RISK OF SUBSEQUENT COLON AND RECTAL CANCER AFTER ~~EXCISION OF RECTOSIGMOID~~ REMOVAL OF ADENOMAS FROM THE RECTOSIGMOID

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ABSTRACT

As a cancer prevention measure, surveillance by repeated colonoscopy is currently recommended for all patients found to have colorectal adenomas. In order to assess the long-term risk of colorectal cancer after polypectomy, a detailed examination was undertaken of 1618 patients (1061 men and 557 women) with rectosigmoid adenomas excised between 1957 and 1980 who did not have such colon surveillance. A total of 23,015 years of follow-up (mean 14.2 years per person) were accrued.

Overall, the incidence of **rectal cancer** was similar to that in the general population (standardized incidence ratio=1.24; 95% confidence interval: 0.7-2.1). However most rectal cancers developed in patients with large (≥ 1cm), tubulovillous, villous or severely dysplastic adenomas which had been incompletely excised without follow-up to monitor for local recurrence. This occurred more frequently in the women leading to significant sex-differences in risk.

Risk of **colon cancer** was twice that in the general population in both men and women. Risk depended on the size, histologic type and, to a lesser extent, the number of adenomas in the rectosigmoid. For 842 patients with either tubulovillous, villous or large (≥1 cm) adenomas, the standardized incidence ratio was 3.6 (95% confidence interval: 2.4-5.0). For the remaining 776 patients having with only small (<1cm), tubular adenomas, the standardized incidence ratio was 0.5 (95% confidence interval: 0.1-1.3). Patients with only small tubular adenomas were therefore considered to be at low risk and the remainder at high risk. The number of adenomas found in the rectosigmoid did not influence the division into risk groups. The risk of development of synchronous and metachronous adenomas in the colon was of the order of 20% to 40% in both low and high risk groups, but the adenomas in the low risk group were mainly small (< 1cm).

These results suggest that endoscopic surveillance for patients with only small, mildly or moderately dysplastic, tubular adenomas may not be rewarding as a cancer prevention measure since the risk of colorectal cancer is low. Colonoscopic surveillance would probably benefit the remaining high risk group, although assessment of the degree of benefit is beyond the scope of this study.

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ABBREVIATIONS

AC:	Ascending colon
CM:	Caecum
DC:	Descending colon
DF:	Degrees of freedom for a chi-squared test
EXP:	Expected number of cases
FAP:	Familial adenomatous polyposis coli
FOB:	Faecal occult blood test
HF:	Hepatic flexure
NHS:	National Health Service
NO:	Number
NS:	Not statistically significant ($p \geq 0.05$)
OBS:	Observed number of cases
OPCS:	Office of Population Censuses and Surveys
RM:	Rectum
RS:	Rectosigmoid region (rectum and distal sigmoid colon)
RR:	Relative risk
SC:	Sigmoid colon
SF:	Splenic flexure
SIR:	Standardized incidence ratio
TA:	Tubular adenoma
TC:	Transverse colon
TVA:	Tubulovillous adenoma
VA:	Villous adenoma
95% CI:	95% confidence interval

CHAPTER ONE

INTRODUCTION

Colorectal cancer is the second most frequent cause of death due to malignant disease in England and Wales accounting for 17,053 deaths in 1989 (OPCS, 1989). Risk increases with age with an approximate doubling of the incidence for each decade after 40 years (Muir et al., 1987). The cumulative probability of developing the disease by age 74 is 3.0% in men and 2.5% in women (Thames Cancer Registry data). Approximately 40% of cancers arise in the rectum.

Despite improvements in the surgical management, there has been only a slight change in the rates of survival over the past 3 decades with only 35% of patients currently surviving 5 or more years (Thames Cancer Registry data). This is mainly because more than 90% of patients already have advanced disease at the time of presentation (Stower & Hardcastle, 1985). Dukes' A stage patients who have only local invasion, have survival rates in excess of 90% compared with only 25% in patients with spread beyond the bowel wall (Jass et al., 1986). Efforts to reduce the mortality have therefore concentrated on detection of invasive disease before metastatic spread has occurred, or on intervening at an even earlier pre-invasive stage and preventing its development.

Some asymptomatic patients with colorectal cancer have increased blood losses in the stool compared with healthy individuals and this finding has led to the development of tests for faecal occult blood (Greegor,1967; 1971). Several prospective studies are evaluating the efficacy of faecal occult blood (FOB) testing as a screening procedure (Flehinger et al., 1988; Hardcastle et al., 1986; Kewenter et al., 1987; Kronberg et al., 1987). Early results indicate that the proportion of Dukes' A cases detected is increased from less than 10% to 30% to 50% (Kronberg et al., 1987; Nivatvongs et al., 1982; Winawer et al., 1982; Hardcastle et al., 1989) and in one study, a 15-year survival rate of 90% was reported (Winawer et al., 1983). The validity of this latter finding in the light of lead-time and length-time biases has been questioned (Simon, 1985). Thus, although results so far are promising, the role of FOB testing in the

screening of average-risk individuals will remain controversial until a reduction in mortality is demonstrated in a controlled clinical trial.

An alternative and possibly complementary approach has focused on preventing the development of the disease by detecting and removing colorectal adenomas, since there is strong evidence that most colorectal adenocarcinomas arise from these pre-existing benign polyps (Morson, 1974; Fenoglio & Lane, 1974).

Possible transformation from the benign to the malignant state has been observed radiologically (Welin et al., 1963; Stryker et al., 1987; Rawlinson et al., 1989), but most of the evidence for the adenoma-carcinoma sequence is indirect based on the observations that: (i) the prevalence of adenomas in autopsy specimens correlates with rates of colorectal cancer in different populations (Correa et al., 1977), (ii) adenomas and adenocarcinomas tend to cluster in the same subsites of the bowel (Cappell & Forde, 1989) being more frequent in the left side of the bowel in younger patients with a right-sided shift with increasing age (Granqvist,1981, Vatn & Stalsberg,1982; Bernstein et al., 1985; Clark et al., 1985), (iii) remnant adenomatous tissue adjacent to a cancer or a focus of invasive cancer within an adenoma are not infrequently found (Grinnell & Lane, 1958; Muto et al., 1974; Shinya & Wolff, 1979).

Patients with familial adenomatous polyposis coli (FAP), a dominantly-inherited condition, have an almost 100% life-time incidence of colorectal cancer. These patients typically have hundreds of adenomas throughout the large bowel (Bussey & Morson, 1967; Bussey, 1975). Studies in patients who refused surgery have shown that the premalignant phase lasts approximately 5 - 10 years (Morson et al., 1983). The existence of a benign phase of relatively long duration allows for the, at least theoretical, possibility of reducing the incidence of the disease through prophylactic polypectomy.

Unfortunately, there are formidable problems with the practical application of this concept. Autopsy surveys indicate that more than 30% of the population over 50 years of age has at least one adenoma (Arminski and McLean,1964; Rickert et al., 1979; Vatn & Stalsberg,1982; Williams et al., 1982). The detection and removal of all adenomas in this large number of at-risk

people would be an enormous task. According to Winawer (1976), 50% of all neoplastic lesions in the colorectum (adenomas and adenocarcinomas) occur within reach of the 25 cm rigid sigmoidoscope. Others have disputed this figure, and a four to five-fold increase in the detection rate of adenomas has been reported with the more recently introduced flexible sigmoidoscopes (60 cm and 65 cm) (Winnan et al., 1980; Wilking et al., 1986). However, approximately one third of neoplasms occur in sites proximal to the splenic flexure and these are accessible only by colonoscopy (Theuerkauf, 1978; Lieberman & Smith, 1988). The reliability with which adenomas may be detected and removed via the colonoscope has made this procedure, when it is available, the first choice in the initial work-up of patients found to have adenomas (Lambert et al., 1984, Aldridge & Sim, 1986). However, its application as a screening tool is limited by its high costs in terms of both equipment and skilled endoscopists (McGill, 1985; Neugut & Forde, 1988). It is also a relatively invasive procedure requiring sedation of the patient and is associated with a small, but significant morbidity and mortality (Macrae et al., 1981).

At present the majority of adenomas are found coincidently during routine examination of patients referred to hospital, so the workload is still manageable. With the wider application of screening by sigmoidoscopy and FOB tests, the number of patients coming to the attention of clinicians will increase. This prediction is based on the findings of the Nottingham group (Hardcastle et al., 1989) which has recently reported that 43% of asymptomatic patients with positive FOB tests harbour adenomas. Furthermore, the American Cancer Society (1980) now recommends screening proctosigmoidoscopy every 3 to 5 years for people over the age of 50 years.

The scale of the problem is further compounded by the finding that, after complete clearing of adenomas from the colorectum by colonoscopy, metachronous adenomas are found in 30% to 60% of patients within 3 to 5 years (Fruhmorgen et al., 1979; Waye & Braunfeld, 1982; Matek et al., 1985; Neugut et al., 1985; Winawer et al., 1986). For this reason, surveillance by colonoscopy at 2 to 4 yearly intervals for all patients with adenomas is currently recommended (Morson et al., 1990) which constitutes a major demand on available resources.

Yet there is little evidence that all patients with adenomas are at an increased risk of cancer. The prevalence of adenomas at autopsy is more than 10 times the lifetime risk of colorectal cancer, so only a small proportion of patients with adenomas will develop cancer. It would be logical therefore to identify a subgroup at increased risk so that the limited resources could be focused on these patients. The malignant potential of an adenoma increases with increasing size, villousness and severity of dysplasia (Enterline et al., 1962; Muto et al., 1975; Shinya & Wolff, 1979). Size, villousness and dysplasia are interrelated (Muto et al., 1975). Tubulovillous and villous adenomas are generally larger than tubular adenomas, and they also tend to be more dysplastic. Furthermore larger adenomas, irrespective of their histology, tend to be more dysplastic. The rate of growth of adenomas varies widely and some remain dormant for long periods of time (Welin et al., 1963; Figiel et al., 1963). Since the majority of adenomas found during autopsy surveys are small, it has been suggested most adenomas remain small and do not become malignant (Welin et al., 1963; Muto et al., 1974). It is possible therefore that patients who are found to have only small adenomas are at low risk of developing cancer.

It would be unwise to leave even a small adenoma untreated, especially if it is within reach of the rigid sigmoidoscope, since 1% of adenomas smaller than 1 cm may contain invasive cancer (Muto et al., 1975) and their removal is quick, easy and relatively safe. However, after excision of prevalent adenomas at entry, there is little evidence that metachronous adenomas present a risk of cancer during the remaining life-span of most patients. Metachronous adenomas, tend to be very small (<5mm), mostly tubular and only mildly dysplastic compared with those found at entry (Waye & Braunfeld, 1982; Matek et al., 1985; Kronberg & Fenger, 1987). The natural history of the small adenomas found at follow-up remains unexplored because, for ethical reasons, they cannot be left untreated and the recommmended intervals between colonoscopic examinations are too short to allow for the malignant potential of new adenomas to be expressed. Several large randomised studies are currently comparing different intervals between follow-up examinations (Matek et al., 1985; Winawer et al., 1986; Williams & Macrae, 1986; Kronberg & Fenger, 1987) since there is a general feeling that the currently recommended intervals err too far on the side of caution for most individuals. However, the endpoint in all of these studies is the recurrence of adenomas rather than the development of cancer, since

even the longest intervals currently under evaluation must be sufficiently short to reduce the risk of cancer to an acceptably low level. Only one study of these studies takes account of the possible heterogeneity with respect to risk of cancer of patients with adenomas by dividing them into high and low-risk categories (Williams & Macrae, 1986). The criteria for this division is based on risks of further adenomas rather than cancers. Thus, at present many endoscopists are engaged in a time consuming process of adenoma-hunting, during which polyps of decreasing size are removed, without any proof that this exercise is preventing cancer. The aim of this study is to try to identify a subgroup of patients with adenomas who are at an increased risk of developing colorectal cancer and would be most likely to benefit from colonoscopic surveillance.

CHAPTER TWO

BACKGROUND TO THE STUDY

2.1 DEFINITIONS:

Polyp: A 'polyp' is a descriptive term for any tumour or elevation which projects above the surface of the surrounding flat normal mucous membrane (Morson & Dawson, 1979). Polyps may appear as pedunculated lesions with a long or short stalk, or the stalk may be entirely absent; they may also be flat or sessile. Polyps with stalks rarely exceed 3 cms in size, but sessile lesions may vary from a few millimetres to 10-15 cms, encompassing the entire circumference of the rectum. Such large tumours are rare and the majority are less than 3-4 cms in diameter. A **diminutive polyp** is a clinical description of a polyp of 5 mm or less of any histological type.

Adenoma: There are several histological types of polyp (Table 1). The neoplastic group, known as adenomas, are the lesions from which the majority of adenocarcinomas of the large bowel are thought to arise. All adenomas, despite their varying macroscopic appearance, share one common distinguishing feature: they all show some degree of epithelial dysplasia. This dysplasia is essentially the same cellular change as that observed in other epithelial surfaces such as the cervix, oesophagus and stomach (Morson & Dawson, 1979; Morson et al., 1983).

In the majority of patients only one or two adenomas are found, although between 3 and 10 adenomas is a relative common finding. Patients with more than 100 adenomas have a rare genetically determined disease known as familial adenomatous polyposis coli (FAP) which carries an almost 100% lifetime risk of colorectal cancer.

Histology: Adenomas may be classified by their histological structure into three groups (WHO, 1976): **tubular, tubulovillous** and **villous** on the basis of subjective microscopic findings. Adenomas are described as tubular if more than 80% are composed of closely packed branched epithelial tubules. They are described as villous if more than 80% of the surface is composed of finger-like processes, each made up of a core of lamina propria covered by epithelial cells

Table 1.A Histological Classification of Colorectal Polyps*

Histogenesis	Single or Isolated Multiple Polyp	Polyposis (> 100 Polyps)
Mucosal Neoplastic	Adenoma	Adenomatosis (familial polyposis coli)
Haemartomatous	Juvenile polyp Peutz-Jegher polyp	Juvenile polyposis Peutz-Jegher syndrome
Inflammatory	Inflammatory polyp	Inflammatory polyposis
Mechanical stress	Mechanical prolapse syndrome (a) Inflammatory 'cap' polyps (b) Solitory ulcer syndrome (c) Large intestinal prolapse	
Uncertain	Metaplastic (hyperplastic polyp)	Metaplastic polyposis Cronkite-Canada syndrome

*from Price AB (1989)

growing vertically towards the bowel lumen. The remainder, with a mixed appearance, are classified as tubulovillous (Konishi & Morson, 1982)

Most adenomas have a tubular type of growth and only about 10% are truly villous. Approximately 20%-30% are tubulovillous, but the relative frequency of the three types depends upon how carefully the polyp is examined. The more sections taken, the greater the chance that villous structures will be found in what otherwise appears to be a tubular type of adenoma, particularly in larger specimens (Morson & Dawson, 1979)

Dysplasia: Irrespective of their growth pattern, dysplasia in adenomas may be graded by cytological and histological criteria into three grades: mild, moderate and severe, the latter being used synonymously with carcinoma in situ (Konishi & Morson, 1982).

Mild dysplasia: The nuclei are elongated, slightly hyperchromatic with a fine chromatin pattern and nucleoli are inconspicuous. The amount of mucin is decreased and the number of mitotic figures is increased. There is irregular glandular arrangement with some branching.

Moderate dysplasia: Nuclei are elliptical, the chromatin is denser. There is nuclear pseudostratification and minor loss of polarity. Mucin is further decreased and reversed goblet cells are seen. There is a tendency towards pleomorphism of the nuclei.

Severe dysplasia: The changes are similar to those of invading adenocarcinoma. The nuclei are large and pleomorphic. The chromatin pattern is diffusely dark or open with clumping of the chromatin. Nucleoli are seen. There is marked pleomorphism, loss of polarity of the nuclei and an increase in the number of mitotic figures. The growth pattern is distorted showing a condensed glandular back-to-back arrangement.

The grading of adenomas is subjective since areas within the same tumour may have different grades of dysplasia and the transition from one area to another is often gradual. Adenomas are usually graded according to the most severe dysplasia seen.

Rectosigmoid: This includes the rectum and that part of the sigmoid colon that is within reach of the 25 cm rigid sigmoidoscope.

Index adenoma(s): The first adenoma(s) detected in a patient either by proctosigmoidoscopy or more extensive examinations such as barium enema or colonoscopy.

Entry time: The date of the initial examination at which the first (index) adenoma(s) is diagnosed.

Synchronous adenoma(s): Adenoma(s) in the proximal part of the colon beyond the reach of the 25 cm sigmoidoscope found at the same time as those diagnosed in the rectosigmoid.

Metachronous adenoma(s): Lesions detected anywhere in the large bowel, but on a different occcasion to the index adenoma(s).

2.2 THE ADENOMA-CARCINOMA SEQUENCE

The recognition that colorectal polyps can become malignant is usually attributed to Virchow (1845), although a hereditary condition associated with multiple polyps, some of which showed malignant change, was described at the beginning of the last century (Munro, 1811; Breschet, 1817). Bland-Sutton (1922) was the first to point out that the term 'polyp' is a merely descriptive term and that several distinct forms exist. However confusion and misuse of the word was still apparent in the 1970s (Morson, 1984). It is not clear who introduced the term 'adenoma', but it was already in use in 1919 (Ewing, 1919). Villous papillomas were regarded as a separate entity with a pronounced tendency towards recurrence and malignant change (Ewing, 1919).

Westhues (1934) made the first detailed histological description of polyps which laid the foundation for the modern classification of benign tumours. He drew a distinction between 'adenomas' which had a potential for becoming malignant and 'hyperplastic' polyps which he said were 'harmless'.

It was not until the early 1950s that it became widely accepted that pedunculated adenomatous polyps had a propensity to develop into cancer; the malignant potential of villous (papillary) adenomas had already been well established. Whether all cancers develop from adenomas and the time required for transformation was not known, and indeed remains unclear today. Jackman and Mayo (1951) maintained that all adenomas given sufficient time develop into carcinomas and that all clinicians should practise cancer prevention by removing polyps. A vogue began in the United States to detect and remove all polyps in the large intestine. Several large screening programmes for healthy individuals were instigated and, because of the improvements in the morbidity associated with abdominal surgery, some surgeons proposed colectomy and ileorectal anastomosis for patients with multiple polyps (Lillihei & Wangensteen, 1955). This policy provoked a backlash from the proponents of a school of thought which questioned the malignant potential of the non-villous pedunculated variety of adenomatous polyp (Spratt et al., 1958; Castleman & Krickstein, 1962). They argued that even when a cancer arises in a stalked adenomatous polyp, it rarely if ever metastasizes (Grinnell & Lane, 1953; Enterline et al., 1962) and that these adenomas should be treated only by local excision without the need for radical surgery.

Soon after his appointment as Consultant Pathologist at St Mark's Hospital, Dr B.C. Morson began his work to clarify the situation, which culminated in the publication of the World Health Organisation blue book on the Histological Classification and Nomenclature of Intestinal Tumours (1976). He made a plea for greater precision in the use of the word 'polyp' and emphasised that an adenoma is the only type of polyp with malignant potential (Morson, 1974). He also stressed that clinically as well as pathologically, it is the presence of invasion that is important in the definition of malignant change because it is only after invasion that metastasis can occur. That pedunculated polyps are capable of metastasis after invasion was demonstrated by Johnson (1978) who showed that 30% to 50% of invasive cancers in pedunculated lesions have positive lymph nodes.

