs)	18.7 yrs (11-30 yrs)		N/S	N/S
(52)	N/S	N/S	45.1 yrs(13-67 yrs)	22.6 yrs (9-50 yrs)		N/A	N/A
(52)	N/S	N/S	N/S	N/S		N/S	N/S
(307)	N/S	N/S	N/S	N/S		0	22.2
(327)	N/S	N/S	N/S	N/S		17.6	21.6
(73)	N/A	N/S	N/A	N/A		N/S	19.5
(299)	No	N/S	53 yrs	9 yrs		0	40
(293)	N/S	N/S	40.7 yrs(16-67 yrs)	18.3 yrs (1-39 yrs)		N/S	N/S
(247)	N/S	N/S	N/S	N/S		N/S	N/S
(356)	N/S	(2-26 yrs)	N/S	N/S		4.4	8
(268)	N/S	9 yrs (1-26 yrs)	N/S	14.8 yrs (9-21 yrs)		N/S	23.5
(233)	N/S	N/S	17.5 yrs(17-18 yrs)	N/S		N/S	5
(314, 315)	N/S	* 23 yrs (5-44 yrs) * 6 yrs	N/S	N/S		N/S	47.1
(285)	N/S	N/S	36.5 yrs(32-41 yrs)	20 yrs (18-22 yrs)		10.2	18.4
(242)	Yes	N/S	57 yrs	19 yrs		9.7	10.1

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(308)	Yes	N/S	51 yrs (46-56 yrs)	13.5 yrs (13-14 yrs)		N/A	N/A
(337)	N/S	N/S	25 yrs (23-27 yrs)	N/S		1.7	20
(255)	N/S	N/S	N/S	16.5 yrs (8-26 yrs)		N/S	N/S
(251)	N/S	N/S	N/S	N/S		N/S	N/S
(273)		N/S	28yrs (27-29 yrs)	9 yrs		N/S	N/S
(342)	N/S	N/S	N/S	N/S		N/S	31.5
(238)	No	N/S	N/S	N/S		0	21.1
(234)	No	(7-14 yrs)	N/S	N/S		0	20.2
(236)	N/S	N/S	N/S	N/S		N/A	N/A
(292)	N/S	N/S	N/S	19.3 yrs (10-42 yrs)		???	58.7
(245)	N/S	N/S	42 yrs	18 yrs (1 month-49 yrs) *		N/S	N/S
(237)	N/A	N/S	N/A	N/A		0	80
(248)	N/S	N/S	28.7 yrs (21-36 yrs)	19.7 yrs (6-32.5 yrs)		N/S	N/S
(311)	Yes	N/S	N/S	N/S		N/S	9.8
(345)	N/S	N/S	N/S	N/S		N/S	46.2
(324)	N/S	N/S	N/S	N/S		N/S	22
(67)	N/S	11.8 yrs	26.6 yrs(16-40.5 yrs)	14.5 yrs (11-22 yrs)		32	35
(287)	N/S	N/S	44.5 yrs(39-50yrs)	> 15 yrs		N/A	N/A

Ref.	Referred cancers included in study?	Duration of follow up mean (range)	Age at cancer diagnosis mean (range)	Duration of colitis at cancer diagnosis mean (range) total	left sided	Panprocto-Colectomy rate (%)	Total Surgery (PPC + other) %
(294)	N/S	N/S	N/S	N/S		4	15
(259)	No	(1-60 yrs)	Varies with age at onset	N/S		7.8	12
(317)	No	N/S	13 yrs	7 yrs		0	61.5
(239)	No	N/S	N/S	N/S		0	0.75

Appendix 2 continued. Further data extracted from papers in the meta-analysis:-

(N/S = Not Stated, N/A = Not Applicable, Freq = Frequency)

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up (%)
	10 yrs	mean 15 yrs	95% CI 20 yrs	30 yrs	All Cases	Extensive / Total UC	
(56)	0.4 (All)	2.5 (All)	13 (All) 22 (Total)	34 (All) 50 (Total)	18.9	26.5	97
(61)	0.7 (0-1.1)	3.4(1.0-5.8)	7.2 (3.6-10.8)	16.5 (9.0-23.96)	8.2	19.2	97
(206)	3.0 6.4 calculated frequency	9.6 (2.6-16.6)	24.2 (11-37.4)	34 (at 25yrs)	30.6	—	N / S
(66)	1.6 (at 8 yrs) 3.5 % calculated frequency	4.5	12.6 (1st attack) 5.5 (whole series)	—	7.3	—	N / S
(339)	Calculated freq=6.7%(whole series):17%(UC>10yrs duration)				N / S		N / S
(55)	5 (total) 25.8 at 25yrs (whole series)	13 (total)	21(total)	42 at 25 yrs (total UC)	N / S		100
(53)	3 (total) 13.1 calculated frequency	12 (total)	23	43 (at 35 yrs)	N / S		80
(42)	0.8 (all)	1.1(all)	1.4 (0.7-2.8) at 18yrs (all) 1.3 at 18 yrs (total)		N / S		100
(36)			8 at 25yrs (3.5-13)	20 (4.5-36)	11.1		95.7
(341)	—	—	2.3	—	2.4 (excluding proctitis)		96
(59)	0.6 (all) 0.8 (total)	3.3 (all) 5.1 (total)	7.7 (all) 11.9 (total)	16.1(all) 25.3 (total)	N / S		100
(71)	—	—	1(all) 5 (total)	4(all) 15 (total) 20 at 35yrs (total)	—	4.3	N / S *
(214)	N / S				2.85 (1.59-4.69)		97.5
(300)	calculated frequency = 0.6 %				3.3		N / S

Ref.	Cumulative cancer incidence (%) All Cases mean 95% CI 10 yrs 15 yrs 20 yrs 30 yrs	Observed / Expected All Cases Extensive / Total UC	Follow up (%)
(54)	Lifetime risk = 3.5% 3.1 (at 25yrs)	0.9 (0.14-1.4) 0.8 (0.29-2.0)	99.9
(326)	Calculated frequency = 0.75 %	1.8 (1.3-2.4)	N/S
(57)	6.6 at 26 yrs (all) 11.4 at 32 yrs (all)	N/S	95.7
(133)	Crude cancer incidence=2.9 %	N/S	N/S
(50)	Calculated frequency = 10.8 %	N/S	94
(323)	Calculated frequency = 3.3 %	—— 30	98.6
(158)	Calculated frequency = 3.1 %	N/S	90
(310)	— — 11(total) 19 (at 34 yrs, all)	N/S	100
(60)	— — — 30 (at 35 yrs, total)	5.7 14.8	100
(283)	— 3 (Total) 5 (Total) 13 (Total at 25 yrs) 5.5 (All cases at 25 yrs)	— 6	99
(275)	Calculated frequency = 0 %	N/A	N/S
(249)	Calculated frequency = 0 %	N/A	100
(64)	0 3 5 9 (at 25 yrs)	N/S	98
(45)	Calculated frequency = 0 %	N/A	N/S
(70)	0.2 (all) 2.8 (all) 5.5 (all) 13.5 (all) 0 (total) 9.3 (total) 13.8 (total)	5.5 <- at 20 yrs -> 13.8	100
(240)	0 (total) 5 (total) 10.3 (total) 30.4 at 28 yrs(total) calculated frequency = 3.1 %	N/S	98

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up
	10 yrs	mean 15 yrs	95% CI 20 yrs	30 yrs	All Cases	Extensive /Total UC	(%)
(149)	—	—	—	—	8.3	23	98
(69)	1 (at 7 yrs)	5	11	—	3.3	—	100
(330)	At 17 yrs all cases = 3.4 At 17 yrs Total UC = 13.2 Calculated frequency = 3.6%				N/S		>94
(281)	Calculated frequency = 2.5%				N/S		100
(260)	Calculated frequency = 2.9%				N/S		N/S
(7)	Calculated frequency = 7.6%				12.5 (me)		100
(295)	Calculated frequency = 6%				N/S		N/S
(340)	All cases 2	3	4 (at 25 yrs)		2.1	——	98%
	Total UC 6	8	10 (at 25 yrs)				
(313)	Calculated frequency = 4.6 % (Total UC) = 1.8 % (All Cases)				——	——	82%
(335)	Calculated frequency = 5.2 %				N/S		100
(284)	Calculated frequency = 5.3 %				N/S		100
(243)	Calculated frequency = 0.5 %				N/S		100
(306)	Calculated frequency = 0 %				N/A		100
(256)	Calculated frequency = 2.9 %				N/S		97.7
(241)	Calculated frequency = 1.8 %				N/S		97
(131)	Calculated frequency = 6 %				N/S		96.3
(124)	Calculated frequency = 1.4 %				N/S		93

Ref.	Cumulative cancer incidence (%) All Cases mean 95% CI 10 yrs 15 yrs 20 yrs 30 yrs	Observed / Expected All Cases Extensive / Total UC	Follow up (%)
(156)	Calculated frequency = 8.8 %	N / S	92
(235)	Calculated frequency = 0 %	N / A	98.2
(144)	Calculated frequency = 0 %	N / A	95.5
(282)	Calculated frequency= 9 %	N / S	80
(274)	Calculated frequency = 1 %	N / S	100
(159)	0.6 (at 7 yrs) 1.6 (at 11-20 yrs) 2.4 (at 21-30 yrs)	N / S	100
(148)	Calculated frequency = 2.8 %	N / S	100
(333)	Calculated frequency = 0 %	N / A	N / S
(58)	Calculated frequency = 4.3 %	N / S	97.7
(147)	Calculated frequency = 4.2 %	N / S	100
(137)	Calculated frequency = 1.7 %	N / S	100
(142)	Calculated frequency = 14.7 %	N / S	100
(136)	Calculated frequency (me) = 5.8 %	N / S	100
(351)	Calculated frequency = 4.8 %	N / S	100
(145)	Calculated frequency = 2.8 %	N / S	97.2
(146)	Calculated frequency = 0.56%	N / S	91.7
(250)	Calculated frequency = 1.63 %	N / S	100
(304)	Calculated frequency = 0.7 %	N / S	N / S

Ref.	Cumulative cancer incidence (%) All Cases mean 95% CI 10 yrs 15 yrs 20 yrs 30 yrs	Observed / Expected All Cases Extensive / Total UC	Follow up (%)
(343)	Calculated frequency = 3.9 %	N/S	N/S
(257)	Calculated frequency = 5.2 %	N/S	100
(350)	Calculated frequency = 5.0 %	N/S	100
(346)	Calculated frequency = 6.6 %	N/S	100
(278)	Calculated frequency = 2.9 %	N/S	N/S
(253)	Calculated frequency = 4.8 %	N/S	63.9
(468)	Calculated frequency = 6.3 %	10.8	100
(297)	Calculated frequency = 0 %	N/S	100
(469)	Calculated frequency = 2.7 %	N/S	100
(320)	Calculated frequency = 2.1 %	N/S	98.7
(252)	Calculated frequency = 0 %	N/S	N/S
(246)	Calculated frequency = 0.97 %	N/S	N/S
(261)	Calculated frequency = 2.75 %	N/S	N/S
(272)	Calculated frequency = 3.9 %	N/S	96.8
(280)	Calculated frequency = 3.7 %	N/S	99.7
(318)	Calculated frequency = 0.8 %	N/S	N/S
(244)	Calculated frequency = 3.1 %	N/S	N/S
(348)	Calculated frequency = 9.6 % (1.4% of all pts with UC)	N/S	100

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up
		mean	95% CI		All Cases	Extensive / Total	(%)
	10 yrs	15 yrs	20 yrs	30 yrs		UC	
(267)	Calculated frequency = 2.78 %				66.7 (surgical) 31.0 (medical)		N / S
(470)	Calculated frequency = 5.4 %				N / S		N / S
(301)	Calculated frequency = 3.8 %				N / S		N / S
(254)	Calculated frequency = 2.0 %				N / S		N / S
(334)	Calculated frequency = 1.4 %				N / S		N / S
(321)	Calculated frequency = 3.9 %				N / S		100
(322)	Calculated frequency = 3.9 %				N / S		N / S
(354)	Calculated frequency = 6.2 %				N / S		71
(336)	Calculated frequency = 4.0 %				N / S		N / S
(305)	Calculated frequency = 5.8 %				N / S		75
(352)	Calculated frequency = 3.4 %				N / S		N / S
(338)	Calculated frequency = 2.5 %				N / S		100
(332)	Calculated frequency = 2.3 %				N / S		97.7
(298)	Calculated frequency = 0.67 %				N / S		88.5
(270)	Calculated frequency = 6.7 %				N / S		N / S
(269)	Calculated frequency = 2.0 %				N / S		100
(312)	Calculated frequency = 4.9 %				N / S		N / S

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up
	mean		95% CI		All Cases	Extensive / Total UC	(%)
	10 yrs	15 yrs	20 yrs	30 yrs			
(289)	Calculated frequency = 3.6 %				N/S		100
(357)	Calculated frequency = 0 %				N/A		N/S
(358)	Calculated frequency = 2.1 %				N/S		N/S
(355)	Calculated frequency = 0 %				N/A		100
(329)	2.1 (all)	—	7.4 (all)	—	N/S		98
(155)	Calculated frequency = 2.2 %				N/S		100
(143)					N/S		91
(319)					N/S		100
(157)	Calculated frequency = 5.2 %				N/S		N/S
(266)	Calculated frequency = 9.7 %				18.9	26.5	N/S
(471)	—	—	7 at 20 yrs (total UC)	—	N/S	19.2 (CI 12.9 - 27.5)	N/S
(264)	Calculated frequency = 1.7 %				N/S		N/S
(271)	Calculated frequency = 0 %				N/A		N/S
(286)	Calculated frequency =7.2 %				N/S		100
(290)	Calculated frequency =11.1 %				N/S		100
(174)	Calculated frequency = 2.1 %				N/S		N/S
(138)	Calculated frequency = 4.7 %				N/S		100
(302)	Calculated frequency = 0.9 %				N/S		N/S

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up (%)
	mean	95% CI			All Cases	Extensive / Total UC	
	10 yrs	15 yrs	20 yrs	30 yrs			
(349)	Calculated frequency = 1 %				N/S		100
(126)	Calculated frequency = 2 %				N/S		N/S
(62)	Calculated frequency = 8.6 %				N/S		100
(279)	Calculated frequency = 5.9 %				N/S		96.5
(303)	Calculated frequency = 4.8 %				N/S		94
(344)	Calculated frequency = 2.9 %				N/S		N/S
(288)	Calculated frequency = 0 %				N/A		N/S
(331)	Calculated frequency = 0.6 %				N/S		98.2
(309)	Calculated frequency = 1.2 %				N/S		N/S
(325)	Calculated frequency = 2.8 %				N/S		N/S
(291)	Calculated frequency = 5.7 %				N/S		N/S
(230)	Calculated frequency = 1.9 %				N/S		N/S
(296)	Calculated frequency = 0 %				N/A		N/S
(276)	Calculated frequency = 0 %				N/A		100
(347)	Calculated frequency = 6.8 %				N/S		N/S
(258)	Calculated frequency = 10.8 %				N/S		N/S
(328)	Calculated frequency = 0.9 %				N/S		N/S
(316)	Calculated frequency = 1 %				N/S		N/S

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up (%)
	mean	95% CI			All Cases	Extensive / Total UC	
	10 yrs	15 yrs	20 yrs	30 yrs			
(277)	Calculated frequency = 6.3 %				N/S		*
(353)	Calculated frequency = 3.3 %				N/S		N/S
(123)	Calculated frequency = 6.3 %				N/S		100
(52)	Calculated frequency = 19.5 %				N/S		100
(52)	Calculated frequency = 1.5 %				N/S		100
(307)	Calculated frequency = 5.6 %				N/S		72.2
(327)	Calculated frequency = 2 %				N/S		N/S
(73)	Calculated frequency = 0 %				N/A		69.1
(299)	Calculated frequency = 10 %				N/S		100
(293)	Calculated frequency = 1.9 %				N/S		N/S
(247)	Calculated frequency = 3.1 %				N/S		N/S
(356)	Calculated frequency = 4.4 %				N/S		
(268)	Calculated frequency = 7.8 %				N/S		98.1
(233)	Calculated frequency = 1.4 %				N/S		90.6
(314, 315)	Calculated frequency = 7.4 %				N/S		89.3
(285)	Calculated frequency = 2 %				N/S		100
(242)	Calculated frequency = 0.2 %				N/S		N/S
(308)	Calculated frequency = 11.1 %				N/S		100

Ref.	Cumulative cancer incidence (%) All Cases mean 95% CI 10 yrs 15 yrs 20 yrs 30 yrs	Observed / Expected All Cases Extensive / Total UC	Follow up (%)
(337)	Calculated frequency = 3.3 %	N/S	N/S
(255)	Calculated frequency = 1.7 %	N/S	N/S
(251)	Calculated frequency = 2.2 %	N/S	N/S
(273)	Calculated frequency = 0.6 %	N/S	N/S
(342)	Calculated frequency = 1.8 %	N/S	92.6
(238)	Calculated frequency = 6.3 %	N/S	100
(234)	Calculated frequency = 3.2 %	N/S	N/S
(236)	Calculated frequency = 4 %	N/S	69.3
(292)	Calculated frequency = 4.2 %	N/S	71.5
(245)	Calculated frequency = 5.4 %	N/S	N/S
(237)	Calculated frequency = 0 %	N/A	100
(248)	Calculated frequency = 4.1 %	N/S	N/S
(311)	Calculated frequency = 1.4 %	N/S	100
(345)	Calculated frequency = 4 %	N/S	N/S
(324)	Calculated frequency = 2.4 %	N/S	100
(67)	1.4 (at 11 yrs) 7.2(at 15 yrs) 8.7 (at 20 yrs) —	N/S	99.1
(287)	Calculated frequency = 14.3 %	N/S	N/S
(294)	Calculated frequency = 4 %	N/S	N/S

Ref.	Cumulative cancer incidence (%) All Cases				Observed / Expected		Follow up (%)
	10 yrs	15 yrs	mean 95% CI 20 yrs	30 yrs	All Cases	Extensive / Total UC	
(259)	—	—	—	30 (at 35 yrs, total)	5.7	14.8	100
(317)	Calculated frequency = 3.8 %				N / S		100
(239)	Calculated frequency = 0.75 %				N / S		97.8

Appendix 3

DATA RETRIEVAL FORM (FOR RISK FACTORS FOR CRC IN UC)

Name: Sex:

Address:

Date of Birth: Age:

Next of kin, address + telephone number:

Consultant: Hospital:

Date of diagnosis of UC: Age at diagnosis of UC:

Extent of UC:

Date of diagnosis of CRC: Age at diagnosis of CRC:

Site of CRC: Stage of CRC at diagnosis:

1) Treatment 5-10 years before	i) 5 ASA preparation	YES / NO
CRC diagnosed:	Dose + frequency	
	ii) Systemic steroid	YES / NO
	Dose + frequency	
	iii) Local steroid	YES / NO
	Dose + frequency	
	iv) Aspirin	YES / NO
	Dose + frequency	

2) Average frequency of contacts with a physician per year over the course of their disease:

3) Number of barium enemas and / or colonoscopies per year:

4) Activity of UC:

- ☐ Silent disease
- ☐ 1 exacerbation / 10 years
- ☐ 1 exacerbation / 1-10 years
- ☐ 1 exacerbation per month to 1 year
- ☐ 1 exacerbation per month
- ☐ Continuous symptoms

5) Smoking history:

- ☐ Never smoked
- ☐ Current smoker
- ☐ Ex - smoker

6) PSC confirmed on ERCP / PTC / Liver biopsy YES / NO

Date of diagnosis of PSC: Age at diagnosis of PSC:

Elevated Alk phos for > 1 year (but no diagnosis of PSC) YES / NO

Highest level of alk phos:

Elevated AST for > 1 year (but no diagnosis of PSC) YES / NO

Highest level of AST:

Elevated ALT for > 1 year (but no diagnosis of PSC) YES / NO

Highest level of ALT:

7) Family members with UC / Crohn's disease YES / NO

Relationship(s):

8) Family members with colorectal cancer: YES / NO

Relationship(s)

Appendix 4

TESTING YOUR KNOWLEDGE OF CROHN'S AND COLITIS .

THE CCKNOW SCORE

This questionnaire will help your doctors and nurses know on which topics you may need more information. This will help make your treatment more effective. Please tick only **one** answer for each question. Thank you.

1. The intestines play an important role in the body but they only work during meal times:-
   a) True
   b) False
   c) Don't know

2. People with inflammatory bowel disease are never allowed to eat dairy products:-
   a) True
   b) False
   c) Don't know

3. Elemental feeds are sometimes used to treat Crohn's disease and ulcerative colitis. They;-
   a) Always contain a lot of fibre
   b) Are very easy to digest
   c) Come in the form of tablets
   d) Don't know

4. Proctitis:-
   a) Is a form of colitis that affects the rectum or back passage only
   b) Is a form of colitis that affects the whole of the large bowel
   c) Don't know

5. When a patient with inflammatory bowel disease passes blood in their stool it means:-
   a) They definitely have bowel cancer
   b) They are having a flare up of their disease
   c) Don't know

6. Patients with inflammatory bowel disease are probably cured if they have been symptom free for 3 years:-
   a) True
   b) False
   c) Don't know

7. Inflammatory bowel disease runs in families :-
   a) True
   b) False
   c) Don't know

8. If patients with inflammatory bowel disease are not careful with their personal hygiene they can pass on their disease to friends and members of the family:-
   a) True
   b) False
   c) Don't know

9. Patients with inflammatory bowel disease can get inflammation in other parts of the body as well as the bowel:-
   a) True
   b) False
   c) Don't know

10. A fistula:-
   a) Is an abnormal track between 2 pieces of bowel or between the bowel and skin
   b) Is a narrowing of the bowel which may obstruct the passage of the contents
   c) Don't know

11. The terminal ileum:-
   a) Is a section of the bowel just before the anus
   b) Is a section of the bowel just before the large intestine
   c) Don't know

12. During a flare up of inflammatory bowel disease:-
   a) The platelet count in the blood rises
   b) The albumin level in the blood rises
   c) The white cell count in the blood falls
   d) Don't know

13. Steroids (such as prednisolone / prednisone / budesonide / hydrocortisone) :-
   a) Can only be taken by mouth
   b) Can be given in the form of an enema into the back passage
   c) Cannot be given directly into the vein
   d) Don't know

14. Steroids usually cause side effects:-

a) only after they have been taken for a long time and in high doses
b) Immediately and even after small doses
c) Which are not permanent and all disappear after treatment is stopped
d) Don't know

15. Immunosuppressive drugs are given to inflammatory bowel disease patients to:-

a) Prevent infection in the bowel by bacteria
b) Reduce inflammation in the bowel
c) Don't know

16. Sulphasalazine:-

a) Controls the level of sulphur in the bloodstream
b) Can be used to reduce the frequency of flare ups
c) Cannot be used to prevent flare ups
d) Don't know

17. An example of an immunosuppresive drug used in inflammatory bowel disease is:-

a) Sulphasalazine
b) Mesalazine
c) Azathioprine
d) Don't know

18. If a woman has Crohn's disease:-

a) She may find it more difficult to become pregnant
b) She should not have children
c) Her pregnancy will always have complications
d) She should stop all medication during her pregnancy
e) Don't know

19. Patients who smoke are more likely to have:-

a) Ulcerative colitis
b) Crohn's disease
c) Don't know

20. Which **one** of the following statements is **false?**

a) Ulcerative colitis can occur at any age
b) Stress and emotional events are linked with the onset of ulcerative colitis
c) Ulcerative colitis is least common in Europeans and North Americans
d) Patients with ulcerative colitis have an increased risk of developing bowel cancer
e) Don't know

21. The examination of the large bowl with a flexible camera is called a:-

a) Barium enema
b) Biopsy
c) Colonoscopy
d) Don't know

22. Male patients who take sulphasalazine:-

a) Have reduced fertility levels that are reversible
b) Have reduced fertility levels that are not reversible
c) The drug does not have any effect on male fertility
d) Don't know

23. The length of the small bowel is approximately:-

a) 2 feet
b) 12 feet
c) 20 feet
d) Don't know

24. The function of the large bowel is to absorb:-

a) Vitamins
b) Minerals
c) Water
d) Don't know

25. Another name for an ileorectal anastomosis operation with formation of a reservoir is:-

a) Purse
b) Pouch
c) Stoma
d) Don't know

26. If a part of the bowel called the terminal ileum is removed during surgery the patient will have impaired absorption of :-

a) Vitamin C
b) Vitamin A
c) Vitamin B12
d) Don't know

27. Patients with IBD need to be screened for cancer of the colon. Which **one** of the following statements about screening is **false ?**

Screening should be offered to all patients with ulcerative colitis:-

a) Which affects only the rectum
b) Which has lasted for 8-10 years
c) Which started before the age of 50
d) Don't know

28. There are millions of tiny "hairs" in the small bowel to increase the absorptive surface. They are called:-

a) Villi
b) Enzymes
c) Bile salts
d) Crypts
e) Don't know

29. Which one of the following is **not** a common symptom of inflammatory bowel disease ?

a) Abdominal pain
b) Change in bowel habit
c) Headache
d) Fever
e) Don't know

30. If a child has inflammatory bowel disease; he/she **probably** will not:-

a) live beyond the age of 45
b) be as tall as his or her friends
c) be as intelligent as his or her friends
d) Don't know

Appendix 5 Questionnaire completed prior to and after intervention (video / leaflet).