At about this time, several groups showed that despite the gross differences in appearance, pedunculated adenomatous polyps and villous adenomas are 'histological variants of the same neoplastic process' (Fung & Golman, 1970; Kaneko, 1972; Muto et al., 1975). On re-examination of 458 pedunculated

polyps originally classified between 1948 and 1962 as adenomatous, Kaneko found that one third contained a villous component. Twenty percent of adenomas with villous components were malignant compared with only 4% of purely adenomatous polyps, but he could not demonstrate that carcinoma had arisen from the villous rather than the adenomatous part of the polyp. It is probable that all polyps begin as sessile lesions and, as they grow, they acquire a pedicle as a result of peristaltic action (Scarborough, 1960). This would explain why most polyps with stalks are found in the sigmoid colon, the site of maximal colonic movement.

By careful examination of almost 2000 tumours with contiguus benign and malignant tissue, Muto et al., (1975) showed that the malignant potential of an adenoma was related more to the size than the presence of a villous component. In their series, only 1% of tumours smaller than 1 cm were malignant compared with almost 50% of those larger than 2 cm. The proportion of malignancy increased from 5% in the tubular adenomas to 40% in the villous type, but that was possibly because the villous adenomas were larger.

The concept that adenomatous polyps and villous adenomas are a single clinical entity is enforced by the observation that regardless of their histological structure, all show characteristics of dysplasia or epithelial atypia; that is, loss of some fundamental control mechanism and as a result, cell division (mitosis) is unrestricted and cell differentiation is incomplete (Fenoglio & Lane, 1974). The manifestations of this abnormality are graded into mild, moderate and severe according to defined criteria (see section 2.1). It is common to see within a single adenoma a gradation of epithelial atypia from mild to severe to carcinomatous change which is powerful evidence for the concept of the adenoma-carcinoma sequence (Lescher et al., 1967; Potet & Soullard, 1971; Muto et al., 1975). It is likely that all carcinomas in the large bowel pass through a stage of severe dysplasia before becoming invasive (Morson, 1983).

Direct observations of the adenoma-carcinoma sequence have been rare because most adenomas are removed immediately upon detection. The condition familial adenomatous polyposis coli (FAP) has been a useful model since the hundreds of adenomas that characterize this disease are indistinguishable from solitary adenomas. The majority of adenomas in FAP

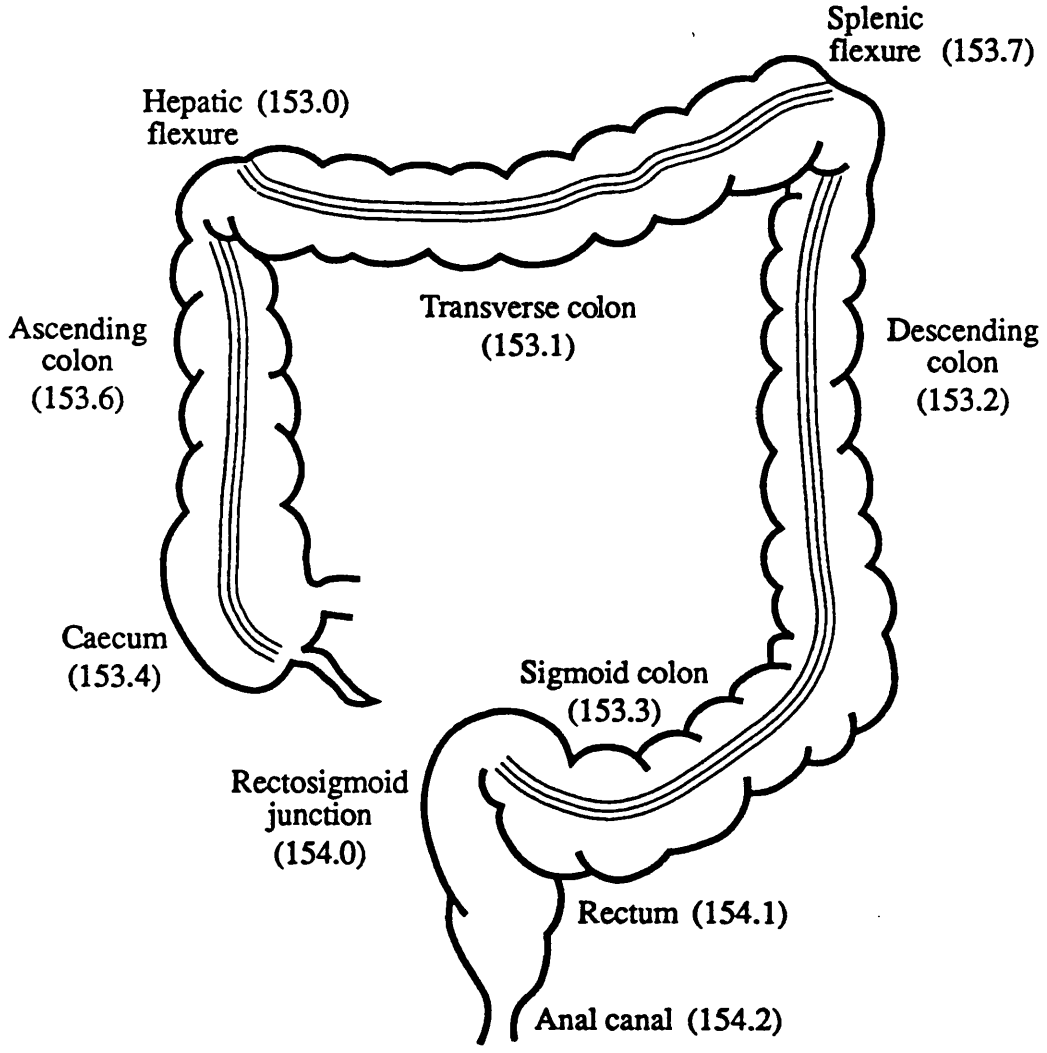
are tubular, occasionally they are tubulovillous and only rarely purely villous. Unless treated by total colectomy and ileo-rectal anastomosis, there is an almost 100% lifetime risk of developing colorectal cancer. The average age of presentation with only benign adenomas is 27 years in FAP compared with 39 years for patients with associated cancer. This suggests that it takes approximately 12 years for adenomas to develop into cancer. Sporadic cancers occur approximately 30 years later, but the average interval between presentation with only benign adenomas and with cancer is of the same order.

Patients with FAP who have refused surgery have enabled direct observation of the time to development of cancer. Of 59 such patients at St Mark's Hospital, 12% developed cancer within 5 years, 25% within 10 years and 50% by 20 years. Thus it seems that the adenoma-carcinoma sequence is a slow process. Furthermore only a tiny proportion of adenomas actually become malignant during the normal lifespan. This is particularly apparent in cases of FAP refusing surgery where there are hundreds or thousands of adenomas but only a few cancers in each individual (Muto et al., 1975).

2.3 DIAGNOSIS OF ADENOMAS

Methods of diagnosing adenomas are largely dependent on their location. By convention, the large bowel is divided into the colon and rectum at the rectosigmoid junction (Figure 1). The location of this arbitrary dividing line varies depending on whether it is defined by a surgeon, clinician or pathologist, but at sigmoidoscopy is considered to be 15 cm from the ano-rectal junction (Goligher, 1980). Therefore considerable confusion exists about the precise location of tumours around the rectosigmoid (Higginson, 1966). This is important because the majority of colorectal cancers occur in this region and because incidence and mortality rates are expressed separately for the two subsites (Waterhouse et al., 1982). In the International Classification of Diseases, (1977), the 3-digit code 153 refers to neoplasms in the colon and 154 for neoplasms in the rectum; subsites within these regions have been allocated 4-figure codes (Figure 1).

Figure 1. Subsites of the large intestine



In parentheses: International classification of Diseases, 9th edition (1977) codes for neoplasms.

2.3.1 Clinical History

In his book 'Diseases of the Rectum and Colon', Mr J.P. Lockhart-Mummary (1934) stated that "in the diagnosis of rectal diseases, the history was of little significance and that everything depended on the physical examination". Although this is an overstatement, it is true to some extent particularly in the diagnosis of adenomas because of the accuracy and ease with which the rectum may be visualised with the sigmoidoscope and because adenomas, unless they are very large do not generally produce symptoms (bleeding being the commonest presentation, though villous adenomas may produce excessive mucus discharge). This statement is not true of the colon and the presence of symptoms, not necessarily related to a polyp, is still the main reason for referral for more extensive examinations of the bowel by radiology or colonoscopy.

2.3.2 Rigid Sigmoidoscopy

The Lloyd-Davies 25 cm length rigid sigmoidoscope is commonly used for routine examinations. However the bowel forms a sharp bend at the rectosigmoid junction (Figure 1) and many patients, particularly women are unable to tolerate passage of the instrument to its full length; examinations may therefore be incomplete (Nichols & Dube, 1982). The distance passed as reported in the patient's notes, is likely to be an over-estimate of the length of the bowel traversed since the rigid sigmoidoscope tends to stretch the bowel wall (Madigan & Halls, 1968).

In several large series from the United States, the average reported depth of insertion was only 17 cm to 20 cm (Nivatvongs & Fryd, 1980; Winnan et al., 1980; Marks et al., 1979). In the United Kingdom, patients are examined with an unprepared bowel in the left lateral position, whereas in the United States the knee-chest position is preferred and patients are often given a saline enema half an hour before examination. Mann et al., (1988) have shown that this method allows passage of the instrument higher into the bowel. It is likely, therefore, that only the rectum, up to and including the rectosigmoid junction, is examined with any degree of reliability.

2.3.3 Barium Enema

Until 1960, the only method available for examining the bowel radiologically was the single contrast barium enema which frequently missed polyps, particularly those smaller than 1 cm. With the single contrast technique, radiographs are taken as the bowel gradually fills with barium. The enema is then evacuated and further radiographs taken of the collapsed colon. With the development of the double contrast 'Malmo' technique (DCBE), the colon could be examined more thoroughly (Welin, 1962). In the double contrast method, the single technique is followed by inflation of the colon with air. The distended bowel then has a thin layer of barium coating the mucosa. Radiographs at this stage usually give a good view of polyps including plaque-like adenomas and carcinomas.

A long debate has ensued between endoscopists and radiologists as to the relative merits of either technique in detecting polyps (Thoeni and Menucke, 1977; Wolff et al., 1975; Ott et al., 1980; Fork, 1981; Williams, 1981; Farrands et al., 1983). Barium enema may be a better method than colonoscopy for detecting relatively flat lesions (Glick et al., 1989), but is generally considered inferior to colonoscopy in the detection of lesions smaller than 1 cm (Williams et al., 1982). A major disadvantage of barium enema is that it only allows visualisation of polyps and a separate procedure is then required for their removal. Further, barium enema appears to be inferior to colonoscopy in the examination of the sigmoid colon in the presence of diverticular disease (Boulos et al., 1985).

2.3.4 Colonoscopy and Flexible Sigmoidoscopy

The introduction of flexible fibro-optic endoscopes of up to 180 cm in length has revolutionised the examination of the large bowel making polyps of almost any size or site accessible for removal (Wolff & Shinya, 1972; Williams, 1981). The shorter 60 to 65 cm flexible sigmoidoscopes were introduced in 1976 (Fath & Winawer, 1986) for examination of the left side of the bowel where the majority of adenomas and cancers occur. Bowel preparation is still required, but sedation is not, so flexible sigmoidoscopy is useful as an Out-Patient procedure. It is also useful for patients unable to tolerate complete colonoscopy or for the follow-up of patients finding the initial examination

unacceptably uncomfortable. Flexible sigmoidoscopy is usually accompanied by a barium enema examination.

Theoretically, colonoscopy allows for the detection and excision of adenomas up to the caecal pole. In practice, about 25% of colonoscopies are technically difficult or painful for the patient. This may cause an inexperienced endoscopist to discontinue the examination, but in specialist centres colonoscopy to the caecum is performed on at least one occasion in more than 90% of the cases (Williams & Macrae,.1986; Kronborg & Fenger, 1987).

2.4 POLYP EXCISION

It is not usually possible from the gross appearance of polyps to distinguish adenomas from other types of non-neoplastic polyps and a biopsy provides an unrepresentative sample, therefore they are usually excised for histological examination.

Methods for polyp excision may be broadly classified as:

1. Endoscopic excision
2. Endo-anal excision
3. Colotomy, and colonic resection

2.4.1 Endoscopic excision.

Endoscopic polypectomy is the usual treatment of choice except for large sessile lesions or pedunculated polyps with thick stalks. Today, this is done via the colonoscope which allows examination of the whole colon for synchronous neoplasms. The operating rigid sigmoidoscope is not commonly used as it only allows access to the distal sigmoid colon.

For pedunculated tumours the diathermy snare is used. The wire loop is pulled over the polyp and gradually tightened around the stalk. The wire cuts through the stalk leaving a small coagulated area which does not usually bleed (Goligher, 1980). An alternative technique is to grasp the pedicle with diathermy forceps and the applied current then achieves the same effect.

For most sessile lesions, fulgaration with a button electrode or diathermy forceps is employed as snaring with the diathermy loop can be dangerous. The polyp is touched and the current switched on for a few seconds. It may be necessary to repeat the performance several times. This method does not provide a tissue specimen for histological examination and does not always guarantee complete destruction of the polyp. A simpler and safer method was developed at St Mark's Hospital, the 'Hot Biopsy' technique (Williams, 1973) for the simultaneous diathermy and biopsy of small sessile polyps. Rare complications include haemorrhage and perforation of the bowel (Macrae et al., 1983).

2.4.2 Endo-anal excision

Large and/or sessile adenomas are usually tubulovillous or villous with an increased likelihood of containing a focus of invasive cancer. The majority are found in the rectosigmoid although they may occur elsewhere within the large bowel. The most reliable way of determining whether malignant degeneration has occurred is by palpation of the lesion, although this is only suitable for adenomas within reach of the examining finger (Goligher, 1980). A biopsy specimen could be taken for proximal lesions within reach of the rigid proctosigmoidoscope, but the accuracy of the histopathological assessment of such biopsies can be quite low (Taylor et al., 1980). If a villous adenoma is clinically suspicious then it should be treated as a cancer.

The choice of method of excision depends on the site, the size, the presence of a stalk and whether the lesion involves the entire circumference of the bowel. For relatively small lesions, local excision is used. Pedunculated polyps in the lower rectum can be removed peranally, while higher lesions are removed via the sigmoidoscope by snaring the stalk, although for polyps with a thick stalk, it is safer to excise peranally as it allows access for controlling bleeding which is a risk with such lesions. For sessile adenomas, contact diathermy using a button electrode or diathermy forceps is necessary. This method is very tedious for large lesions; several sessions may be necessary to treat the entire lesion and recurrences occur in 20% to 50% of cases (Thomson, 1977; McCabe et al., 1973; Galandiuk et al., 1987 Christiansen et al., 1979; Pollard et al., 1988).

Methods for more extensive lesions have changed considerably over the years. Originally, complete excision of the rectum by the abdomino-perineal appoach and a permanent colostomy was favoured. When originally introduced, this operation had a high mortality rate (Miles, 1910) and was therefore only slowly adopted by surgeons in general, but by the 1950s had become a commonly used method (Gabriel, 1952). Anterior resection also called the 'Mayo Clinic' or 'Dixon's' method (Dixon, 1948) was employed with the objective of preserving the anal sphincters and, until the introduction of stapling restoration of bowel continuity, was difficult to achieve for lesions in the lower rectum. An alternative technique based on the transphincteric approach (Mason, 1970) was not favoured.

Submucosal excision, first introduced by Soave (1964) and modified by Parks (1966; 1973) has become the treatment of choice. It allows complete excision of the adenoma; although, for circumferential lesions and those in the upper rectum, it can be technically difficult. It is less traumatic than previous methods and appears to be associated with fewer recurrences (Thomson, 1977; Pollard et al., 1988). Until the introduction of this latter method, the choice was between radical surgery with a relatively high morbity and mortality rate or local methods which were associated with a high risk of recurrence and the possibility of development of cancer.

2.4.3 Colotomy and Colonic resection

In the pre-colonoscopy era the only way to remove adenomas detected by barium enema was via the trans-abdominal route. Colotomy and polypectomy used to be the most commonly employed method. The colon was opened in the region of the polyp with a 2" to 3" longitudinal incision. This procedure was considered by some to be relatively safe with a mortality of less than 1% (Judd & Carlisle, 1953; Swinton & Weakley, 1963), although a morbidity of around 20% made it difficult to come to a decision as to whether to remove a polyp found by barium enema. Another problem with this technique was that synchronous adenomas were not seen and recurrences often occurred, so it was recommended that a 'generous' segmental resection or even a total colectomy be performed (Welch, 1951, Judd & Carlisle, 1953; Lillihei & Wangensteen, 1955: Teicher & Abrahams, 1956). An alternative approach was to make two or more longitudinal incisions usually in the transverse colon at

the hepatic flexure and in the sigmoid colon and introduce a sterile sigmoidoscope in both directions at each colotomy wound (Deddish, 1953, Bacon & Peale, 1956).

Since the introduction of colonoscopy these drastic measures are rarely needed. The abdominal approach may still be necessary for large pedunculated polyps which are inaccessible endoscopically because of a fold or when there is risk of bleeding following snaring. Large villous adenomas not suitable for local per-anal excision or in the colon would require more radical surgery in the form of colonic resection because of the high rate of malignancy in these lesions.

2.5 SURVEILLANCE FOR PATIENTS WITH ADENOMAS

By the early 1970s it had become generally accepted that the majority of colorectal carcinomas arise in pre-existing adenomas (Morson, 1974; Fenoglio & Lane, 1974) and that prevention of colorectal cancer by prophylactic polypectomy was at least a theoretical possibility. Evidence in support of this supposition was, and remains, sparse. Gilbertson reported an 85% reduction in the incidence of rectal cancer in a large screening series of 21,000 subjects subjected to regular follow-up proctosigmoidoscopy and polypectomy (Gilbertson, 1974; Gilbertson & Nelms, 1978). A significant reduction in the incidence of colorectal cancer within reach of the rigid sigmoidoscope was also reported by organisers of the Kaiser Permanente Multiphasic Check-up Study (Dales et al., 1979; Friedman et al., 1986) in which subjects were randomly allocated to a screened and non-screened control group. However, both studies suffered from methodological problems and the validity of their findings has been questioned (Miller, 1987; Neugat & Pita, 1988; Ow et al., 1989).

Until the 1970s, only rectal polyps were easily accessible for removal and colonic polyps were observed radiologically until they grew large or showed signs suggestive of malignancy. The introduction of the colonoscope and endoscopic polypectomy techniques made polyps of any size and site within the colorectum amenable to treatment (Williams, 1983) and it became possible to attempt cancer prevention throughout the large bowel.

However the availability of this new technology gave rise to formidable logistic problems (Kern, 1976; Williams, 1983). There was mounting evidence that the "presence of adenomas represents an abnormal mucosa with a tendency to produce more adenomas and cancers at other sites" (Rider et al., 1959). This was the first indication that, after excision of adenomas and carcinomas, patients might remain susceptible to the development of cancer for the remainder of their lives. Patients with colorectal cancer were shown to be at an increased risk of having a second colorectal cancer either synchronously or metachronously (Bussey et al., 1967; Heald & Bussey, 1975; Burns, 1980). While studies in patients with colorectal polyps detected by proctosigmoidoscopy and/or barium enema who had a repeat examination 4 to 9 years later, indicated that polyps recur in approximately 20% to 40% (Rider et al.,1959; Kirsner et al., 1960; Brahme et al., 1974; Henry et al.,1975).

These findings were confirmed in more recent studies of patients having repeat colonoscopy. The rate of recurrence of polyps within 3 years after endoscopic-removal of all visible polyps was reported to be of the order of 30% in patients with a single polyp and 60% if multiple polyps were present at the initial colonoscopy (Fruhmorgen et al., 1979; Waye & Braunfeld, 1982; Matek et al., 1985; Neugut et al., 1985; Winawer et al., 1986). Approximately 10% of these so-called recurrences were thought to be polyps missed at the inital examination and it was suggested that two colonoscopies are required to achieve a 'clean colon' free of all visible polyps (Waye and Braunfeld, 1982; Williams, 1983; Kronborg & Fenger, 1987). However, as a result of these observations, follow-up by regular colonoscopy is now recommended for all patients with colorectal adenomas (Morson et al., 1990).

Autopsy and endoscopy studies indicate that adenomas are present in at least 10% of individuals aged over 40 years, and that the prevalence increases with age, such that by 60 years of age approximately one third are affected (Eide & Stalsberg, 1978; Rickert et al., 1979; Williams et al., 1982: Lambert et al., 1984). To offer prophylactic polypectomy followed by surveillance colonoscopy to all those at risk would be a formidable task, graphically illustrated by Kern (1976) in his presidential address to the American Gastroenterological Association when he visualized "an endless train of people colonoscoping each other, end to end, like elephants in a circus".

It appears, though, that many practitioners have lost sight of the primary purpose of colonoscopic polypectomy which is the prevention of cancer rather than the removal of polyps. The basic premise for colonoscopic surveillance is that polypectomy may be equated with cancer prevention. In a recent review of the results of the Kaiser Permanente Multiphasic Check-up Study, Selby et al (1989), noted that the lower incidence of colorectal cancer could not be ascribed to polypectomy at screening proctosigmoidoscopy since the rates of detection and removal of polyps were the same in the screened and non-screened groups. Preliminary results from the on-going 'National Polyp Study' (Winawer et al., 1986), in which patients are randomised to either one or two colorectal examinations within the first 3 years after entry, indicate that, compared with adenomas at entry, new adenomas detected at follow-up tend to be mostly diminutive (<5 mm), and only mildly dysplastic (O'Brien et al., 1990). Radiological studies suggest that the rate of growth of small adenomas is very slow and some may stay dormant for long periods (Welin et al., 1963; Figiel et al., 1963). There is little evidence that these small adenomas pose a risk of cancer during the remaining lifetime of the majority of patients.

There have been a few studies of cancer risk in patients treated in the pre-colonoscopy era when follow-up after adenoma-excision was not routine. Most do not specify the histology of the removed polyps, but they do give an indication of the low risk of subsequent cancer after excision of adenomas. In an early study (Colvert & Brown, 1948), 2.5% of patients with polyps in the rectum developed rectal cancer within 5 years, although what proportion might have been recurrences of inadequately excised lesions is not clear. Prager et al (1974) observed 12 cancers in 305 patients followed for 15 years, an incidence of 4%, but all except one of these cancers occurred in the unexamined colon. In a long-term follow-up study of 751 patients with small polyps excised from the rectosigmoid at the Mayo Clinic in Rochester, Minnesota (Spencer et al., 1984), there were 18 cancers (2.4%), but only 7 of the cancers (0.9%) occurred in the area from which polyps had been excised at entry. In a similar series, also from the Mayo Clinic (Lotfi et al., 1986), of 323 patients with histologically diagnosed adenomas, a proportion of which were larger than 1 cm, colorectal cancer developed in 20; again, though, only 8 of the cancers (2.5%) were within reach of the rigid sigmoidoscope. Thus it seems that the long-term risk of subsequent cancer in the area of the colorectum rendered free of polyps is less than 3%. Colonoscopic studies

indicate that new adenomas appear in approximately one third of patients after achieving a 'clean colon' (Fruhmorgen et al., 1979; Waye & Braunfeld, 1982; Winawer et al., 1986), therefore, 90% of patients with new adenomas are not destined to develop cancer. In many cases, therefore, the small adenomas being detected at follow-up are being removed with no benefit to the patients in terms of reducing cancer risk.

However, endoscopists are faced with a dilemma. Without firm evidence of the absence of risk of cancer in an individual patient with adenomas, it would not be considered ethical in the light of current recommendations to withhold colonoscopic surveillance where it is available. Furthermore, there are anecdotal reports of carcinomas appearing within a short period of achieving a clean colon (Matek et al., 1985; Kronborg & Fenger, 1987). It is not clear whether these cancers have arisen in missed adenomas or whether in some cases, progression is rapid. It does seem, however, that while the majority of patients may be at very low risk of developing subsequent cancer after achieving a clean colon at entry, there is a small proportion which is at high risk and for this group colonoscopic surveillance is warranted.

There are several large randomized studies in progress cautiously extending the intervals between examinations (Winawer et al., 1986; Williams & Macrae, 1986; Kronberg & Fenger, 1987). These studies are unlikely to be able to distinguish between the few high risk and the majority of low risk patients since preliminary results suggest that even with the longest intervals, very few newly detected adenomas exceed 1 cm in size (O'Brien et al., 1990;, Macrae et al., 1990). The reason is that, ethically, the intervals between examinations must be sufficiently short to prevent the manifestation of the malignant potential of adenomas even in high-risk patients.

Thus there is a need to undertake a long-term follow-up study in patients with adenomas excised on a single occasion without subsequent follow-up examinations. The aim of such a study would be to identify the characteristics at presentation of patients who are at increased risk of developing cancer and who might benefit from colonoscopic surveillance, and conversely, to identify a sub-group at low risk possibly requiring no follow-up.

CHAPTER THREE

AIMS AND PLAN OF THE STUDY

3.1 AIMS

The author had the opportunity to study the long-term risk of colorectal cancer in a large cohort of patients with rectosigmoid adenomas excised at proctosigmoidoscopy at a time when surveillance of patients with adenomas was not routine practice.

The specific aims were:

1. To measure the relative risk of subsequent rectal and colon cancer compared with the general population following excision of rectosigmoid adenomas, in the absence of endoscopic surveillance.

2. To determine whether the number, size, histology and the grade of dysplasia of rectosigmoid adenomas are predictive of the risk of subsequent rectal or colon cancer.

3. To determine whether patients with rectosigmoid adenomas can be divided into:

   a) a subgroup at low risk of rectal or colon cancer who possibly require no surveillance after adenoma-excision at entry

   b) a subgroup at substantially increased risk who may benefit from regular colonoscopic surveillance to prevent the development of cancer.

It is hoped that these findings will be used to formulate a more rational and cost-effective surveillance policy for patients with adenomas diagnosed at sigmoidoscopy.

3.2 PLAN OF THE STUDY

All patients presenting at St Mark's Hospital between 1957 and 1980 in whom colorectal adenomas were diagnosed were to be considered for inclusion. Patients aged over 85 years or with any concurrent disease associated with increased risk of developing colorectal cancer were to be excluded.

It was to be assumed that all cancers and adenomas detected within the first two years of diagnosis of an index adenoma were present at entry. For this reason, patients with cancer developing within two years of entry or with less than two years of follow-up were to be excluded from the analysis of future cancer risk. Similarly, all adenomas detected within the first two years were to be cumulated to give the total number, the largest size, the most villous histology and the most severe grade of dysplasia present at entry. For consistency, the histopathology of all polyps were to be re-examined by a single observer (Dr B. C. Morson) at the start of the study in January 1985.

Patients were to be categorised according to the type of examinations they had within two years of entry as follows: proctosigmoidoscopy only, proctosigmoidoscopy plus barium enema, and colonoscopy. Patients undergoing colonoscopy or colotomy excision of adenomas from the colon were to be excluded from the main analysis, but the adenomas detected at colonoscopy were to be recorded for a subsidiary analysis.

Although there was no surveillance policy for adenomas, a proportion of patients continued to attend the hospital and underwent subsequent clinical examinations. All such examinations and adenomas thereby detected and removed were to be recorded. Patients subsequently undergoing colonoscopy examinations were to be censored at that point, but any cancers detected at the first colonoscopy examination were to be included as endpoints. The clinical status at the end of the study, where not available from the hospital records, was to be obtained from the National Health Services Central Register at the Office of Populations, Censuses and Surveys.

Patients were to be considered at risk of developing cancer from two years after entry until their 86th birthday, death, a colonoscopy examination or the end of the study in May 1988, whichever occurred first. The observed number of cases of cancer in the study subjects were to be compared with the

expected number calculated from age, sex and calendar year-specific incidence rates for the general population.

Risks for rectal and colon cancer were to be analysed separately because the natural course of the development of rectal cancer is interrupted by the excision of rectosigmoid adenomas, while that of cancer of the colon is largely unaffected. Relative risks were to be analysed separately for men and women, by age and according to the number (single, two or more adenomas), size (< 1cm, 1-2 cm, >2cm), histology (tubular, tubulovillous, villous) and grade of dysplasia (mild, moderate, severe). The independent effects of each of the adenoma characteristics were to be examined in a Cox's proportional hazards model. In this way, two risk groups were to be identified: a 'High-Risk' and a 'Low-Risk' group for rectal and for colon cancer separately.

It was proposed to confirm the validity of the risk-groups so defined by examining, in subsidiary analyses, the risk of synchronous adenomas in patients undergoing colonoscopy at entry (and excluded from the main analysis) and of metachronous adenomas in patients having colonoscopy during follow-up at two or more years after entry (and censored from the main analysis).

CHAPTER FOUR

METHODS

4.1 PATIENTS

Every patient presenting at St Mark's Hospital during the period 1957 to 1980 in whom colorectal adenomas were diagnosed was considered for entry. The year of the appointment of Dr B.C. Morson as Consultant Pathologist was chosen as the starting date for recruitment since he initiated a policy requiring biopsy of all colorectal polyps and set up a system for recording the histopathology. Recruitment was stopped in 1980 when the 'Neoplastic Polyp Follow-up' study (Williams & Macrae, 1986) began and colonoscopic surveillance of all patients with colorectal adenomas became routine practice at the hospital.

The pathology records included the full name, sex and date of birth, hospital record number and a pathology number unique to each patient. Slides of specimens from each patient were stored in pathology number order, so that all specimens from a patient were retained in a single location. Where the specimen was a polyp, the site from which it was removed and its size (maximum diameter) after fixation were also recorded.

Dr Morson's assistant, Dr H.J.R. Bussey, also maintained a separate card record system. This included every patient found to have one or more colorectal polyps and allowed for the identification of all the patents in the cohort under study. In addition to information from the pathology records, the patient record cards included the procedure which identified the polyp: rigid sigmoidoscopy, barium enema, colonoscopy, flexible sigmoidoscopy, or at operation, including the reason for the operation and findings. Whenever a patient attended St Mark's Hospital, the relevant patient card was updated.

The hospital records for each patient were examined in order to verify the information recorded on the record cards and to supplement missing data. Patients found to have had an adenocarcinoma at or before the time of presentation were excluded from further analysis. Patients with either anal cancer or cancer at another site at presentation, or with any concurrent

disease associated with increased risk of large bowel cancer such as familial adenomatous polyposis or inflammatory bowel disease were also excluded as were patients aged over 85 years.

4.2 DESCRIPTION AND HISTOPATHOLOGICAL GRADING OF ADENOMAS

The number and location of the excised adenomas were ascertained from the patients' hospital notes. The size was taken from the patients' notes as estimated clinically and confirmed by measuring the maximum diameter of the fixed specimen, which is generally slightly smaller than the fresh specimen because of the method of embedding the tumour (Konishi & Morson, 1982). Where the polyp was fulgurated and only a biopsy was available, the size was taken from the notes as estimated clinically. For the purpose of this study, size was classified as less than 1 cm, 1-2 cm or greater than 2 cm.

Adenomas were classified by their histological structure into three groups: tubular, tubulovillous and villous, according to WHO criteria. The dysplasia of the adenomas was graded as mild, moderate or severe (Section 2.1). In order that there should be uniform grading, specimen slides from every polyp removed from patients in this study were examined by a single observer (Dr B.C.Morson). In many instances this involved recutting a section from the original paraffin block. As a result of the re-examination of the pathology, a few polyps initially classified as adenomas were reclassified as metaplastic polyps. In cases where there were only metaplastic polyps and no other adenomas, the patients were excluded from the study. The histopathological grading was undertaken blind, that is without knowledge of the ultimate clinical status of the patients.

4.3 COVARIATES AT ENTRY

The number, size, histology and grade of dysplasia of the adenomas detected were the covariates to be examined for their effect on the future risk of rectal and colon cancer. Patients with more than one adenoma at entry were categorised according to the largest size, the most villous histology and the most severe grade of dysplasia recorded.

4.3.1 Influence of the Type of Examination at Entry.

The accuracy of detection of adenomas is dependent upon the extent of the bowel examination. Those patients examined solely by rigid sigmoidoscopy had adenomas removed from the rectosigmoid only, while the status of the proximal part of the colon was not known. Among those who additionally had barium enema examination, the majority had adenomas excised from the rectosigmoid only via the sigmoidoscope, particularly before the introduction of colonoscopy to the hospital. In the few patients who had colotomy excision of adenomas, the covariates relating to the future risk of cancer were based not only on rectal, but also on colonic adenomas. In patients who had colonoscopy, adenomas were removed both from the rectum and the colon.

The postulated relationship between the number of adenomas removed at entry and subsequent colorectal cancer is therefore confounded or distorted (Susser, 1973) by the type of examination given. On the one hand, the number of adenomas found at entry and therefore the risk-factor score, is increased with the extent of examination, but since all adenomas detected were generally removed, more extensive examination of the bowel was expected to have been associated with decreased future risk of cancer. For this reason, patients were classified into three groups based on the type of examination they had at entry, as follows:

Group 1: Proctosigmoidoscopy only
Group 2: Proctosigmoidoscopy plus barium enema
  (i) polyp excision via the rigid sigmoidoscope only
  (ii) polyp excision via colotomy
Group 3: Colonoscopy.

Patients could be divided into those from whom adenomas were removed from the rectosigmoid only [Groups 1 and 2(i)] and those from whom adenomas were also removed from the colon [Groups 2(ii) and 3].

An assumption implicit in this study is that removal of adenomas reduces the risk of cancer at that site. In patients in whom adenomas were removed by sigmoidoscopy, it is possible that the risk of rectal cancer could be less than

that of age and sex-matched members of the general population, a proportion of whom will have undetected adenomas in the rectum. Alternatively, if the risk of cancer from recurrent adenomas is important for this group, the risk of rectal cancer may be higher than that of the general population.

Adenomas from only the distal part of the sigmoid colon may be removed by proctosigmoidoscopy. As a result, it is unlikely that risk of colon cancer would be much lower than that of the general population, but it may be higher if adenomas in the rectum are index lesions pointing to increased risk of other lesions in the unexamined colon.

However, the risk of subsequent cancer of the colon may be lower than the general population in patients undergoing colonoscopy or colotomy excision in whom adenomas were excised from the colon [Groups 2(ii) and 3]. Risk in these patients would need to be analysed separately. Since these patients constituted only a small proportion of the total, it was decided to exclude from the main analysis for cancer risk all patients from whom adenomas were removed from the colon beyond the reach of the sigmoidoscope either by colonoscopy or colotomy. Records of excluded patients having colonoscopy examinations at entry were however analysed for a subsidiary study of the probablity of having synchronous adenomas in the proximal colon (Section 5.6.5).

The remainding patients were a relatively homogeneous group which had adenomas removed from the rectosigmoid only.

4.3.2 The Two-year Rule

Not all adenomas were excised at the first visit to the hospital, although most adenomas were removed within a year after presentation in the vast majority of patients having proctosigmoidoscopy only. For patients having barium enema examinations in whom there were colonic polyps, there was often a time-lag before all adenomas detected were removed. In the pre-colonoscopy era, a delay was likely to have arisen because of the seriousness of the nature of the decision to perform a laparotomy. Unless the barium enema findings were unequivocal and the adenoma looked highly suspicious, another barium enema was often performed. After the introduction of

colonoscopy, patients would usually be put on a waiting list unless the case was urgent. It was decided, therefore, that all adenomas found within the first two years after presentation should be considered to have been present at entry (synchronous) and the cumulated number, size, histology and grade of dysplasia used as covariates for estimating future risk. This was an important decision since all adenomas found after two years were treated as metachronous (Section 2.1).

The two-year rule was also used for segregating patients into examination groups. Thus, patients having a colonoscopy within two years of entry were classified as colonoscopy patients (Group 3) and were excluded from the main analysis, those with a barium enema but no colonoscopy within two years as barium enema patients (Group 2) and if a colotomy was performed the patient was excluded, and those with no colonoscopy or barium enema within two years as the proctosigmoidoscopy group (Group 1).

If cancer was detected within two years of entry, it was assumed that the cancer was present at entry and the patient was excluded from the study. Patients were considered to be at risk from two years after entry and those with less than of two years follow-up were excluded.

4.3.3 Incidence of Rectosigmoid Adenomas

The incidence of rectosigmoid adenomas in St Mark's Hospital outpatients was calculated for selected years during the period of recruitment up to 1973 when colonoscopy was introduced at the hospital. Prior to this time adenomas were only rarely removed from the colon proximal to the distal sigmoid. The total number of outpatients for each year was obtained from the Hospital registration books located in the Archives Department at St Bartholomew's Hospital.

4.4 FOLLOW-UP

The majority of patients were discharged after investigation and treatment of the condition for which they were referred. Therefore the clinical status of the patients, except where known, was requested from the National Health Service Central Register (NHSCR) for England and Wales which, wherever possible, provided details of all deaths (date and causes) and cancer registrations (date of diagnosis and site or type).

All National Health Service patients have an identification number. At the NHSCR, each registry entry is denoted with a symbol indicating the local Family Practitioner Committee (FPC) for the area in which the patient is currently on an NHS doctor's list, or the reason (death, embarkation) for removal from that FPC's list. Since 1971 arrangements have been made for cancer registrations reported by all regional registries to be added to the relevant patient NHS registry entry. Thus, it is now possible to be informed of post-1971 cancer registrations in addition to deaths.

All follow-up information on a patient relates to his NHSCR entry. In a substantial proportion of cases the NHS number was not in a patient's hospital notes. In these cases staff at the NHSCR had to attempt to find a number using their alphabetic indexes. There are two lists, one for persons born before 29 September 1939, and another for everyone born subsequently. All persons born in the UK after 29 September 1939 were automatically given an NHS number at birth, but patients born before that time, or who were born outside the UK, only had an NHS number if they registered with a general practitioner. Where the NHS number could not be traced, the patient's status could not be ascertained and they were censored at the time they were last seen.

Whenever notification of a registration or death certificate for colorectal cancer was received in which the site was stated as "colon, site not specified", further information was requested from the hospital where the diagnosis was made in an attempt to obtain a more precise diagnosis. It was not possible to obtain such information for patients dying at home for whom the death certificate was the first indication of the cancer.

4.4.1 Examinations during Follow-up

Colonoscopy: From 1980, patients found to have adenomas were sent routinely for a colonoscopy. This policy also applied to patients returning to the hospital with new or recurrent symptoms who had had adenomas removed in the past. At this time, the 'Neoplastic Polyp Follow-up Study' (Williams & Macrae, 1986) was started, and patients who had had adenomas removed in the past were invited to have a colonoscopy and to participate in the study.

The aim of colonoscopy is to produce a completely clean colon and rectum with no visible adenomas remaining. Thereafter, the intervals between examinations are designed to reduce the risk of cancer to almost zero. Adenomas were removed initially from the rectosigmoid only and the status of the rest of the colon was unknown. Subsequent examination and removal of adenomas from the colon should have a profound effect on the future risk of colon cancer. Therefore, it seemed reasonable to censor all patients having colonoscopy, although any cancers diagnosed were included as endpoints in the analysis.

Proctosigmoidoscopy and/or Barium enema: The aim of this study was to estimate the future risk of cancer in the absence of colonoscopic surveillance. Patients in this study were given no special surveillance for their adenomas and the majority were discharged after the initial complaint which led to their referral to St Mark's Hospital had been resolved. However, a significant proportion of patients had one or more routine proctosigmoidoscopies two or more years after entry and, in a small proportion, barium enema as well. These patients were not censored from the study. In some of these patients, polyps were found and removed and it could be argued that this consitituted a form of surveillance. Therefore, all routine examinations undertaken during follow-up and all adenomas thereby detected were ascertained by examination of the patients' hospital notes, and the effects of these examinations on the subsequent risk of cancer estimated.