Age---------Sex----------Member of NACC? YES / NO

We are conducting a research project into what people with ulcerative colitis know about bowel cancer and having a colonoscopy. We would like you to answer the following questions. This is totally confidential and will not affect your care in any way. Please answer the questions on your own and tick only one answer for each question. Thank you.

1. Do you think that people are at an increased risk of getting bowel cancer because they have ulcerative colitis ?
   a) Yes -------
   b) No -------
   c) Don't know -------

2. Do you think a person with ulcerative colitis can have bowel cancer and still feel well?
   a) Yes -------
   b) No -------
   c) Don't know -------

3. Who do you think is most at risk of getting bowel cancer?
   a) People with colitis affecting a portion of the colon----------
   b) People with colitis affecting most of the colon----------
   c) The risk is the same for everyone----------

4. Do you think it is possible to screen for early bowel cancer by having a colonoscopy?
   a) Yes -------
   b) No -------
   c) Don't know -------

5. Do you think if you take your colitis medication regularly you can reduce your risk of getting bowel cancer ?
   a) Yes -------
   b) No -------
   c) Don't know -------

Please turn over

6. When do you think the risk of bowel cancer becomes large enough to start having regular colonoscopies?

a) As soon as colitis is diagnosed----------
b) After about ten years of colitis----------
c) After about twenty years of colitis----------

7. If your colitis has been trouble free, do you think that you still need a colonoscopy ?

a) Yes -------
b) No -------
c) Don't know -------

8. Do you think that you will be completely put to sleep before having a colonoscopy?

a) Yes -------
b) No -------
c) Don't know -------

9. Do you think that you are likely to open your bowels during the colonoscopy?

a) Yes -------
b) No -------
c) Don't know -------

10. Do you think you will be told the results of the biopsies immediately after the colonoscopy has finished?

a) Yes -------
b) No -------
c) Don't know -------

11. Do you think that if you have had a normal colonoscopy you will need another one in the future ?

a) Yes -------
b) No -------
c) Don't know -------

12. If you were booked to have a colonoscopy in the future, do you think you would attend ?

a) Yes -------
b) No -------
c) Don't know -------

Appendix 6

Preventing Bowel Cancer in Ulcerative Colitis and Having a Colonoscopy

Bowel cancer and ulcerative colitis

For many years it has been known that some people with ulcerative colitis develop cancer of the colon. The chance of cancer developing is greater in people with extensive disease which has been present for more than 8 to 10 years. The longer the colitis goes on the greater the risk of colon cancer.

Patients can feel totally well if they have early bowel cancer. They won't necessarily know that there is anything wrong, just as the doctor can't tell if you have bowel cancer simply by talking to you or performing a physical examination.

Preventing Bowel cancer in ulcerative colitis

Some research has suggested that taking your colitis medications regularly, even when you feel well, can reduce the chances of you developing bowel cancer. Another way to reduce the chance of getting bowel cancer is to have regular camera examinations of the large bowel. These are called colonoscopies. At the moment a colonoscopy is the best test to detect early bowel cancer.

What is a colonoscopy?

A colonoscopy involves passing an endoscope into your bottom. A colonoscope is a long flexible tube about as thin as your index finger with a light on the end. The doctor can see the lining of the bowel and can look for early changes in the bowel which might suggest cancer.

Before the colonoscopy

The bowel has to be prepared for the colonoscopy. The days before the test you will need to take the bowel preparation which will be sent to you. This is a laxative that clears out the bowel and will enable the doctor to get a clear view.

The day of the test

1. You must have someone to bring you in for the test and someone to take you home.
2. A nurse will greet you and explain the test in full, and will answer any questions.
3. You will be asked to change into a gown and will wear this during the test.

During the test

When you are in the endoscopy room the doctor will ask you to sign the consent form. This states that you understand the procedure and the complications associated with it and agree to it.

You will be given a sedative injection which relaxes you but does not put you out completely. Having the sedative means you must not:-

1. drive a car or ride a bicycle
2. operate machinery for 24 hours after the test
3. make important decisions or sign any documents for 24 hours after the test

The colonoscope is passed gently into your bottom and the doctor will steer the instrument through the bowel. Air is used to inflate the bowel and you may feel some wind like discomfort as though you want to go to the toilet. As your bowel is empty this won't happen but some of the air may escape. This is perfectly normal so there's no need to feel embarrassed.

The colonoscopy usually takes 10 - 15 minutes. Once the doctor has had a good look around the bowel he will take several small biopsies. These are small samples of tissue for analysis. This is totally painless.

After the colonoscopy

The doctor will be able to tell you what has been found at the colonoscopy but the biopsy report takes a few days to come through. You will need another outpatient appointment to receive the biopsy result.

It is always reassuring when you've had a normal colonoscopy but it is important to know that you should have a colonoscopy once every 1 or 2 years if you have extensive ulcerative colitis.

Appendix 7 (See attached video)

Appendix 8 **SCREENING PRACTICES OF BRITISH**

GASTROENTEROLOGISTS IN ULCERATIVE COLITIS.

This survey is designed to investigate different approaches to screening across the United Kingdom in ulcerative colitis. It may help determine the reasons why detection rates of dysplasia and colonic cancer vary across the country.

The questionnaire is coded so as to ensure anonymity. The code is held by an independent monitor. Its use however will allow re-mailing to encourage a good response rate. Thank you for taking the time to complete this questionnaire.

Jayne Eaden (Research Fellow in Gastroenterology).
John Mayberry (Consultant Physician).

	YES	NO
1. Do you practice colonic surveillance in ulcerative colitis ?	☐	☐
2. Does your centre maintain a register of people in surveillance programs ?	☐	☐
3. Is this register computerized ?	☐	☐
4. Is there a specific doctor, nurse or manager who keeps the surveillance list up to date ?	☐	☐
5. Do you have a system for contacting people who default from follow up ?	☐	☐
6. Do you enter patients into a screening program who have:-		
a) Pan colitis / disease proximal to the splenic flexure ?	☐	☐
b) Left sided colitis ?	☐	☐
c) Proctitis ?	☐	☐

7. If the answers to any of the previous stem were yes; please state after how many years of disease you commence surveillance colonoscopies on your patients with:-

a) Pancolitis / disease proximal to the splenic flexure ----------

b) Left sided colitis ----------

c) Proctitis ----------

	YES	NO
8. Do you enter people into a screening program who are:-		
a) Under 50 years of age at diagnosis ?	☐	☐
b) Aged 50 years and older at diagnosis ?	☐	☐
c) Both of the above ?	☐	☐
9. Do you routinely offer patients with disease of more than 10 years duration a prophylactic colectomy ?	☐	☐
10. Do you routinely perform a colonoscopy on **all** your patients with ulcerative colitis after 10 years of disease to reassess the extent of their disease ?	☐	☐

11. When performing a surveillance colonoscopy; how many routine biopsies do you take ?

0-5☐ 6-10☐ 11-15☐ 16-20☐ More (please specify) ☐

12. Is routine screening in your unit **mainly** conducted by :-

a) An accredited gastroenterologist ? ☐

b) A trainee gastroenterologist ? ☐

c) An accredited colorectal surgeon ? ☐

d) A trainee surgeon ? ☐

Please **tick one box only** for the following questions:-

13. Are the biopsies you take reviewed **mainly** by :-

    a) A general pathologist ? ☐

    b) A pathologist specializing in gastrointestinal pathology ? ☐

14. You see a 45 year old woman in your outpatient clinic who was diagnosed with ulcerative colitis at the age of thirty. She has ulcerative colitis involving the whole colon (as seen at colonoscopy at the time of diagnosis). She is in complete remission on asacol and has had no relapse for 5 years. Do you :-

    a) Arrange to review her in outpatients one year ? ☐

    b) Stop her asacol and review her in outpatients in one year ? ☐

    c) Arrange a flexible sigmoidoscopy ? ☐

    d) Wait until she develops new colonic symptoms before performing any endoscopic procedure in the future ? ☐

    e) Arrange a colonoscopy ? ☐

    f) Offer her a prophylactic colectomy ? ☐

15. You have performed a colonoscopy on a fifty year old woman who has had pancolitis for 30 years. She is totally asymptomatic and the appearances at colonoscopy were those of quiescent disease. The biopsies confirm this with no evidence of dyplasia or malignancy. Do you :-

    a) Repeat the colonoscopy in five years time ? ☐

    b) Repeat the colonoscopy in three years time ? ☐

    c) Repeat the colonoscopy in one years time ? ☐

    d) Repeat the colonoscopy **only** if the patient develops new colonic symptoms ? ☐

16. You have performed a colonoscopy on a fifty year old man who has had ulcerative colitis affecting the left side of the colon for 20 years. The appearances at the time of the examination were those of quiescent disease. The histology from the colonic biopsies show low grade dysplasia. Do you :-

a) Recommend he has a colectomy in the near future? ☐

b) Repeat the colonoscopy in the next 3-6 months and if low grade dysplasia **is confirmed** recommend he has a colectomy? ☐

c) Repeat the colonoscopy in the next 3-6 months and if low grade dysplasia is **not found** return to surveillance colonoscopy ? ☐

17. You have performed a colonoscopy on a sixty year old man who has had pan-colitis for 20 years. The appearance at colonoscopy was unremarkable apart from a DALM in the transverse colon. The histology from the colonic biopsies show low grade dysplasia. Do you :-

a) Recommend he has a colectomy in the near future ? ☐

b) Repeat the colonoscopy in the next 3-6 months and if low grade dysplasia **is confirmed** recommend he has a colectomy ? ☐

c) Repeat the colonoscopy in the next 3-6 months and if low grade dysplasia is **not found** return to surveillance colonoscopy ? ☐

18. You have performed a colonoscopy on a thirty year old woman who has had pan-colitis for 15 years. The appearances at colonoscopy were unremarkable. The histology from the colonic biopsies show high grade dysplasia. Do you :-

a) Recommend she has a colectomy in the near future ? ☐

b) Repeat the colonoscopy and if high grade dysplasia **is confirmed** recommend she has a colectomy ? ☐

c) Repeat the colonoscopy in the next 3-6 months and if high grade dysplasia is **not found** return to surveillance colonoscopy ? ☐

THANK YOU

References

1. Wilks S. Morbid appearances in the intestines of Miss Bankes. Medical Times Gazette 1859;19:264-5.

2. Hurst AF. Ulcerative colitis. Guy's Hospital Report 1921;71:24-41.

3. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol 1989;24 (supplement 170):2-15.

4. Shivananda S, Hordijk ML, Ten Kate FJW, Probert CSJ, Mayberry JF. Differential diagnosis of inflammatory bowel disease. A comparison of various diagnostic classifications. Scand J Gastroenterol 1991;26:167-73.

5. O'Morain C, Tobin A, Leen E, Suzuki Y, O'Riordan T. Criteria of case definition in Crohn's disease and ulcerative colitis. Scand J Gastroenterol 1989;24 (supplement 170):7-11.

6. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. BMJ 1955;2:1041-8.

7. Sedlack RE, Nobrega FT, Kurland LT, Sauer WG. Inflammatory colon disease in Rochester, Minnesota 1935-1964. Gastroenterology 1972;62:935-41.

8. Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. World J Surg 1980;4:189-93.

9. Evans JG, Acheson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. Gut 1965;6:311-24.

10. Stowe SP, Redmond SR, Stormont JM. An epidemiologic study of inflammatory bowel disease in Rochester New York: Hospital incidence. Gastroenterology 1990;98:104-10.

11. Jewell DP. Sleisenger MH, Fordtran JS, editors. Gastriointestinal Disease. Pathophysiology, Diagnosis and Management. Fifth ed. Philadelphia: W.B. Saunders Company; 1993; 64, Ulcerative colitis. p. 1305-30.

12. Gilat T, Ribak J, Benaroya Y, Zemishlany Z, Weissman I. Ulcerative colitis in the Jewish population of Tel-Aviv Yafo I: Epidemiology. Gastroenterology 1974;66:335-42.

13. Acheson ED. The distribution of ulcerative colitis and regional enteritis in United States Veterans with particular reference to the Jewish religion. Gut 1960;1:291-3.

14. Roth M-P, Petersen GM, McElree C, Feldman E, Rotter JI. Geographic origins of Jewish patients with inflammatory bowel disease. Gastroenterology 1989;97:900-4.

15. Odes HS, Fraser D, Krawiec J. Incidence of idiopathic ulcerative colitis in Jewish population subgroups in the Beer Sheva region of Israel. Am J Gastroenterol 1987;82:854-8.

16. Logan R. Allan RN, Rhodes JM, Hanauer SB, Keighley MRB, Alexander-Williams J, Fazio VW, editors. Inflammatory Bowel Diseases. Third ed. New York: Churchill Livingstone; 1997; 6, Epidemiology: smoking and oral contraception. p. 47-52.

17. Koutroubakis I, Pena AS. Allan RN, Rhodes JM, Hanauer SB, Keighley MRB, Alexander-Williams J, Fazio VW, editors. Inflammatory Bowel Diseases. Third ed. New York: Churchill Livingstone; 1997;Genetics of inflammatory bowel disease. p. 13-33.

18. Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut 1988;28:990-6.

19. Mayberry JF, Ballantyne KC, Hardcastle JD, Mangham C, Pye G. Epidemiological study of asymptomatic inflammatory bowel disease: the identification of cases during a screening programme for colorectal cancer. Gut 1989;30(4):481-3.

20. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. BMJ 1959;1:387-94.

21. Svartz N. Experiences with salazopyrine. Nord Med 1941;11:2261-4.

22. Misiewicz JJ, Lennard-Jones JE, Connell AM, Baron JH, Avery-Jones F. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. Lancet 1965;1:185-8.

23. Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine. Gut 1973;14:923-6.

24. Ireland A, Jewell DP. Sulphasalazine and the new salicylates. Eur J Gastroenterol Hepatol 1989;1:43-47.

25. Thomson AB. New developments in the use of 5-aminosalicylic acid in patients with inflammatory bowel disease. Aliment Pharmacol Ther 1991;5:449-70.

26. Lichtiger S, Present DH, Kornbluth A, Gelernt I. Cyclosporin in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841-5.

27. Connell AM, Lennard-Jones JE, Misiewicz JJ, Baron JH, Avery Jones F. Comparison of acetarsol and prednisolone-21-phosphate suppositories in the treatment of idiopathic proctitis. Lancet 1965;i:238-9.

28. Forbes A, Britton TC, House IM, Gazzard BG. Safety and efficacy of acetarsol suppositories in unresponsive proctitis. Aliment Pharmacol and Ther 1989;3:553-6.

29. Steinhardt AH, Brezinski A, Baker JP. Treatment of refractory ulcerative proctosigmoiditis with butyrate enemas. Am J Gastroenterol 1994;89:179-83.

30. Pullan RD, Rhodes J, Ganesh S, Mani V, Morris JS, Williams GT, Newcombe RG, Russell MAH, Feyerabend C, Thomas GAO, et al. Transdermal nicotine for active ulcerative colitis. N Engl J Med 1994;330:811-5.

31. Sandborn WJ, Tremaine WJ, Offord KP, Lawson GM, Petersen BT, Batts KP, Croghan IT, Dale LC, Schroeder DR, Hurt RD. Transdermal nicotine for mildly to moderately active ulcerative colitis. Ann Intern Med 1997;126:364-71.

32. Thomas GAO, Rhodes J, Mani V, Williams GT, Newcombe RG, Russell MAH, Feyerabend C. Transdermal nicotine as maintenance therapy for ulcerative colitis. N Engl J Med 1995;332:988-92.

33. Evans RC, Wong VS, Morris AI, Rhodes JM. Treatment of corticosteroid-resistant ulcerative colitis with heparin - a report of 16 cases. Aliment Pharmacol Ther 1997;11:1037-40.

34. Torkvist L, Thorlacius H, Sjoqvist U, Bohman L, Lapidus A, Flood L, Agren B, Raud J, Lofberg R. Low molecular weight heparin as adjuvant therapy in active ulcerative colitis. Aliment Pharmacol Ther 1999;13:1323-8.

35. Greenstein AJ, Aufses AH. Differences in pathogenesis, incidence and outcome of perforation in inflammatory bowel disease. Surg Gynecol Obstet 1985;160:63-9.

36. Prior P, Gyde SN, Macartney JC, Thompson H, Waterhouse JAH, Allan RH. Cancer morbidity in ulcerative colitis. Gut 1982;23:490-7.

37. Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. Gut 1967;8:423-34.

38. Langman MJ. Epidemiology of cancer of the large intestine. Proc R Soc Med 1966;59:132-4.

39. Edling NPG, Eklof O. Distribution of malignancy in ulcerative colitis. Gastroenterology 1961;41:465-6.

40. Connell WR, Talbot IC, Harpaz N, Britto N, Wilkinson KH, Kamm MA, Lennard-Jones JE. Clinicopathological characteristics of colorectal carcinoma complicating ulcerative colitis. Gut 1994;35(10):1419-23.

41. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1963;4:299-315.

42. Hendriksen C, Kreiner S, Binder V. Long term prognosis in ulcerative colitis - based on results from a regional patient group from the county of Copenhagen. Gut 1985;26:158-63.

43. Binder V, Both H, Hansen PK, Hendriksen C, Kreiner S, Torp-Pedersen K. Incidence and prevalence of ulcerative colitis and Crohn's disease in the county of Copenhagen, 1962 to 1978. Gastroenterology 1982;83:563-8.

44. Powell-Tuck J, Ritchie JK, Lennard-Jones JE. The prognosis of idiopathic proctitis. Scand J Gastroenterol 1977;12:727-32.

45. Ritchie JK, Powell-Tuck J, Lennard-Jones JE. Clinical outcome of the first ten years of ulcerative colitis and proctitis. Lancet 1978;i:1140-3.

46. Gyde S, Prior P, Dew NJ, Sauders V, Waterhouse JAH, Allan RN. Mortality in ulcerative colitis. Gastroenterology 1982;83:36-43.

47. Probert C, Jayanthi V, Wicks A, Mayberry J. Mortality in patients with ulcerative colitis in Leicestershire, 1972-1989. An epidemiological study. Dig Dis Sci 1993;38:538-41.

48. Crohn B, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). Am J Med Sci 1925;170:220-8.

49. Robinson RJ, Hart AR, Mayberry JF. Cancer surveillance in ulcerative colitis: a survey of patients' knowledge. Endoscopy 1996;28:761-2.

50. Michener WM, Gage RP, Sauer WG, Stickler GB. The prognosis of chronic ulcerative colitis in children. N Engl J Med 1961;265:1075-9.

51. Nugent FW, Haggitt RC, Colcher H, Kutteruf GC. Malignant potential of chronic ulcerative colitis. Gastroenterology 1979;76:1-5.

52. Yardley JH, Keren DF. "Precancer" lesions in ulcerative colitis. A retrospective study of rectal biopsy and colectomy specimens. Cancer 1974;34:835-44.

53. Devroede GJ, Taylor WF, Sauer WG, Jackman RJ, Stickler GB. Cancer risk and life expectancy of children with ulcerative colitis. N Engl J Med 1971;285:17-21.

54. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. Gastroenterology 1992;103:1444-51.

55. De Dombal FT, Watts J, Watkinson G, Goligher JC. Local complications of ulcerative colitis: stricture, pseudopolyposis and carcinoma of colon and rectum. BMJ 1966;1:1442-7.

56. Greenstein AJ, Sachar DB, Smith H, Pucillo A, Papatestas AE, Kreel I, Geller SA, Janowitz HD, Aufses AH. Cancer in universal and left-sided ulcerative colitis: factors determining risk. Gastroenterology 1979;77:290-4.

57. Katzka I, Brody RS, Morris E, Katz S. Assessment of colorectal cancer risk in patients with ulcerative colitis: experience from a private practice. Gastroenterology 1983;85:22-9.

58. Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. Lancet 1983;ii:149-52.

59. Mir-Madjlessi SH, Farmer RG, Easley KA, Beck GJ. Colorectal and extracolonic malignancy in ulcerative colitis. Cancer 1986;58:1569-74.

60. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990;323:1228-33.

61. Gyde SN, Prior P, Allan RN, Stevens A, Jewell DP, Truelove SC, Lofberg R, Brostrom O, Hellers G. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. Gut 1988;29:206-17.

62. Sugita A, Sachar DB, Bodian C, Ribeiro MB, Aufses Jr AH, Greenstein AJ. Colorectal cancer in ulcerative colitis. Influence of anatomical extent and age at onset on colitis-cancer interval. Gut 1991;32:167-9.

63. Ransohoff DF. Colon cancer in ulcerative colitis. Gastroenterology 1988;94:1089-91.

64. Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams, CB. Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. Gut 1990;31:800-6.

65. Lennard-Jones JE. Young GP, Rozen P, Levin B, editors. Prevention and Early Detection of Colorectal Cancer. W B Saunders Company Limited. London; 1996;Prevention of cancer in inflammatory bowel disease. p. 217-38.

66. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Part IV:Carcinoma of the Colon. Gut 1964;5:15-22.

67. Michener WM, Farmer RG, Mortimer EA. Long-term prognosis of ulcerative colitis with onset in childhood or adolescence. J Clin Gastroenterol 1979;1:301-5.

68. Greenstein AJ, Sachar DB, Smith H. Patterns of neoplasia in Crohn's disease and ulcerative colitis. Cancer 1980;46:403-7.

69. Kvist N, Jacobsen O, Kvist HK, Norgaard P, Ockelmann HH, Schou G, Jarnum S. Malignancy in ulcerative colitis. Scand J Gastroenterol 1989;24:497-506.

70. Gilat T, Fireman Z, Grossman A, Hacohen D, Kadish U, Ron E, Rozen P, Lilos P. Colorectal cancer in patients with ulcerative colitis. A population study in central Israel. Gastroenterology 1988;94:870-7.

71. Maratka Z, Nedbal J, Kocianova J, Havelka J, Kudramann J, Hendl J. Incidence of colorectal cancer in proctocolitis: a retrospective study of 959 cases over 40 years. Gut 1985;26:43-9.

72. Suzuki K, Muto T, Masaki T, Morioka Y. Microspectrophotometric DNA analysis in ulcerative colitis with special reference to its application in diagnosis of carcinoma and dysplasia. Gut 1990;31:1266-70.

73. Watanabe H, Hiwatashi N, Yamagata S. Clinical observations on ulcerative colitis. Tohoku J Exp Med 1977;123:197-213.

74. Pinczowski D, Ekbom A, Baron J, Yuen J, Adami HO. Risk factors for colorectal cancer in patients with ulcerative colitis: A case-control study. Gastroenterology 1994;107:117-20.

75. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large bowel cancer. J Natl Cancer Inst 1991;83:355-8.

76. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, Booker SV, Robinson CR, Offerhaus GJA. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313-6.

77. Lashner BA, Heidenreich PA, SU GL, Kane SV, Hanauer SB. Effect of folate supplementation on the incidence of dysplasia and cancer in chronic ulcerative colitis. Gastroenterology 1989;97:255-9.

78. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE, Willett WC. Folate, methionine and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85:875-83.

79. Bauer WM, Brzezinski A, Rybicki L, et al. Folic acid is associated with a favourable Dukes' stage in colorectal cancer in ulcerative colitis. [Abstract] Gastroenterology 1999;116:(4)G1642

80. Le Leu RK, McIntosh GH, Young GP. Effect of folate deficiency on formation of azoxymethane-induced aberrant crypt foci in the rat colon. [Abstract] Gastroenterology 1999;116:(4)G1973

81. Connell WR, Kamm MA, Dickson M, Balkwill AM, Ritchie JK, Lennard-Jones JE. Longterm neoplasia risk after treatment in inflammatory bowel disease. Lancet 1994;343:1249-52.

82. Aadland E, Schrumpf E, Fausa O, Elgjo K, Heilo A, Aakhus T, Gjone E. Primary sclerosing cholangitis: A long-term follow-up study. Scand J Gastroenterol 1987;22:655-64.

83. Brentnall TA, Haggitt RC, Rabinovitch PS, Kimmey MB, Bronner MP, Levine DS, Kowdley KV, Stevens MB, Crispin DA, Emond M, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996;110:331-8.

84. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis. A risk factor for the development of dysplasia and DNA aneuploidy. Gastroenterology 1992;102:1877-80.

85. Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. Gut 1997;41(4):522-5.

86. Shetty K, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. Am J Gastroenterol 1999;94:1643-9.

87. Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis. Evidence for increased neoplastic potential. Hepatology 1995;22:1404-8.

88. D'Haens GR, Lashner BA, Hanauer SB. Pericholangitis and sclerosing cholangitis are risk factors for dysplasia and cancer in ulcerative colitis. Am J Gastroenterol 1993;88:1174-8.