4.5 ANALYSIS OF THE DATA

The following analyses were performed:

1. Examination of the distribution of the covariates (number, size, histology and grade of dysplasia of rectosigmoid adenomas) in men and women and according the age at entry and of the inter-relationships between the covariates.

2. It has been argued that St Mark's Hospital, being a tertiary care institution, attracts patients who differ in many ways from the general population and that comparisons with community rates are not valid. In order to examine this assertion, the all-cause mortality of the patients in this cohort was compared to that of the population of the North-East Thames region, using age, sex and calendar-specific rates for the period under study (1957-1988).

3. Estimation of the cumulative risk of developing rectal and colon cancer within 5, 10, and 20 years after entry in men and women.

4. Estimation of the standardized incidence ratios (SIRs) for rectal and colon cancer separately in men and women. Univariate comparisons of SIRs according to age at entry (< 50, 50-59, 60-69, ≥70 years) and the number (single vs multiple), size (< 1cm, 1-2 cm, > 2 cm) histology (tubular, tubulovillous, villous) and grade of dysplasia (mild, moderate, severe) of rectosigmoid adenomas at entry.

5. Analysis of the independent effects of risk factors in a Cox's proportional hazards model in order to identify subgroups of patients at high-risk and low-risk of rectal cancer ('High-Risk$_{rectal}$') and ('Low-Risk$_{rectal}$') and of colon cancer ('High-Risk$_{colon}$' and 'Low-Risk$_{colon}$').

6. Division of patients into a group at 'Low-Risk' of developing either rectal or colon cancer for whom minimum surveillance may be recommended and a 'High-Risk' group for whom regular surveillance may be warranted.

4.5.1 Subsidiary Analyses

1. Examination of the prevalence of synchronous colonic adenomas in patients having colonoscopy at entry and excluded from the main analysis for cancer risk. Patients who were found to have rectosigmoid adenomas were divided into those with only small (<1cm) tubular adenomas ('Low-Risk$_{colon}$') and those with either large (≥1cm), tubulovillous or villous adenomas ('High-Risk$_{colon}$'). The prevalence and characteristics of the colonic adenomas detected synchronously at entry in the 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' groups were compared.

2. Patients undergoing colonoscopy two or more years after entry were censored from the main analysis at the time of the first follow-up colonoscopy but the adenomas detected at the first follow-up colonoscopy were used as endpoints in a study of the prevalence and characteristics of metachronous adenomas in 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' groups.

3. Estimation of the effect of subsequent clinical examination and excision of adenomas 2 or more years after entry on the future risk of colorectal cancer. Two methods for assessing the hypothetical number of cancers prevented by subsequent examinations were used.

   (i) In the first method, the SIRs for patients who were not re-examined were compared with the SIRs for those who were. The adjusted expected number of cancers in the examined group (in the absence of follow-up) was then calculated.

   (ii) Only patients who had adenomas excised had the natural course of the development of colorectal cancer interfered with. Therefore, the second approach considered was to calculate the hypothetical number of extra cancers which might have occurred if those adenomas had been left in-situ instead of being removed.

   Very little is known about the growth-rate and malignant transformation of adenomas smaller than 1 cm. The few small studies that exist (Figiel et al., 1963; Welin et al., 1963) indicate that the growth is very slow and some remain dormant for long periods. Adenomas larger than 1 cm pose a greater threat since 25% contain a focus of

malignancy (Muto et al., 1975) and a proportion are actually growing. Growth was observed in 37% of a large series of adenomas left in-situ in the pre-colonoscopy era and monitored radiologically for up to 20 years (Stryker et al., 1987). More importantly, the cumulative risk of cancer at the polyp site was 2.5% at 5 years, 8% at 10 years and 24% at 20 years.

Stryker's findings were used to estimate the number of cancers which may have been prevented by excision of the adenomas during follow-up. Stryker provided information only on adenomas larger than 1 cm. In an attempt to avoid underestimating the possible number of cancers prevented by excision of adenomas particularly in the 'Low-Risk' group for which a minimum follow-up policy might be appropriate, all adenomas were considered to be at risk (not just those 1 cm or larger). Tubulovillous, villous or severely dysplastic adenomas smaller than 1 cm were considered to have the same risk as adenomas of 1 cm or larger and designated 'At Risk' adenomas. It was assumed that mildly or moderately dysplastic tubular adenomas smaller than 1 cm take 5 years to grow to 1 cm, therefore the risks associated with the 'At-Risk' adenomas were applied to the small, tubular, mildly or moderately dysplastic adenomas with a time-lag of 5 years.

The risk associated with an 'At Risk' adenoma was assumed to begin at the time of its excision and to increase with time for the remainder of the patient's life or to the end of the study. For the first 5 years, 0.005 of a cancer was added for each year at risk, for the next 5 years, 0.011 of a cancer and for the next 10 years 0.016 of a cancer added for each year at risk. The same method was used for the remaining adenomas, but no risk was accrued for the first 5 years after adenoma-excision.

4.6 STATISTICAL METHODS

In all statistical tests, a p value of less than 0.05 was taken as significant.

4.6.1 Comparisons of Means

To test for the equality of means, a t-test was performed in MINITAB where the pooled variance estimator was used. A check on the assumption of equal variances was made using the appropriate F statistic. Where the number of means to be compared was greater than 2, a one-way analysis of variance was carried out, again using MINITAB.

4.6.2 Comparisons of Proportions

For tables (r rows and c columns) the standard chi-squared test for heterogeneity was carried out

$$X^2=\Sigma_{j=1}^{c}\ \Sigma_{i=1}^{r}\ (O_{ij}-E_{ij})^2/E_{ij}$$

where i indexes rows and j indexes columns, and O_{ij} and E_{ij} are the observed and expected frequencies. X^2 is distributed approximately as $\chi^2_{(r-1)(c-1)}$.

To test a hypothesis of trend in a 2 x k table (k > 2), Armitage's (1955) trend test was used which has an approximate χ^2_1 distribution.

With r x c tables (r > 2 and c > 2) where it was of interest to see if there was a positive association down the rows and across the columns, a log-linear model was used following the example of McCullagh and Nelder (1983, p104). Under the null hypothesis of no trend there is the model with Poisson errors:

$$H_0: \log n_{ij} = \alpha_i + \beta_j$$

where n_{ij} is the expected number in the cell (i,j). If there is a positive association, then γ is expected to be significantly greater than zero where

$$H_1: \log n_{ij} = \alpha_i + \beta_j + ij\gamma.$$

The likelihood ratio statistic for $\gamma=0$ vs $\gamma\neq0$ is then distributed approximately as χ^2_1. Below this is also referred to as a trend test.

4.6.3 Standardized Incidence Ratios

The program MAN-YEARS (Coleman et al., 1986) was used to compare the observed number of cases of colon and rectal cancer in the cohort with the expected number from the South Thames Region, London. Sex and age-specific rates (5-yearly age intervals) for the 4 calendar periods: 1963-1966, 1967-1971, 1973-1977, 1978-1982, were obtained from 'Cancer Incidence in Five Continents (Waterhouse et al., 1976; 1982; Muir et al.,1987) (Tables 2, 3).

The method used was described in Breslow & Day (1987). Basically, it involved calculating separately for each sex, the amount of observation time in each age and calendar-period category for each individual in the cohort, and adding these contributions for all the cohort members to obtain the total number of person-years of observation in each category. The expected number of cases for that category was calculated by multiplying the total number of person-years at risk by the standard rate for that category. The person-years at risk and the expected numbers of cases for each of the age-calendar period categories were computed and summed for all of the cohort members to give the total expected numbers of cases adjusted for age, sex and calendar period. The ratio of the observed number of deaths in the cohort to the expected number is the standardized incidence ratio (SIR), the weighted sum of the sex, age and calendar period-specific ratios.

The MAN-YEARS program allowed for separate estimates of expected numbers by sex for successive risk intervals after entry, for each calendar period and each age-group. Patients were censored on their 86th birthday.

Table 2. Sex, Age, Calendar Year-Specific Incidence Rates of Rectal Cancer in the South Thames Region, London (per Million Population)

Age	1963-66	1967-71	1973-77	1978-82
Men				
20-	3	1	1	3
25-	7	3	3	0
30-	11	5	16	9
35-	17	25	35	23
40-	62	39	36	40
45-	68	95	85	80
50-	153	168	163	151
55-	302	256	316	283
60-	469	400	461	447
65-	688	622	747	704
70-	1106	910	988	972
75-	1552	1278	1372	1295
80-	1873	1580	1638	1584
Women				
20-	1	1	0	1
25-	4	3	1	5
30-	9	10	12	8
35-	26	17	16	14
40-	41	35	39	32
45-	73	83	81	97
50-	142	114	140	136
55-	235	202	201	221
60-	318	278	307	285
65-	502	322	471	385
70-	621	537	537	568
75-	818	678	706	689
80-	990	821	989	993

Sources: Waterhouse et al., 1976;1982: Muir et al., 1987

Table 3. Sex, Age, Calendar Year-Specific Incidence Rates of Colon Cancer in the South Thames Region, London (per Million Population)

Age	1963-66	1967-71	1973-77	1978-82
Men				
20-	5	5	7	3
25-	10	9	8	3
30-	26	20	24	16
35-	59	39	51	40
40-	86	98	79	56
45-	135	137	141	142
50-	221	222	250	245
55-	326	354	385	387
60-	506	512	528	516
65-	748	638	844	741
70-	1110	968	1116	1057
75-	1428	1437	1462	1501
80-	1870	1746	2108	1977
Women				
20-	5	3	7	9
25-	9	10	8	6
30-	21	28	28	17
35-	36	44	44	38
40-	69	82	95	63
45-	117	124	156	111
50-	199	181	214	213
55-	291	342	352	373
60-	489	527	504	504
65-	778	711	808	867
70-	1307	1008	1218	1278
75-	1721	1530	1773	1775
80-	2129	1897	2218	2183

Sources: Waterhouse et al., 1976;1982: Muir et al., 1987

A FORTRAN program was written to censor cases lost to follow-up and those undergoing colonoscopy examinations prior to performing the MAN-YEARS program. The significance of the observed SIR was computed by the MAN-YEARS program by assuming that the observed number of cases (D) is approximately Poisson-distributed with a mean and variance equal to the expected number (E).

Exact confidence limits for the observed SIRs were obtained by finding the lower limits (μ_L) and the upper limits (μ_U) for the mean of the Poisson-distributed observation O from Pearson and Hartley (1966) and than calculating $SIR_L = \mu_L/E$ and $SIR_U = \mu_U/E$.

4.6.4 Comparisons of Standardized Incidence Ratios

The standard global chi-squared statistic was used to test for heterogeneity between k SIR's.

$$\chi^2_{k-1} = \Sigma_{k=1}^{K} \frac{(O_k - E_k^*)^2}{E_k^*}$$

where E_k^* is the 'adjusted expected value' for each observation O_k (Breslow & Day, 1987, p 96) such that $\Sigma E_k^* = \Sigma O_k$

Armitage's test was used to detect the presence of a trend in SIRs with increasing exposure:

$$\chi^2_1 = \frac{\{\Sigma_{k=1}^{K} x_k (O_k - E_k^*)\}^2}{\Sigma_{k=1}^{K} x_k^2 E_k^* - (\Sigma_{k=1}^{K} x_k E_k^*)^2 / \Sigma O_k}$$

A point estimate for the relative risk (ψ) was taken as the ratio of the SIR at level k and the SIR at the baseline level (k=1).

Exact confidence intervals for the relative risk (ψ) were obtained from tables of confidence intervals for proportions (Beyer, 1968)

4.6.5 Survival Analysis

The product-limit or Kaplan Meier method was employed using the program TRIAL. The differences between the survival curves were tested using Peto and Peto's (1972) logrank test.

The Cox's regression or proportional hazards model (Cox, 1972) was used to identify a subgroup of the characteristics of the excised adenomas making a significant contribution to the risk of subsequent cancer. A forward stepwise regression procedure (BMDP 2L) was used.

CHAPTER FIVE

RESULTS

5.1 PATIENTS AND EXCLUSIONS

The study was based on 2172 patients (1422 men and 750 women) who presented at St Mark's Hospital between 1957 and 1980 with no previous history of adenocarcinoma of the large bowel and who were found to have one or more adenomas in the colon or rectum. Based on a sample of 4 years during the period of recruitment to this study (1960, 1966, 1970, 1973), the incidence of colorectal adenomas in patients presenting in the Out-Patients' department at St Mark's Hospital was approximately 2% (Table 4).

Ten patients who were aged over 85 years were excluded from the study (Table 5). Also excluded were patients with associated adenocarcinoma (10 cases), anal cancer (10 cases), cancer at another site (2 cases), or inflammatory bowel disease (5 cases). After re-examination of the histopathology of the polyps removed at entry, 3 further cases were excluded, either because their polyps had been wrongly classified as adenomas or because the pathology specimen was unavailable.

Patients with less than two years colorectal cancer-free follow-up were also excluded (206 cases); three of these patients developed large bowel cancer within 2 years which was assumed to be present at entry, a further 103 patients died of another cause, and 100 patients could not be followed up, either because they had emigrated (17 patients) or because their NHS number could not be traced (83 patients). A further 308 patients (14.2%) had adenomas removed at entry from the colon beyond the reach of the rigid sigmoidoscope (244 by colonoscopy and 64 by colotomy) and were also excluded from the study. The patients examined by colonoscopy within two years of entry were, however, included in a subsidiary analysis (section 5.6.5).

This study concerns the remaining 1618 patients with adenomas in the rectum and distal sigmoid colon only who were followed for at least 2 years. There were almost twice the number of men as women in this cohort (1061 men and 557 women). Their ages at entry ranged from 21 to 84 years and the

Table 4.Incidence of Adenomas in Men and Women Presenting at St Mark's Hospital in Selected Years Between 1957 and 1980

Year of Admission	Total Patients			No.(%) with Adenomas	
	Men	Women	M:F ratio	Men	Women
1960	2716	1516	1.8	42 (1.5)	21 (1.4)
1966	2256	1056	2.1	53 (2.3)	31 (2.9)
1970	2228	1176	1.9	46 (2.1)	21 (1.8)
1973	2220	1368	1.6	38 (1.7)	21 (1.5)
Total	9420	5116	1.8	179 (1.9)	94 (1.8)

Table 5. Exclusions from the Study.

	Men	Women	Total
Entered into the study	1061	557	1618
Excluded:			
Age over 85 years	6	4	10
Cancer or inflammatory bowel disease	23	4	27
No adenoma or no pathology specimen	3	0	3
Follow-up less than 2 years:			
Developed colorectal cancer	3	0	3
Died of another cause	75	28	103
Emigrated	11	6	17
No trace	52	31	83
Colonoscopy	150	94	244
Colotomy	40	24	64
Total seen at entry	1422	750	2172

men were significantly younger than the women (mean age 56.9 ± 11.0 years for men, 59.7 ± 11.4 years for women; $p < 0.001$) (Table 6).

5.2 ADENOMAS AT ENTRY

Adenomas removed within two years of presentation were considered to be present at entry and were cumulated to give the total number, the largest size, the most villous histology and the most severe grade of dysplasia.

In 96% of patients (1556 cases), adenomas were excised on a single occasion, in 3.65% of patients (59 cases) on 2 occasions and in 3 patients (0.2% of cases) on 3 occasions. Adenomas were excised within a year of entry in 97% of patients.

5.2.1 Adenoma Features by Age and Sex

Number: More than 85% of patients, both male and female, had just a single adenoma in the rectosigmoid at presentation (Table 7). There was a significant increase in the multiplicity of adenomas with age in the men but not in the women (Table 8). However, overall there was no significant difference between the sexes even after adjustment for age ($p=0.06$) (Table 7).

Size: The largest adenoma in more than half of cases was less than 1 cm in diameter and only 11% had an adenoma larger than 2 cm. There was a significant increase with age in the size of the largest adenoma in both men and women, although adenomas in the women were larger than those in the men at all ages (Table 9). Even after adjustment for age, therefore, the adenomas in the women were significantly larger than those in the men ($p=0.002$).

Histology: More than 50% of both men and women had only tubular adenomas (Table 7). There was a significant increase with age in both men and women in the proportion of patients with tubulovillous or villous histology; although at all ages, the proportion of women with at least one tubulovillous or villous adenoma exceeded that of men (Table 10).

Table 6.Sex and Age at Entry of 1618 Patients Entered into the Study.

Age(Years) at Entry	Number(%) of Patients Men	Women	Total
20-29	9 (0.8)	3 (0.5)	12 (0.7)
30-39	62 (5.8)	27 (4.8)	89 (5.5)
40-49	202 (19.0)	85 (15.3)	287 (17.7)
50-59	324 (30.5)	137 (24.6)	461 (28.5)
60-69	326 (30.7)	190 (34.1)	516 (31.9)
70-79	127 (12.0)	99 (17.8)	226 (14.0)
80+	11 (1.0)	16 (2.9)	27 (1.7)
Total	1061(100.0)	557(100.0)	1618 (100.0)

Table 7. Number, Size, Histology and Grade of Dysplasia of Adenomas at Entry in Men and Women.

Adenomas at Entry	Men No.(%)	Women No.(%)	(% age-adjusted*)	Total
Number				
1	907(85.5)	488(87.6)	(87.6)	1395(86.2)
2	119(11.2)	56(10.1)	(10.0)	175(10.8)
3+	35(3.3)	13(2.3)	(2.4)	48(3.0)
Chi-square+:	heterogeneity	(2df) 3.4	p=0.18	ns
	trend	(1df) 3.4	p=0.06	
Size				
<1cm	661(62.3)	288(51.7)	(52.7)	949(58.6)
1-2cm	307(28.9)	190(34.1)	(34.0)	497(30.7)
>2cm	93(8.8)	79(14.2)	(13.3)	172(10.6)
Chi-square+:	heterogeneity	(2df) 14.0	p=0.0009	
	trend	(1df) 14.0	p=0.0002	
Histology				
Tubular	710(66.9)	311(55.8)	(57.9)	1021(63.1)
Tubulovillous	262(24.7)	168(30.2)	(29.2)	430(26.6)
Villous	89(8.4)	78(14.0)	(12.9)	167(10.3)
Chi-square+:	heterogeneity	(2df) 15.8	p=0.0001	
	trend	(1df) 15.7	p=0.0004	
Dysplasia				
Mild	662(62.4)	301(54.0)	(55.0)	963(59.5)
Moderate	309(29.1)	196(35.2)	(34.4)	505(31.2)
Severe	90(8.5)	60(10.8)	(10.6)	150(9.3)
Chi-square+:	heterogeneity	(2df) 6.5	p=0.39	ns
	trend	(1df) 5.7	p=0.17	ns
Total	1061(100.0)	557(100.0)		1618(100.0)

* adjusted to the age of the men
\+ after age adjustment

Table 8. Multiplicity of Adenomas at Entry According to Age and Sex

Age (years)	Total Patients	Number (%) Patients Number of Adenomas 1	2	3
Men				
<50	273	250 (91.6)	20 (7.3)	3 (1.1)
50-59	324	275 (84.9)	37 (11.4)	12 (3.7)
60-69	326	273 (83.7)	40 (12.3)	13 (4.0)
70+	138	109 (79.0)	22 (15.9)	7 (5.1)
Women				
<50	115	103 (89.6)	10 (8.7)	2 (1.7)
50-59	137	126 (92.0)	7 (5.1)	4 (2.9)
61-69	190	168 (88.4)	17 (8.9)	5 (2.6)
70+	115	91 (79.1)	22 (19.1)	2 (1.7)

Chi-square:
Heterogeneity (6df) men: 17.1, p=0.047; women: 25.8;p=0.02
Trend (1df): men: 9.6, p=0.002; women: 2.7,p=0.10

Table 9. Size of Adenomas at Entry According to Age and Sex

Age (years)	Total Patients	No.(%) Patients Size of Adenomas <1 cm	1-2 cm	>2 cm
Men				
<50	273	199 (72.9)	61 (22.3)	13 (4.8)
50-59	324	206 (63.6)	90 (27.8)	28 (8.6)
60-69	326	196 (60.1)	98 (30.1)	32 (9.8)
70+	138	60 (43.5)	58 (42.0)	20 (14.5)
Women				
<50	115	64 (55.7)	39 (33.9)	12 (10.4)
50-59	137	68 (49.6)	54 (39.4)	15 (11.0)
61-69	190	108 (56.8)	55 (29.0)	27 (14.2)
70+	115	48 (41.7)	42 (36.5)	25 (21.7)

Chi-square tests:
Heterogeneity (6df): men: 31.3,p<0.0001; women: 12.1,p=0.06
Trend (1df): men: 27.7,p<0.0001; women: 5.8,p=0.02

Table 10. Histology of Adenomas at Entry According to Age and Sex

Age (years)	Total Patients	No(%) Patients Histology of Adenomas Tubular	Tubulovillous	Villous
Men				
<50	273	199 (72.9)	65 (23.8)	9 (3.3)
50-59	324	226 (69.8)	73 (22.5)	25 (7.7)
60-69	326	208 (63.8)	87 (26.7)	31 (9.5)
70+	138	77 (55.8)	37 (26.8)	24 (17.4)
Women				
<50	115	73 (63.5)	29 (25.2)	13 (11.3)
50-59	137	79 (57.7)	41 (29.9)	17 (12.4)
61-69	190	113 (59.5)	56 (29.5)	21 (11.1)
70+	115	46 (40.0)	42 (36.5)	27 (23.5)

Chi-square tests:
Heterogeneity (6df): men: 37.3,p<0.0001; women: 24.0,p<0.0001
Trend (1df): men: 22.9,p<0.0001; women: 13.8,p=0.0002

Again, even after adjustment for age, adenomas in the women were significantly more villous than in the men (p=0.001) (Table 7).

Grade of Dysplasia: Most adenomas in both men and women were only mildly dysplastic (59%). The increase in severity of dysplasia with age was more pronounced in the men than in the women (Table 11). This was primarily because at younger ages women had a higher proportion of adenomas with moderate or severe dysplasia. After adjustment for age, significantly more women than men had moderately or severely dysplastic adenomas (p=0.02) (Table 7).

Conclusion: Adenomas in the women were more likely to be either large, villous or moderately or severely dysplastic. Almost half of the men had only a mildly or moderately tubular adenoma compared with a third of the women (Table 12), while 10% more women than men (28% versus 18%) had at least one adenoma which was either larger than 2 cm, villous or severely dysplastic.

5.2.2 Inter-relationships Between Size, Histology and Grade of Dysplasia

There was a highly significant relationship between the size and histology (p<0.0001) and between the size and grade of dysplasia (p<0.0001) of the excised adenomas (Table 13); 47% of adenomas larger than 2 cm had a villous histology and 26% were severely dysplastic compared with only 1.5% and 2% respectively of adenomas smaller than 1 cm.

Villous adenomas tended to be larger than tubulovillous, but their similarity in other respects was emphasised by the finding that similar proportions of adenomas with each type had moderate or severe dysplasia; 40% of tubulovillous adenomas were moderately dysplastic compared with 46% of villous adenomas. The corresponding proportions for severe dysplasia were 16.0% and 16.2% respectively (Table 14).

Histology, although an important determinant of severity of dysplasia, did not have an effect independent of size. Within each histological type, there

Table 11. Grade of Dysplasia of Adenomas at Entry According to Age and Sex

Age (years)	Total Patients	No.(%) Patients Grade of Dysplasia Mild	Moderate	Severe
Men				
<50	273	194 (71.1)	65 (23.8)	14 (5.1)
50-59	324	213 (65.7)	83 (25.6)	28 (8.6)
60-69	326	192 (58.9)	104 (31.9)	30 (9.2)
70+	138	63 (45.7)	57 (41.3)	18 (13.0)
Women				
<50	115	75 (65.2)	30 (26.1)	10 (8.7)
50-59	137	70 (51.1)	51 (37.2)	16 (11.7)
61-69	190	102 (53.7)	67 (35.3)	21 (11.0)
70+	115	54 (47.0)	48 (41.7)	13 (11.3)

Chi-square tests:
Heterogeneity (6df): men: 27.8,p<0.0001; women: 7.8,p=0.09
Trend (1df): men: 24.6,p<0.0001; women: 4.4,p=0.36

Table 12. Grade of Dysplasia According to Histology of Adenomas at Entry in Men and Women

Histology	Number (%) Patients Grade of Dysplasia Mild	Moderate	Severe	Total Patients
Men				
Tubular	517(48.7)	159(15.0)	34(3.2)	710(66.9)
Tubulovillous	113(10.7)	107(10.1)	42(4.0)	262(24.7)
Villous	32(3.0)	43(4.0)	14(1.3)	89(8.4)
Total	662(62.4)	309(29.1)	90(8.5)	1061(100.0)
Women				
Tubular	192(34.5)	99(17.8)	20(3.6)	311(55.8)
Tubulovillous	78(14.0)	63(11.3)	27(4.9)	168(30.2)
Villous	31(5.6)	34(6.1)	13(2.3)	78(14.0)
Total	301(54.1)	196(35.2)	60(10.8)	557(100.0)

Chi-square:
Heterogeneity(4df): men:107.1, p<0.0001; women: 23.3, p<0.0001
Trend (1df): men: 96.9, p<0.0001; women: 28.6, p<0.0001

Table 13. Histology and Grade of Dysplasia of Adenomas at Entry According to Size

Size	Total Patients	No.(%) Patients Histology* TVA	VA	Grade of Dysplasia Moderate	Severe
<1cm	949	158(16.6)	15(1.6)	210(22.1)	22(2.3)
1-2cm	497	195(39.2)	72(14.5)	213(43.3)	84(16.9)
>2cm	172	77(44.8)	80(46.5)	80(46.5)	44(25.6)

*TVA=Tubulovillous, VA=Villous

Chi-square		
Heterogeneity(4df):	538.7,p<0.0001	293.4,p<0.0001
Trend (1df):	490.0,p<0.0001	269.7,p<0.0001

Table 14. Grade of Dysplasia of Adenomas at Entry According to Histology

Histology	Total Patients	No.(%) Patients Grade of Dysplasia Mild	Moderate	Severe
Tubular	1021	709(69.4)	258(25.3)	54(5.3)
Tubulovillous	430	191(44.4)	170(39.5)	69(16.0)
Villous	167	42(25.1)	77(46.1)	27(16.2)

Chi-square
Heterogeneity(4df): 128.0,p<0.0001
Trend (1df): 134.2,p<0.0001

was an increase in the proportion of severely dysplastic adenomas with increasing size (Table 15). Whereas for a given size, there was no consistent increase with increasing villousness in the proportion with severe dysplasia. Notwithstanding this finding, the main differences in the probability of having severe dysplasia were between adenomas less than or greater than 1 cm (19% vs 2% respectively) or between tubular and tubulovillous or villous adenomas (16% vs 5% respectively).

5.2.3 Relationships with Multiplicity

There was a significant association ($p<0.0001$) between the multiplicity of rectosigmoid adenomas and the severity of dysplasia. Severe dysplasia was seen in 8% of patients with a single adenoma, 15% of patients with two adenomas and 21% of patients with 3 or more adenomas in the rectum or distal sigmoid (Table 16).

There was also an association between the multiplicity of adenomas and the largest size ($p<0.0001$) and the most villous histology ($p<0.0001$). In the majority of patients from whom a single adenoma was excised, the size of that adenoma was less than 1 cm (Table 16). Conversely, most patients with two or more adenomas had at least one which was larger than 1 cm. In patients with a single adenoma, that adenoma was tubulovillous or villous in 35% (Table 17). This proportion increased with increasing numbers of adenomas, rising to 80% in patients with 5 or more adenomas in the rectum or distal sigmoid. An association of histological type with multiplicity was also observed in the 244 patients who had a colonoscopy examination within two years of entry and were excluded from the main analysis (Table 17). However, the observed association between increasing numbers of adenomas and increasing risk of villous histology is consistent with an approximately constant risk per adenoma. If the risks per adenoma are independent, and the probability of having tubulovillous or villous histology is approximately 35% for a single adenoma, then according to the probability theory (Armitage & Berry, 1987), the risk of having at least one tubulovillous or villous adenoma in the presence of 2 adenomas would be 57.75% and for 3 adenomas 72%. The observed risks were slightly lower than these values (Tables 16 & 17).

Table 15.Number (%) of Patients with Severely Dysplastic Adenomas at Entry According to Histology and Size

Histology	<1 cm Total	<1 cm No.(%)	1-2 cm Total	1-2 cm No.(%)	2 cm Total	2 cm No.(%)	Total Total	Total No.(%)
Tubular	776	16(2.1)	230	34(14.8)	15	4(26.7)	1021	54(5.3)
Tubulovillous	158	6(3.8)	195	39(20.0)	77	24(31.2)	430	69(16.0)
Villous	15	0(0.0)	72	11(15.3)	80	16(20.0)	167	27(16.2)
Total	949	22(2.3)	497	84(16.9)	172	44(25.6)	1618	150(10.8)

Table 16. Size, Histology and Grade of Dysplasia According to the Number of Adenomas at Entry

Number of Adenomas	Total Patients	Size >1cm	Histology+ TVA/VA	Grade of Dysplasia Moderate	Severe
1	1395	535(38.4)	483(34.6)	409(29.3)	113(8.1)
2	175	102(58.3)	87(49.7)	73(41.7)	26(14.9)
3-4	43	28(65.1)	23(53.5)	22(51.2)	9(20.9)
5-9	5	4(80.0)	4(80.0)	1(20.0)	2(40.0)

+TVA=Tubulovillous, VA=Villous

Chi-square			
Heterogeneity(3df):	38.96,p<0.0001	24.5,p<0.0001	*50.2,p<0.0001
Trend (1df):	37.33,p<0.0001	23.2,p<0.0001	40.9,p<0.0001

*6df

Table 17. Multiplicity and Histology of Adenomas in 244 Patients Having Colonoscopy at Entry*

Number of Adenomas	Total patients	No.(%) Patients Tubulovillous adenomas	Villous adenomas
1	135	30 (22.2)	8 (5.9)
2	58	21 (36.2)	3 (5.2)
3-4	38	12 (31.6)	5 (13.2)
5-9	13	8 (61.5)	3 (23.1)
Total	244	71 (29.1)	19 (7.8)

* these patients were excluded from the main analysis for cancer risk

Chi-square
Heterogeneity (3df): 18.7, p=0.0003
Trend (1df): 15.5, p=0.0014

5.2.4 Summary

Eighty-five percent of both men and women had just a single rectosigmoid adenoma. The size, villousness and grade of dysplasia increased with age in both men and women. However, even after adjustment for the older age of the women, adenomas in the women were significantly larger, more villous and more dysplastic. Significant correlations were observed between all of the adenoma features under study (number, size, histology and grade of dysplasia).

5.3 FOLLOW-UP

The 1618 patients had a total 23,015 person-years of (passive) follow-up, a mean of 14.2 ± 6.9 years per patient (including the first two years after entry). 1494 were followed for at least 5 years, 1114 for at least 10 years, 742 for at least 15 years and 400 for at least 20 years (Table 18). The follow-up times for the men and women were similar (mean 14.1 ± 7.2 years and 14.3 ± 6.9 years respectively, p=0.62).

An adenocarcinoma of the large bowel developed in 50 patients (3.1%); there were 14 rectal cancers (0.9%) and 36 colon cancers (2.2%). Fifty-eight percent of patients were censored due to: death from another cause (43.4%), colonoscopy examination during follow-up (12%), and loss to follow-up (3%). Almost 40% of the patients were alive and free of colorectal cancer on their 86th birthday or at the end of the study, May 1988 (Table 19).

5.3.1 All-Cause Mortality Compared with the General Population.

Excluding the first two years after entry, there were 517 deaths among the men compared with an expected 495 over the 23-year period of follow-up; among the women there were 225 deaths compared with an expected 197 (Table 20). Thus the standardized mortality ratios were not significantly different from 1.00 in either sex (p=0.102, p=0.31, respectively for men and women).

Table 18. Length of follow-up after entry

Follow-up	No.(%) of Patients		
	Men	Women	Total
At least 5 years	974 (91.8)	520 (93.4)	1494 (92.3)
At least 10 years	720 (67.9)	394 (70.7)	1114 (68.9)
At least 15 years	482 (45.4)	260 (46.7)	742 (45.9)
At least 20 years	268 (25.3)	137 (24.6)	405 (25.0)
At least 25 years	101 (9.5)	40 (7.2)	141 (8.7)
At least 30 years	16 (1.5)	9 (1.6)	25 (1.5)

Table 19. Outcome

	No.(%) of Patients		
	Men	Women	Total
Developed rectal cancer	3 (0.3)	11 (2.0)	14 (0.9)
colon cancer	20 (1.9)	16 (2.9)	36 (2.2)
Died of another cause	496 (46.7)	207 (37.2)	703 (43.4)
Lost to follow-up	14 (1.3)	21 (3.8)	35 (2.1)
Emigrated	11 (1.0)	4 (0.7)	15 (0.9)
Colonoscopy examination	122 (11.5)	70 (12.6)	192 (11.9)
Alive and free of colorectal cancer*	395 (37.2)	228 (40.9)	623 (38.5)
Total	1061 (100.0)	557 (100.0)	1618 (100.0)

* at the end of the study (May, 1988) or at age 86 years whichever was the soonest

Table 20. Cumulated Observed and Expected Deaths from All Causes at Intervals after Entry

Time (years)	Men Obs	Exp	SMR (95%CI)*	Women Obs	Exp	SMR (95%CI)
3- 4	61	64.9	0.94(0.66-1.32)	20	25.6	0.78(0.48-1.21)
5- 9	151	136.6	0.96(0.75-1.20)	62	64.6	0.96(0.67-1.36)
10-15	145	127.9	1.13(0.89-1.43)	53	51.4	1.03(0.70-1.51)
16-19	96	87.2	1.10(0.82-1.47)	59	35.7	1.65(1.09-2.50)
20-24	64	58.3	1.10(0.77-1.57)	31	19.6	1.58(0.90-2.78)
Total	517	494.8	1.04(0.91-1.18)	225	196.9	1.14(0.94-1.38)

SMR=Standardized Mortality Ratio

5.3.2 Subsequent Clinical Examinations

Colonoscopy: 192 patients were censored because they had a colonoscopy during the course of their follow-up, a mean of 7.9 ± 4.6 years after entry. The reasons for colonoscopy were as follows: 125 (65%) were invited to participate in the 'Neoplastic Polyp Follow-up Study' (Williams & Macrae, 1986), a further 45 (23%) attended the hospital because of unrelated conditions and were then referred for colonoscopy because of the new policy after 1980 to undertake colonoscopic surveillance in patients with a history of adenomas. Of the remaining 22 patients, 16 had colonoscopy at another hospital and the indication was not known, 2 had anaemia, 2 had altered bowel habit and in the other 2 cases cancer was suspected. As a result of the colonoscopy examinations, one colon cancer was diagnosed and this was included in the analysis.

The number, size, histology or the dysplasia of the rectosgmoid adenomas did not appear to influence either the decision for or the timing of the colonoscopy after entry (Tables 21 & 22). At the first colonoscopy, further adenomas were detected in 78 (41%) of patients and in 20 patients the adenomas were 1 cm or larger (see Section 5.6.4).

Proctosigmoidoscopy/Barium Enema: A total of 697 patients (43%) had further colorectal examinations during follow-up, but were not censored: 509 (31%) had proctosigmoidoscopy only and 188 (12%) barium enema examination(s) in addition. As a result of these examinations, a total of 49 adenomas were detected (28 in the rectum, 12 in the sigmoid colon and 9 in the rest of the colon). The effects of subsequent examinations and removal of adenomas on the risks of rectal and colon cancer are examined in Section 5.7.1.

Table 21. Number(%) of Patients Having Colonoscopy at Follow-up According to the Characteristics of Adenomas at Entry.

		No. (%) of Patients		
		Total	Colonoscopy	χ^2
Number	single	1395	161 (11.5)	1.02
	multiple	223	31 (13.9)	p=0.31
Size	<1cm	949	101 (10.6)	6.04 *
	1-2cm	497	75 (15.1)	p=0.014
	>2cm	172	16 (9.3)	
Histology	tubular	1021	138 (13.5)	4.99 *
	tubulovillous	430	40 (9.3)	p=0.25
	villous	167	14 (8.4)	
Dysplasia	mild	963	104 (10.8)	3.75 *
	moderate	505	72 (14.3)	p=0.053
	severe	150	16 (10.7)	

* for trend

Table 22.Time after Entry To First Follow-up Colonoscopy According to the Characteristics of Adenomas at Entry

Adenomas at Entry		Years to Examination	
Number	single	7.9 + 4.4	t=0.07,
	multiple	7.9 + 4.8	p=0.94
Size	<1cm	7.7 + 4.2	*F=0.49,
	1-2cm	7.9 + 4.5	p=0.61
	>2cm	8.9 + 5.6	
Histology	tubular	7.9 + 4.2	*F=0.06,
	tubulovillous	8.0 + 5.1	p=0.94
	villous	7.6 + 4.9	
Dysplasia	mild	8.2 + 4.7	*F=0.65,
	moderate	7.8 + 4.3	p=0.52
	severe	6.9 + 2.6	

*Analysis of variance test

5.4 PATIENTS DEVELOPING COLORECTAL CANCER:

Summaries of the clinical characteristics of the patients developing rectal and colon cancer are described in Tables 23 and 24.

The proportion of women developing cancer was almost twice that of the men (4.4% vs 2.5%). The mean age at entry of the men developing cancer did not differ significantly from that of the men not developing cancer (60.0 ± 9.1 vs 57.3 ± 11.1, p = 0.12); the same was true for the women (62.7 ± 9.9 vs 59.8 ± 11.3, p = 0.13). The mean time to development of cancer after entry was 9.6± 5.8 years for the men and 12.5 ± 6.5 years for the women (p=0.167).

5.4.1 Survival Curves

Based on the Kaplan Meier curves, the cumulative probability of developing rectal cancer at 5, 10 and 20 years after entry was 0%, 0.2% and 0.4% respectively for men and 0%, 0.4% and 4% for women (Figure 2). Because of the small number of events it was not possible to put confidence limits on these risks, but there was a significant difference between the survival curves for men and women (p=0.0005).