89. Pinczowski D, Ekbom A. Is there an increased risk of colorectal cancer among ulcerative colitis patients with primary sclerosing cholangitis? Gastroenterology 1995;108:A29

90. Loftus EV, Sandborn WJ, Tremaine WJ, Mahoney DW, Zinsmeister AR, Offord KP, Melton LJ. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis. Gastroenterology 1996;110:432-40.

91. Higashi H, Yanaga K, Marsh JW, Tzakis A, Kakizoe S, Starzl TE. Development of colon cancer after liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. Hepatology 1990;11(3):477-80.

92. Bleday R, Lee E, Jessurun J, Heine J, Wong WD. Increased risk of early colorectal neoplasms after hepatic transplant in patients with inflammatory bowel disease. Dis Colon Rectum 1993;36:908-12.

93. Loftus EV, Jr., Aguilar HI, Sandborn WJ, Tremaine WJ, Krom RA, Zinsmeister AR, Graziadei IW, Wiesner RH. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. Hepatology 1998;27(3):685-90.

94. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: A case-control study. Gastroenterology 1998;115:1079-83.

95. Rosenberg SG. Sackett DL, Haynes RB, editors. Compliance with Therapeutic Regimens. Baltimore: John Hopkins; 1976;Patient education - an educator's view. p. 93-9.

96. Mazzuca SA. Does patient education in chronic disease have therapeutic value? J Chronic Dis 1982;35:521-9.

97. Lange A, Haslbeck E, Andus T, Bregenzer N, Gross V, Scholmerich J, Lamparter-Lang R. Ambulatory education of patients with Crohn's disease / ulcerative colitis. Z Gastroenterol 1996;34:411-5.

98. Mansfield JC, Tanner AR, Bramble MG. Information for patients about inflammatory bowel disease. J R Coll Physicians Lond 1997;31:184-7.

99. Probert CSJ, Mayberry JF. Inflammatory bowel disease: patients' expectations in the 1990's. J R Soc Med 1991;84:131-2.

100. Martin A, Leone L, Castagliuolo I, Di Mario F, Naccarato R. What do patients want to know about their inflammatory bowel disease? Ital J Gastroenterol 1992;24:477-80.

101. Agre P, Kurtz RC, Krauss BJ. A randomised trial using videotape to present consent information for colonoscopy. Gastrointest Endosc 1994;40:271-6.

102. Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW 3rd, Philips JA 3rd. Teaching about cystic fibrosis carrier screening by using written and video information. Am J Hum Genet 1995;57:171-81.

103. Kim S, Stewart JF, Emond MJ, Reynolds AC, Leen MM, Mills RP. The effect of a brief education program on glaucoma patients. J Glaucoma 1997;6:146-51.

104. Wood RY. Breast self-examination proficiency in older women: measuring the efficacy of video self-instruction kits. Cancer Nurs 1996;19:429-36.

105. Surawy C. Knowledge about diabetes in type 1 patients is related to metabolic control. Diabet Med 1989;6:784-6.

106. Schlatter S, Ferrans CE. Teaching program effects on high phosphorus levels in patients receiving haemodialysis. Am Nurses Nephrol Assoc J 1998;25:31-6.

107. Hardcastle JD, Farrands PA, Balfour TW, Chamberlain J, Amar SS, Sheldon MG. Controlled trial of faecal occult blood testing in the detection of colorectal cancer. Lancet 1983;ii:1-4.

108. Jones SC, Gallacher B, Lobo AJ, Axon ATR. A patient knowledge questionnaire in inflammatory bowel disease. J Clin Gastroenterol 1993;17:21-4.

109. Probert CS, Frisby S, Mayberry JF. The role of educational videos in gastroenterology. J Clin Gastroenterol 1991;13:620-1.

110. Mayberry MK, Mayberry JF. Value of patient self-help groups in gastroenterology. Current Medical Literature: Gastroenterol 1991;10:159-61.

111. Hawkey GM, Hawkey CJ. Effect of information leaflets on knowledge in patients with gastrointestinal diseases. Gut 1989;30:1641-6.

112. Mayberry JF, Rose J, Rhodes J. Assessment of a patient information booklet on ulcerative colitis. Ital J Gastroenterol 1989;21:193-5.

113. Rees JEP, Mayberry JF, Calcraft B. What the patient wants to know about Crohn's disease. J Clin Gastroenterol 1983;5:221-2.

114. Scholmerich J, Sedlak P, Hoppe-Seyler P, Gerok W. The information needs and fears of patients with inflammatory bowel disease. Hepatogastroenterology 1987;34:182-5.

115. Agre P, McKee K, Gargon N, Kurtz RC. Patient satisfaction with an informed consent process. Cancer Pract 1997;5:162-7.

116. O'Donnell CR, O'Donnell L, San Doval A, Duran R, Labes K. Reductions in STD infections to an STD clinic visit. Using video-based education to supplement provider interactions. Sex Transm Dis 1998;25:161-8.

117. Soetikno RM, Provenzale D, Lennert LA. Studying ulcerative colitis over the World Wide Web. Am J Gastroenterol 1997;92:457-60.

118. Eaden JA, Ward B, Mayberry JF. The use of the Internet amongst gastroenterology out-patients. Postgrad Med J 1998;74:701

119. Mackenburg M, Hobbie C. Patient education on the Web. J Pediatr Health Care 1997;11:89-91.

120. Kipp DE, Radel JD, Hogue JA. The Internet and the nutritional scientist. Am J Clin Nutr 1996;64:659-62.

121. Meade CD. Producing videotapes for cancer education: methods and examples. Oncol Nurs Forum 1996;23:837-46.

122. Axon ATR. Screening and surveillance of ulcerative colitis. Gastrointest Endosc Clin N Am 1997;7(1):129-45.

123. Blackstone MO, Riddell RH, Rogers G, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology 1981;80:366-74.

124. Brostrom O, Lofberg R, Ost A, Reichard H. Cancer surveillance of patients with long-standing ulcerative colitis: a clinical, endoscopical and histological study. Gut 1986;27:1408-13.

125. Riddell RH. Screening strategies in gastrointestinal cancer. Scand J Gastroenterol Suppl 1990;175:177-84.

126. Choi PM, Nugent FW, Schoetz DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology 1993;105:418-24.

127. Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, et al. Dysplasia in inflammatory bowel disease: Standardised classification with provisional clinical applications. Hum Pathol 1983;14:931-66.

128. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis ? Lancet 1994;343:71-4.

129. Choi PM. Predominance of rectosigmoid neoplasia in ulcerative colitis and its implication on cancer surveillance. Gastroenterology 1993;104:666-7.

130. Lashner BA, Hanauer SB, Silverstein MD. Optimal timing of colonoscopy to screen for cancer in ulcerative colitis. Ann Intern Med 1988;108:274-8.

131. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology 1994;107:934-44.

132. Fochios SE, Sommers SC, Korelitz BI. Sigmoidoscopy and biopsy in surveillance for cancer in ulcerative colitis. Journal of Clinical Gastroenterology 1986;8(3 Pt 1):249-54.

133. Hughes RG, Hall TJ, Block GE, Levin B, Moossa AR. The prognosis of carcinoma of the colon and rectum complicating ulcerative colitis. Surg Gynecol Obstet 1978;146:46-8.

134. Riddell RH, Morson BC. Value of sigmoidoscopy and biopsy in detection of carcinoma and premalignant change in ulcerative colitis. Gut 1979;20:575-80.

135. Slater G, Greenstein AJ, Gelernt I, Kreel I, Bauer J, Aufses AH, Jr. Distribution of colorectal cancer in patients with and without ulcerative colitis. Am J Surg 1985;149(6):780-2.

136. Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulcerative colitis: The predictive value of low grade dysplasia. Gastroenterology 1992;103:431-8.

137. Choi PM, Zelig MP. Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention. Gut 1994;35:950-4.

138. Dickinson RJ, Dixon MF, Axon ATR. Colonoscopy and the detection of dysplasia in patients with longstanding ulcerative colitis. Lancet 1980;ii:620-2.

139. Gumaste V, Sachar DB, Greenstein AJ. Benign and malignant colorectal strictures in ulcerative colitis. Gut 1992;33:938-41.

140. Reiser JR, Waye JD, Janowitz HD, Harpaz N. Adenocarcinoma in strictures of ulcerative colitis without antecedent dysplasia by colonoscopy. Am J Gastroenterol 1994;89(1):119-22.

141. Choi PM, Kim WH. Colon cancer surveillance. Gastroenterol Clin North Am 1995;24(3):671-87.

142. Fuson JA, Farmer RG, Hawk WA, Sullivan BH. Endoscopic surveillance for cancer in chronic ulcerative colitis. Am J Gastroenterol 1980;73:120-6.

143. Lashner BA, Silverstein MD, Hanauer SB. Hazard rates for dysplasia and cancer in ulcerative colitis. Results from a surveillance program. Dig Dis Sci 1989;34:1536-41.

144. Leidenius M, Kellokumpu I, Husa A, Sipponen P. Dysplasia and carcinoma in longstanding ulcerative colitis: an endoscopic and histological surveillance programme. Gut 1991;32:1521-5.

145. Lofberg R, Brostrom O, Karlen P, Tribukait B, Ost A. Colonoscopic surveillance in long-standing total ulcerative colitis - a 15 year follow-up study. Gastroenterology 1990;99:1021-31.

146. Lynch DAF, Lobo AJ, Sobala GM, Dixon MF, Axon ATR. Failure of colonoscopic surveillance in ulcerative colitis. Gut 1993;34:1075-80.

147. Nugent FW, Haggitt RC, Gilpin PA. Cancer surveillance in ulcerative colitis. Gastroenterology 1991;100:1241-8.

148. Rosenstock E, Farmer RG, Petras R, Sivak MV, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. Gastroenterology 1985;89:1342-6.

149. Rutegard J, Ahsgren L, Stenling R, Janunger KG. Cancer surveillance in an unselected population. Scand J Gastroenterol 1988;23:139-45.

150. Axon ATR. Cancer surveillance in ulcerative colitis - a time for reappraisal. Gut 1994;35:587-9.

151. Collins RH, Feldman M, Fordtran JS. Colon cancer, dysplasia and surveillance in patients with ulcerative colitis: a critical review. N Engl J Med 1987;316:1654-8.

152. Gyde S. Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs. Gut 1990;31:1089-92.

153. Thirlby RG. Colonoscopic surveillance for cancer in patients with chronic ulcerative colitis: is it working ? Gastroenterology 1991;100:570-2.

154. Sackett DL, Whelan G. Cancer risk in ulcerative colitis: Scientific requirements for the study of prognosis. Gastroenterology 1980;78:1632-5.

155. Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefit. Gut 1988;29:325-31.

156. Sugita A, Greenstein AJ, Ribeiro MB, Sachar DB, Bodian C, Panday AKN, Szporn A, Pozner J, Heimann T, Palmer M, et al. Survival with colorectal cancer in ulcerative colitis. A study of 102 cases. Ann Surg 1993;218:189-95.

157. Gyde SN, Prior P, Thompson H, Waterhouse JAH, Allan RN. Survival of patients with colorectal cancer complicating ulcerative colitis. Gut 1984;25:228-31.

158. Jonsson B, Ashgren L, Andersson LO, Stenling R, Rutegard J. Colorectal cancer surveillance in patients with ulcerative colitis. Br J Surg 1994;81:689-91.

159. Rozen P, Baratz M, Fefer F, Gilat T. Low incidence of significant dysplasia in a successful endoscopic surveillance program of patients with ulcerative colitis. Gastroenterology 1995;108:1361-70.

160. Provenzale D, Kowdley KV, Arora S, Wong JB. Prophylactic colectomy or surveillance for chronic ulcerative colitis ? A decision analysis. Gastroenterology 1995;109:1188-96.

161. Lashner BA, Kane SV, Hanauer SB. Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. Am J Gastroenterol 1990;85:1083-7.

162. Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson PG, Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. Gut 1998;42:711-4.

163. Axon AT, Lynch DA. Surveillance for ulcerative colitis does not and cannot work. Gastroenterology 1994;106(4):1129-31.

164. Koobatian GJ, Choi PM. Safety of surveillance colonoscopy in long-standing ulcerative colitis. Am J Gastroenterol 1994;89:1472-5.

165. Walker AR, Whynes DK, Chamberlain JO, Hardcastle JD. The hospital costs of diagnostic procedures for colorectal cancer. J Clin Epidemiol 1991;44:907-14.

166. Wagner JL, Herdman RC, Wadhwa S. Cost effectiveness of colorectal cancer screening in the elderly. Ann Intern Med 1991;115:807-17.

167. Atkin WS, Cuzick J, Northover JMA, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 1993;341:736-40.

168. Day NE, Miller AB, Parkin DM. How much can the NHS afford to spend to save a life or to avoid a severe disability? Lancet 1985;i:280-1.

169. Sonnenberg A, El-Serag HB. Economic aspects of endoscopic screening for intestinal precancerous conditions. Gastrointest Endosc Clin N Am 1997;7:165-84.

170. Butt JH, Price A, Williams CB. Allan RN, Norman R. editors. Inflammatory Bowel Diseases. Edinburgh: Churchill Livingstone; 1983; Dysplasia and cancer in ulcerative colitis. p. 140-53.

171. Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS, Dean PJ, Kimmey M, Perera DR, Rabinovitch PS. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology 1992;103:1611-20.

172. Kim CY, Fleischer DE. Colonic chromoscopy. A new perspective on polyps and flat adenomas. Gastrointest Endosc Clin N Am 1997;7:423-37.

173. Messmann H, Knuchel R, Baumler W, Holstege A, Scholmerich J. Endoscopic fluorescence detection of dysplasia in patients with Barrett's oesophagus, ulcerative colitis or adenomatous polyps after 5-aminolevulinic acid-induced protoporphyrin IX sensitisation. Gastrointest Endosc 1999;49:97-101.

174. Manning AP, Bulgim OR, Dixon MF, Axon AT. Screening by colonoscopy for colonic epithelial dysplasia in inflammatory bowel disease. Gut 1987;28:1489-94.

175. Melville DM, Jass JR, Shepherd NA, Northover JMA, Capellaro D, Richman PI, Lennard-Jones JE, Ritchie JK, Andersen SN. Dysplasia and deoxyribonucleic acid aneuploidy in the assessment of precancerous changes in chronic ulcerative colitis. Observer variation and correlations. Gastroenterology 1988;95:668-75.

176. Dixon MF, Brown LJR, Gilmour HM, Price AB, Smeeton NC, Talbot IC, Williams GT. Observer variation in the assessment of dysplasia in ulcerative colitis. Histopathology 1988;13:385-97.

177. Lofberg R, Brostrom O, Karlen P, Ost A, Tribukait B. DNA aneuploidy in ulcerative colitis: reproducibility, topographic distribution, and relation to dysplasia. Gastroenterology 1992;102(4 Pt 1):1149-54.

178. Levine DS, Rabinovitch PS, Haggitt RC, Blount PL, Dean PJ, Rubin CE, Reid BJ. Distribution of aneuploid cell populations in ulcerative colitis with dysplasia or cancer. Gastroenterology 1991;101(5):1198-210.

179. Klump B, Holzmann K, Kuhn A, Borchard F, Sarbia M, Gregor M, Porschen R. Distribution of cell populations with DNA aneuploidy and p53 protein expression in ulcerative colitis. Eur J Gastroenterol Hepatol 1997;9:789-94.

180. Markowitz J, McKinley M, Kahn E, Stiel L, Rosa J, Grancher K, Daum F. Endoscopic screening for dysplasia and mucosal aneuploidy in adolescents and young adults with childhood onset colitis. Am J Gastroenterol 1997;92:2001-6.

181. Shapiro BD, Lashner BA. Cancer biology in ulcerative colitis and potential use in endoscopic surveillance. Gastrointest Endosc Clin N Am 1997;7(3):453-68.

182. Harpaz N, Peck AL, Yin J. p53 protein expression in ulcerative colitis-associated colorectal dysplasia and carcinoma. Hum Pathol 1994;25:1069-74.

183. Lang SM, Stratakis DF, Heinzlmann M, Heldwein W, Wiebecke B, Loeschke K. Molecular screening of patients with long standing extensive ulcerative colitis: detection of p53 and Ki-*ras* mutations by single strand conformation polymorphism analysis and differential hybridisation in colonic lavage fluid. Gut 1999;44:822-5.

184. Burmer GC, Rabinovitch PS, Haggitt RC. Neoplastic progression in ulcerative colitis: histology, DNA content, and loss of a p53 allele. Gastroenterology 1992;103:1602-10.

185. Boland CR, Lance P, Levin B. Abnormal goblet cell glycoconjugates in rectal biopsies associated with with an increased risk of neoplasia in patients with ulcerative colitis: early results of a prospective study. Gut 1984;25:1364-71.

186. Fozard JB, Dixon MF, Axon AT, Giles GR. Lectin and mucin histochemistry as an aid to cancer surveillance in ulcerative colitis. Histopathology 1987;11(4):385-94.

187. Ahnen DJ, Warren GH, Greene LJ, Singleton JW, Brown WR. Search for a specific marker of mucosal dysplasia in chronic ulcerative colitis. Gastroenterology 1987;93(6):1346-55.

188. Allen DC, Foster H, Orchin JC. Immunohistochemical staining of colorectal tissues with monoclonal antibodies to ras oncogene p21 product and carbohydrate determinant antigen 19-9. J Clin Pathol 1987;40:157-62.

189. Fischbach W, Mossner J, Seyschab H. Tissue carcinoembryonic antigen and DNA aneuploidy in precancerous and cancerous colorectal lesions. Cancer 1990;65:1820-4.

190. Frykholm G, Enbled P, Pahlman L. Expression of the carcinoma associated antigen CA 19-9 and CA 50 in inflammatory bowel disease. Dis Colon Rectum 1987;30:545

191. Thor A, Itzkowitz SH, Schlom J. Tumour associated glycoprotein (TAG-72) expression in ulcerative colitis. Int J Cancer 1989;43:810-5.

192. Meltzer SJ, Mane SM, Wood PK. Activation of c-Ki-ras in human gastrointestinal dysplasias determined by polymerase chain reaction products. Cancer Res 1990;50:3727-30.

193. Greenwald BD, Harpaz N, Yin J. Loss of heterozygosity affecting the p53, Rb2 and mcc/apc tumour supressor gene loci in dysplastic and cancerous ulcerative colitis. Cancer Res 1992;52:741-5.

194. Yin J, Harpaz N, Tong Y. p53 point mutation in dysplastic and cancerous ulcerative colitis lesions. Gastroenterology 1993;104:1633-9.

195. Itzkowitz SH, Yuan M, Montgomery CK, Kjeldsen T, Takahashi HK, Bigbee WL, Kim YS. Expression of Tn, sialosyl Tn, and T antigens in human colon cancer. Cancer Res 1989;49:197-204.

196. Itzkowitz SH, Marshall A, Kornbluth A, Harpaz N, McHugh JB, Ahnen D, Sachar DB. Sialosyl-Tn antigen: initial report of a new marker of malignant progression in long-standing ulcerative colitis. Gastroenterology 1995;109:490-7.

197. Itzkowitz SH, Young E, DuBois D, Harpaz N, Bodian C, Chen A, Sachar DB. Sialosyl-Tn antigen is prevalent and precedes dysplasia in ulcerative colitis: a retrospective case-control study. Gastroenterology 1996;110:694-704.

198. Karlen P, Young E, Brostrom O, Lofberg R, Tribukait B, Ost K, Bodian C, Itzkowitz S. Sialyl-Tn antigen as a marker of colon cancer risk in ulcerative colitis: relation to dysplasia and DNA aneuploidy. Gastroenterology 1998;115:1395-404.

199. Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD, Melvin WT. Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res 1997;57(14):3026-31.

200. Sackett DL. Bias in analytic research. J Chronic Dis 1979;32:51-63.

201. Whelan G. Ulcerative colitis. What is the risk of developing colorectal cancer? Aust N Z J Med 1991;21:71-7.

202. Whelan G. Cancer risk in ulcerative colitis: Why are results in the literature so varied ? Clin Gastroenterol 1980;9:469-76.

203. Butt JH, Lennard-Jones JE, Ritchie JK. A practical approach to the risk of cancer in inflammatory bowel disease. Reassure, watch or act? Med Clin North Am 1980;64:1203-20.

204. Lennard-Jones JE. Colitic cancer: Supervision, surveillance or surgery? Gastroenterology 1995;109:1388-91.

205. Lennard-Jones JE. Compliance, cost and common sense limit cancer control in colitis. Gut 1986;27:1403-7.

206. Kewenter J, Ahlman H, Hulten L. Cancer risk in extensive ulcerative colitis. Ann Surg 1978;188:824-8.

207. The University of York. NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness: CRD guidelines for those carrying out or commissioning reviews. 1996; York Publishing Services Ltd.

208. Sharp SJ. Meta-analysis regression. Stata Technical Bulletin 1998;42:16-22.

209. Sharp SJ, Sterne JAC. Meta-analysis. Stata Technical Bulletin 1997;38:9-14.

210. Stata Statistical Software. [computer program]. Stata Corp. College Station. Texas: Stata Corporation; 1997;

211. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121-45.

212. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random effects regression model for meta-analysis. Stat Med 1995;14:395-411.

213. Collett D. Modelling Survival Data in Medical Research. London: CRC Press LLC; 1993.

214. Perrson PG, Bernell O, Leijonmarck CE, Farahmand BY, Hellers G, Ahlbom A. Survival and cause specific mortality in inflammatory bowel disease:a population based cohort study. Gastroenterology 1996;110:1339-45.

215. Bonnevie O, Riis P, Anthonisen P. An epidemiological study of ulcerative colitis in Copenhagen county. Scand J Gastroenterol 1968;3:432-8.

216. Mosbech J. Mortality from ulcerative colitis in Denmark. Gastroenterology 1960;39:690-3.

217. Svartz N. The treatment of ulcerative colitis. Gastroenterology 1954;26(1):26-8.

218. Bargen JA, Dixon CF. Chronic ulcerative colitis with associated carcinoma. Arch Surg 1935;30:854-64.

219. Bargen JA. Chronic ulcerative colitis associated with malignant disease. Arch Surg 1928;17:561-76.

220. Cattell RB. Indications for colectomy in ulcerative colitis. Surg Clin North Am 1944;24:656-60.

221. Coffey RJ. Multiple polyposis associated with chronic ulcerative colitis:a clinicopathological study. Procedings of the Staff Meetings of the Mayo Clinic 1939;14:11-3.

222. Devroede GJ, Dockerty MB, Sauer WG, Jackman RJ, Stickler GB. Cancer of the colon in patients with ulcerative colitis since childhood. Can J Surg 1972;15:369-74.

223. Hinton JM. Risk of malignant change in ulcerative colitis. Gut 1966;7:427-32.

224. Sauer WG, Bargen JA. Chronic ulcerative colitis and carcinoma. JAMA 1949;141:982-5.

225. Shands WC, Dockerty MB, Bargen JA. Adenocarcinoma of the large intestine associated with chronic ulcerative colitis. Surg Gynecol Obstet 1952;94:302-10.

226. Muto T, Konishi F. Shiratori T, Nakano H, editors. Inflammatory Bowel Disease. Tokyo: University & Tokyo Press; 1984; Carcinoma in ulcerative colitis. p. 151-60.

227. Sauer WG, Bargen JA. Chronic ulcerative colitis followed by carcinoma: report of twenty-six cases. Staff Meetings of the Mayo Clinic 1944;311-5.

228. Bargen JA, Coffey RJ. Two intestinal carcinomas in the same case of chronic ulcerative colitis and the management of the resulting obstruction. Med Clin North Am 1935;19:403-9.

229. Brooke BN. Malignant change in ulcerative colitis. Diseases of the Colon and Rectum 1961;4:393-8.

230. Lynn DH. The relationship of chronic lesions to carcinoma of the colon-chronic ulcerative colitis. Int Abstract Surg 1945;81:269-76.

231. Poley JR. Chronic inflammatory bowel disease in children and adolescents: Part II. South Med J 1978;71:1123-33.

232. Poley JR. Chronic inflammatory bowel disease in children and adolescents: Part I. South Med J 1978;71:935-48.

233. Bargen JA, Kennedy RLJ. Chronic ulcerative colitis in children. Postgrad Med 1955;17:127-31.

234. Bargen JA, Jackman RJ, Kerr JG. Studies on the life histories of patients with chronic ulcerative colitis (thrombo-ulcerative colitis) with some suggestions for treatment. Ann Intern Med 1938;12:339-52.

235. Bonnevie O, Binder V, Anthonisen P, Riis P. The prognosis of ulcerative colitis. Scand J Gastroenterol 1974;9:81-91.

236. Cave HW. Late results in the treatment of ulcerative colitis. Am Surg 1946;124:716-24.

237. Helmholz HF. Chronic ulcerative colitis in childhood. Am J Dis Child 1923;26:418-30.

238. Jackman RJ, Bargen JA, Helmholz HF. Life histories of ninety-five children with chronic ulcerative colitis. Am J Dis Child 1940;59:459-67.