The corresponding risks for colon cancer at 5, 10 and 20 years after entry were 0.3%, 1.2%, 2.9% for men and 0.6%, 1.4%, 5.5% for women (Figure 3). The survival curves for the men and women were not significantly different (p=0.21)

5.4.2 Subsites of the Cancers

The subsites of the 50 colorectal cancers which developed subsequent to adenoma-excision are shown in Table 25. Twenty-eight percent of the cancers occurred in the rectum or rectosigmoid area, a further 22% in the distal colon (sigmoid and descending colon) and 28% in the proximal colon (proximal to the splenic flexure). In the remaining 22% of cases, the subsite of the cancer within the colon was not known. Almost three times as many women as men had cancers in the rectum or at the rectosigmoid junction (41% versus 13%); conversely 3 times as many men as women had cancers in the distal colon (35% versus 11%). The proportion of cases with either proximal colon cancers or colon cancer with a site not specified was similar

Table 23.Summary Description of Patients Developing Rectal Cancer

Case No.	Cancer Site	Sex	Adenomas at Entry Number	Sites	Size	Hist	Dysp	Year of Entry	Age at Entry	Yrs to Cancer
1	RM	M	1	RM	>2cm	VA	mod	1958	63	6
2	RM	M	1	RM	1-2cm	TVA	mod	1962	63	9
3	RM	M	1	RM	1-2cm	TVA	mild	1970	59	12
4	RM	F	1	RM	>2cm	VA	sev	1958	63	11
5	RM	F	1	RM	>2cm	VA	sev	1968	63	11
6	RM	F	1	RM	>2cm	TVA	sev	1962	53	11
7	RM	F	1	RM	1-2cm	VA	mod	1967	56	9
8	RM	F	1	RM	1-2cm	TVA	mod	1963	62	16
9	RM	F	2	RM,RM	1-2cm	TVA	mild	1960	39	18
10	RM	F	2	RM,RM	1-2cm	TA	mod	1963	67	17
11	RM	F	1	RM	1-2cm	TA	sev	1958	76	9
12	RM	F	1	RM	<1cm	TA	sev	1958	49	18
13	RM	F	1	RM	<1cm	TA	mild	1958	50	18
14	RM	F	2	RM,RM	<1cm	TA	mild	1973	66	13

Abbreviations:
Sites:RM=rectum
Histology: TA=tubular,TVA=tubulovillous,VA=villous
Dysplasia: Mod=moderate,Sev=severe

Table 24. Summary Description of Patients Developing Colon Cancer

Case No.	Cancer Site	Sex	Adenomas at Entry Number	Sites	Size	Hist	Dysp	Year of Entry	Age at Entry	Yrs to Cancer
1	CM	M	1	RM	1-2cm	TA	mild	1963	62	14
2	CM	M	1	RM	<1cm	TVA	mild	1962	50	22
3	CM	M	1	SC	<1cm	TVA	mild	1966	74	6
4	TC	M	1	RM	<1cm	TA	mild	1962	55	9
5	TC	M	1	SC	1-2cm	TA	mod	1961	48	7
6	TC	M	2	RM,SC	<1cm	TVA	mod	1961	56	6
7	TC	M	3	SC,SC,SC	>2cm	VA	mod	1958	61	12
8	DC	M	1	SC	1-2cm	TA	mild	1961	58	17
9	SC	M	2	RM,RM	1-2cm	TVA	mod	1970	55	3
10	SC	M	2	RM,RM	<1cm	TVA	mod	1965	56	7
11	SC	M	3	ALL RM	>2cm	TVA	sev	1973	59	4
12	SC	M	1	RM	>2cm	VA	mild	1973	80	4
13	SC	M	2	RM,SC	1-2cm	TVA	mod	1977	68	3
14	SC	M	2	RM,SC	1-2cm	TA	sev	1958	55	7
15	SC	M	1	RM	<1cm	TA	mod	1961	61	20
16	C;SNS	M	1	RM	1-2cm	TA	mod	1964	68	8
17	C;SNS	M	1	SC	<1cm	TVA	mod	1965	63	17
18	C;SNS	M	2	RM,SC	>2cm	VA	mod	1969	55	15
19	C;SNS	M	3	RM,RM,RM	<1cm	TVA	mod	1960	49	18
20	C;SNS	M	4	4x SC	1-2cm	TVA	sev	1963	64	21
21	CM	F	1	SC	<1cm	TA	mild	1967	67	15
22	CM	F	1	SC	>2cm	TA	mod	1965	69	13
23	CM	F	1	RM	<1cm	TVA	mod	1961	70	16
24	TC	F	1	SC	>2cm	VA	mild	1963	37	12
25	AC	F	1	RM	>2cm	TVA	mod	1976	73	3
26	HF	F	1	SC	>2cm	VA	mild	1964	76	19
27	HF	F	1	RM	>2cm	TVA	sev	1957	57	19
28	DC	F	1	RM	1-2cm	VA	mod	1963	66	10
29	SC	F	1	SC	<1cm	VA	mild	1959	66	7
30	SC	F	1	RM	<1cm	TA	mild	1964	59	19
31	C;SNS	F	1	SC	<1cm	VA	mod	1958	67	15
32	C;SNS	F	1	RM	>2cm	TVA	mod	1957	75	4
33	C;SNS	F	2	RM,RM	>2cm	TVA	mod	1960	70	6
34	C;SNS	F	1	SC	1-2cm	VA	mild	1969	55	8
35	C;SNS	F	1	RM	1-2cm	TVA	mild	1958	49	30
36	C;SNS	F	1	RM	<1cm	TVA	mild	1967	74	5

Abbreviations:
Sites: RM=rectum, SC=sigmoid colon, DC=descending colon, SF=splenic flexure, TC=transverse colon, HF=hepatic flexure, AC=ascending colon, CM=caecum, C;SNS=colon, site not specified
Histology: TA=tubular, TVA=tubulovillous, VA=villous
Dysplasia: Mod=moderate, Sev=severe

Figure 2. Cumulative risk of rectal cancer at intervals after entry

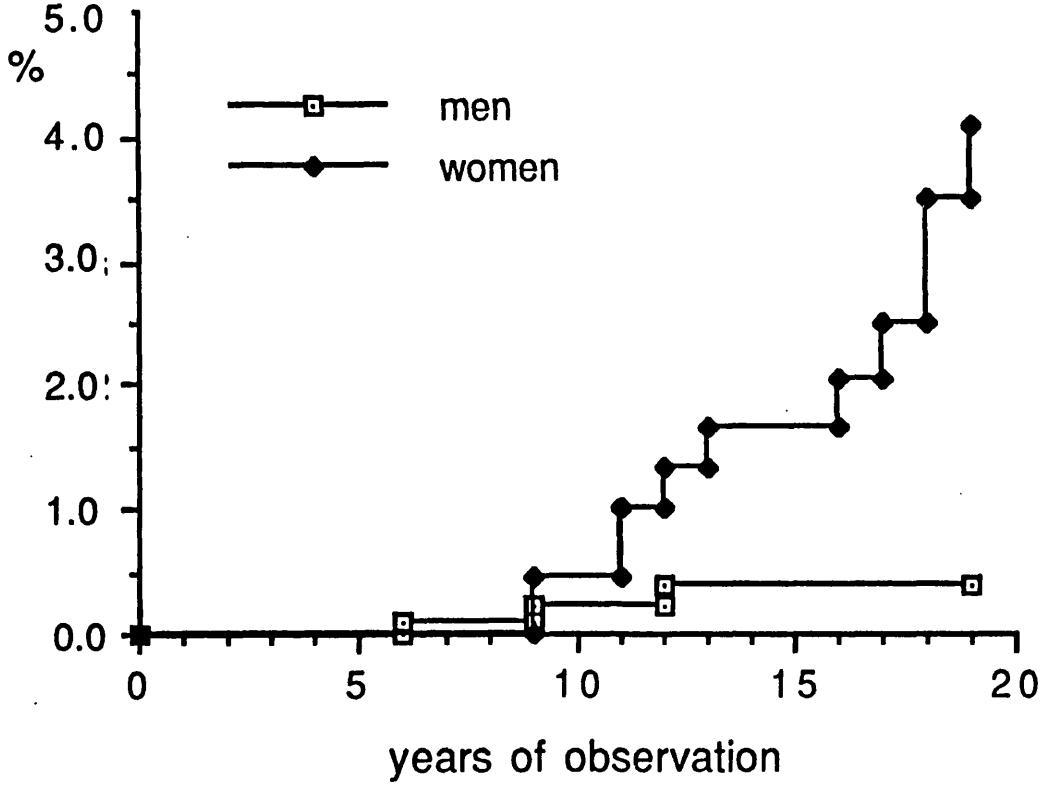


Figure 3. Cumulative risk of colon cancer at intervals after entry.

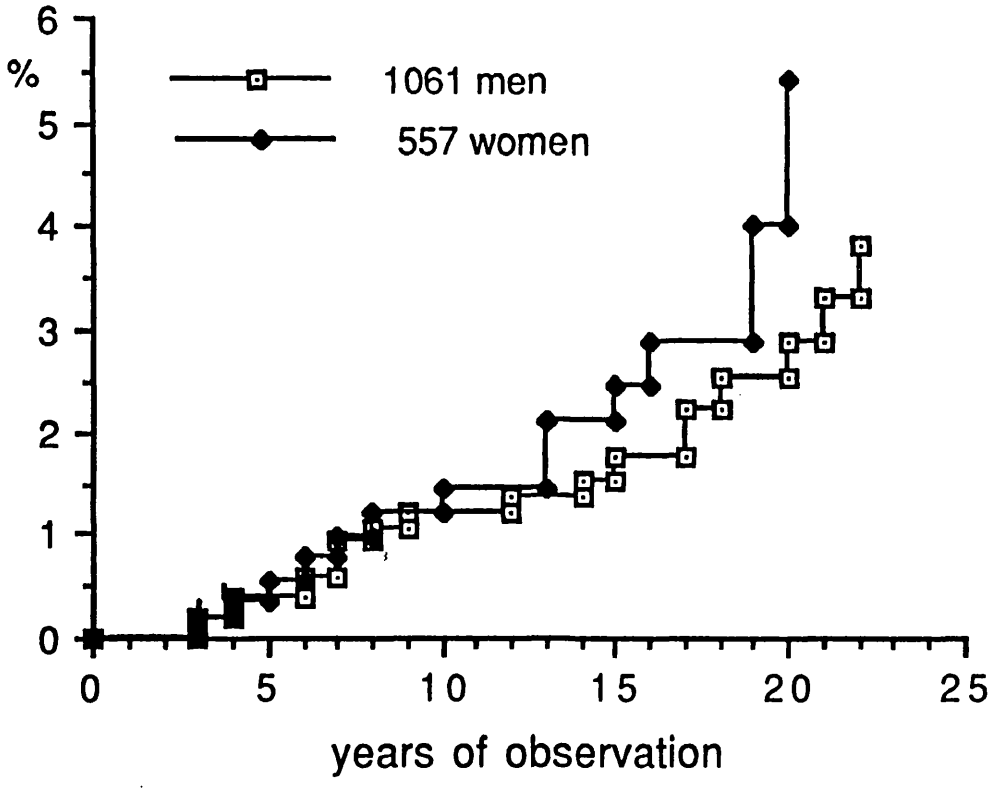


Table 25. Subsites of the Colorectal Cancers

Site of Cancer	Number(%) of Cases Men	Women	Total
Rectum+Rectosigmoid	3 (13.0)	11 (40.7)	14 (28.0)
Sigmoid Colon	6 (26.1)	2 (7.4)	8 (16.0)
Desending Colon	2 (8.7)	1 (3.7)	3 (6.0)
Transverse Colon	4 (17.4)	1 (3.7)	5 (10.0)
Hepatic Flexure	- (0.0)	2 (7.4)	2 (4.0)
Ascending Colon	- (0.0)	1 (3.7)	1 (2.0)
Caecum	3 (13.0)	3 (11.1)	6 (12.0)
Colon,site not specified	5 (21.7)	6 (22.2)	11 (22.0)
Total	23(100.0)	27(100.0)	50(100.0)

in the two sexes (30% versus 28% for proximal colon cancer; 22% for both men and women for colon cancer, site unspecified).

5.4.3 Standardized Incidence Ratios for Rectal and Colon Cancer

In comparing risks of cancer of the study group with the general population, patients were censored on their 86th birthday. Colon cancer developed in one woman at the age of 96 years, therefore there was one less colon cancer in the analysis of relative risks compared with internal comparisons (Table 26).

Overall, the risk of developing rectal cancer was no higher than that of the general population; there were 14 cases compared with 11.3 expected (SIR=1.2; 95% CI=0.7-2.1). The risk of colon cancer, on the other hand, was approximately doubled (S.I.R.=2.1, 95% CI: 1.5-3.0, $p<0.001$); there were 35 cases compared with 16.3 expected.

5.5 FACTORS INFLUENCING THE RISK OF RECTAL CANCER

5.5.1 UNIVARIATE ANALYSES

Sex and Age: Only three cases of rectal cancer occurred in the 1061 men compared with an expected 8.3 (SIR= 0.36 (95% CI: 0.07-1.1) (Table 26), suggesting that following excision of adenomas, men may be at a lower risk than the general population of developing rectal cancer.

The women, on the other hand, were at a significantly increased risk; there were 11 cases compared with only 3.0 expected (SIR=3.63; 95% CI: 1.8-6.5). The SIR for rectal cancer in the women was ten times higher than that in the men (RR=10.1; 95% CI: 2.7-56.9 $p<0.0001$).

The relative risks of rectal cancer compared to the general population did not show any significant trend with age at entry in either sex (Table 27). Thus, the significant difference in risk between the sexes was not due to the older age at entry of the women.

Table 26. Standardized Incidence Ratios for Rectal and Colon Cancer in Men and Women

	Cancer Cases			
	Observed	Expected	SIR	(95% CI)
Rectal cancer				
Men	3	8.27	0.36	(0.07-1.06)
Women	11	3.03	3.63	(1.81-6.49)
Total	14	11.30	1.24	(0.68-2.08)
Colon Cancer				
Men	20	10.35	1.93	(1.18-2.98)
Women	15	5.91	2.54	(1.42-4.19)
Total	35	16.26	2.15	(1.50-2.99)
Colorectal Cancer				
Men	23	18.62	1.23	(0.78-1.85)
Women	26	8.94	2.90	(1.90-4.26)
Total	49	27.56	1.78	(1.35-2.39)

Relative risk (95% CI) for women vs men for:
Rectal cancer: 10.08 (2.7-56.9) p= <0.0001
Colon cancer: 1.32 (0.6-2.7) p= 0.21
Colorectal cancer: 2.36 (1.2-4.1) p= 0.0001

Table 27. Standardized Incidence Ratios for Rectal Cancer According to Age at Entry

Age (years)	Total Number of Patients	Rectal Cancer Observed	Expected	SIR	(95% CI)
Men					
<50	273	0	1.25	0.00	(0.00-2.95)
50-59	324	1	2.50	0.40	(0.01-2.22)
60-69	326	2	3.28	0.61	(0.07-2.20)
70+	138	0	1.24	0.00	(0.00-2.98)
Women					
<50	115	1	0.35	2.86	(0.07-15.91)
50-59	137	4	0.75	5.33	(1.45-13.65)
60-69	190	5	1.27	3.94	(1.27- 9.19)
70+	115	1	0.66	1.51	(0.04- 8.44)

Chi-square tests:
Heterogeneity (2df): men: 1.65,p=0.29; women: 1.50,p=0.0001
Trend (1df): men: 0.02,p=0.47; women: 0.15,p=0.47

Numbers of adenomas: Risk of rectal cancer was not influenced by the number of rectosigmoid adenomas in either sex (Table 28). The three rectal cancers in the men occurred in patients with only one adenoma. In the women the risk was significantly higher than in the general population, both in those with a single adenoma (SIR=3.40; 95% CI: 1.5-6.4) and those with multiple adenomas (SIR=5.56; 95% CI: 0.7-20.0).

Size: All of the rectal cancers in the men occurred in patients with adenomas larger than 1 cm in diameter at entry (Table 29), although even in this group the risk was still not significantly higher than the general population (SIR=1.00; 95% CI: 0.2-2.9). However, it is important to note the very low risk of rectal cancer in the men with only small adenomas (<1 cm). Not a single cancer occurred in 661 men compared with 5.3 expected rendering them at a significantly lower risk than the general population ($p<0.01$).

In the women, on the other hand, the risk of rectal cancer was significantly higher than in the general population among those with adenomas larger than 1 cm at entry (SIR=4.67; 95% CI: 1.9-9.6), but was also raised, although not significantly so, in women with small adenomas (SIR=2.61; 95% CI: 0.7-6.7).

Histology: Two of the rectal cancers in the men occurred in patients with tubulovillous adenomas and one in a patient with a villous adenoma, though the risk was not significantly raised in any of the histological groups (Table 30). Women with tubulovillous or villous adenomas had significantly increased relative risks (SIR=4.04 and 7.50 respectively), but risk was also raised, although not significantly so, in women with only tubular adenomas (SIR=2.44; 95% CI: 0.7-6.2).

Grade of dysplasia: Two of the men developing rectal cancer had moderately dysplastic adenomas and one patient had mild dysplasia (Table 31).

In the women, severe dysplasia was associated with a fourteen-fold increase (95% CI: 4.6-33.3), moderate dysplasia with a three-fold increase (95% CI: 0.59-8.43) and mild dysplasia with a two-fold increase in risk (95% CI: 0.4-5.3).

Table 28. Standardized Incidence Ratios for Rectal Cancer According to the Number of Adenomas at Entry

	Total Patients	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
1	907	3	7.06	0.42 (0.09-1.24)
2+	154	0	1.22	0.00 (0.00-3.02)
Women				
1	488	9	2.65	3.40 (1.55-6.44)
2+	69	2	0.36	5.56 (0.67-20.05)
Total				
1	1395	12	9.71	1.24 (0.64-2.16)
2+	223	2	1.58	1.26 (0.15-4.57)

Relative risk (95% CI) for 2+ vs 1 = 1.0 (0.1-4.6) p=0.64

Table 29. Standardized Incidence Ratios for Rectal Cancer According to the Size of Adenomas at Entry

	Total Patients	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
<1cm	661	0	5.29	0.00 (0.00-0.70)
1-2cm	307	3	2.23	1.34 (0.28-3.93)
>2cm	93	0	0.75	0.00 (0.00-4.92)
Women				
<1cm	288	4	1.53	2.61 (0.71-6.69)
1-2cm	190	4	1.09	3.67 (1.00-9.39)
>2cm	79	3	0.41	7.32 (1.51-21.39)
Total				
<1cm	949	4	6.82	0.59 (0.16-1.50)
1-2cm	497	7	3.32	2.11 (0.85-4.34)
>2cm	172	3	1.16	2.59 (0.53-7.56)

Chi-square
Heterogeneity (2df): 5.74, p=0.06
Trend (1df): 5.26, p=0.02

Table 30. Standardized Incidence Ratios for Rectal Cancer According to the Histology of Adenomas at Entry

	Total Patients	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
Tubular	710	0	5.53	0.00 (0.00-0.60)
Tubulovillous	262	2	2.09	0.95 (0.12-3.45)
Villous	89	1	0.65	1.54 (0.04-8.57)
Women				
Tubular	311	4	1.64	2.44 (0.66-6.24)
Tubulovillous	168	4	0.99	4.04 (1.10-10.34)
Villous	78	3	0.40	7.50 (1.54-21.92)
Total				
Tubular	1021	4	7.17	0.56 (0.15-1.43)
Tubulovillous	430	6	3.08	1.95 (0.71-4.24)
Villous	167	4	1.05	3.81 (1.04-9.75)

Chi-square
Heterogeneity (2df): 8.72, p=0.013
Trend (1df): 8.70, p=0.002

Table 31.Standardized Incidence Ratios for Rectal Cancer According to the Grade of Dysplasia of Adenomas at Entry

	Total Patients	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
Mild	662	1	5.25	0.19 (0.00-1.06)
Moderate	309	2	2.40	0.83 (0.10-3.01)
Severe	90	0	0.63	0.00 (0.00-5.86)
Women				
Mild	301	3	1.65	1.82 (0.37-5.31)
Moderate	196	3	1.04	2.88 (0.59-8.43)
Severe	60	5	0.35	14.29 (4.63-33.34)
Total				
Mild	963	4	6.90	0.58 (0.16-1.48)
Moderate	505	5	3.44	1.45 (0.47-3.39)
Severe	150	5	0.98	5.10 (1.65-11.91)

Chi-square
Heterogeneity: 10.40, p=0.005
Trend: 8.71, p=0.003

Year of entry into the study: The patients were divided into similar-sized groups according to the year of entry into the study: 1957-64 (568 patients); 1965-71 (557 patients); 1972-80 (493 patients). The risk of rectal cancer in the men was below unity in each period, but because of small numbers the confidence intervals included unity in each period (Table 32). The risk was near unity for the women for all periods except for 1957-64 when 8 cases were diagnosed compared with an expected 1.28 (SIR= 6.25 (95% CI: 2.7-12.3). Thus increased risk in the women was confined to those treated before 1965.

Summary: Compared with the women, the 1061 men in this study had a significantly lower risk of developing rectal cancer after adenoma-excision. Almost 50% of the men were followed to their death, for an average of 14.1 years, and only 3 developed rectal cancer, one third of that expected for the local population.

Because of the low risk of rectal cancer in the men and only 3 observed cancers, it is difficult to say much about what factors influenced risk. However, all 3 of the men developing rectal cancer had either large ($\geq$1 cm), tubulovillous or villous adenomas.

The 557 women in this series were at a 3.6-fold increased risk. The women were followed for an average of 14.3 years and 11 cancers developed where only 3.0 were expected. Eight of the 11 cancers occurred in women whose adenomas were treated before 1965. Size, histology and grade of dysplasia were all risk factors, but multiplicity was not.

5.5.2 MULTIVARIATE ANALYSIS AND DIVISION OF PATIENTS INTO RISK CATEGORIES

The independent effects of the covariates were examined in a Cox's proportional hazards model (Table 33). After adjustment for sex ($p<0.001$), the strongest predictor of risk was dysplasia ($p=0.004$) followed by histology ($p=0.08$). The complete model was given by

$$h(t; \text{model}) = h_0(t) \exp (1.64 \text{ sex} + 1.02 \text{ histology} + 0.85 \text{ dysplasia})$$

Table 32.Standardized Incidence Ratios for Rectal Cancer According to the Year of Entry

Year of Entry	Total	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
1957-1964	383	2	3.81	0.52 (0.06-1.89)
1965-1971	371	1	3.03	0.33 (0.01-2.38)
1972-1980	307	0	1.42	0.00 (0.00-2.60)
Women				
1957-1964	185	8	1.28	6.25 (2.69-12.31)
1965-1971	186	2	1.16	1.72 (0.21- 6.22)
1972-1980	186	1	0.61	1.64 (0.04- 9.13)
Total				
1957-1964	568	10	5.09	1.96 (0.94-3.61)
1965-1971	557	3	4.19	0.72 (0.14-2.09)
1972-1980	493	1	2.03	0.49 (0.01-2.74)

Table 33.Cox's Proportional Hazards Model for Rectal Cancer

	Step 0	Step 1		Step 2	
	Approximate $\chi 2$	Approximate $\chi 2$		Approximate $\chi 2$	
	to Enter	to Enter	to Remove	to Enter	to Remove
Sex	11.02		11.02		8.55
Age	3.50	1.72		1.47	
Number	0.05	0.06		0.01	
Size	6.59	4.17		0.94	
Histology (2 gps)	7.80	5.44		3.13	
Dysplasia	10.87	8.41			8.41
Variable selected:-	Sex	Dysplasia		Histology	
Improvement $\chi 2$ (1df)	11.02	8.41		3.13	
	p=0.0009	p=0.0037		p=0.077	

On the basis of this model, the patients were divided into a 'Low-Risk$_{rectal}$' and 'High-Risk$_{rectal}$' group. Because of the high degree of correlation between size and histology, size was also considered in the division of patients into the risk groups. Thus the 'Low-Risk$_{rectal}$' group comprised patients with small, mildly or moderately dysplastic, tubular adenomas and the 'High-Risk$_{rectal}$' group, the remainder with either large ($\geq$ 1cm), tubulovillous, villous or severely dysplastic adenomas.

None of the cancers in the men and only 2 of the 11 cancers in the women developed in the 'Low-Risk$_{rectal}$' group, confirming this to be a particularly low-risk group (Table 34). Among the 'High-Risk$_{rectal}$' patients, only the women were at increased risk (SIR=4.8; 95% CI: 2.2-9.1). Although all 3 of the cancers in the men developed in the 'High-Risk$_{rectal}$' group, the relative risk was still no higher than that of the general population (SIR=0.75; 95% CI: 0.15-2.2).

5.5.3 Investigation of the possible reasons for the high rate of rectal cancer among the women.

The finding that the men in 'High-Risk$_{rectal}$' group were not at increased risk, while the women with similar adenomas were, together with the observation that the enhanced risk in the women was confined to those treated before 1965, prompted a more thorough examination of the circumstances surrounding the excision of adenomas at entry in the women developing rectal cancer by means of a nested case-control study.

The shape of the adenomas, the method of excision, the completeness of excision and the length of follow-up of the 14 cases were compared to controls selected from the remaining patients in the cohort as described in the Appendix.

It was found that only one of the cases had had any clinical follow-up after excision and this was for just 18 months. Furthermore, a significantly higher proportion of the cases had sessile adenomas which had been inadequately excised. The adenomas in all 3 of the male cases and in 3 of the 11 female cases had merely been biopsied and not excised. Five further cases (all female) had large sessile adenomas which had been treated by fulgaration only.

Table 34.Standardized Incidence Ratios for Rectal Cancer in 'Low-Risk$_{rectal}$' and'High-Risk$_{rectal}$' Groups

	Total Patients	Rectal Cancer Obs	Exp	SIR (95% CI)
Men				
'Low-Risk$_{rectal}$'	536 (50.5)	0	4.25	0.00 (0.00-0.90)
'High-Risk$_{rectal}$'	525 (49.5)	3	4.02	0.75 (0.15-2.18)
Women				
'Low-Risk$_{rectal}$'	224 (40.2)	2	1.16	1.72 (0.21-6.22)
'High-Risk$_{rectal}$'	333 (59.8)	9	1.87	4.81 (2.20-9.09)
Total				
'Low-Risk$_{rectal}$'	760 (47.0)	2	5.41	0.37 (0.04-1.33)
'High-Risk$_{rectal}$'	858 (53.0)	12	5.89	2.04 (1.05-3.56)

Low-Risk$_{rectal}$ = small (< 1cm),mildly or moderately dysplastic, tubular
High-Risk$_{rectal}$= large (≥ 1cm). tubulovillous, villous or severely dysplastic

Relative risk (95% CI) for 'High-Risk$_{rectal}$)' vs 'Low-Risk$_{rectal}$' =5.51 (1.2-50.1) p=0.006

The principal differences between the men and women resided in the proportions with sessile and inadequately excised adenomas. A similar proportion of men and women had no follow-up, but this appeared to matter less in the men since their adenomas were more likely to have been pedunculated with a low risk of recurrence after excision.

5.5.4 Effect of Clinical Follow-Up in 'Low-Risk$_{rectal}$' and 'High-Risk$_{rectal}$' groups.

Patients were divided into those who were discharged within two years of entry and those who continued to attend the hospital and had repeated rectal examinations. Such patients were considered to be 'followed-up' whatever the purpose of their attendance at the hospital. A total of 697 patients (43%) had follow-up examinations. It was found that increased risk was confined to the 'High-Risk$_{rectal}$' group who had no 'follow-up' examinations, confirming the findings of the case-control study. It was also noted that the standardized incidence ratios in both men and women in the 'Low-Risk$_{rectal}$' group were low, even in the absence of follow-up (Table 35).

5.5.5 Summary and Conclusions

Overall, the risk of rectal cancer was no higher than the general population, but there profound sex differences. The risk in the men was only one third of that of the general populaton, while the women were at a more than three-fold increased risk. Increased risk was confined to patients with either large ($\geq$ 1cm), tubulovillous, villous or severely dysplastic adenomas. The women were older than the men and their adenomas were larger, more villous and more dysplastic. However, these differences did not account for the ten-fold higher risk in the women since men with such adenomas were not at increased risk.

A matched case-control study demonstrated that after accounting for age and the characteristics of adenomas at entry, the morphology of the adenoma, the adequacy of excision and follow-up after excision were the strongest additional risk factors. A larger proportion of the women had sessile and inadequately excised adenomas which accounted for their increased risk. A similar

Table 35. Standardized Incidence Ratios for Rectal Cancer With and Without Follow-up Examinations in 'Low-Risk$_{rectal}$' and 'High-Risk$_{rectal}$' Groups

	Rectal Cancer		
	Obs	Exp	SIR (95% CI)
'Low-Risk$_{rectal}$'			
No Follow-up	2	3.82	0.52 (0.06-1.89)
Follow-up	0	1.75	0.00 (0.00-2.11)
'High-Risk$_{rectal}$'			
No Follow-up	10	3.46	2.89 (1.39-5.31)
Follow-up	1	2.67	0.37 (0.01-2.09)

*'Low-Risk$_{rectal}$'= small,mildly or moderately dysplastic,tubular
'High-Risk$_{rectal}$'=tubulovillous,villous,large (≥ 1cm) or severely dysplastic

proportion of men and women (60%) had no follow-up after adenoma-treatment, but this mattered less in the men because most of their adenomas were adequately excised.

Thus, it may be concluded that, if all adenomas detected within reach of the rigid sigmoidoscope are adequately excised and patients are monitored for local recurrence if the adenomas are either sessile, large (≥ 1cm) tubulovillous, villous or severely dysplastic, then the risk of subsequent rectal cancer may be lower than that of the general population.

5.6 FACTORS INFUENCING THE RISK OF COLON CANCER

5.6.1 UNIVARIATE ANALYSES

Sex and Age: Unlike rectal cancer, the SIRs for colon cancer did not differ between the sexes, being approximately two for both men and women and significantly higher than the general population (Table 26). There was no significant trend in the SIRs with age in either sex (Table 36).

Numbers of adenomas: The risk of colon cancer in men with more than one adenoma was more than six times that of the general population (SIR=6.6; 95% CI: 3.2-12.2) while the risk in men with a single adenoma was similar to that of the general population (SIR=1.1; 95% CI: 0.5-2.1) (Table 37).

In the women, on the other hand, the risk of colon cancer was not influenced by the number of adenomas in the rectum, the relative risk being higher in women with single rather than multiple adenomas.

Size : Men and women with adenomas larger than 1 cm were at significantly increased risk of colon cancer (SIR=3.4; 95% CI: 1.9-4.8). Patients with only small (<1cm) adenomas were at a similar risk to the general population (Table 38).

In men and women together, there was a significant trend (p=0.002) of increasing risk with increasing size and the risk associated with an adenoma 1 cm or larger was 2.2 times greater than that with only a small adenoma (95% CI: 1.0-4.6).

Histology: The relative risks associated with tubulovillous or villous histology were of a similar order of magnitude, 4 and 5 respectively (Table 39). Villous adenomas were associated with higher risk in women. Men and women with tubular adenomas were at no extra risk.

There was a highly significant trend of increasing risk with increasing villousness (p=0.0001), and patients with either a tubulovillous or villous adenoma were at 4 times the risk of colon cancer (95% CI: 1.9-9.7) compared with those with only tubular adenomas.

Table 36. Standardized Incidence Ratios for Colon Cancer According to Age at Entry

Age (years)	Total Patients	Colon Cancer Obs	Exp	SIR (95% CI)
Men				
<50	273	2	1.56	1.28 (0.15-4.63)
50-59	324	9	3.07	2.93 (1.34-5.55)
60-69	326	7	4.14	1.69 (0.68-3.48)
70+	138	2	1.57	1.27 (0.15-4.60)
Women				
<50	115	2	0.62	3.22 (0.39-11.64)
50-59	137	3	1.43	1.39 (0.43- 6.13)
60-69	190	5	2.50	2.00 (0.64- 4.67)
70+	115	5	1.35	3.70 (1.20- 8.64)

Chi-square tests

Heterogeneity (2df):	men 2.18,p=0.06	women 1.22,p=0.86
Trend (1df):	men 0.26,p=0.97	women 0.02,p=0.95

Table 37. Standardized Incidence Ratios for Colon Cancer According to the Number of Adenomas at Entry

	Total Patients	Colon Cancer Obs	Exp	SIR (95% CI)
Men				
1	907	10	8.84	1.13 (0.54-2.08)
2+	154	10	1.51	6.62 (3.18-12.18)
Women				
1	488	14	5.15	2.72 (1.48-4.56)
2+	69	1	0.75	1.33 (0.03-7.43)
Total*				
1	1395	24	13.99	1.71 (1.10-2.55)
2+	223	11	2.26	4.87 (2.43-8.71)

*Relative risk (95% CI) for 2+ vs 1 = 2.85 (1.26-6.02), p=0.011

Table 38. Standardized Incidence Ratios for Colon Cancer According to Size of Adenomas at Entry.

	Total Patients	Colon Cancer Obs	Exp	SIR	(95% CI)
Men					
<1cm	661	8	6.64	1.20	(0.52- 2.37)
1-2cm	307	8	2.79	2.87	(1.24- 5.67)
>2cm	93	4	0.93	4.30	(1.17-11.01)
Women					
<1cm	288	6	2.98	2.01	(0.74- 4.38)
1-2cm	190	3	2.13	1.41	(0.29- 4.12)
>2cm	79	6	0.80	7.50	(2.75-16.32)
Total*					
<1cm	949	14	9.62	1.45	(0.79- 2.44)
1-2cm	497	11	4.92	2.23	(1.12- 4.00)
>2cm	172	10	1.73	5.78	(2.77-10.63)

*Chi-square
Heterogeneity(2 df): 12.04 p=0.002
Trend (1 df): 9.78 p=0.002

Table 39. Standardized Incidence Ratios for Colon Cancer According to Histology of Adenomas at Entry.

	Total Patients	Colon Cancer Obs	Exp	SIR (95% CI)
Men				
Tubular	710	7	6.93	1.01 (0.40-2.08)
Tubulovillous	262	10	2.61	3.83 (1.84-7.05)
Villous	89	3	0.81	3.70 (0.96-10.83)
Women				
Tubular	311	3	3.20	0.93 (0.19-2.74)
Tubulovillous	168	7	1.92	3.64 (1.46-7.51)
Villous	78	5	0.78	6.41 (2.09-14.96)
Total*				
Tubular	1021	10	10.13	0.99 (0.47-1.81)
Tubulovillous	430	17	4.53	3.75 (2.18-6.00)
Villous	167	8	1.59	5.03 (2.17-9.91)

*Chi-square
Heterogeneity: 17.1, p=0.0002
Trend: 16.3, p=0.0001

Grade of dysplasia: Both moderate and severe dysplasia were associated with a relative risk of approximately 3, but no excess risk was seen for mild dysplasia. There was a slight trend of increasing risk with increasing severity of dysplasia (p=0.01) (Table 40).

5.6.2 MULTIVARIATE ANALYSIS AND DIVISION OF PATIENTS INTO RISK CATEGORIES

In men and women considered together, multiplicity, large size, villous histology, and moderate or severe dysplasia of adenomas in the rectosigmoid were univariate risk factors for the future development of cancer in the colon. These variables were highly correlated and it was not clear whether a Cox's proportional hazards model would be of use in discriminating individual predictors of more value than others. Histology (tubular versus tubulovillous/villous) was marginally the strongest predictor of risk ($p<0.0001$). This was followed by age as a continuous variable ($p<0.0002$). The number of adenomas excised (1 vs 2 or more adenomas) was a weak additional predictor ($p= 0.04$) (Table 41). The complete proportional hazards model was given by:-

$$h(t; \text{model}) = h_0(t) \exp (0.06 \text{ age} + 0.81 \text{ number} + 1.34 \text{ histology})$$

There was an approximate doubling of risk with increasing age for each decade ($\exp 0.06*10 = 1.82$) in this group of adenoma patients as is observed in the general population (Thames Cancer Registry data). After controlling for age, the odds ratio for tubulovillous or villous versus tubular histology was 3.8 and for multiple versus single adenomas 2.2. Four groups of patients were defined based on the above model.

1) single, tubular
2) multiple, tubular
3) single, tubulovillous or villous
4) multiple, tubulovillous or villous

The risks relative to the general population in men and women in each of the groups are shown in Table 42.

Table 40. Standardized Incidence Ratios for Colon Cancer According to Grade of Dysplasia of Adenomas at Entry

	Total Patients	Obs	Exp	Colon Cancer SIR (95% CI)
Men				
Mild	662	6	6.57	0.91 (0.33-1.99)
Moderate	309	11	2.99	3.68 (1.84-6.58)
Severe	90	3	0.78	3.85 (0.79-11.24)
Women				
Mild	301	7	3.21	2.18 (0.87-4.49)
Moderate	196	6	2.03	2.95 (1.08-5.70)
Severe	60	2	0.68	2.94 (0.35-10.62)
Total*				
Mild	963	13	9.78	1.33 (0.71-2.27)
Moderate	505	17	5.02	3.39 (1.97-5.42)
Severe	150	5	1.46	3.42 (1.11-7.99)
*Chi-square				
Heterogeneity	7.49	p=0.024		
Trend	6.39	p=0.011		

Table 41.Cox's Proportional Hazards Model for Colon Cancer

	Step 0	Step 1		Step 2	
	Approx.χ^2 to Enter	Approximate χ^2 to Enter	to Remove	Approximate χ^2 to Enter	to Remove
Sex	1.42	0.00		0.01	
Age	18.02	13.86			12.07
Number	8.92	4.35		4.35	
Size	13.14	1.26		0.79	
Histology (3 gps)	19.61	0.51		0.80	
Histology (2 gps)	20.71		16.00		14.40
Dysplasia	6.68	1.81		0.99	
Variable selected:-	Histology (2 gps)	Age		Number	
Improvement χ^2(1df)	20.71	13.86		4.35	
	p <0.001	p=0.0002		p=0.04	

Table 42. Standardized Incidence Ratios for Colon Cancer According to Histology and Multiplicity of Adenomas at Entry

	Total Number (%) Patients		Colon Cancer Obs	Exp	SIR	(95% CI)
Men						
Tubular single	634	(59.8)	6	6.21	0.97	(0.35-1.88)
multiple	76	(7.2)	1	0.72	1.39	(0.03-7.74)
TVA or VA single	273	(25.7)	4	2.62	1.53	(0.42-3.91)
multiple	78	(7.3)	9	0.79	11.39	(5.21-21.62)
Women						
Tubular single	278	(49.9)	3	3.79	0.79	(0.22-3.14)
multiple	33	(5.9)	0	0.41	0.00	(0.00-9.00)
TVA or VA single	210	(37.7)	11	2.35	4.68	(2.34-8.37)
multiple	36	(6.5)	1	0.35	2.85	(0.07-15.91)
Total*						
Tubular single	912	(56.4)	9	9.00	1.00	(0.46-1.90)
multiple	109	(6.7)	1	1.13	0.88	(0.02-4.93)
TVA or VA single	483	(29.8)	15	4.97	3.02	(1.69-4.98)
multiple	114	(7.1)	10	1.14	8.77	(4.21-16.13)

TVA=tubulovillous, VA=villous
*Chi-square
Heterogeneity (3 df): 24.9, p=<0.0001
Trend (1df): 14.9, p= 0.0001

These groups were further defined. The group comprising patients with only a single, tubular adenoma were at the same risk of developing colon cancer as the general population confirming them to be a low risk group. However 9 cancers occurred in this group and in 5 of these cases the original adenomas were larger than 1 cm. The histological classification of adenomas is heterogeneous and is defined according to the most villous histology seen in a specimen. Because of sampling error, misclassification of large adenomas is more likely to occur (Fung & Goldman, 1970). Furthermore, the histology and size of adenomas are highly correlated, therfore, it seemed inappropriate that a low-risk group should include patients with adenomas of 1 cm or larger. Therefore four new groups were defined in order of increasing risk:-

'Low-Risk$_{colon}$'	1) single small (< 1cm) tubular
	2) multiple small (< 1cm) tubular
'High-Risk$_{colon}$'	3) single, large (≥ 1cm) or tubulovillous or villous
	4) multiple, large (≥ 1cm) or tubulovillous or villous

The risk of colon cancer for patients in the Groups 1 and 2 (Low-Risk$_{colon}$) who had only small tubular adenomas (single or multiple) was lower although not significantly so than the general population (Table 43); only 4 cases occurred compared with an expected 7.8 (SIR=0.51; 95% CI: 0.1-1.3). Patients with multiple small tubular adenomas appeared to be at no increased risk, but there only 64 cases, too few to be confident about this finding.