239. Lagerkrantz R. Ulcerative colitis in children. Acta Paediatr 1949;37 (Supplement 75):89-151.

240. Lennard-Jones JE, Morson BC, Ritchie JK, Shove DC, Williams CB. Cancer in colitis: assessment of the individual risk by clinical histological criteria. Gastroenterology 1977;73:1280-9.

241. Lennard-Jones JE, Parrish JA, Misiewicz JJ, Ritchie JK, Swarbrick ET, Williams CB. Prospective study of outpatients with extensive colitis. Lancet 1974;i:1065-7.

242. Maratka Z. Ulcerative colitis and carcinoma of the colon. Gastroenterology 1961;40:854-5.

243. Nedbal J, Maratka Z. Ulcerative proctocolitis in Czechoslovakia. Am J Proctol 1968;19:106-14.

244. Rice-Oxley JM, Truelove S. Complications of ulcerative colitis. Lancet 1950;i:607-11.

245. Sloan WP, Bargen JA, Baggentoss AH. Local complications of chronic ulcerative colitis based on the study of 2000 cases. Mayo Clinic Proc 1950;25:240-4.

246. Storgaard L, Bischoff N, Henriksen FW, Fischerman K, Jarnum S. Survival rate in Crohn's disease and ulcerative colitis. Scand J Gastroenterol 1979;14:225-30.

247. Svartz N, Ernberg T. Cancer coli in cases of colitis ulcerosa. Acta Medica Scandinavia 1949;135:444-7.

248. Tidrick RT, Hickey RC. The catastrophic complications of ulcerative colitis:cancer, perforation and massive bleeding. J Iowa Med Soc 1956;46:485-92.

249. Ashgren L, Jonsson B, Stenling R, Rutegard J. Prognosis after early onset of ulcerative colitis. A study from an unselected patient population. Hepatogastroenterolgy 1993;40:467-70.

250. Aylett S. Cancer and ulcerative colitis. BMJ 1971;2:203-5.

251. Bargen JA. Complications and sequelae of chronic ulcerative colitis. Ann Intern Med 1929;3:335-52.

252. Binder V, Bonnevie O, Gertz TCL, Krasilnikoff PA, Vestermark S, Riis P. Ulcerative colitis in children: treatment, course and prognosis. Scand J Gastroenterol 1973;8:161-7.

253. Brown ML, Kasich AM, Weingarten B. Complications of chronic ulcerative colitis. Am J Dig Dis 1951;18:52-4.

254. Cattell RB, Boehme EJ. The importance of malignant degeneration as a complication of chronic ulcerative colitis. Gastroenterology 1947;8:695-710.

255. Culinan ER, MacDougall IP. The natural history of ulcerative colitis. Lancet 1957;i:487-9.

256. Dawson IMP, Pryse-Davies J. The development of carcinoma of the large intestine in ulcerative colitis. Br J Surg 1959;47:113-28.

257. Dukes CE, Lockhart-Mummery HE. Practical points in the pathology and surgical treatment of ulcerative colitis. A critical review. Br J Surg 1957;45:25-36.

258. Edling NPG, Eklof O. Radiologic findings and prognosis in ulcerative colitis. Acta Chir Scand 1961;121:299-308.

259. Ekbom AM. Cancer risk in inflammatory bowel disease. Can J Gastroenterol 1995;9:23-6.

260. Fennessy JJ, Sparberg MB, Kirsner JB. Radiological findings in carcinoma of the colon complicating chronic ulcerative colitis. Gut 1968;9:388-97.

261. Goldgraber MB, Kirsner JB. Carcinoma of the colon complicating ulcerative colitis. Report of ten cases. Dis Colon Rectum 1964;7:336-44.

262. Goldgraber MB, Kirsner JB. Carcinoma of the colon in ulcerative colitis. Cancer 1964;17:657-65.

263. Goldgraber MB, Humphreys EM, Kirsner JB, Palmer WL. Carcinoma and ulcerative colitis: a clinical-pathologic study. II Statistical Analysis. Gastroenterology 1958;34:840-6.

264. Goligher JC, De Dombal FT, Watts JM, et al. Williams &, Wilkins I, editors. Ulcerative Colitis. Baltimore; 1968;p. 175-188.

265. Greenstein AJ, Sachar DB. Cancer in inflammatory bowel disease. Surv Dig Dis 1983;1:8-18.

266. Greenstein AJ, Sachar DB, Smith H, Janowitz HD, Aufses AH. A comparison of cancer risk in Crohn's disease and ulcerative colitis. Cancer 1981;48:2742-5.

267. Kiefer ED, Eytinge EJ, Johnson AC. Malignant Degeneration in Chronic Ulcerative Colitis. Gastroenterology 1951;19:51-7.

268. King RC, Linder AE, Pollard HM. Chronic ulcerative colitis in childhood. A follow-up study. Arch Dis Child 1959;34:257-61.

269. Kirsner JB, Palmer WL, Maimon SN, Ricketts WE. Clinical course of chronic nonspecific ulcerative colitis. JAMA 1948;137:922-8.

270. Lahey FH. The management of ulcerative colitis. Postgrad Med 1950;8:93-100.

271. Lennard-Jones JE. The clinical outcome of ulcerative colitis depends on how much of the colonic mucosa is involved. Scand J Gastroenterol 1983;18 (supplement 88):48-53.

272. MacDougall IPM. Ulcerative colitis and carcinoma of the large intestine. BMJ 1954;i:852-4.

273. Renshaw RJF, Brownell TS. Carcinoma complicating ulcerative colitis. Cleve Clin Q 1945;12:123-7.

274. Rutegard JN, Ahsgren LR, Janunger KG. Ulcerative colitis: colorectal cancer risk in an unselected population. Ann Surg 1988;6:721-4.

275. Aktan H., Paykoc Z., Ertan A. Ulcerative colitis in Turkey: clinical review of sixty cases. Diseases of the Colon and Rectum 1970;13:62-5.

276. Al-Nakib B, Radhakrishnan S, Jacob GS, Al-Liddawi H, Al-Ruwaih A. Inflammatory bowel disease in Kuwait. Am J Gastroenterol 1984;79:191-4.

277. Albrechtsen D, Bergan A, Gjone E, Nygaard K. Elective surgery for ulcerative colitis: colectomy in 158 patients. Scand J Gastroenterol 1981;16:825-31.

278. Bacon HE, OuYang LM, Carroll PT, Bates BA, Villalba G, McGregor RA. Non-specific ulcerative colitis with reference to mortality, morbidity, complications and long-term survivals following colectomy. Am J Surg 1956;92:688-95.

279. Baker WNW, Glass RE, Ritchie JK, Aylett SO. Cancer of the Rectum following colectomy and ileorectal anastomosis for ulcerative colitis. Br J Surg 1978;65:862-8.

280. Banks BM, Korelitz BI, Zetzel L. The course of nonspecific ulcerative colitis: review of twenty years' experience and late results. Gastroenterology 1957;32:983-1012.

281. Bargen JA, Gage RP. Carcinoma and ulcerative colitis: prognosis. Gastroenterology 1960;39:385-93.

282. Biasco G, Brandi G, Pagannelli GM, Rossini FP, Santucci R, Di Febo G, Miglioli M, Risio M, Labate AMM, Babara L. Colorectal cancer in patients with ulcerative colitis. A prospective cohort study in Italy. Cancer 1995;75:2045-50.

283. Brostrom O, Lofberg R, Nordenvall B, Ost A, Hellers G. The risk of colorectal cancer in ulcerative colitis. An epidemiologic study. Scand J Gastroenterol 1987;22:1193-9.

284. Bruce D, Cole WH. Complications of ulcerative colitis. Ann Surg 1962;155:768-79.

285. Carleson R, Fristedt B, Philipson J. A follow-up investigation of a 20-year primary material. Acta Medica Scandinavia 1962;172:647-56.

286. Cattell RB, Sachs E. Surgical treatment of ulcerative colitis. JAMA 1948;137:929-33.

287. Cazacu M, Dejica D, Badea R, Secas N, Tudose M, Ban A. Colorectal cancer and pre-existing pathological conditions: ulcerative colitis, Crohn's disease, colonic diverticulosis and polyposis. A retrospective analysis of 286 surgical patients. Rom J Gastroenterol 1997;6:239-41.

288. Chuttani HK, Nigam SP, Sama SK, Dhanda PC, Gupta PS. Ulcerative colitis in the tropics. BMJ 1967;4:204-7.

289. Colcock BP, Mathiesen WL. Complications of the surgical treatment of chronic ulcerative colitis. Arch Surg 1956;72:399-404.

290. Counsell PB, Dukes CE. The association of chronic ulcerative colitis and carcinoma of the rectum and colon. Br J Surg 1952;39:485-95.

291. Dennis C, Karlson KE. Cancer risk in ulcerative colitis: formidability per patient-year of late disease. Surgery 1961;50:568-71.

292. Dennis C, Karlson KE. Surgical measures as supplements to the management of idiopathic ulcerative colitis: cancer, cirrhosis and arthritis as frequent complications. Surgery 1952;32:892-912.

293. Diaz RJ, Farmer RG, Brown CH. Carcinoma of the colon and ulcerative colitis. Am J Dig Dis 1965;10:643-56.

294. Dolcini H, Arabehety JT, Stapler NM. Ulcerative colitis. Follow-up of 100 patients with some comments on the general features of this disease in Argentina. Am J Proctol 1967;18:132-5.

295. Farmer RG, Hawk WA, Turnbull RB. Carcinoma associated with mucosal ulcerative colitis and with transmural colitis and enteritis (Crohn's disease). Cancer 1971;28:289-92.

296. Feder IA. Chronic ulcerative colitis: an analysis of 88 cases. Am J Dig Dis 1938;2:239-45.

297. Felsen J, Wolarsky W. Chronic ulcerative colitis and carcinoma. Arch Intern Med 1949;84:293-304.

298. Flood CA, Lepore MJ, Hiatt RB, Karush A. Prognosis in chronic ulcerative colitis. J Chronic Dis 1956;4:267-82.

299. Fung WP, Monteiro EH, Murugasu JJ, Ng KC, Kho KM, Lee SK. Non-specific ulcerative colitis in Chinese and Indians in Singapore. Med J Aust 1971;2:361-5.

300. Gilat T, Zemishlany Z, Ribak J, Benaroya Y, Lilos P. Ulcerative colitis in the Jewish population of Tel-Aviv Yafo II: The rarity of malignant degeneration. Gastroenterology 1974;67:933-8.

301. Gleckler WJ, Brown CH. Carcinoma of the colon complicating chronic ulcerative colitis. Gastroenterology 1950;14:455-64.

302. Granqvist S, Gabrielsson N, Sundelin P, Thorgeirsson T. Precancerous lesions in the mucosa in ulcerative colitis. A radiographic, endoscopic and histopathologic study. Scand J Gastroenterol 1980;15:289-96.

303. Grundfest SF, Fazio V, weiss RA, Jagelman D, Lavery I, Weakley FL, Turnbull RB. The risk of cancer following colectomy and ileorectal anastomosis for extensive mucosal ulcerative colitis. Ann Surg 1981;193:9-14.

304. Hayes MA. Chronic ulcerative colitis and associated carcinoma. Am J Surg 1949;77:363-70.

305. Hickey RC, Tidrick RT. Cancer in patients with chronic ulcerative colitis. Cancer 1958;11:35-9.

306. Hijmans JC, Enzer NB. Ulcerative colitis in childhood. A study of 43 cases. Pediatr 1962;29:389-403.

307. Holowach J, Thurston DL. Chronic ulcerative colitis in childhood. J Pediatr 1956;48:279-91.

308. Hurt LE. The relationship of chronic ulcerative colitis to malignancy. Ann Surg 1954;139:838-43.

309. Johnson TM, Orr TG. Carcinoma of the colon secondary to chronic ulcerative colitis. Am J Dig Dis 1948;15:21-3.

310. Johnson WR, McDermott FT, Hughes ESR, Pihl EA, Milne BJ, Price AB. Carcinoma of the colon and rectum in inflammatory disease of the intestine. Surg Gynecol Obstet 1983;156:193-7.

311. Kapel O. Medical and modern surgical treatment of chronic ulcerative colitis. Acta Medica Scandinavia 1950;138:328-39.

312. Kasich AM, Weingarten B, Brown ML. Malignant degeneration in ulcerative colitis. Med Clin North Am 1949;33:1421-37.

313. Kochhar R, Goenka MK, Kaushik SP, Gupta NM, Nagi B, Mehta SK. Colorectal carcinoma in Indian patients with idiopathic ulcerative colitis. Eur J Cancer Prev 1992;1:293-6.

314. Korelitz BI, Gribetz D, Danziger I. The prognosis of ulcerative colitis with onset in childhood. I. The pre-steroid era. Ann Intern Med 1962;57:582-91.

315. Korelitz BI, Gribetz D. The prognosis of ulcerative colitis with onset in childhood. II. The steroid era. Ann Intern Med 1962;57:592-7.

316. Kusakcioglu O, Kusakcioglu A, Oz F. Idiopathic ulcerative colitis in Istanbul: clinical review of 204 cases. Dis Colon Rectum 1979;22:350-5.

317. Ladd WE, Fothergill LD. Idiopathic ulcerative colitis in children. Med Clin North Am 1935;19:1673-83.

318. Lanfranchi GA, Brignola C, Michelini M, Campieri M, Bazzochi G, Benatti A, Cortini C, Labo G, Parmeggiani A. Clinical course of ulcerative colitis in Italy. Digestion 1980;20:106-10.

319. Lashner BA, Provencher KS, Bosdech JM, Brzezinski A. Worsening risk for the development of dysplasia or cancer in patients with chronic ulcerative colitis. Am J Gastroenterol 1995;90:377-80.

320. Lindner AE, King RC, Bolt RJ. Chronic ulcerative colitis. A clinical appraisal and follow-up study. Gastroenterology 1960;39:153-60.

321. Lumb G, Protheroe RHB. Ulcerative colitis. A pathologic study of 152 surgical specimens. Gastroenterology 1958;34:381-407.

322. Lyons AS, Garlock JH. The relationship of chronic ulcerative colitis to carcinoma. Gastroenterology 1951;18:170-8.

323. MacDougall IPM. The cancer risk in ulcerative colitis. Lancet 1964;ii:655-8.

324. Maltby EJ, Dickson RC, O'Sullivan PM. The use of ACTH and cortisone in idiopathic ulcerative colitis. Can Med Assoc J 1956;74:4-9.

325. McMillan WO, Garbutt JT, Ruffin JM. Problems of cancer in ulcerative colitis. South Med J 1968;61:526-8.

326. Mellemkjaer L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK. Cancer in patients with ulcerative colitis. Int J Cancer 1995;60:330-3.

327. Micames C, Zaiter J, Nigaglioni A. Clinico-epidemiological features of 102 cases of ulcerative colitis in Puerto Rico. Bol Asoc Med P R 1983;75:106-9.

328. Mir-Madjlessi SH, Forouzandeh B, Ghadimi R. Ulcerative colitis in Iran: a review of 112 cases. Am J Gastroenterol 1985;80:862-6.

329. Moody GA, Jayanthi V, Probert CSJ, Mackay H, Mayberry JF. Long term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. Eur J Gastroenterol Hepatol 1996;8:1179-83.

330. Nefzger MD, Acheson ED. Ulcerative colitis in the United States army in 1944. Gut 1963;4:183-92.

331. Odes HS, Fraser D, Krawiec J. Ulcerative colitis in the Jewish population of Southern Israel 1961-1985: epidemiological and clinical study. Gut 1987;28:1630-6.

332. Patterson M, Castiglioni L, Sampson L. Chronic ulcerative colitis. A review of 43 patients beginning in children and teenagers. Am J Dig Dis 1971;16:289-97.

333. Radhakrishnan S, Zubaidi G, Daniel M, Sachdev GK, Mohan AN. Ulcerative colitis in Oman: a prospective study of the incidence and disease pattern from 1987 to 1994. Digestion 1997;58:266-70.

334. Ricketts WE, Palmer WL. Complications of chronic non-specific ulcerative colitis. Gastroenterology 1946;7:55-66.

335. Rosenqvist H, Lagerkrantz R, Ohrling H, Edling N. Ulcerative colitis and carcinoma coli. Lancet 1959;i:906-8.

336. Russell IS, Hughes ESR. Carcinoma of the colon complicating ulcerative colitis. Aust N Z J Surg 1961;30:306-11.

337. Schlesinger B, Platt J. Ulcerative colitis in childhood and a follow-up study. Proc R Soc Med 1958;51:733-4.

338. Skyring A, Roberts R. Childhood ulcerative colitis: an epidemiological study in N S W. Med J Aust 1965;52:955-60.

339. Slaney G, Brooke BN. Cancer in ulcerative colitis. Lancet 1959;ii:694-8.

340. Stewenius J, Adnerhill I, Anderson H, Ekelund GR, Floren CH, Fork FT, Janzon L, Lindstrom C, Ogren M. Incidence of colorectal cancer and all cause mortality in non-selected patients with ulcerative colitis and indeterminate colitis in Malmo, Sweden. Int J Colorectal Dis 1995;10:117-22.

341. Stonnington CM, Phillips SF, Zinsmeister AR, Melton III, LJ. Prognosis of chronic ulcerative colitis in a community. Gut 1987;28:1261-6.

342. Strombeck JP. The surgical treatment of ulcerative colitis. Acta Chir Scand 1949;98:414-27.

343. Svartz N, Gillnas T. In which phase of ulcerative colitis does colonic cancer occur? Am J Dig Dis 1958;3:537-48.

344. Tandon BN, Mathur AK, Mohapatra LN, Tandon HD, Wig KL. A study of the prevalence and clinical pattern of non-specific ulcerative colitis in northern India. Gut 1965;6:448-53.

345. Thompson JE. Ulcerative colitis. South Med J 1961;54:801-7.

346. Thorlakson RH. Carcinoma of the colon and rectum associated with chronic ulcerative colitis. Surg Gynecol Obstet 1956;103:41-50.

347. Turunen MJ, Jarvinen HJ. Cancer in ulcerative colitis: what failed in follow-up? Acta Chir Scand 1985;151:669-73.

348. Van Heerden JA, Beart RW. Carcinoma of the colon and rectum complicating chronic ulcerative colitis. Dis Colon Rectum 1980;23:155-9.

349. Vilien M, Jorgensen MJ, Ouyang Q, Schlichting P, Linde J, Riis P, Binder V. Colonic epithelial dysplasia or carcinoma in a regional group of patients with ulcerative colitis of more than 15 years duration. J Intern Med 1991;230:259-63.

350. Warren S, Sommers SC. Pathogenesis of ulcerative colitis. Am J Pathol 1949;25:657-79.

351. Waye JD. Dysplasia and ulcerative colitis - A colonoscopic study. Scand J Gastroenterol 1983;18 (supplement 88):44-7.

352. Weckesser EC, Chinn AB. Carcinoma of the Colon Complicating Chronic Ulcerative Colitis. JAMA 1953;152:905-8.

353. Welch CE, Hedberg SE. Colonic cancer in ulcerative colitis and idiopathic colonic cancer. JAMA 1965;191:815-8.

354. Wheelock FC, Warren R. Ulcerative colitis. Follow-up studies. N Engl J Med 1955;252:421-5.

355. Willard JH, Pessel JF, Hundley JW, Bockus HL. Prognosis of ulcerative colitis. JAMA 1938;111:2078-83.

356. Lagerkrantz R. Follow-up investigation of children with ulcerative colitis. With special reference to indications for surgical therapy. Acta Paediatr 1955;44:302-17.

357. Feher M. Drobini S, Feher M, editors. Recent Progress in the Study of Disorders of the Colon and Rectum. Budapest: Akademiai Kiado; 1972; Prognosis of Ulcerative Colitis. p. 389-93.

358. Pronay G, Molnar P, Horvath A, et al. Drobini S, Feher M, editors. Recent Progress in the Study of Disorders of the Colon and Rectum. Budapest: Akademiai Kiado; 1972; Diagnosis and Prognosis of Proctitis and Ulcerative Colitis. p. 395-9.

359. Office of National Statistics. 1993 Cancer Statistics Registrations. London. The Stationary Office. 1993; p.24 Series MB1 26.

360. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

361. Bansal P, Sonnenberg A. Risk factors for colorectal cancer in inflammatory bowel disease. Am J Gastroenterol 1996;91:44-8.

362. Eaden JA, Abrams K, Ekbom A, Jackson E, Mayberry JF. Colorectal cancer prevention in ulcerative colitis: a case-control study. Aliment Pharmacol Ther 2000;14:145-53.

363. Lashner BA, Provencher KS, Seidner DL, Knesebeck A, Brzezinski A. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. Gastroenterology 1997;112:29-32.

364. Greenberg ER, Baron JA, Freeman Jr DH, Mandel JS, Haile R. Reduced risk of large bowel adenomas among aspirin users. J Natl Cancer Inst 1993;85:912-5.

365. Martinez ME, McPherson RS, Levin B, Annegers JF. Aspirin and other nonsteroidal anti-inflammatory drugs and risk of colorectal adenomatous polyps among endoscoped individuals. Cancer Epidemiol Biomarkers Prev 1995;4:703-7.

366. Thun MJ, Namboodira MM, Heath CW. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325:1593-6.

367. Bus PJ, Nagtegaal ID, Verspaget HW, Lamers CBHW, Geldof H, Van Krieken JHJM, Griffioen G. Mesalazine-induced apoptosis of colorectal cancer: on the verge of a new chemopreventive era? Aliment Pharmacol Ther 1999;13:1397-402.

368. Probert CSJ, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. An epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire, 1972-89. Gut 1992;33:687-93.

369. Logan RFA, Little J, Hawtin PG, Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: Case-control study of subjects participating in the Nottingham faecal occult blood screening programme. BMJ 1993;307:285-9.

370. Kauppi M, Pukkala E, Isomaki H. Low incidence of colorectal cancer in patients with rheumatoid arthritis. Clin Exp Rheumatol 1996;14:551-3.

371. Barnes CJ, Cameron IL, Hardman WE, Lee M. Non-steroidal anti-inflammatory drug effect on crypt cell proliferation and apoptosis during initiation of rat colon carcinogenesis. Br J Cancer 1998;77:573-80.

372. Davis AE, Patterson F, Crouch R. The effect of therapeutic drugs used in inflammatory bowel disease on the incidence and growth of colonic cancer in the dimethylhydrazine rat model. Br J Cancer 1992;66:777-80.

373. Catnach SM, Rutter KRP, Bown RL. Colorectal carcinoma in patients with ulcerative colitis and recent colonoscopy. Gut 1993;34:1148-9.

374. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331:1669-74.

375. Probert CSJ, Jayanthi V, Bhakta P, Wicks ACB, Mayberry JF. How necessary is colectomy? An epidemiological study of the surgical management of ulcerative colitis amongst different ethnic groups in Leicestershire. Eur J Gastroenterol Hepatol 1993;5:17-20.

376. Sinclair TS, Brunt PW, Mowat NAG. Nonspecific proctocolitis in Northeastern Scotland: a community study. Gastroenterology 1983;85:1-11.

377. Moser G, Tillinger W, Sachs G, Genser D, Maier-Doberberger T, Spiess K, Wyatt J, Vogelsang H, Lochs H, Gangl A. Disease-related worries and concerns: a study on outpatients with inflammatroy bowel disease. Eur J Gastroenterol Hepatol 1995;7:853-8.

378. Eaden JA, Ward B, Smith H, Mayberry JF. Are we telling patients enough? A pilot study to assess patient information needs in a gastroenterology outpatient department. Eur J Gastroenterol Hepatol 1998;10:63-7.

379. Smart H, Mayberry J, Calcraft B, Morris JS, Rhodes J. Effect of information booklets on patients' anxiety levels and consultation rates in Crohn's disease. Public Health 1986;100:184-6.

380. Chambers JK, Boggs DL. Development of an instrument to measure knowledge about kidney function, kidney failure and treatment options. Am Nurses Nephrol Assoc J 1993;20:637-50.

381. Devind GM, Binik YM, Mandin H, Letourneau PK, Hollomby DJ, Barre PE, Prichard S. The kidney disease questionnaire: a test for measuring patient knowledge about end-stage renal disease. J Clin Epidemiol 1990;43:297-307.

382. Dunn SM, Bryson JM, Hoskins PL, Alford JB, Handelsman DJ, Turtle JR. Development of the Diabetes Knowledge (DKN) Scales: forms DKNA, DKNB and DKNC. Diabetes Care 1984;7:36-41.

383. Meadows KA, Fromson B, Gillespie C, Brewer A, Carter C, Lockington T, Clark G, Wise PH. Development, validation and application of computer-linked knowledge questionnaires in diabetes education. Diabet Med 1988;5:61-7.

384. Reisine S, Lewis C, Tibbles L, Donald M, Rippey R. Self-administered patient questionnaire for assessing knowledge about joint arthroplasty prior to surgery. Arthritis Care Res 1992;5:8-12.

385. Vaeth PA. Women's knowledge about breast cancer. Am J Clin Oncol 1993;16:446-54.

386. Mayberry JF, Morris JS, Calcraft B, Rhodes J. Information assessment by patients of a booklet on Crohn's disease. Public Health 1995;99:239-42.

387. Bryman A; Cramer D. Qualitative Data Analysis for Social Scientists. London: Routledge; 1994.

388. Streiner DL; Norman GL. Health Measurement Scales: a practical guide to their development and use. Oxford: Oxford University Publications; 1989.

389. Flesch R. A new readability yardstick. J Appl Psychol 1948;32:221-33.

390. Altman DG. Practical Statistics for Medical Research. 7th ed. London: Chapman & Hall; 1996.

391. Somerville KW, Logan RFA, Edmond M, Langman MJS. Smoking and Crohn's disease. BMJ 1984;289:954-6.

392. Levi AJ, Fisher AM, Hughes L, Henry WF. Male infertility due to sulphasalazine. Lancet 1979;ii:276-8.

393. Nwokolo CU, Tan WC, Andrews HA, Allan RA. Surgical resections in parous patients with distal ileal and colonic Crohn's disease. Gut 1994;35:220-3.

394. Kish L. Survey Sampling. New York: John Wiley & Sons,Inc; 1965.

395. Moody GA, Eaden JA, Bhakta P, Sher K, Mayberry JF. The role of complementary medicine in European and Asian patients with inflammatory bowel disease. Public Health 1998;112(4):269-71.

396. Stein SH; Rood RP. Stein SH and Rood RP, editors.Inflammatory Bowel Disease. A guide for patients and their families. Second ed. Philadelphia. New York. Lippincott-Raven; 1999.

397. Moody GA, Mayberry JF. Disinterest in local self help groups amongst patients with inflammatory bowel disease. Int J Colorectal Dis 1993;8:181-3.

398. Choy DK, Tong M, Ko F, Ho A, Chan J, Leung R, Lai CK. Evaluation of the efficacy of a hospital-based asthma education programme in patients of low socioeconomic status in Hong Kong. Clin Exp allergy 1999;29:84-90.

399. Haines ST. Patient education: a tool in the outpatient management of deep vein thrombosis. Pharmacotherapy 1998;18:158-64.

400. Tan AS, Yong LS, Wan S, Wong ML. Patient education in the management of diabetes mellitus. Singapore Med J 1997;38:156-60.

401. HamajimaN, Tajima K, Morishita M, Hyodo C, Sakakibara N, Kawai C, Moritaka S. Patient's expectations of information provided at cancer hospitals in Japan. Jap J Clin Oncol 1996;26:362-7.

402. Eaden JA, Abrams K, Ekbom A, et al. Colorectal cancer prevention in ulcerative colitis: a case-controlled study. [Abstract] Gut 1999;44:(supplement 1)W169

403. Eaden JA, Shears J, Mayberry JF. Preventing bowel cancer in ulcerative colitis: a patients guide. [Abstract] Gut 1999;44:(supplement 1)V574

404. Healton CG, Messeri P. The effect of video interventions on improving knowledge and treatment compliance in the sexually transmitted disease clinic setting. Sex Transm Dis 1993;20:70-6.

405. Herrmann KS, Kreuzer H. A randomized prospective study on anxiety reduction by preparatory disclosure with and without a video film show about a planned heart catheterization. Eur Heart J 1989;10:753-7.

406. Baggerly J, Crockett MJ. Managing an educational video production: practical considerations. Rehabil Nurs 1991;16:141-3.

407. Meade CD, McKinney WP, Barnas GP. Educating patients with limited literacy skills: the effectiveness of printed and videotaped materials about colon cancer. Am J Public Health 1994;84(1):119-21.

408. Stalonas PM, Keane TM, Foy DW. Alcohol education for inpatient alcoholics: a comparison of live, videotape, and written presentation modalities. Addict Behav 1979;4:223-9.

409. Pace PW, Henske JC, Whitfill BJ, Andrews SM, Russell ML, Probstfield JL, Insull W Jr. Videocassette use in diet instruction. J Am Diet Assoc 1983;83:166-9.

410. Vogler RE, Weissbach TA, Compton JV, Martin GT. Integrated behaviour change techniques for problem drinkers in the community. J Consult Clin Psychol 1977;45:267-79.

411. Kleemeier CP, Hazzard AP. Videotaped parent education in pediatric waiting rooms. Patient Educ Couns 1984;6:122-4.

412. Audit Commision. What seems to be the matter: communication between hospitals and patients. London: HMSO. 1993;

413. Cherkin DC, Deyo RA, Street JH, Hunt M, Barlow W. Pitfalls of patient education. Limited success of a program for back pain in primary care. Spine 1996;21:345-55.

414. Castaldini M, Saltmarch M, Luck S, Sucher K. The development and pilot testing of a multimedia CD-ROM for diabetes education. Diabetes Educ 1998;24:285-96.

415. Liedholm H, Linne AB, Agelii L. The development of an interactive education program for heart failure patients: the Kodak Photo CD Portfolio concept. Patient Educ Couns 1996;29:199-206.

416. Lofberg R. Endoscopy findings in ulcerative colitis. How to manage ulcerative colitis. A quick reference guide. 1996; Synergy Medical Education.

417. Lashner BA. Colorectal cancer in ulcerative colitis patients: survival curves and surveillance. Cleve Clin J Med 1994;61:272-5.

418. McLeod RS, Churchill DN, Lock AM, Vanderburgh S, Cohen Z. Quality of life of patients with ulcerative colitis preoperatively and postoperatively. Gastroenterology 1991;101:1307-13.

419. Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-8.

420. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. Am J Gastroenterol 1997;92:204-11.

421. Fozard JBJ, Dixon MF. Colonoscopic surveillance in ulcerative colitis - dysplasia through the looking glass. Gut 1989;30:285-92.

422. Bernstein CN, Weistein WM, Levine DS, Shanahan F. Physician's perceptions of dysplasia and approaches to surveillance colonoscopy in ulcerative colitis. Am J Gastroenterol 1995;90:2106-14.

423. Axon ATR. Colonic cancer surveillance in ulcerative colitis is not essential for every patient. Eur J Cancer 1995;31A(7-8):1183-6.

424. Butt JH, Morson B. Dysplasia and cancer in inflammatory bowel disease. Gastroenterology 1981;80:865-8.

425. Ransohoff DF, Riddell RH, Levin B. Ulcerative colitis and colonic cancer: problems in assessing the diagnostic usefulness of mucosal dysplasia. Dis Colon Rectum 1985;28:383-8.

426. Dundas SAC, Kay R, Beck S, Cotton DWK, Coup AJ, Slater DN, Underwood JCE. Can histopathologists reliably assess dysplasia in chronic inflammatory bowel disease ? J Clin Pathol 1987;40:1282-6.

427. Melville DM, Jass JR, Morson B.C., Pollock DJ, Richman PI, Shepherd NA, Ritchie JM, Love SB, Lennard-Jones JE. Observer study of the grading of dysplasia in ulcerative colitis: Comparison with clinical outcome. Hum Pathol 1989;20:1008-14.

428. Machin D; Campbell M; Fayers P, et al. Sample size tables for clinical studies. Second ed. Oxford: Blackwell Sciences Limited; 1997.

429. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York: Wiley; 1981.

430. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

431. McCluggage WG, Walsh MY, Thornton CM, Hamilton PW, Date A, Caughley LM, Bharucha H. Inter- and intra-observer variation in the histopathological reprting of cervical squamous intraepithelial lesions using a modified Bethesda grading system. Br J Obset Gynaecol 1998;105:206-10.

432. O'Sullivan JP, Ismail SM, Barnes WS, Deer AR, Gradwell E, Harvey JA, Husain OA, Kocjan G, McKee G, Olafsadotir R, et al. Inter- and intra-observer variation in the reporting of cervical smears: specialist cytopathologists versus histopathologists. Cytopathology 1996;7:78-89.

433. Hamilton PW, Bartels PH, Thompson D, Anderson NH, Montironi R, Sloan JM. Automated location of dysplastic fields in colorectal histology using image texture analysis. J Pathol 1997;182:68-75.

434. Banks PA, Present DH. Surveillance in ulcerative colitis: Is it worthwhile? Does it save lives? Or does it just give discontent? Inflamm Bowel Dis 1995;1:84-5.

435. Itzkowitz SH. Inflammatory bowel disease and cancer. Gastroenterol Clin North Am 1997;26(1):129-39.

436. A nationwide survey of observer variaton in the diagnosis of thin cutaneous malignant melanoma including the MIN terminology. J Clin Pathol 1997;50:202-5.

437. Andrew A, Wyatt JI, Dixon MF. Observer variation in the assessment of chronic gastritis according to the Sydney system. Histopathology 1994;24:317-22.

438. Brown LJR, Smeeton NC, Dixon MF. Assessment of dysplasia in colorectal adenomas: an observer variation and morphometric study. J Clin Pathol 1985;38:174-9.

439. Burnett RA, Swanson Beck J, Howatson SR. Observer variability in the histopathological reporting of malignant broncial biopsies. [Abstract] J Pathol Suppl 1994;173:39

440. Colloby PS, Fletcher A, West KP. Interobserver variation in the measurement of Breslow depth in thin primary cutaneous malignant melanomas. [Abstract] J Pathol 1990;160:154

441. Hartman G, McCormick F, Sundaresan M. The subjective nature of diagnosing coeliac disease. [Abstract] J Pathol 1995;175:104

442. Ismail SM, Colcough AB, Dinnen JS, Eakins D, Evans DMD, Gradwell E, O'Sullivan JP, Summerell JM, Newcombe RG. Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. BMJ 1989;298:707-10.

443. Lessels AM, Burnett RA, Howatson SR. Observer variability in the histopathological reporting of prostatic needle biopsy specimens. [Abstract] J Pathol 1996;178:7

444. Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, Lewin K, Weinstein WM, Antonioli DA, Goldman H, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Hum Pathol 1988;19:166-78.

445. Sloane JP, Ellman R, Anderson TJ. Consistency of histopathological reporting of breast lesions detected by screening: findings of the UK National External Quality Assessment (EQA) Scheme. UK National Co-ordinating Group for Breast Screening Pathology. [Abstract] Eur J Cancer 1994;30:1414-9.

446. Lesna M. Assessing diagnostic errors: when is suspension of a pathologist justified? J Clin Pathol 1998;51:649-51.

447. Stanley MW. Quality and liabilty issues with the Papanincolau smear: the role of professional organisations in reform initiatives. Arch Pathol Lab Med 1997;121:327-30.

448. Fozard JBJ, Quirke P, Dixon MF, Giles GR, Bird CC. DNA aneuploidy in ulcerative colitis. Gut 1986;27:1414-8.

449. Allen DC, Biggart JD, Orchin JC, Foster H. An immunoperoxidase study of epithelial marker antigens in ulcerative colitis with dysplasia and carcinoma. J Clin Pathol 1985;38:18-29.

450. Allen DC, Hamilton PW, Watt PC, Biggart JD. Morphometrical analysis in ulcerative colitis with dysplasia and carcinoma. Histopathology 1987;11(9):913-26.

451. Furness PN. The use of digital images in pathology. J Pathol 1997;183:253-63.

452. Hickman D, Pope J, Patil SD, Fakis G, Smelt V, Stanley LA, Payton M, Unadkat JD, Sim E. Expression of arylamine N-acetyltransferase in human intestine. Gut 1998;42:402-9.

453. Rieder CR, Ramsden DB, Williams AC. Cytochrome P450 1B1 mRNA in the human cental nervous system. Mol pathol 1998;51:138-42.

454. McKay JA, Melvin WT, AhSee AK, Ewen SWB, Greenlee WF, Marcus CB, Burke MD, Murray GI. Expression of cytochrome P450 CYP1B1 in breast cancer. FEBS Lett 1995;374:270-2.

455. Savas U, Bhattacharyya KK, Christou M, Alexander DL, Jefcoate CR. Mouse cytochrome P450EF, representative of a new 1B subfamily of cytochrome P450s. Cloning, sequence determination and tissue expression. J Biol Chem 1994;269:14905-11.

456. Shen Z, Liu J, Wells RL, Elkind MM. cDNA cloning, sequence analysis and induction by aryl hydrocarbons of a murine cytochrome P450 gene, CYP1B1. DNA Cell Biol 1994;(13):763-9.

457. Sutter TR, Yong MT, Hayes CL, Wo YYP, Jabs EW, Li X, Yin H, Cody CW, Greenlee WF. Complete cDNA sequence of a human dioxin-inducible mRNA identifies a new subfamily of cytochrome P450 that maps to chromosome 2. J Biol Chem 1994;(269):13092-9.

458. Bertheau P, Cazals-Hatem D, Meignin V, de Roquancourt A, Verola O, Lesourd A, Sene C, Brocheriou C, Janin A. Variability of immunohistochemical reactivity on stored paraffin slides. J Clin Pathol 1998;51:370-4.

459. Mason DY, Cordell JL, Pulford KAF. Bullock GR, Petrusz P, editors. Techniques in Immunocytochemistry. Volume 2. London: Academic Press; 1983; Production of monoclonal antibodies for immunocytochemical use. p. 175-216.

460. Ekbom A, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 1990;336:357-9.

461. Sachar DB. Cancer in Crohn's disease: dispelling the myths. Gut 1994;35:1507-8.

462. Stahl TJ, Schoetz Jr DJ, Roberts PL, Coller JA, Murray JJ, Silverman ML, Veidenheimer MC. Crohn's disease and carcinoma: increasing justification for surveillance? Dis Colon Rectum 1992;35:850-6.

463. Matsui T, Iida M, Suekane H, Tominaga M, Yao T, Sakurai T, Seo M, Okada M, Nomiyama Y, Fuchigami T. The long-term follow-up study of Japanese patients with ulcerative colitis. (Japanese). Jap J Gastroenterol 1993;90:134-43.

464. Martins P, Soares C, Batista A. Idiopathic proctocolitis. Follow-up (1-13 years) of 71 patients. Acta Med Port 1990;3:159-63.

465. Nahas SC. Colonoscopy and digital cytometry in the clinical assessment of prolonged non-specific ulcerative rectocolitis. Revista do Hospital das Clinicas 1994;49:152-6.

466. Clayton DG; Hills M. Methods in Statistical Analysis. Oxford: Oxford University Press; 1993.

467. Thompson SG. Why sources of heterogeneity in meta-analyses should be investigated. BMJ 1994;309:1351-5.

468. Bargen JA, Sauer WG, Sloan WP, Gage RP. The development of cancer in chronic ulcerative colitis. Gastroenterology 1954;26:32-7.

469. Goldgraber MB, Humphreys EM, Kirsner JB, Palmer WL. Carcinoma and ulcerative colitis: a clinical-pathologic study. I Cancer Deaths. Gastroenterology 1958;34:809-39.

470. Sloan WP, Bargen JA, Gage RP. Life histories of patients with chronic ulcerative colitis: a review of 2000 cases. Gastroenterology 1950;16:25-38.

471. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut 1994;35:1590-2.

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The Crohn's and Colitis Knowledge Score: A Test for Measuring Patient Knowledge in Inflammatory Bowel Disease

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OBJECTIVE: The aim of this study was to develop a valid and reliable questionnaire assessing patient knowledge of inflammatory bowel disease (IBD) and its treatment—the Crohn's and Colitis Knowledge (CCKNOW) Score.

METHODS: A total of 30 multiple choice questions were constructed into a draft questionnaire. This was piloted on a random selection of participants with differing IBD knowledge levels: junior doctors, nurses, and ward clerks. Factor analysis eliminated questions with poor discriminant ability. The resulting 24-item questionnaire (CCKNOW score) was retested on the three groups, and a Kruskal-Wallis test determined the questionnaire's ability to discriminate between the groups. Reliability and readability were tested using Cronbach's α and the Flesch Kincaid reading score. The validated CCKNOW was then tested on patients from the Leicestershire IBD database.

RESULTS: CCKNOW scores differed significantly across the groups of doctors, nurses, and ward clerks (median 22, 16, and five, respectively) $T = 40.35$, $p < 0.0001$. The reliability was very good with a Cronbach's α of 0.95 and the readability was also high. The median score on the CCKNOW for IBD patients was 10, with no significant difference between ulcerative colitis and Crohn's disease. Patients who are members of NACC (National Association of Crohn's and Colitis) achieve statistically significantly higher scores than do nonmembers (difference in medians 4, 95% confidence interval 4–6, $p < 0.0001$).

CONCLUSIONS: The CCKNOW score provides a valuable index of overall knowledge. It is self-administered and psychometric tests show it to be valid, reliable, and readable. It may be used in the future as a tool to evaluate patient education programs. (Am J Gastroenterol 1999;94: 3560–3566. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

Patient knowledge and understanding varies widely in inflammatory bowel disease (IBD). Some patients show evidence of advance reading about IBD and its treatment options. Others do not possess even a basic understanding of their condition and have virtually no recall of previous discussions with their physician. A working knowledge of their disease and its management is essential for patients with chronic disorders such as IBD. Such knowledge can positively influence quality of life, social activity, and ability to cope and comply with treatment (1–3). Various studies from Europe have demonstrated that patients with IBD want detailed information on both social and medical aspects of their disease (4–9). In addition there is evidence that providing patients with such information can reduce consultation rates and decrease anxiety levels (10).

It would seem that patient education should therefore be an integral part of comprehensive IBD care. Before the general introduction of individual or group based education programs (whether for newly diagnosed or established IBD patients) we should have an index that can evaluate them objectively. If patients have good knowledge of their disease and manage their condition appropriately, one would hope that they would have fewer disease complications. However, objectives such as complications of disease provide very late and imprecise guides of knowledge deficits. Consequently there is a need for an efficient and reliable tool that can assess deficiencies in knowledge so that patient education programs can be designed and evaluated comprehensively.

Although there is growing interest in patient education in IBD there are few published scales which measure such knowledge (11). In contrast much research has been conducted on the development of assessment tools in other areas of medicine: most notably diabetes mellitus and end stage renal failure (12–17). In type 1 diabetes mellitus glycosylated hemoglobin concentration was inversely correlated with patient scores for overall knowledge (18), and it seems reasonable to predict that increased knowledge of IBD may be lead to fewer complications and better self-management.

The aim of this study was to develop a valid and reliable self-administered questionnaire to assess patient knowledge of IBD and its treatment. Additional aims were that the test

be easy to administer and score and that it require only basic reading skills. This article initially presents an analysis and discussion of the development, discriminant validity, and internal reliability of the instrument developed for that purpose: the Crohn's and Colitis Knowledge Score (CCKNOW score). The article goes on to report the findings when the questionnaire was posted to patients with IBD from the Leicestershire IBD patient database.

MATERIALS AND METHODS

The procedure used to develop the questionnaire was divided into four stages, as follows.

1. The Development of Knowledge Areas to Be Assessed

The areas to be covered by the test were based on key elements in the educational materials used in our clinics. The effects of these educational booklets have already been assessed in previous studies (19, 20), and they were initially developed after consultation with several clinicians with an interest in IBD. The booklets deal with symptoms, investigations, theories of etiology, and medical and surgical treatment.

2. Preparation of Multiple Choice Questions

Forty multiple choice questions were developed, each defining specific knowledge to be evaluated in the following areas of IBD management: a) general IBD understanding, b) medication, c) diet, and d) complications of IBD. All multiple choice questions were reviewed by physicians to consider their relevance to patient assessment. A number of questions were revised, resulting in a total of 30 questions being included for evaluation in the assessment of patient knowledge levels (see Appendix 1). The revised set of 30 questions consisted of general knowledge, including anatomy and investigation (16), medication (6), diet (2), and complications of IBD (6). Only two questions were specific to either Crohn's disease or ulcerative colitis (UC) and, thus, the majority of the questions should have been answerable by all respondents.

3. Pilot Study of Draft Multiple Choice Questions

Participants were randomly selected from three groups that were expected to differ in IBD-relevant knowledge and included a) 17 junior doctors (most knowledgeable), b) 16 state registered nurses (moderately knowledgeable), and c) 20 ward clerks (least knowledgeable). Each participant was sent a questionnaire with a covering letter explaining the purpose of the study and stressing the confidentiality of the answers. The questionnaires were self-administered and returned anonymously.

4. Analysis of Returned Questionnaires and Multiple Choice Question Selection and Revision

Scoring of the CCKNOW was one point for each correct answer with no negative marking. Questions were analyzed by factor analysis to maximize valid discrimination (21). Factors with an eigenvalue >1 were chosen and the interpretation of the factorial structure was based on factor loadings ≥0.5. The revised CCKNOW score was then retested on doctors, nurses, and ward clerks so that new summary scores for the groups could be determined.

Criterion related validity was assessed via a Kruskal-Wallis test, a nonparametric one way analysis of variance, as the data from the three groups were not normally distributed (as demonstrated by the Shapiro-Wilk test). This test was used to demonstrate the statistical significance of the difference in scores between the three groups. The reliability of the CCKNOW Score was tested by calculating the internal consistency using Cronbach's alpha—an index of inter-item consistency that can vary between 0 and 1, with higher values reflecting higher levels of internal consistency (22). Readability of the test questionnaire was determined using the Flesch Kincaid reading score (23).

Once the CCKNOW Score was validated it was posted to 647 IBD patients who were randomly selected from the Leicestershire IBD patient database and are of mixed social class and ethnic background. The IBD patients in Leicestershire are cared for by one of seven gastroenterologists and so no single consultant (and his practice) could have influenced the results. Correlation between knowledge score and membership of The National Association of Crohn's and Colitis patient self-help group (NACC) was performed. The data were assessed for nonnormality using the Shapiro-Wilk test, the level of statistical significance between the groups subsequently assessed using the Mann-Whitney U-test and 95% confidence intervals (CI) were calculated (24).

RESULTS

The mean and median scores, 95% confidence intervals, and standard deviations of the participants in the pilot study are shown in Table 1. Junior doctors had higher scores than staff nurses, who in turn did better than ward clerks. The factor analysis resulted in five factors with an eigenvalue >1. For each of these factors, questions with a factor loading >0.5 were regarded as acceptable for inclusion in the final questionnaire. Questions with a factor loading of <0.5 were rejected. From this analysis, six items were deemed to be unsuitable for inclusion (questions 1, 5, 8, 14, 19, and 21). The redrafted questionnaire consisted of 24 multiple choice questions covering five objectives. Eight questions related to general IBD knowledge, five to medication, four to anatomy, five to disease complications, and two related to diet. The revised 24-item CCKNOW score was retested on doctors, nurses, and ward clerks. The junior doctors obtained a median score of 22, nurses 16, and ward clerks 5 (Table 1).

Internal consistency was assessed in two ways. First, a Kruskal-Wallis test indicated that the 24-item CCKNOW scores differed significantly across the three groups, $T = 40.35$ (adjusted for ties), $p < 0.0001$. Secondly, Cronbach's α was very high, at 0.95. The readability of the CCKNOW score was also very good. The test questionnaire scored

Table 1. Results of the Pilot CCKNOW Score for Junior Doctors, Staff Nurses, and Ward Clerks on 30- and 24-Item Multiple Choice Questionnaires

		Mean (95% CI)	Median (95% CI)	SD
Junior doctors	30 items	27.3 (26.4–28.2)	28.0 (27.0–28.0)	1.8
(n = 17)	24 items	21.9 (21.1–22.7)	22.0 (21.0–23.0)	1.6
Staff nurses	30 items	20.6 (19.0–22.2)	20.5 (19.0–23.0)	3.3
(n = 16)	24 items	15.9 (14.2–17.6)	16.0 (14.0–18.0)	3.4
Ward clerks	30 items	9.5 (6.9–12.1)	8.0 (7.0–12.0)	5.9
(n = 20)	24 items	6.1 (3.9–8.3)	5.0 (3.0–8.0)	5.1

CCKNOW = Crohn's and Colitis Knowledge.

favorably in that it was classified as being easy to read (score of 77.9/100); only 13% of the sentences were passive, and it had a reading grade level of 4.4.

The validated CCKNOW score was then further tested on the patient group described previously. Overall, 354 questionnaires were returned (response rate, 55%). A total of 200 patients had ulcerative colitis and 154 had Crohn's disease. Of the patients, 182 of 290 respondents were members of NACC (response rate, 63%) and 172 of 357 were nonmembers (response rate, 48%).

The median score for IBD patients was 10 (95% CI, 9–10), with no significant difference in the scores for patients with UC and Crohn's disease (median 9; 95% CI, 9–10 and median 10; 95% CI, 9–11, respectively). The CCKNOW scores for patients by disease and membership of NACC are shown in Table 2. Using the Shapiro-Wilk W test, the data from these groups were found to be from a nonnormal distribution, and so nonparametric tests were utilized (Mann-Whitney U test).

Patients who are members of NACC, whether they have UC or Crohn's disease, achieve significantly better scores than nonmembers with a difference in median scores of 4.0, $p < 0.0001$ (95% CI, 4–6). Patients with IBD who do not belong to NACC have only slightly higher knowledge levels than ward clerks (lay persons), with median scores of 8 and 5, respectively. Members of NACC score more highly, with knowledge levels approaching those of nurses (12 and 16 respectively). As questionnaires were posted anonymously, it was not possible to trace which subjects returned their questionnaires. However, 80 respondents added their names and addresses to the questionnaire and with their permission we reviewed their medical notes to determine whether duration of disease affected the CCKNOW score. We found that duration of disease bore no correlation to the CCKNOW score with respondants having IBD for 2 yr being just as likely to have a low/high score as someone who had had IBD for 20 yr.

Considering the group as a whole, mixed levels of understanding were ascertained from the general knowledge section of the questionnaire. Most patients (78%) realized that just because they may have been symptom free for 3 yr, they were not cured of their condition, and the vast majority (96%) knew that they could not pass on their disease to family members if they were not careful about personal hygiene. However 72% of patients were unaware that IBD runs in families, 47% did not understand that IBD can affect parts of the body other than the bowel, and 77% did not know that smoking was associated with Crohn's disease. Fifty-eight percent were not aware that a child with IBD may be shorter than his/her friends, with these responders actually believing that they may be either less intelligent or may not live beyond the age of 45 yr.

Regarding medication, there was some confusion between the different types of drug used to treat IBD. Of the patients, 60% understood the role of immunosuppressive drugs, but 76% thought that sulphasalazine and mesalazine were examples of such drugs. In addition, 68% knew that sulphasalazine was used to reduce the frequency of relapse, but only 26% were aware that it can reversibly reduce male fertility. Concerning steroids, 49% did not know that these agents can be administered rectally and intravenously as well as orally; 56% thought that side effects from steroids started immediately (even after small doses), and that all side effects disappeared after they were discontinued.

Table 2. CCKNOW Scores for IBD Patients by Disease and Membership Status in NACC (on 24-Item Multiple Choice Questionnaire)

	Mean (95% CI)	Median (95% CI)	SD
Ulcerative colitis, NACC (n = 96)	12.4 (11.4–13.4)	12.5 (10.0–14.0)	5.0
Crohn's disease, NACC (n = 86)	12.6 (11.5–13.7)	12.0 (11.0–14.0)	5.3
Ulcerative colitis, nonmember (n = 104)	7.9 (7.2–8.6)	8.0 (7.0–9.0)	3.8
Crohn's disease, nonmember (n = 68)	7.8 (6.8–8.8)	7.5 (6.0–9.0)	4.0

CCKNOW = Crohn's and Colitis Knowledge; IBD = inflammatory bowel disease; NACC = National Association of Crohn's and Colitis.

As far as complications of IBD are concerned, 78% were unaware as to which patients were at increased risk for bowel cancer and, therefore, should be under surveillance, with 7% believing that if they passed blood in their stools they definitely had bowel cancer. In addition, 58% did not understand what a fistula was, and 79% did not realize that a woman with Crohn's disease may have difficulty becoming pregnant.

DISCUSSION

In developing the CCKNOW score four criteria were chosen as goals. These included a) reliability, b) validity, c) ease of administration, and d) readability. The 24-item CCKNOW score displays high levels of reliability, as estimated by the coefficient α, and validity is also high with the Kruskal-Wallis test, demonstrating its ability to significantly discriminate doctors from nurses and could separate both of these groups from ward clerks. The CCKNOW score has a good readability score, which makes it ideal as a self-administered tool for assessing patient knowledge levels. The 55% response rate for the CCKNOW score was lower than we hoped, but this is not unexpected for a postal survey after a single mailing (25).

The CCKNOW score provides a robust index of overall knowledge and could be used in the future to evaluate patient education programs. It allows a comparatively inexpensive assessment of knowledge status for entire IBD populations, thereby freeing specialist IBD educators for more individual and goal-oriented teaching tasks. Those who wish to assess IBD knowledge on a single occasion may use the 24-item version. If users wish to conduct repeated assessments (for example, before and after an education program), two parallel 12-item versions may be developed for this purpose. Although there will be areas that will concern most patients (such as the cancer risk), each patient will require knowledge relating to different aspects of his or her disease. The CCKNOW will help individual clinicians to identify those topics to which they should give added attention during their general discussions with the patients under their care. As we have shown that knowledge is independent of disease duration, it is clear that patient education needs to be an ongoing process, with reiteration of important issues in IBD at each clinic visit. In addition to the standard doctor-patient consultation, knowledge may be imparted in through other media. Patients are enthusiastic about accepting educational material in a variety of forms, and a significant improvement in understanding can be achieved by the use of both videos and information leaflets. Written and video educational materials can be used without face-to-face consultations to inform most people about their disease and screening for complications. Video tapes provide a consistent form of teaching, are a familiar medium to most patients and can communicate concepts in a realistic and visual manner. A major advantage to video-based approaches is that educational benefits for patients can be achieved without imposing additional burdens on physicians to spend more time in educating and counseling patients about their disease. Another effective method of imparting information would be to employ specialist IBD nurses whose role would be to identify and address any knowledge deficits of the patient while liaising with the doctor to inform him or her of any areas raising specific concerns.

An additional use for the CCKNOW score may be to initiate discussions in self-help groups and in seminar-based teaching sessions. Most knowledge assessment tools in other specialities have been used to evaluate education programs and, through feedback, to correct patients' knowledge deficits. The CCKNOW score may be used to assess the knowledge not only of patients but also of family members. Educating spouses could result in greater understanding and an increase in the practical support given to patients in their home environments.

The CCKNOW was developed along similar lines to tests of knowledge in other areas of medicine (12–17) in that we defined crucial knowledge content, excluded questions of poor discriminatory ability and carried out various psychometric tests that have shown the CCKNOW questionnaire to have very promising properties. In the field of diabetic medicine, the CCQ-1 (15, 18), has been used to discriminate between performance in home monitoring, general management and overall scores stratified on a basis of patients' HbA_1 levels. In nephrology, the KDQ and CKKT (12, 13) have been used to establish the knowledge base of established dialysis patients for whom concordance with dietary, fluid, medication, or treatment regimens remains an ongoing challenge. It is understandable that good diabetic control can be achieved by education, as such patients have direct control of their own treatment. The treatment of IBD may be regarded as less complicated for the patient, but many patients self-medicate during exacerbations and a significant proportion turn to alternative medicines (26). Increasing knowledge in IBD may not have the same impact as in diabetes, although it should help to improve compliance with medication and colonic cancer screening programs.

We believe that all patients with IBD need to have a comprehensive knowledge base, although it could be argued that it is unnecessary to burden a patient with too much information. For example, a patient with distal colitis may not need to know about fibrostenotic Crohn's disease or the risk of colorectal cancer. We appreciate this point of view, but the CCKNOW has only five questions that are specific to either Crohn's disease or ulcerative colitis, with most being appropriate to both conditions. In addition, limiting patient knowledge and protecting patients against any anxiety-provoking issues may be seen as paternalistic. American gastroenterologists inform their patients of the CCFA (Crohn's and Colitis Foundation of America), which is a patient self-help organization similar to the NACC in Britain. Their official publication, written specifically for people with IBD (27), is a 213-page book that comprehensively covers many aspects of IBD and is readily available to

patients and their families. With the increasing recognition of the role that patients must play in therapy and the need for concordance rather than simple compliance, it is important to supply patients with accurate and detailed information about a range of aspects of their disease.

Our CCKNOW score compares favorably with the IBD Knowledge Questionnaire (KQ) developed by Jones *et al.* (11), with both questionnaires having high levels of reliability (Cronbach's α 0.95 and 0.84, respectively). Unlike the KQ, in the development of the CCKNOW we excluded questions that the majority of people got wrong as well as those on which most participants scored correctly, as we felt that both were poor discriminators of knowledge between groups. Some readers may feel that even if questions are well understood by the majority of patients (and thus have little discriminatory value), they should still be included as it may be dangerous not to detect patients whose knowledge is deficient in crucial areas. However, the questions excluded by factor analysis, with the exception of questions 5 and 14 are not "crucial areas of knowledge," and question 14 was phrased in an ambiguous way and could be modified in any future version of the CCKNOW. Thus, we do not believe that the CCKNOW misses patients whose knowledge is inadequate in important areas.

Both the CCKNOW and KQ found that patients with Crohn's disease were more knowledgeable than those with ulcerative colitis, whereas we found no difference between the groups. We believe that our results may be more representative, as we tested the CCKNOW on a significantly larger patient group. Both questionnaires identified similar misconceptions among the IBD population: namely, it found that there was general confusion concerning medication and a widespread belief that IBD does not run in families. The study by Hawkey and Hawkey of information leaflets also found confusion about the familial occurrence of IBD (28).

The lack of knowledge displayed by patients in the second part of this study gives no reason to be complacent about patients' current understanding of IBD. Indeed, similar findings have been reported for breast cancer, in which patients, despite having been treated for the disease, continue to have significant deficiencies in their knowledge (17). The higher scores achieved by NACC members is not unexpected, as they have greater access to information, and membership in itself suggests that they may be more motivated to learn. It may be argued that NACC members scored higher because they may have suffered more disease complications and may have had their disease for a longer period of time compared with nonmembers. This would appear not to be the case, as many NACC members enroll as new patients, *i.e.*, early after diagnosis, and have not had IBD for a sufficient time to develop complications. Indeed 19% of patients from a study in Leicester did not attend NACC meetings, as they believed that they were too ill (29). In addition many members are only transient, drawing from the group for a while and withdrawing once their needs are met (30).

We are aware that further support of the questionnaires' validity and reliability will be based largely on its continued use in the clinical setting. Even so, it is obvious that there are large deficits in patients' knowledge, which must be addressed if we hope to achieve better self-management of IBD. Although the CCKNOW score tests knowledge, it is not a measure of behavior (*e.g.*, adherence to therapeutic regimens) or of medical outcomes (*e.g.*, reduced frequency of complications). Research currently is in progress examining a potential role for the CCKNOW score in these issues.

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REFERENCES

1. Lange A, Haslbeck E, Andus T, et al. Ambulatory education of patients with Crohn's disease/ulcerative colitis. Zeitschrift für Gastroenterologie 1996;34:411–5.
2. Mazzuca SA. Does patient education in chronic disease have therapeutic value? J Chron Dis 1982;35:521–9.
3. Moser G, Tillinger W, Sachs G, et al. Disease-related worries and concerns: A study on outpatients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 1995;7:853–8.
4. Eaden JA, Ward B, Smith H, et al. Are we telling patients enough? A pilot study to assess patient information needs in a gastroenterology outpatient department. Eur J Gastroenterol Hepatol 1998;10:63–7.
5. Mansfield JC, Tanner AR, Bramble MG. Information for patients about inflammatory bowel disease. J R Coll Phys London 1997;31:184–7.
6. Martin A, Leone L, Castagliuolo I, et al. What do patients want to know about their inflammatory bowel disease? Ital J Gastroenterol 1992;24:477–80.
7. Probert CSJ, Mayberry JF. Inflammatory bowel disease: patients' expectations in the 1990's. J R Soc Med 1991;84: 131–2.
8. Rees JEP, Mayberry JF, Calcraft B. What the patient wants to know about Crohn's disease. J Clin Gastroenterol 1983;5: 221–2.
9. Scholmerich J, Sedlak P, Hoppe-Seyler P, et al. The information needs and fears of patients with inflammatory bowel disease. Hepatogastroenterology 1987;34:182–5.
10. Smart H, Mayberry J, Calcraft B, et al. Effect of information booklets on patients' anxiety levels and consultation rates in Crohn's disease. Public Health 1986;100:184–6.
11. Jones SC, Gallacher B, Lobo AJ, et al. A patient knowledge questionnaire in inflammatory bowel disease. J Clin Gastroenterol 1993;17:21–4.
12. Chambers JK, Boggs DL. Development of an instrument to measure knowledge about kidney function, kidney failure and treatment options. Am Nurses Nephrol Assoc J 1993;20:637–50.
13. Devind GM, Binik YM, Mandin H, et al. The kidney disease questionnaire: A test for measuring patient knowledge about end-stage renal disease. J Clin Epidemiol 1990;43:297–307.
14. Dunn SM, Bryson JM, Hoskins PL, et al. Development of the Diabetes Knowledge (DKN) Scales: Forms DKNA, DKNB and DKNC. Diabetes Care 1984;7:36–41.
15. Meadows KA, Fromson B, Gillespie C, et al. Developmen validation and application of computer-linked knowledg

questionnaires in diabetes education. Diabetic Med 1988;5: 61–7.
16. Reisine S, Lewis C, Tibbles L, et al. Self-administered patient questionnaire for assessing knowledge about joint arthroplasty prior to surgery. Arthitis Care Res 1992;5:8–12.
17. Vaeth PA. Women's knowledge about breast cancer. Am J Clin Oncol 1993;16:446–54.
18. Surawy C. Knowledge about diabetes in type 1 patients is related to metabolic control. Diabetic Med 1989;6:784–6.
19. Mayberry JF, Morris JS, Calcraft B, et al. Information assessment by patients of a booklet on Crohn's disease. Public Health 1995;99:239–42.
20. Mayberry JF, Rose J, Rhodes J. Assessment of a patient information booklet on ulcerative colitis. Ital J Gastroenterol 1989;21:193–5.
21. Bryman A, Cramer D. Qualitative data analysis for social scientists. London: Routledge, 1994.
22. Streiner DL, Norman GL. Health measurement scales: A practical guide to their development and use. Oxford: Oxford University Publications, 1989.
23. Flesch R. A new readability yardstick. J Appl Psychol 1948; 32:221–33.
24. Altman DG. Practical statistics for medical research. 7th ed. London: Chapman & Hall, 1996.
25. Kish L. Survey sampling. New York: John Wiley & Sons, 1965.
26. Moody GA, Eaden JA, Bhakta P, et al. The role of complementary medicine in European and Asian patients with inflammatory bowel disease. Public Health 1998;112:269–71.
27. Stein SH, Rood RP. Inflammatory bowel disease. A guide for patients and their families, 2nd ed. New York: Lippincott-Raven, 1999.
28. Hawkey GM, Hawkey CJ. Effect of information leaflets on knowledge in patients with gastrointestinal diseases. Gut 1989;30:1641–6.
29. Moody GA, Mayberry JF. Disinterest in local self help groups amongst patients with inflammatory bowel disease. Int J Colorectal Dis 1993;8:181–3.
30. Mayberry MK, Mayberry JF. Value of patient self-help groups in gastroenterology. Current Medical Literature: Gastroenterol 1991;10:159–61.

APPENDIX 1: TESTING YOUR KNOWLEDGE OF CROHN'S AND COLITIS: THE CCKNOW SCORE

This questionnaire will help your doctors and nurses know on which topics you may need more information. This will help make your treatment more effective. Please tick only *one* answer for each question. Thank you.

1. The intestines play an important role in the body but they only work during meal times:
   a) True
   b) False
   c) Don't know
2. People with inflammatory bowel disease are never allowed to eat dairy products:
   a) True
   b) False
   c) Don't know
3. Elemental feeds are sometimes used to treat Crohn's disease and ulcerative colitis. They:
   a) Always contain a lot of fibre
   b) Are very easy to digest
   c) Come in the form of tablets
   d) Don't know
4. Proctitis:
   a) Is a form of colitis that affects the rectum or back passage only
   b) Is a form of colitis that affects the whole of the large bowel
   c) Don't know
5. When a patient with inflammatory bowel disease passes blood in their stool it means:
   a) They definitely have bowel cancer
   b) They are having a flare up of their disease
   c) Don't know
6. Patients with inflammatory bowel disease are probably cured if they have been symptom free for 3 years:
   a) True
   b) False
   c) Don't know
7. Inflammatory bowel disease runs in families:
   a) True
   b) False
   c) Don't know
8. If patients with inflammatory bowel disease are not careful with their personal hygiene they can pass on their disease to friends and members of the family:
   a) True
   b) False
   c) Don't know
9. Patients with inflammatory bowel disease can get inflammation in other parts of the body as well as the bowel:
   a) True
   b) False
   c) Don't know
10. A fistula:
    a) Is an abnormal track between 2 pieces of bowel or between the bowel and skin
    b) Is a narrowing of the bowel which may obstruct the passage of the contents
    c) Don't know
11. The terminal ileum:
    a) Is a section of the bowel just before the anus
    b) Is a section of the bowel just before the large intestine
    c) Don't know
12. During a flare up of inflammatory bowel disease:
    a) The platelet count in the blood rises
    b) The albumin level in the blood rises
    c) The white cell count in the blood falls
    d) Don't know
13. Steroids (such as prednisolone/prednisone/budesonide/hydrocortisone):
    a) Can only be taken by mouth
    b) Can be given in the form of an enema into the back passage

c) Cannot be given directly into the vein
d) Don't know

14. Steroids usually cause side effects:
a) only after they have been taken for a long time and in high doses
b) Immediately and even after small doses
c) Which are not permanent and all disappear after treatment is stopped
d) Don't know

15. Immunosuppressive drugs are given to inflammatory bowel disease patients to:
a) Prevent infection in the bowel by bacteria
b) Reduce inflammation in the bowel
c) Don't know

16. Sulphasalazine:
a) Controls the level of sulphur in the bloodstream
b) Can be used to reduce the frequency of flare ups
c) Cannot be used to prevent flare ups
d) Don't know

17. An example of an immunosuppresive drug used in inflammatory bowel disease is:
a) Sulphasalazine
b) Mesalazine
c) Azathioprine
d) Don't know

18. If a woman has Crohn's disease:
a) She may find it more difficult to become pregnant
b) She should not have children
c) Her pregnancy will always have complications
d) She should stop all medication during her pregnancy
e) Don't know

19. Patients who smoke are more likely to have:
a) Ulcerative colitis
b) Crohn's disease
c) Don't know

20. Which one of the following statements is false?
a) Ulcerative colitis can occur at any age
b) Stress and emotional events are linked with the onset of ulcerative colitis
c) Ulcerative colitis is least common in Europeans and North Americans
d) Patients with ulcerative colitis have an increased risk of developing bowel cancer
e) Don't know

21. The examination of the large bowel with a flexible camera is called a:
a) Barium enema
b) Biopsy
c) Colonoscopy
d) Don't know

22. Male patients who take sulphasalazine:
a) Have reduced fertility levels that are reversible
b) Have reduced fertility levels that are not reversible
c) The drug does not have any effect on male fertility
d) Don't know

23. The length of the small bowel is approximately:
a) 2 feet
b) 12 feet
c) 20 feet
d) Don't know

24. The function of the large bowel is to absorb:
a) Vitamins
b) Minerals
c) Water
d) Don't know

25. Another name for an ileorectal anastomosis operation with formation of a reservoir is:
a) Purse
b) Pouch
c) Stoma
d) Don't know

26. If a part of the bowel called the terminal ileum is removed during surgery the patient will have impaired absorption of:
a) Vitamin C
b) Vitamin A
c) Vitamin B12
d) Don't know

27. Patients with IBD need to be screened for cancer of the colon. Which one of the following statements about screening is false?
Screening should be offered to all patients with ulcerative colitis:
a) Which affects only the rectum
b) Which has lasted for 8–10 years
c) Which started before the age of 50
d) Don't know

28. There are millions of tiny "hairs" in the small bowel to increase the absorptive surface. They are called:
a) Villi
b) Enzymes
c) Bile salts
d) Crypts
e) Don't know

29. Which one of the following is not a common symptom of inflammatory bowel disease?
a) Abdominal pain
b) Change in bowel habit
c) Headache
d) Fever
e) Don't know

30. If a child has inflammatory bowel disease; he/she probably will not:
a) live beyond the age of 45
b) be as tall as his or her friends
c) be as intelligent as his or her friends
d) Don't know

How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance

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Background: **The aim of this study was to assess the colorectal cancer surveillance practices of British gastroenterologists for patients with ulcerative colitis.**
Methods: **A questionnaire that investigated aspects of surveillance in patients with ulcerative colitis was mailed to all consultant gastroenterologists in the U.K. (n = 413).**
Results: **Three hundred forty-one questionnaires were returned (response rate 83%). Ninety-four percent of consultants practice cancer surveillance in ulcerative colitis, with 35% maintaining a registry of patients in surveillance programs. All gastroenterologists perform surveillance in patients with pancolitis, 24% in those with left-sided colitis and 2% in patients with proctitis. The mean duration of disease before surveillance is commenced is 9.2 years for pancolitis and 12.4 years for left-sided colitis ($p < 0.0001$). Only 4% of gastroenterologists routinely offer patients with disease of more than 10 years' duration a prophylactic colectomy. Colonoscopies are conducted by an accredited gastroenterologist in 65% of cases and biopsies are reviewed by specialists in gastrointestinal pathology in 45%. When histology reveals low-grade dysplasia only 4% advise colectomy and when high-grade dysplasia is found 53% recommend colectomy. Sixteen percent of gastroenterologists were unaware of the significance of a dysplasia associated lesion or mass.**
Conclusion: **The majority of gastroenterologists practice surveillance on a disorganized basis. There is inconsistency in the management of patients with dysplasia and education of gastroenterologists is needed. (Gastrointest Endosc 2000;51:123-8.)**

Patients with ulcerative colitis (UC) are at increased risk of colorectal carcinoma.[1-3] Many clinicians practice colonoscopic surveillance in this group of patients in the hope of detecting an early cancer at a surgically curable stage. However, much debate surrounds the efficacy of surveillance programs in UC.[4-6] These programs were widely introduced without the benefit of randomized controlled trials needed to assess their efficacy and cost-effectiveness. It would now be unethical to randomize patients into a study of the benefits of surveillance, and the only acceptable approach is to critically appraise current practices in surveillance.

The recognized drawbacks of surveillance programs in UC include poor patient compliance, difficulties of detecting and interpreting dysplasia, and the magnitude of the false-negative problem (i.e., some cancers will be missed). However, colonoscopies are relatively safe procedures with few complications occurring during surveillance programs.[7] In addition, there is some evidence that surveillance can detect cancers at an earlier stage.[8,9] More recently a case control study by Karlen et al.[10] has found that surveillance may reduce colorectal cancer mortality, although the results were not statistically significant. These recent studies give impetus to identify the reasons for the general failure of surveillance programs in UC.

Surveillance is best performed during periods of disease remission to eliminate the difficulty of differentiating reactive changes from low-grade dysplasia (LGD).[11] Periodic colonoscopy should begin at 8 to 10 years' duration of disease for extensive colitis and 15 to 20 years for left-sided disease.[12] The current recommendation is to perform surveillance examinations regularly at 1- to 2-year intervals.[12] Some have advocated an alternative schedule to use the better duration-independent increase in cancer risk.[13,14] They suggest a gradual decrease in the surveillance interval from every 3 years for the second decade of disease to yearly by the fourth decade of disease, particularly in patients whose initial studies are negative.[13,14] During a colonoscopy a full examination should be performed with a careful inspection of the entire colonic mucosa. Thereafter, taking 2 to 4 biopsy specimens randomly at 10 cm intervals from the

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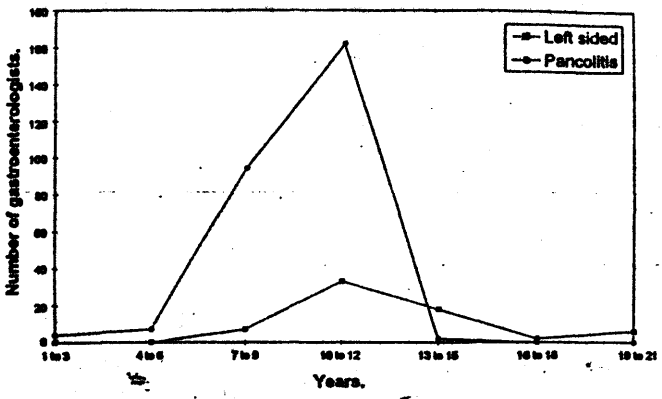

Figure 1. Duration of disease at which surveillance is initiated.

entire length of the colon is currently recommended.[12] Particular attention should be paid to elevated masslike lesions (dysplasia associated lesion or mass [DALMs]) because there is an increased likelihood that such areas may harbor dysplasia or carcinoma.[15,16] If such a lesion is present, additional biopsy specimens should be taken from the area. Any ambiguity in histologic biopsy interpretation should be clarified by a second experienced pathologist. If severe dysplasia or a DALM is discovered at any time, then colectomy is indicated.[15,17] Patients need to be aware that surveillance cannot guarantee a reduced cancer risk but rather that it offers a reasonable chance of detecting precancerous changes or cancer at an asymptomatic stage.[18]

The aims of this study were to determine the surveillance practices of British gastroenterologists for patients with UC. National data were collected using a postal questionnaire. In addition to the overall analysis of data, the possibility of differences in practice between consultants in teaching and district hospitals was investigated. The information from respondents at the same institutions was examined to see whether there was consistency and agreement within the workplace.

METHODS

A questionnaire to assess the surveillance practices of gastroenterologists for colorectal cancer in patients with UC was developed and a pilot study was conducted with 30 consultant gastroenterologists in the Trent region. In the light of their comments the questionnaire was modified and new questions added. This included the introduction of short case scenarios whose purpose was to confirm the validity of earlier questions and to elicit the management practice of gastroenterologists when finding LGD, dysplasia with a DALM and high-grade dysplasia (HGD) at colonoscopy. Last, 6 color photographs of features that may be seen at a colonoscopy were shown. Three of these photographs were from an endoscopy unit library (taken with patient's consent) and the others were scanned from

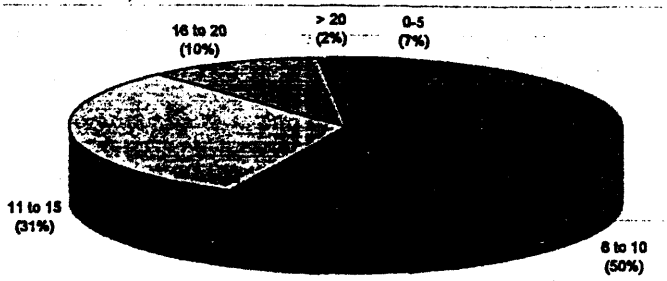

Figure 2. Number of biopsies taken at colonoscopy.

a reference guide for endoscopists with the publisher's permission.[19] Respondents were asked which features would lead them to take a further biopsy in addition to routine random biopsies from the colon. The modified questionnaire was mailed to all consultant gastroenterologists in the United Kingdom. Altogether there were 3 mailings at intervals of approximately 6 weeks.

Statistical analysis

The data were analyzed using Arcus statistical software. Comparison of proportions was assessed by the chi-square test. Differences in time intervals at which surveillance is commenced were analyzed using a Mann-Whitney test. The probability values quoted are 2-tailed.

RESULTS

After three mailings 341 questionnaires were returned (response rate 83%). In 42 cases the questionnaires were not completed for reasons such as the consultant did not see patients with inflammatory bowel disease. This left 298 questionnaires that were analyzed, 90 from teaching hospital consultants and 208 from district hospitals.

Overall surveillance practice

Ninety-four percent of consultant gastroenterologists (physicians) state they practice colorectal cancer surveillance for patients with UC, with 35% maintaining a registry of patients undergoing surveillance. Of these registries, 49% are computerized with the rest probably being compiled using a card index format. Only 17% of hospitals have a specific doctor/nurse who keeps the surveillance list up to date and 61% have a system for contacting people who default from follow-up.

All doctors who practice surveillance do so in all patients with total colitis, 24% enter patients who have left-sided disease into a program and 2% perform surveillance examinations in patients with proctitis. The mean duration of disease before surveillance is commenced is 9.2 years (range 1 to 15 years) for total colitis and 12.4 years (range 7 to 20 years) for left-sided colitis (Fig. 1). Mann-Whitney test normalized statistic (adjusted for ties) is 7.8, $p < 0.0001$: median difference = 2 (95% CI [1, 3]). Age

Table 1. The management of patients with abnormal histology after a surveillance colonoscopy

	Management		
Histology	Colectomy (%)	Colectomy if histology confirmed at second colonoscopy (%)	Return to surveillance if histology not confirmed (%)
LGD	4	25	71
LGD + DALM	30	37	33
HGD	53	42	5

at diagnosis of colitis seems to have limited bearing on a clinician's decision to conduct surveillance because 96% of gastroenterologists enter patients into a program when colitis is diagnosed at 50 years of age and older (all consultants performing surveillance in patients who developed colitis before the age of 50 years).

When asked whether they routinely offered patients with disease of more than 10 years' duration a prophylactic colectomy, only 4% of doctors gave a positive response. Many more doctors (46%) stated that they routinely perform a colonoscopy on all patients with UC after 10 years of disease to reassess the extent of their colitis.

Each gastroenterologist completing a questionnaire was asked to indicate (by ticking 1 of 4 boxes) which *single* group *mainly* conducted routine surveillance in the department. Despite these instructions, 2 categories or more were chosen by 29% of respondents. Surveillance is mainly conducted by an accredited gastroenterologist in 65% of programs. Four percent are conducted mainly by a trainee and 10% by a trainee and consultant together. In 13% of hospitals colonoscopies are performed by a mixture of accredited gastroenterologists and consultant surgeons. The remainder are carried out by a combination of consultant surgeons, surgical trainees and subconsultants.

Respondents were asked how many biopsies they routinely take for histologic assessment when performing a surveillance colonoscopy. Most (50%) take between 6 and 10 biopsies from the whole colon, with 31% taking between 11 and 15. The pattern among the remainder can be seen in Figure 2. The histologic slides are interpreted by a general pathologist in 55% of cases and by a pathologist specializing in GI pathology in 45% of cases.

Clinical scenarios

The first clinical scenario posed the problem of what to do with a 45-year-old woman who had suffered from UC for 15 years. She had total colitis, had been symptom free for 5 years and had colonoscopy only when the disease was first diagnosed. This vignette provided a check on how many consultants routinely performed a colonoscopy to reassess extent of disease after 10 years. Sixty-eight percent would arrange a colonoscopy, with 17% also reviewing the patient 1 year later. This result agreed favorably with earlier responses on the questionnaire.

To elicit the interval between repeat colonoscopies in surveillance programs, scenario two posed the case of a patient who had pancolitis for 30 years with quiescent disease and normal histology at colonoscopy. Most (55%) would repeat the examination in 3 years, 27% repeated the test after 1 year, 10% after 5 years and 8% only if the patient developed new colonic symptoms.

Three further scenarios determined how gastroenterologists manage patients who have abnormal histology at surveillance colonoscopy. The results are summarized in Table 1. When faced with LGD after a normal colonoscopy the majority of gastroenterologists (71%) repeat the colonoscopy within 3 to 6 months and if LGD is not found, return to routine surveillance. Only 4% would recommend a colectomy in the near future after discussion with the patient. The remainder advise a colectomy if LGD is confirmed at a second colonoscopy.

If LGD is found at colonoscopy along with the endoscopic appearance of a DALM, the response differs widely. In this situation 30% of doctors recommend a colectomy, 37% advise a colectomy only if LGD is confirmed at a second examination and 33% stated they would return to surveillance if LGD was not found at a second evaluation. Sixteen percent of consultant gastroenterologists conceded they were not aware of the meaning/implication of a DALM. With the finding of HGD on biopsy 53% of consultants advise their patients to have a colectomy, 42% only advise colectomy if HGD is established at a second colonoscopy and 5% would return to surveillance if HGD was not confirmed at a second evaluation.

Targeted biopsies

In addition to random biopsies taken from around the colon, participants were asked to indicate which features at colonoscopy would lead them to take

extra biopsies. Six color photographs depicted different pathologies: acute inflammation, a DALM, a carcinoma, normal tissue, a scarred colon and a pseudopolyp. All gastroenterologists would obtain biopsies from the carcinoma and the vast majority (98%) from the DALM. Ninety-two percent also took a sample from the pseudopolyp. Most doctors (86%) obtained biopsies of the inflamed colon and 48% took a sample from the scarred colon. Fifteen percent of consultants also procured biopsies from normal tissue and 11% of respondents indicated they would take a biopsy based on the findings depicted in every picture.

Teaching versus district hospital gastroenterologists

There was little variation between responses from gastroenterologists in teaching and district hospitals. Only three aspects of surveillance were significantly different between the groups. A greater number of trainees (10%) carry out colonoscopies in teaching hospitals than in district hospitals (2%) (Yates corrected chi-square = 7.83, $p < 0.0005$). Correspondingly, more colonoscopies are conducted by accredited gastroenterologists in district hospitals, 70% in district compared with 54% in teaching hospitals (Yates corrected chi-square = 5.9, $p < 0.02$). Pathologists specializing in GI disease are more likely to review biopsies in teaching hospitals (80%) than district general hospitals (40%) (Yates corrected chi-square = 57, $p < 0.00001$). The remaining difference lay in the management of patients with LGD. There is a trend for gastroenterologists in district hospitals to return patients to surveillance much more readily than consultants in teaching hospitals who are likely to advise a colectomy if repeat histology confirms LGD (chi-square for trend = 8.1, $p = 0.04$ with 3 degrees of freedom).

Many institutions have more than one gastroenterologist and replies from consultants within the same hospitals were compared. There were 23 teaching and 35 district hospitals with more than one respondent. One third of consultants in both categories disagreed about the facilities available in their departments. They failed to agree on whether a registry of patients in surveillance programs existed, whether that registry was computerized, whether anyone kept the list up to date and whether a system was in place for contacting defaulters.

DISCUSSION

This study is the first to investigate the surveillance practices of British gastroenterologists for colorectal cancer in patients with UC. Ninety-four percent of gastroenterologists say they practice surveillance but it is carried out in an ad hoc and disorganized fashion. Although the increased risk of colorectal cancer in UC is universally recognized, there is no unanimity among gastroenterologists with regard to the surveillance process[20] and thus we predictably found wide variation in the surveillance practices of British gastroenterologists. Indeed with the current emphasis on evidence-based practice it is salutary to observe that not a single randomized controlled study has been undertaken to test the hypothesis that "colonoscopic surveillance in ulcerative colitis works."[5,6,13] However, this is unlikely to ever be achieved for ethical and cost reasons.

Not only is there uncertainty about the facilities available within units but also about how surveillance should be conducted and abnormalities dealt with. Only half the respondents in this study routinely determine extent of disease after 10 years' duration. The majority of gastroenterologists who practice surveillance rightly commence surveillance in patients with total colitis 3 to 4 years earlier than when the disease is left-sided. However, there is again a wide variation in practice with some initiating surveillance immediately after diagnosis and others waiting for 15 years after the onset of UC. Because the hazard rate for cancer increases with duration of disease, intervals between screening tests should not be uniform.[14] The ideal interval has yet to be established, but it has been suggested that a colonoscopy every 3 years during the second decade of disease, every 2 years in the third decade and every year thereafter would be reasonable. Our study has shown that 10% of gastroenterologists wait 5 years between examinations and 8% wait until a patient develops new symptoms. This is far too long because cancer can occur within 2 years of an examination.[21] Cancer/dysplasia detection rates could be improved by screening patients every 6 to 12 months but the cost-effectiveness of such a protocol would need to be assessed.

Colectomy rate is one of the main determinants of cancer risk in a population of patients with UC. However, only 4% of British gastroenterologists routinely offer patients a prophylactic colectomy after 10 years of disease. Although some may consider this proposal "ridiculous" it is worth bearing in mind that countries with an aggressive policy toward the disease, such as Denmark, have some of the lowest rates of colonic cancer in UC.[22,23] With improved surgical techniques quality of life for patients after surgery has also improved and is high irrespective of the surgical procedure.[24]

It is not known to what extent dysplastic changes are unequivocally detectable at colonoscopy. Failure

of a biopsy from one wall to show dysplasia does not guarantee its absence on the opposite wall. Therefore, the number of biopsies taken at each colonoscopy is a factor in the detection of dysplasia or carcinoma. The majority of respondents only took between 6 and 10 biopsies at colonoscopy. Previous studies have suggested that as many as 33 biopsies are required to achieve 90% confidence in detecting dysplasia if present.[21] Even if multiple biopsies are taken at 10 cm intervals, only 0.05% of the entire area of the colon is sampled.[25] The interpretation of histology in UC is critical to the success of surveillance programs. It is not known whether pathologists who specialize in GI disease achieve a greater degree of accuracy when assessing colonic biopsies compared with general pathologists. This is currently being evaluated by our research group because the implication would be for an increased workload in specialist units.

The skills of endoscopists in recognizing pathologic alterations at colonoscopy appear reasonably good. On the whole, appropriate biopsies were taken in this study, although 11% of endoscopists took biopsies from all lesions in the assessment and 92% obtained specimens from the pseudopolyp. Although colonoscopists appear to be reasonable at interpreting pathology, the ability of endoscopists to *detect* pathology during a colonoscopy is outside the realm of this study. However, dysplasia is notoriously difficult to detect, with flat dysplasia most often occurring in apparently "healthy" mucosa. Significant miss rates for adenomas less than 1 cm in diameter have been reported and so smaller, more subtle lesions may be easily overlooked.[26]

The management of dysplasia is not straightforward. Ideally the finding should be discussed with the patient and a joint decision made about management.[13] It is widely accepted that HGD is an indication for colectomy because the probability of concurrent cancer is high.[13] It is therefore disturbing that only 53% of doctors in this study advised immediate colectomy when a patient had HGD. No one wishes to suggest unnecessary surgery, but dysplastic areas detected during one colonoscopy may not be found during a follow-up examination. If there is doubt about the diagnosis, a second pathologist should review the histology before a decision is made.

Equally perturbing is the management of DALMs. These lesions take on a number of appearances and have a high propensity for malignancy.[15] Sixteen percent of gastroenterologists were unaware of their significance, with many managing the lesion in an unacceptable way by pursuing surveillance and not colectomy when it is detected. The finding of LGD in flat mucosa may also be an indication for colectomy because the 5-year predictive value of LGD for either cancer or HGD is as high as 54%.[21] Despite this, 71% of respondents advocated continued surveillance with only 4% recommending a colectomy. These findings are similar to those of Bernstein et al.,[27] who also discovered a lack of understanding of dysplasia and its management among American gastroenterologists.

It would appear that continued education of gastroenterologists concerning the many aspects and pitfalls of surveillance is needed. At present there is no uniformity in the surveillance practices of British gastroenterologists for colonic cancer in patients with UC. If surveillance continues in this disorganized fashion, cancers will continue to be missed and the process and its practitioners will be discredited. It could be argued that surveillance programs fail because of poor patient compliance because nonattendees are much more likely to develop cancer.[28] This is a legitimate concern and is one of the problems that need to be addressed when deciding how to improve the whole process. Nevertheless, it would be a disservice to our patients if we use this excuse to allow surveillance to continue to be conducted in a poorly standardized manner.

REFERENCES

1. Devroede GJ, Taylor WF, Sauer WG, Jackman RJ, Stickler GB. Cancer risk and life expectancy of children with ulcerative colitis. N Engl J Med 1971;285:17-21.
2. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Part IV: Carcinoma of the colon. Gut 1964;5:15-22.
3. Kewenter J, Ahlman H, Hulten L. Cancer risk in extensive ulcerative colitis. Ann Surg 1978;188:824-8.
4. Axon AT, Lynch DA. Surveillance for ulcerative colitis does not and cannot work. Gastroenterology 1994;106:1129-31.
5. Collins RH, Feldman M, Fordtran JS. Colon cancer, dysplasia and surveillance in patients with ulcerative colitis: a critical review. N Engl J Med 1987;316:1654-8.
6. Gyde S. Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs. Gut 1990;31:1089-92.
7. Koobatian GJ, Choi PM. Safety of surveillance colonoscopy in long-standing ulcerative colitis. Am J Gastroenterol 1994;89: 1472-5.
8. Choi PM, Nugent FW, Schoetz DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology 1993;105: 418-24.
9. Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. Gut 1990; 31:800-6.
10. Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson PG, Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? a population based case control study. Gut 1998;42:711-4.
11. Riddell RH, Goldman H, Ranshoff DF, et al. Dysplasia in inflammatory bowel disease: standardised classification with provisional clinical applications. Hum Pathol 1983;14:931-66.
12. Riddell RH. Screening strategies in gastrointestinal cancer. Scand J Gastroenterol Suppl 1990;175:177-84.

13. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet 1994;343:71-4.
14. Lashner BA, Hanauer SB, Silverstein MD. Optimal timing of colonoscopy to screen for cancer in ulcerative colitis. Ann Intern Med 1988;108:274-8.
15. Blackstone MO, Riddell RH, Rogers G, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology 1981;80:366-74.
16. Brostrom O, Lofberg R, Ost A, Reichard H. Cancer surveillance of patients with long-standing ulcerative colitis: a clinical, endoscopical and histological study. Gut 1986;27:1408-13.
17. Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis: experience over 15 years. Lancet 1983;2:149-52.
18. Lennard-Jones JE. Prevention of cancer in inflammatory bowel disease. In: Young GP, Rozen P, Levin B, editors. Prevention and early detection of colorectal cancer. London: W B Saunders Company Limited; 1996. p. 217-38.
19. Lofberg R. Endoscopy findings in ulcerative colitis: how to manage ulcerative colitis—a quick reference guide. Synergy Medical Education; 1996.
20. Gyde SN, Prior P, Allan RN, et al. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. Gut 1988;29:206-17.
21. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology 1994;107:934-44.
22. Hendriksen C, Kreiner S, Binder V. Long term prognosis in ulcerative colitis-based on results from a regional patient group from the county of Copenhagen. Gut 1985;26:158-63.
23. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. Gastroenterology 1992;103:1444-51.
24. McLeod RS, Churchill DN, Lock AM, Vanderburgh S, Cohen Z. Quality of life of patients with ulcerative colitis preoperatively and postoperatively. Gastroenterology 1991;101:1307-13.
25. Rosenstock E, Farmer RG, Petras R, Sivak MV, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. Gastroenterology 1985;89:1342-6.
26. Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, et al. Colonoscopic miss rates of adenomas determined by back-to back colonoscopies. Gastroenterology 1997;112:24-8.
27. Bernstein CN, Weistein WM, Levine DS, Shanahan F. Physician's perceptions of dysplasia and approaches to surveillance colonoscopy in ulcerative colitis. Am J Gastroenterol 1995;90:2106-14.
28. Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefit. Gut 1988;29:325-31.

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Colorectal cancer prevention in ulcerative colitis: a case-control study

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SUMMARY

Background: The risk of colorectal cancer (CRC) in ulcerative colitis (UC) increases with extent and duration of disease. Identifying other risk factors would allow targeting of sub-groups at greatest risk, enabling more cost-effective surveillance.

Methods: We conducted a case-control study comparing 102 cases of CRC in UC with matched controls. Odds ratios (OR) for cancer risk were estimated by conditional logistic regression. A multivariate model assessed the contribution of individual variables.

Results: Regular 5-aminosalicylic acid (5-ASA) therapy reduces cancer risk by 75% (OR 0.25, 95% CI: 0.13–0.48, $P < 0.00001$). Adjusting for other variables, taking mesalazine regularly reduces risk by 81% (OR 0.19, 95% CI: 0.06–0.61, $P = 0.006$) and visiting a hospital doctor more than twice a year also reduces risk (OR 0.16, 95% CI: 0.04–0.60, $P = 0.007$). Considering variables independently, having a family history of sporadic CRC in any relative increases risk fivefold (OR 5.0, 95% CI: 1.10–22.82, $P < 0.04$).

Conclusions: CRC risk among UC patients can be reduced by regular therapy with 5-ASA medication. Colonoscopic surveillance may be best targeted on those unable to take 5-ASAs (e.g. due to allergy) and those with a positive family history of CRC.

INTRODUCTION

Colorectal cancer is one of the most serious complications of ulcerative colitis (UC). The risk becomes significant after 8–10 years of colitis and increases at a rate of 0.5–1% between the second and fourth decades of disease.[1] After 40 years of pancolitis approximately 25–30% of patients will have developed colorectal cancer.[2] The risk of colorectal cancer is not related to duration of disease alone but also to its extent.[3, 4] However, the severity and frequency of attacks do not confer an increased risk.[5, 6] There is some evidence that if the onset of UC is at a young age, the risk of malignant transformation is increased independent of either disease duration or anatomic extent, although this is disputed.[2, 7–9]

Several studies have suggested that if patients with UC also have primary sclerosing cholangitis they may be at a higher risk of developing colorectal cancer.[10–12] The evidence for other potential risk factors is scarce. A positive family history of colon cancer,[13, 14] smoking[15] and folate depletion[14, 16] may affect the occurrence of colorectal cancer. Aspirin is thought to have an anti-neoplastic effect in the large bowel[17] and regular consumption of low-dose aspirin reduces the risk of adenomatous polyps and fatal colon cancer in the general population.[18, 19] There is growing evidence that the chronic consumption of aminosalicylates, in particular sulphasalazine, may also provide some protection against colorectal cancer in patients with ulcerative colitis through a similar mechanism of action.[15, 20–22]

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As these studies are few in number we wished to investigate this hypothesis further whilst also studying the effect of other 5-ASA compounds that have previously been neglected.

The optimal study design for defining risk factors would be a prospective, controlled study. However, given the long time needed for sufficient cancers or dysplasias to develop in a surveillance programme, as well as ethical concerns about withholding surveillance colonoscopy or 5-ASA medications from the control group, we must still rely on case-control studies to offer the best approximation of colorectal cancer risk factors in ulcerative colitis. With this in mind we aimed to assess the risk factors thought to play a part in the development of colorectal cancer in UC and to build a statistical model that would identify the most hazardous combination of factors.

MATERIALS AND METHODS

The investigation was designed as a retrospective matched case-control study. In order to identify cases, one author (J.E.) contacted consultant gastroenterologists across England and Wales and asked for permission to review the medical records of their patients with known colorectal cancer complicating UC. Nineteen gastroenterologists (eight from teaching hospitals and 11 from district general hospitals) who were interested in the study agreed to a search of their patient records and/or pathology databases. Once potential cases had been identified the same author visited each hospital and systematically recorded various details from each patient's record on a pro forma.

Cases and controls

For subjects to be included in the study the diagnosis of UC had to be confirmed clinically, histologically and radiologically. The criteria used were those established by Lennard-Jones.[23] Cases who were deceased at the time of the study were included provided the medical notes had not been destroyed. Cases were excluded if they had been referred with a diagnosis of CRC where UC was an incidental finding and if full case note documentation was not available.

From 133 cases collected, 102 met the inclusion criteria and these were matched with controls from the Leicestershire inflammatory bowel disease patient database, which was rigorously assembled during the late 1980s using established international diagnostic criteria.[24] The matching criteria were (i) sex; (ii) age within 10 years; (iii) extent of disease at the time of diagnosis of UC; and (iv) duration of disease within a 5-year window. In addition controls had to have an intact colon and not have a colorectal cancer at the time of diagnosis of the case. It was not possible to match cases with a control from the same hospital as most hospitals do not have a database of their IBD patients.

Data collection

Information was extracted from all in-patient and out-patient medical records for each subject from the date of diagnosis of UC until the date of the patient's cancer diagnosis. The data for cases were extracted and recorded in the same manner by one author (J.E.). Data from control notes were independently extracted by two authors (J.E and E.J.) as a quality control check that data retrieval was uniform and accurate. All medical notes (whether or not they pertained to UC) were reviewed so that a comprehensive history, in particular family history, could be obtained. Data extracted included:

(a) Age at diagnosis of UC.

(b) Pharmacotherapy: treatment for the 5–10 years prior to the development of cancer including 5-ASA preparations, corticosteroids (systemic and local) and aspirin. If there was a significant period of time (≥ 1 year) during which a subject was not taking medication, either because it had been stopped by a doctor or if a subject was documented as being a poor complier with medication, they were recorded as not taking regular medication.

(c) Average frequency of contacts with a hospital physician or surgeon per year over the course of their disease.

(d) Number of barium enemas and colonoscopic examinations during follow-up of their UC.

(e) Activity of UC: each subject was placed into one of six categories as follows: (i) silent disease; (ii) one exacerbation every 10 years; (iii) one exacerbation per 1–10 years; (iv) one exacerbation per month to 1 year; (v) one exacerbation per month; and (vi) continuous symptoms. In the final calculations this variable was reduced to three categories (see Table 2) to prevent small sample sizes in the statistical analysis.

(f) Smoking history at the time of diagnosis of UC.

(g) Presence of primary sclerosing cholangitis (PSC) confirmed at endoscopic retrograde cholangio-pancreatography percutaneous transhepatic cholangiography/liver biopsy. Serological values of raised liver function tests for more that 1 year (in the absence of PSC) were also recorded.

(h) Positive family history of IBD and colorectal cancer.

For cases, the age at cancer diagnosis and its site and stage were also recorded. We would have liked to investigate the effect of folate on colorectal cancer risk. After examining 20 sets of notes it was obvious that folate levels were not routinely measured/recorded in the medical notes and therefore this variable was not studied further.

Statistical analysis

The study was designed to have a power of 80% to detect an odds ratio of 2.5 at the level of 5% significance assuming a prevalence of 65% for each risk factor in the control group. Conditional logistic regression was used to compute estimates of odds ratio (OR) as a measure of association between various exposures and colorectal cancer, together with 95% confidence intervals. Risk parameters b–f were analysed as categorical variables in the final analysis. Model development used changes in minus twice the log-likelihood to assess the contribution of individual variables in a forward selection procedure, with variables being added to the model if the change was statistically significant at the 5% level.

RESULTS

The characteristics of cases and controls are summarized in Table 1. The mean age at the time of diagnosis of colorectal cancer was 57.4 years (s.d. ± 12.9) and the mean interval between diagnosis of UC and colorectal cancer was 16.1 years (s.d. ± 9.7). For controls the mean duration of disease was 16 years (s.d. ± 9.4). Fifty-seven per cent of cancers were located in the rectosigmoid with the remainder evenly distributed around the rest of the colon. Typically, over the course of their disease, cases were much less likely to take medication on a regular basis, had fewer contacts with their hospital physician and had fewer colonoscopic examinations. Subjects with cancer had more family members with a history of sporadic colorectal cancer but the activity of disease, number of barium enemas and family history of IBD did not differ significantly between cases and controls. The number of subjects with primary sclerosing cholangitis and raised serological liver function tests was small and therefore could not be investigated further. Of the 51 cases who took a 5-ASA compound on a regular basis, 37 took sulphasalazine (six patients < 2 g/day, 31 patients ≥ 2 g/day), 12 took mesalazine (one patient < 1.2 g/day, 11 patients ≥ 1.2 g/day) and two took other drugs. In comparison, of the 84 controls receiving a 5-ASA compound, 39 took sulphasalazine (seven patients < 2 g/day, 32 patients ≥ 2 g/day), 43 took mesalazine (five patients < 1.2 g/day, 38 patients ≥ 1.2 g/day) and two took other drugs.

The independent effect of each variable on the odds ratio of developing colonic cancer is shown in Table 2. The most significant finding was the strong protective association of regular 5-ASA therapy, reducing cancer risk by 75% (OR 0.25, 95% CI: 0.13–0.48, $P < 0.000001$). When individual 5-ASA drugs and their doses were analysed, mesalazine at a dose of 1.2 g/day or greater reduced colorectal cancer risk by 91% compared to no treatment (OR 0.09, 95% CI: 0.03–0.28, $P < 0.00001$) and was also protective when taken at lower doses (OR 0.08, 95% CI: 0.08–0.85, $P = 0.04$). The benefits of sulphasalazine were less pronounced and an effect was only evident for a dose of 2 g day or greater (OR 0.41, 95% CI: 0.18–0.92, $P = 0.03$). Other 5-ASA medications had a non-significant protective effect. Frequent visits to see a hospital doctor were also highly protective (OR 0.098, 95% CI: 0.03–0.29, $P < 0.000001$), as was having between one and two colonoscopies over the history of their colitis (OR 0.22, 95% CI: 0.09–0.55, $P < 0.001$). Systemic and local steroid therapy also have a statistically significant protective role but a dose–response effect was not demonstrated for either route of administration. Smoking history, particularly being an ex-smoker at the time UC was diagnosed, was associated with a non-significant protective effect. A positive family history of colorectal cancer in any family member increased cancer risk by a factor of five (OR 5.00, 95% CI: 1.10–22.82, $P < 0.04$), but when only first-degree relatives were considered this fell to 3.5 and was no longer significant (OR 3.50, 95% CI: 0.73–16.85, $P = 0.11$). Aspirin use had a minimal protective role which was not statistically significant, but this may be due to the small numbers taking this therapy in our study.

Table 1. Characteristics of cases and controls

	Cases [*n* (%)]	Controls [*n* (%)]
Sex		
Males	64 (63)	64 (63)
Females	38 (37)	38 (37)
Ethnic origin		
Caucasian	96 (94)	58 (57)
Asian	6 (6)	44 (43)
Age at diagnosis of UC		
< 15	3 (3)	1 (1)
15–29	27 (27)	22 (22)
30–49	36 (35)	42 (41)
50+	36 (35)	37 (36)
Mean age at diagnosis of UC (s.d.)	41.33 (± 16.8)	43.59 (± 16.1)
Mean duration of disease (s.d.)	16.1 (± 9.7)	16 (± 9.4)
Extent at diagnosis		
Proctitis	6 (6)	5 (5)
Left sided	34 (33)	33 (32)
Subtotal/total	62 (61)	64 (63)
Physician/surgeon contacts per year		
< 1	32 (31)	9 (9)
1–2	59 (58)	58 (57)
2+	11 (11)	35 (34)
Number of colonoscopies (over UC history)		
< 1	26 (26)	8 (8)
1–2	42 (41)	64 (63)
2+	34 (33)	30 (29)
Number of barium enemas (over UC history)		
< 1	19 (19)	26 (26)
1–2	57 (56)	56 (55)
2+	26 (26)	20 (20)
Activity of UC		
Silent disease	22 (22)	20 (20)
1 exacerbation 10 years	38 (37)	41 (40)
1 exacerbation 1–10 years	31 (30)	30 (29)
More frequent	11 (11)	11 (11)
Smoking history at diagnosis of UC		
Never smoked	76 (74)	68 (67)
Current smoker	11 (11)	12 (12)
Ex-smoker	15 (15)	22 (22)
Primary sclerosing cholangitis	1 (1)	0
Raised liver function tests (no PSC)	12 (12)	11 (10.8)
Family history of colorectal cancer	10 (10)	2 (2)
Family history of IBD	5 (5)	5 (5)
Pharmacotherapy		
Regular use of 5-ASA preparation	51 (50)	84 (82)
Regular use of systemic steroid	5 (5)	19 (19)
Regular use of local steroid	8 (8)	18 (18)
Regular use of aspirin *	4 (4)	5 (5)

Table 2. Independent effect of characteristics on colorectal cancer risk

Variable		Odds ratio	95% CI	*P*-value
Smoking	Smoked at time UC diagnosed (compared to non-smoker)	0.71	0.28–1.8	0.47
	Ex-smoker when UC diagnosed (compared to non-smoker)	0.53	0.23–1.22	0.14
5-ASA	No	—	—	—
	Yes	0.25	0.13–0.48	< 0.00001
	Mesalazine (< 1.2 g/day)	0.08	0.08–0.85	0.04
	Mesalazine (≥ 1.2 g/day)	0.09	0.03–0.28	< 0.00001
	Sulphasalazine (< 2 g day)	0.56	0.17–1.84	0.34
	Sulphasalazine (≥ 2 g day)	0.41	0.18–0.92	0.03
	Other (e.g. olsalazide, balsalazide)	0.40	0.04–3.58	0.41
Systematic steroid	Yes (compared to none)	0.26	0.01–0.70	0.008
Local steroid	Yes (compared to none)	0.44	0.19–1.02	0.06
Aspirin	Yes (compared to none)	0.80	0.21–2.98	0.74
Contact with hospital doctor	1 to 2 visits per year (compared to none)	0.32	0.14–0.76	0.009
	More than 2 visits per year (compared to none)	0.098	0.03–0.29	< 0.00001
Barium enema	Any (compared to none)	1.07	0.88–1.29	0.50
Colonoscopy	1 to 2 over course of disease (compared to none)	0.22	0.09–0.55	0.001
	More than 2 over course of disease (compared to none)	0.42	0.16–1.10	0.08
Raised alk phos (no PSC)		1.14	0.41–3.15	0.80
Family history of colorectal cancer	Any relative	5.00	1.10–22.82	0.04
	1st degree relative	3.50	0.73–16.85	0.11
Activity of disease	1 exacerbation 10 years	0.85	0.40–1.82	0.67
	1 exacerbation 1–10 years	0.95	0.35–2.60	0.92
	1 exacerbation month–1 year (or more frequent)	0.93	0.34–2.60	0.90

Table 3. Adjusted odds ratios for most influential variables

Variable		Odds ratio	95% CI	*P*-value
5-ASA	None	—	—	—
	Yes	0.47	0.22–1.00	0.05
Contact with hospital doctor	< 1	—	—	—
	1 to 2 per year over the course of disease	0.43	0.16–1.15	0.09
	> 2 per year over the course of disease	0.19	0.06–0.65	0.008
CRC in any relative	No	—	—	—
	Yes	6.38	0.97–41.96	0.05
Colonoscopies after diagnosis	< 1	—	—	—
	1 to 2 over the course of disease	0.27	0.09–0.77	0.02
	> 2 over the course of disease	0.52	0.17–1.56	0.24
After adjustment for individuals 5-ASA drugs	None	—	—	—
Mesalazine	< 1.2 g day	0.18	0.02–1.92	0.16
	≥ 1.2 g day	0.19	0.06–0.61	0.006
Sulphasalazine	< 2 g day	0.93	0.22–3.91	0.92
	≥ 2 g day	0.85	0.32–2.26	0.75
Other	Variable doses	1.21	0.08–18.97	0.89
Contact with hospital doctor	< 1	—	—	—
	1 to 2 per year over the course of disease	0.42	0.15–1.18	0.10
	> 2 per year over the course of disease	0.16	0.04–0.60	0.007
CRC in any relative	No	—	—	—
	Yes	6.84	0.80–58.60	0.08
Colonoscopies after diagnosis	< 1	—	—	—
	1 to 2 over the course of disease	0.33	0.11–1.01	0.05
	> 2 over the course of disease	0.55	0.18–1.71	0.30

A suitable model was developed to assess the contribution of the variables in a forward selection procedure. The final model included regular 5-ASA therapy, frequent contacts with a hospital doctor, a positive family history of sporadic colonic cancer in any relative and one to two colonoscopies over the course of UC history. Table 3 shows the effect of these variables, in terms of odds ratios, adjusted for the other variables in the model. Regular consumption of mesalazine at a dose of 1.2 g/day or greater (OR 0.19, 95% CI: 0.06–0.61, $P = 0.006$) and frequent visits to a hospital physician (OR 0.16, 95% CI: 0.04–0.60, $P = 0.007$) confer the greatest benefit after adjusting for the other variables. We investigated the possibility of all interactions between the variables in the final model and none was statistically significant at the 5% level.

As all the controls in this study came from one area (Leicester) we carried out a further analysis stratified by case to assess whether this may have biased the results. There were 12 case–control pairs in which both the case and control were from Leicester. These data were compared with the other 90 pairs where the control came from Leicester but the case came from elsewhere. Regarding 5-ASA medication the independent OR for non-Leicester pairs was 0.25 (95% CI: 0.13–0.51, $P = 0.0001$) and for Leicester pairs was 0.2 (95% CI: 0.02–1.71, $P = 0.14$). It is interesting to note that the point estimate is therefore lower for the Leicester pairs, with the analysis only losing its statistical significance due to a small numbers effect. Looking specifically at mesalazine ≥ 1.2 g day, the OR for non-Leicester pairs was 0.14 (95% CI: 0.05–0.41, $P = 0.0003$) and for Leicester pairs was 0.25 (95% CI: 0.03–2.24, $P = 0.2$). The effect is not as marked in the Leicester pairs but 5-ASA is still protective (again the statistical significance is lost due to a small numbers effect).

There were 44 Asian control patients compared to six Asian cases. We therefore conducted a stratified analysis based on ethnicity to assess if this may have biased the results. There were 57 pairs where both the case and control were Caucasian and an analysis of the independent effect of 5-ASA medication on these pairs gave an OR of 0.30 (95% CI: 0.13–0.65, $P = 0.003$). Regular consumption of mesalazine at a dose of ≥ 1.2 g day was also still highly protective with an OR of 0.1 (95% CI: 0.02–0.39, $P = 0.001$). Having 1–2 colonoscopies over the course of their disease was protective (OR = 0.16, 95% CI: 0.05–0.55, $P = 0.003$) as were frequent visits to a hospital doctor (OR = 0.17, 95% CI: 0.04–0.65, $P = 0.01$).

Finally we performed a stratified analysis to assess if there was any difference in the results from teaching vs. district hospitals. There were 29 pairs where the case and control came from teaching hospitals and 73 pairs where the case alone was from a district hospital. 5-ASAs were protective in both groups with identical odds ratios of 0.25. The effect of mesalazine (≥ 1.2 g/day) also gave similar results with an OR of 0.1 in teaching hospitals (95% CI: 0.01–0.78, $P = 0.03$) and 0.18 in district hospitals (95% CI: 0.06–0.53, $P = 0.02$).

DISCUSSION

Colorectal cancer (CRC) risk in patients with UC can be substantially reduced by taking 5-ASA therapy on a regular basis. After adjusting for other variables, mesalazine is particularly effective, reducing the cancer risk by 81%. This protective effect is independent of dose but becomes statistically significant for 1.2 g/day or greater. The benefits of sulphasalazine are not as pronounced and a significant effect is only seen at higher doses (≥ 2 g day). These protective effects are independent of disease activity. A family history of sporadic colorectal cancer in any relative is associated with a fivefold increased risk, although this did not quite reach statistical significance after adjustment for other variables in the analysis. Systemic and local steroid use also have an inverse relationship with the development of colorectal cancer although their effects were not as influential in the model analysis.

Previous studies[5, 20–22] have suggested a protective role for sulphasalazine against the development of colorectal cancer and recent research has shown that mesalazine selectively induces apoptosis of tumour cells in sporadic colorectal cancer.[23] Our study not only agrees with these findings, but has also allowed an analysis of the effects of other 5-ASA compounds, and has demonstrated that mesalazine exerts an even greater protective effect than sulphasalazine. It is postulated that NSAIDs and 5-ASA compounds work in a similar way and may reduce CRC risk by inhibiting mucosal prostaglandin synthesis.[25] This is supported by three lines of research. Firstly, there is a reduced risk of large bowel adenomas among aspirin and NSAID users.[17, 18, 26] Secondly, NSAIDs decrease the number and size of colorectal adenomas in patients with familial adenomatous polyposis[27] and the morbidity and mortality rates for CRC are

low in patients on chronic NSAIDs.[25, 28] Finally, NSAIDs have been shown to decrease the number and size of chemically induced colon adenomas and carcinomas in experimental animal studies.[29, 30] In our study only 3.9% of cases and 4.9% of controls were taking aspirin. These small numbers limit any interpretation of its role. However, it does mean that the beneficial effects of 5-ASA compounds are not due to the co-incidental use of aspirin.

Patients who see a hospital doctor of any grade frequently and have at least one colonoscopy are less likely to develop bowel cancer. However, these actions do not necessarily reduce the risk of malignancy *per se* and probably represent markers for compliance. This is also likely to be associated with a high compliance taking prescribed medication. Thus, a protective effect found for pharmacological agents may be an underestimation, as the controls are more likely to be compliant even in this respect compared with cases. As controls appear to be more compliant than cases, one may wonder whether this was because the controls were aware that they were part of the Leicestershire database and thus were more motivated or health conscious than the cases, who were followed in a greater variety of practice settings without a cohesive database registry. However, we feel that this is unlikely as the database is used entirely for epidemiological evaluations and is not used for clinical follow-up.

A higher colonoscopy rate among the controls reinforces our results because it makes it unlikely that this group will have a high frequency of undetected cancers. Although colonoscopy has not been proven to be of beneficial effect with regard to reducing the colorectal mortality in this patient group, it is a consistent finding in most studies that being subjected to a surveillance programme upgrades the Duke stage when the cancers are diagnosed.[31–33] In some reported studies of surveillance, cancers are still missed even with 6 monthly examinations and patients should understand that a colonoscopy is not an absolute guarantee against malignant transformation.[34, 35]

A positive family history of CRC is an established risk factor for the disease in the general population[36] and in our study having any family member with a sporadic colonic cancer increased the risk for patients with UC by a factor of five. The relationship was not maintained during the development of a model, and became non-significant when we analysed first-degree relatives only, but this may be a small numbers effect. Indeed research from the Mayo clinic has shown that a family history of colorectal cancer in first-degree relatives was twice as common in UC patients with CRC than in UC controls matched for extent and duration of colitis.[11]

The strengths of our study include a uniform approach to data retrieval and the retrieval of all medical notes for both cases and controls. A second investigator independdently extracted data from control notes using the same pro forma, as a quality control check that the information had been retrieved accurately. A national database of IBD patients does not exist in the UK, and thus case identification could not have been carried out by any other method than the one chosen. Controls were identified from our local database and thus in some instances differed in geographical location and ethnicity from the cases. We do not feel this had a bearing on our results. We have shown that the odds ratio for 5-ASA medication is actually lower in the 12 pairs from Leicester compared with the other 90 pairs, the analysis only losing its statistical significance due to a small numbers effect. Furthermore when we analysed the data after removing Asian cases and controls from the investigation we found that 5-ASA medication (including mesalazine), frequent visits to a hospital doctor and 1–2 colonoscopies were all still highly protective against colorectal cancer in the colitis population. In addition, there have been no documented studies stating that colorectal cancer risk differs in a non-Caucasian population or varies with geographical location across the UK. Indeed Kochhar's study[37] from India stated that the crude incidence of CRC in Asian UC patients was comparable to the 3–4% incidence reported from Anglo-Saxon countries.

A factor that is crucial to consider in studies of cancer risk in UC is the colectomy rate in the population studied. If the colectomy rate was higher in Leicester compared to other geographic areas, that would eliminate patients from the pool at risk for developing CRC and leave behind only very low-risk individuals as controls. Probert's study[17] demonstrates a similar colectomy rate for patients in Leicestershire (in particular Asians) compared with reported rates for St Marks[38] and North-East Scotland[39] and thus this should not be a source of bias in our study.

Criticisms could be levelled at the methods of determining the length and dosage of pharmacological therapy continuously over long periods of time. This is a valid criticism because doses differ with duration of disease and therefore an average dose was estimated for each subject over the course of their colitis. If there was

any doubt whatsoever as to whether a subject was taking medication (or if they had their treatment discontinued for longer than 1 year) they were classed as non-compliers and so our findings are based on subjects clearly identified as taking medication on a regular and virtually continuous basis. Patients who had their medication temporarily interrupted (e.g. a pregnant woman who feared adverse drug effects to the foetus) were recorded as being compliant. All retrospective studies that rely on retrieving information from medical records are subject to some inaccuracies (e.g. in medication usage) and it could be suggested that direct patient interview would be more suitable. However, this is not possible in our study as some cases and controls were deceased. Also, patient recall of facts is fraught with inaccuracies and would introduce another source of bias. We feel that the medical record is the most legitimate source of data as it provides a contemporary record made at the time of consultation.

The strong associations that we found for regular 5-ASA therapy and frequent visits to a hospital physician and the risk of developing colorectal cancer are likely to have an important impact on care programmes and screening for colorectal cancer in patients suffering from ulcerative colitis. The cost-effectiveness of a colonoscopic surveillance programme in ulcerative colitis has been questioned by many authors.[40–42] Physicians may choose to better target colonoscopic surveillance on those who are at greatest risk, i.e. those unable to take regular 5-ASAs (for example due to allergy), have a positive family history of CRC and perhaps have primary sclerosing cholangitis. Likewise it should be possible to reduce the frequency of examinations in those at lower risk. We believe that this effort and expense may be better directed at educating and encouraging patients to take their medication regularly. Such an approach should be supported by hospital-based follow-up for all patients' although patients have to take a modicum of responsibility for their illness. The combination of seeing a hospital doctor on a regular basis, compliance with medication and attendance at colonoscopy offers the greatest degree of protection against colorectal cancer that patients can control themselves.

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REFERENCES

1 Ransohoff DF, Colon cancer in ulcerative colitis. Gastroenterology 1988; 94: 1089–91.
2 Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990; 323: 1228–33.
3 Bargen JA, Gage RP. Carcinoma and ulcerative colitis: prognosis. Gastroenterology 1960; 39: 385–93.
4 Gyde SN, Prior P, Allan RN, *et al.* Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. Gut 1988; 29: 206–17.
5 Katzka I, Brody RS, Morris E, Katz S. Assessment of colorectal cancer risk in patients with ulcerative colitis: experience from a private practice. Gastroenterology 1983; 85: 22–9.
6 Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. Lancet 1983; ii: 149–52.
7 Gilat T, Fireman Z, Grossman A, *et al.* Colorectal cancer in patients with ulcerative colitis. A population study in central Israel. Gastroenterology 1988; 94: 870–7.
8 Greenstein AJ, Sachar DB, Smith H, *et al.* Cancer in universal and left-sided ulcerative colitis: factors determining risk. Gastroenterology 1979; 77: 290–4.
9 Sugita A, Sachar DB, Bodian C, Ribeiro MB, Aufses AH Jr, Greenstein AJ. Colorectal cancer in ulcerative colitis. Influence of anatomical extent and age at onset on colitis–cancer interval. Gut 1991; 32: 167–9.
10 Brentnall TA, Haggitt RC, Rabinovitch PS, *et al.* Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996; 110: 331–8.
11 Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis. A risk factor for the development of dysplasia and DNA aneuploidy. Gastroenterology 1992; 102: 1877–80.
12 Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. Gut 1997; 41: 522–5.
13 Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: A case-control study. Gastroenterology 1998; 115: 1079–83.
14 Lashner BA, Heidenreich PA, Su GL, Kane SV, Hanauer SB. Effect of folate supplementation on the incidence of dysplasia and cancer in chronic ulcerative colitis. Gastroenterology 1989; 97: 255–9.

15 Pinczowski D. Ekbom A. Baron J. Yuen J. Adami HO. Risk factors for colorectal cancer in patients with ulcerative colitis: A case-control study. Gastroenterology 1994; 107: 117–20.
16 Lashner BA. Provencher KS. Seidner DL. Knesebeck A. Brzezinski A. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. Gastroenterology 1997; 112: 29–32.
17 Greenberg ER. Baron JA. Freeman DH Jr. Mandel JS. Haile R. Reduced risk of large bowel adenomas among aspirin users. J Natl Cancer Inst 1993; 85: 912–15.
18 Martinez ME. McPherson RS. Levin B. Annegers JF. Aspirin and other nonsteroidal anti-inflammatory drugs and risk of colorectal adenomatous polyps among endoscoped individuals. Cancer Epidemiology, Biomarkers & Prevention 1995; 4: 703–7.
19 Thun MJ. Namboodira MM. Heath CW. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991; 325: 1593–6.
20 Bansal P. Sonnenberg A. Risk factors for colorectal cancer in inflammatory bowel disease. Am J Gastroenterol 1996; 91: 44–8.
21 Moody GA. Jayanthi V. Probert CSJ. Mackay H. Mayberry JF. Long term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. Eur J Gastroenterol Hepatol 1996; 8: 1179–83.
22 Bus PJ. Nagtegaal ID. Verspaget HW. *et al.* Mesalazine-induced apoptosis of colorectal cancer: on the verge of a new chemopreventive era? Aliment Pharmacol Ther 1999; 13: 1397–1402.
23 Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol 1989; 24: 2–15.
24 Probert CSJ. Jayanthi V. Pinder D. Wicks AC. Mayberry JF. An epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. 1972–89. Gut 1992; 33: 687–93.
25 Rosenberg L. Palmer JR. Zauber AG. Warshauer ME. Stolley PD. Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large bowel cancer. J Natl Cancer Inst 1991; 83: 355–8.
26 Logan RFA. Little J. Hawtin PG. Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: Case-control study of subjects participating in the Nottingham faecal occult blood screening programme. Br Med J 1993; 307: 285–9.
27 Giardiello FM. Hamilton SR. Krush AJ. *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993; 328: 1313–16.
28 Kauppi M. Pukkala E. Isomaki H. Low incidence of colorectal cancer in patients with rheumatoid arthritis. Clin Exper Rheumatol 1996; 14: 551–3.
29 Barnes CJ. Cameron IL. Hardman WE. Lee M. Non-steroidal anti-inflammatory drug effect on crypt cell proliferation and apoptosis during initiation of rat colon carcinogenesis. Br J Cancer 1998; 77: 573–80.
30 Davis AE. Patterson F. Crouch R. The effect of therapeutic drugs used in inflammatory bowel disease on the incidence and growth of colonic cancer in the dimethylhydrazine rat model. Br J Cancer 1992; 66: 777–80.
31 Choi PM. Nugent FW. Schoetz DJ. Silverman ML. Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology 1993; 105: 418–24.
32 Karlen P. Kornfeld D. Brostrom O. Lofberg R. Persson PG. Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. Gut 1998; 42: 711–14.
33 Catnach SM. Rutter KRP. Bown RL. Colorectal carcinoma in patients with ulcerative colitis and recent colonoscopy. Gut 1993; 34: 1148–9.
34 Lennard-Jones JE. Compliance, cost and common sense limit cancer control in colitis. Gut 1986; 27: 1403–7.
35 Fuchs CS. Giovannucci EL. Colditz GA. Hunter DJ. Speizer FE. Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994; 331: 1669–74.
36 Kochhar R. Goenka MK. Kaushik SP. Gupta NM. Nagi B. Mehta SK. Colorectal carcinoma in Indian patients with idiopathic ulcerative colitis. Eur J Cancer Prev 1992; 1: 293–6.
37 Probert CSJ. Jayanthi V. Bhakta P. Wicks ACB. Mayberry JF. How necessary is colectomy? An epidemiological study of the surgical management of ulcerative colitis amongst different ethnic groups in Leicestershire. Eur J Gastroenterol Hepatol 1993; 5: 17–20.
38 Ritchie JK. Powell-Tuck J. Lennard-Jones JE. Clinical outcome of the first ten years of ulcerative colitis and proctitis. Lancet 1978; i: 1140–3.
39 Sinclair TS. Brunt PW. Mowat NAG. Nonspecific proctocolitis in Northeastern Scotland: A community study. Gastroenterology 1983; 85: 1–11.
40 Axon ATR. Cancer surveillance in ulcerative colitis – a time for reappraisal. Gut 1994; 35: 587–9.
41 Collins RH. Feldman M. Fordtran JS. Colon cancer, dysplasia and surveillance in patients with ulcerative colitis: a critical review. N Engl J Med 1987; 316: 1654–8.
42 Clyde S. Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs. Gut 1990; 31: 1089–92.