Among the remaining patients with either a tubulovillous, villous or large (≥1cm) adenoma (High-Risk$_{colon}$) there were 31 cases compared with an expected 8.50 (SIR=3.65; 95% CI: 2.4-5.0). Men with multiple adenomas in addition to one that was either large, tubulovillous or villous were at a nine-fold increased risk and colon cancer was diagnosed in 10% of this group of men. Among the women with tubulovillous, villous or large adenomas, the risk was the same whether or not multiple adenomas were present. Notwithstanding the very high risks in the men in group 4, the major differences were between patients with only small (< 1 cm) tubular adenomas and those with tubulovillous, villous or large (≥ 1 cm) adenomas.

Table 43. Standardized Incidence Ratios for Colon Cancer According to Histology, Size and Multiplicity of Adenomas at Entry

	Total Number (%) Patients		Colon Cancer Obs	Exp	SIR	(95% CI)
Men						
Small and tubular single	501	(47.2)	2	5.02	0.40	(0.05-1.44)
multiple	45	(4.2)	0	0.38	0.00	(0.00-9.71)
Large or TVA or VA single	406	(38.3)	8	3.81	2.10	(0.90-4.14)
multiple	109	(10.3)	10	1.13	8.85	(4.25-16.2
Women						
Small and tubular single	211	(37.9)	2	2.13	0.94	(0.11-3.39)
multiple	19	(3.4)	0	0.22	0.00	(0.00-16.7
Large or TVA or VA single	277	(49.7)	12	3.03	3.96	(2.05-6.92)
multiple	50	(9.0)	1	0.53	1.89	(0.05-10.5
Total*						
Small and tubular single	712	(44.0)	4	7.15	0.56	(0.15-1.43)
multiple	64	(4.0)	0	0.60	0.00	(0.00-6.15)
Large or TVA or VA single	683	(42.2)	20	6.84	2.92	(1.79-4.52)
multiple	159	(9.8)	11	1.66	6.63	(3.30-11.8

TVA=tubulovillous, VA=villous
*Chi-square
Heterogeneity (3df): 29.1,p<0.0001
Trend (1 df):23.1,p<0.0001

5.6.3 Risk of Proximal Colon Cancer

In the present study, adenomas were excised from the most distal few centimetres of the sigmoid colon only suggesting that the presence of a tubulovillous, villous or large adenoma within reach of the rigid sigmoidoscope is predictive of cancer in more proximal regions. However, of the 36 colon cancers, 8 developed in the sigmoid colon and in a further 11, the subsite within the colon was not specified (Table 25). It is theoretically possible that these cancers could have arisen at the sites of the previously excised adenomas. Local recurrence is more likely after excision of large, tubulovillous or villous adenomas in which case the risk groups defined above would be more a factor of the inadequate excision of the original adenomas rather than predictive of cancer at a remote site in the colon beyond the reach of the rigid sigmoidoscope.

This possibility was considered unlikely for two reasons:
1) The remaining 17 cancers occurred at defined sites between the descending colon and the caecum (Table 25). The proportion of patients with a tubulovillous, villous or large adenoma was similar in the 19 cases with cancers in the sigmoid colon or colon, site not specified and the 17 cancers in defined proximal sites (89.5% vs 88% respectively).

2) The relative risk of proximal colon cancer in the group with large, tubulovillous or villous adenomas was 6 times higher than in the group with only small tubular adenomas (95% CI: 2.3-55.0; p=0.01) (Table 44).

Thus it seems that the presence of a tubulovillous, villous or large adenoma is predictive of cancer in more proximal parts of the colon. This supposition was confirmed in subsidiary analyses of two groups of patients undergoing colonoscopy. The first group had colonoscopy during follow-up and was censored at that point and the other group were examined by colonoscopy at entry and was excluded from the main analysis.

Table 44.Standardized Incidence Ratios for Cancer of the Proximal Colon**

	Proximal Colon Cancer		
	Obs	Exp	SIR (95% CI)
Men			
Small, tubular	1	2.11	0.47 (0.01-2.64)
Large or TVA or VA+	7	1.95	3.59 (1.44-7.39)
Women			
Small, tubular	1	1.09	0.92 (0.02-5.11)
Large or TVA or VA	7	1.80	3.89 (1.56-8.01)
Total*			
Small, tubular	2	3.20	0.62 (0.07-1.74)
Large or TVA or VA	14	3.75	3.73 (2.04-6.26)

* Relative risk = 6.02 (95%CI:2.3-55.0)
** Caecum to descending colon.
+TVA=tubulovillous, VA=villous

5.6.4 Metachronous Adenomas Detected by Colonoscopy during Follow-up

A total of 192 patients were examined by colonoscopy two or more years after entry and any adenomas detected were excised. 89 (46%) of these patients had only small (< 1cm) tubular adenomas in the rectosigmoid at entry ('Low-Risk$_{colon}$'), while the remaining 103 (54%) were 'High-Risk$_{colon}$' patients with either a large (≥ 1cm), tubulovillous or villous adenoma. The adenomas found at the first follow-up colonoscopy in the two risk groups were compared. This was felt to be a valid comparison since the decision to refer a patient for colonoscopy during follow-up did not appear to be influenced by the characteristics of the adenomas removed at entry (Table 21). Furthermore the mean times to colonoscopy were similar in the 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' groups (7.55 ± 3.8 years vs 8.25 ± 4.9 years, p=0.27)

A similar proportion of patients in the 'Low-Risk$_{colon}$ and the 'High-Risk$_{colon}$' groups had at least one metachronous adenoma detected at colonoscopy (35% versus 46% respectively, p=0.13) (Table 45). However, patients in the 'High-Risk$_{colon}$' group were much more likely to have a large (≥1cm) adenoma (16% vs 4.5% respectively; p=0.01). The proportions of patients with adenomas with tubulovillous or villous histology or with moderate or severe dysplasia did not differ significantly between the risk groups. However, an 'At-Risk' adenoma (≥1cm, tubulovillous, villous or severely dysplastic) was observed in 8% of the 'Low-Risk$_{colon}$' group compared with 20% of the 'High-Risk$_{colon}$' group (p=0.01).

5.6.5 Synchronous Colonic Adenomas Detected by Colonoscopy at Entry

There were 244 patients who were examined by colonoscopy within 2 years of entry who were excluded from the main analysis. Of these, 182 (75%) had at least one adenoma in the rectum or sigmoid colon (Table 46). One third (61/182) had only small tubular adenoma(s) in the rectosigmoid and were comparable to the 'Low-Risk$_{colon}$' group, while the other two-thirds (122/182) had either a large (≥1cm) tubulovillous or villous adenoma and were comparable to the 'High-Risk$_{colon}$' group.

Table 45. Metachronous Adenomas Detected at Follow-up Colonoscopy in 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' Groups*

Adenomas at Entry	Total Patients Examined	Number(%) of Patients with Metachronous Adenomas				
		Total	Size ≥1cm	Histology TVA/VA	Dysplasia Mod/Severe	'At Risk' Adenoma*
'Low-Risk$_{colon}$'	89	31 (34.8)	4 (4.5)	5 (5.6)	4 (4.5)	7 (7.9)
'High-Risk$_{colon}$'	103	47 (45.6)	16 (15.6)	8 (7.8)	9 (8.7)	21 (20.4)
Chisquare		2.3	6.2	0.35	1.4	6.1
p value		0.1	0.01	0.55	0.2	0.01

* 'Low-Risk$_{colon}$' small (< 1cm) and tubular
'High-Risk$_{colon}$' (≥ 1cm) or tubulovillous or villous
'At-Risk\s\do2' large (≥ 1cm), tubulovillous, villous or severely dysplastic

Table 46. Synchronous Colonic Adenomas Detected during Colonoscopy at Entry in 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' Groups*

Adenomas in the Rectum or Sigmoid colon	Number of Patients Examined	Number(%) of Patients with Colonic Adenomas				
		Total	Size >=1cm	Histology TVA/VA	Dysplasia Mod/Severe	'At Risk' Adenoma*
'Low-Risk$_{colon}$'	61	13 (21.3)	1 (1.6)	0 (-.-)	4 (6.6)	4 (6.6)
'High-Risk$_{colon}$'	121	45 (37.2)	22 (18.2)	11 (9.1)	17 (14.0)	28 (23.1)
chisquare		4.9	10.0	5.9	2.2	7.6
p value		0.03	0.001	0.01	0.15	0.006

* 'Low-Risk$_{colon}$': small (< 1cm) and tubular
'High-Risk$_{colon}$': large (≥ 1cm) or tubulovillous or villous
'At-Risk': large (≥ 1cm), tubulovillous, villous or severely dysplastic

There was an almost two-fold difference in the proportion of patients in the 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' groups with at least one synchronous colonic adenoma (21% vs 37% respectively; p=0.03). Furthermore, the characteristics of the synchronous adenomas differed profoundly. Only 2% of the 'Low-Risk$_{colon}$' group had an adenoma larger than 1 cm compared with 18% in the 'High-Risk$_{colon}$' group (p=0.001). None of the patients in the 'Low-Risk$_{colon}$' group had a synchronous tubulovillous or villous adenoma compared with 9% for the 'High-Risk$_{colon}$' group (p=0.01). The proportions of patients with moderately or dysplastic adenomas did not differ significantly between the groups (7% and 14% respectively; p=0.15). However, an 'At-Risk ' adenoma was observed synchronously in 23% of the 'High-Risk$_{colon}$' group compared with only 6% (4 cases) in the 'Low-Risk$_{colon}$' group (p=0.006).

Thus, synchronous colonic adenomas were less frequent in patients with only small tubular adenoma(s) in the rectum or sigmoid colon compared with those with either a large tubulovillous, villous or large adenoma. Furthermore, in the 'Low-Risk$_{colon}$' group, the synchronous adenomas were mainly small and of low malignant potential.

5.6.6 Summary and Conclusions

Overall in this cohort which comprised patients who had adenomas excised from the rectosigmoid only, the risk of subsequent colon cancer was approximately double that expected from the general population. There was no difference in risks between men and women. Risk increased with age, but at a similar rate to the general population. In univariate analyses, all the covariates under study (number, size, histology and grade of dysplasia) were associated with increased for colon cancer. However, in a multivariate Cox's proportional hazards model, histology (tubulovillous or villous vs tubular) was the strongest predictor, followed by size which was highly correlated with histology. The number of adenomas present was only a weak additional predictor while grade of dysplasia was of no extra value.

Two risk groups were identified: a 'Low-Risk$_{colon}$' group comprising patients with only small (< 1cm) tubular adenomas and a 'High-Risk$_{colon}$' group comprising patients with either a large, tubulovillous or villous adenoma. Risk in the 'Low-Risk$_{colon}$' was only half that of the general population

whereas the 'High-Risk$_{colon}$' group were at a 3.6-fold increased risk. The number of adenomas present did not alter the division into risk groups: patients in the 'Low-Risk$_{colon}$' group were at low risk even if multiple adenomas were present, while those in the 'High-Risk$_{colon}$' group were at high risk even if there was only a single adenoma present.

Patients in both risk groups were at a high risk of having synchronous and metachronous adenomas in the colon, but the adenomas in the 'Low-Risk$_{colon}$' group were mainly small and of low malignant potential compared with those in the 'High-Risk$_{colon}$' group.

5.7 DEFINITION OF A 'HIGH-RISK' AND 'LOW-RISK' GROUP FOR BOTH RECTAL AND COLON CANCER

This study has demonstrated that risk of subsequent rectal cancer is related to the size, histology and dyplasia of the adenomas found at entry, while risk of colon cancer is related to the size and histology and, to a much lesser extent, the number of adenomas at entry. It seemed appropriate, therefore, in defining a 'Low-Risk' group for both rectal and colon cancer to take into consideration all the characteristics of the adenomas at entry that are associated with increased risk of colon or rectal cancer, namely: number, size, histology and grade of dysplasia. Number was included as a precaution even though its contribution to risk after accounting for size and histology was small. However, there were only 64 cases with multiple, small tubular adenomas so the risk for this group could not be determined with any certainty.

Thus a 'Low-Risk' group was defined to include patients with only a single, small (< 1 cm), mildly or moderately dysplastic, tubular adenoma. This group comprised 46% of the men and 37% of the women (Table 47). The risk of rectal and colon cancer was no higher than that of the general population in either the men or women. Only 1 of the 14 rectal cancers and only 4 of the 35 colon cancers occured in this group. The overall risk of colorectal cancer in this 'Low-Risk' group for men and women combined was less than half of that of the general population (SIR=0.4; 95% CI: 0.1-1.0).

The remaining patients with either multiple, large (≥1 cm), tubulovillous, villous or severely dysplastic adenomas at entry were defined as the 'High-Risk' group. Risk of colon cancer was 2.8 times that in the general population in both men and women. Risk of rectal cancer was high only in the women (SIR=4.7; 95% CI: 2.1-8.9?). In the men, the risk was no higher than the general population, confirming that even in patients with 'High-Risk' adenomas, the risk may be reduced to that of the general population if the original adenomas detected at proctosigmoidoscopy at entry are completely excised and the rectum is re-examined at intervals to check for recurrences.

Table 47. Standardized Incidence Ratios for Rectal and Colon Cancer in the 'Low-Risk' and 'High-Risk' Groups*

	Number(%) Patients	Rectal Cancer Obs	Rectal Cancer SIR	Colon Cancer Obs	Colon Cancer SIR	Colorectal Cancer Obs	Colorectal Cancer SIR
Men							
'Low-Risk'	491 (46.3)	0	0.00	2	0.40	2	0.22
'High-Risk'	570 (53.7)	3	0.69	18	3.42	21	2.16
Women							
'Low-Risk'	206 (37.0)	1	0.94	2	0.86	3	0.96
'High-Risk'	351 (63.0)	10	5.08	13	3.47	23	3.96
Total							
'Low-Risk'	697 (43.1)	1	0.20	4	0.51	5	0.41
'High-Risk'	921 (56.9)	13	2.07	31	3.44	44	2.83

*'Low-Risk': single, small (< 1cm), mildly or moderately dyplastic tubular adenoma
'High-Risk': either multiple, large, tubulovillous, villous or severely dysplastic adenomas

5.7.1 Impact of Subsequent Examinations on Risk of Colorectal Cancer.

Almost half of the patients in this study (697/1618-43%) had one or more clinical examinations after entry for recurrence of symptoms (see section 5.3.2). The theoretical possibility that these examinations may have had a beneficial effect on the subsequent risk of cancer and may have been responsible for low risk status of the 'Low-Risk' group was investigated.

It was found that while such examinations did reduce the subsequent risk of colorectal cancer in both 'Low-Risk' and 'High-Risk' patients (Table 48), the effects were much more profound in the 'High-Risk' group. The standardized incidence ratio for 'High-Risk' patients having no further examinations was 3.9 compared with 1.5 in those having examinations ($p=0.008$). For 'Low-Risk' patients the corresponding values were 0.6 and 0.0 respectively ($p>0.1$). Thus, although all 5 of the colorectal cancers in the 'Low-Risk' group occurred among those not examined further, the cancer risk in this unexamined group was still no higher than in the general population.

The adenomas detected provided additional evidence that subsequent clinical examinations have a more profound effect on reducing risk in 'High-Risk' compared with 'Low-Risk' patients. Overall, 49 adenomas were detected, 36 in 'High-Risk' and 13 in 'Low-Risk' patients (Table 49). Only 18 of these adenomas were 1 cm or larger and only one of these large adenomas occurred in a 'Low-Risk' patient. Similarly of the 21 adenomas detected which were either large ($\geq$1cm), tubulovillous, villous, or severely dysplastic (At-Risk adenomas), only 3 were detected in 'Low-Risk' patients

An estimate of the number of cancers possibly prevented by undertaking such examinations was calculated using the methods described in Section 4.5.1. In the first method, the expected number of cases in the subsequently examined group was adjusted by the SIR for the not-examined group to give adjusted expected values for the examined group (Table 48). This produced only 2 extra cancers in the 'Low-Risk' group.(3.35 x 0.61 = 2.0) compared with 15 extra cancers in the 'High-Risk' group [6.55 x 3.87 = 25.3 (adjusted observed number in the examined group)-10 (actual observed) =15].

Table 48. Standardized Incidence Ratios for Colorectal Cancer in 'Low-Risk' and 'High-Risk' Groups According to Subsequent Clinical Examinations Undertaken after Entry.

	Total Patients	Obs	Exp	SIR
'Low-Risk'				
No Subsequent Examinations	440	5	8.16	0.61
Subsequent Examinations	257	0*	3.35	0.00
'High-Risk'				
No Subsequent Examinations	481	34	8.78	3.87
Subsequent Examinations	440	10*	6.55	1.53

'Low-Risk' :Single, mildly or moderately dyplastic small (< 1cm) tubular adenoma
'High-Risk':Multiple, large (≥ 1cm), tubulovillous, villous or severely dysplastic

* Adjusted expected value: 'Low-Risk' = 3.35 x 0.61 = 2.0
'High-Risk'= 6.55 x 3.87 = 25.3

Table 49. Adenomas Detected at Subsequent Examination after Entry in 'High-Risk' and 'Low-Risk' Patients and the Hypothetical Risk of Cancer Associated with these Adenomas*

	Adenomas Detected after Entry			
	Total Number	Size (≥ 1cm)	'At Risk'	Hypothetical Extra Cancers
Rectum				
'High-Risk	16	6	6	1.67
'Low-Risk	12	1	3	0.47
Colon				
'High-Risk'	20	11	12	3.15
'Low-Risk'	1	0	0	0.01
Colorectum				
'High-Risk'	36	17	18	4.82
'Low-Risk'	13	1	3	0.48

'Low-Risk' single,small (< 1cm),mildly or moderately dyplastic, tubular
'High-Risk' multiple,large (≥ 1cm), tubulovillous, villous or severely dysplastic

* Calculated using the findings of Stryker et al., 1987

The second method was based on the observation of Stryker et al (1987) that the risk of cancer in adenomas left in-situ is 2.5% at 5 years, 8% at 10 years and 24% at 20 years (see section 4.5.1). As a result, it was estimated that 4.82 cancers were prevented by adenoma-excision in the 'High-Risk' group compared with 0.48 in the 'Low-Risk' group (Table 49).

Thus the first method suggested that 2 cancers may have been prevented in the 'Low-Risk' group by adenoma-removal compared with 0.48 using the second method. Using the higher figure, the adjusted overall SIR for colorectal cancer was still only 0.6 and no higher than in the general population. In the 'High-Risk' group, there was a greater discrepancy in the hypothesised number of cancers prevented by adenoma-removal: 15 using the first method versus 4.8 using the second method. Whichever figure is chosen, this group remains at more than 3 times the risk of the general population.

CHAPTER SIX

DISCUSSION

6.1 SOURCES OF BIAS AND VALIDITY OF THE METHOD

6.1.1 Selection Bias

In this study, the relative risk of either rectal or colon cancer was calculated as a ratio of the observed number of cases in the study group to the expected number calculated from age, sex and calendar year-specific rates for the general population. This method was used since the main objective of the study was to determine whether persons with adenomas in the rectosigmoid constitute a special group with respect to their risk of developing colorectal cancer compared to the general population, therefore requiring regular surveillance by colonoscopy as is currently recommended (Lambert et al., 1984; Holtzman et al., 1987; Kinzie et al., 1988).

Ideally, it might have been preferable to have used a preselected asymptomatic cohort from the general population, but no such cohort existed. An alternative option was to consider this clinical series since at present, virtually all adenomas are detected coincidentally in patients presenting with bowel or other symptoms. Unlike the United States, it is not current practice in this country to undertake screening sigmoidoscopy in asymptomatic individuals without a history of colorectal adenomas or cancer. Therefore, this series would seem to be similar to the type of patient who is most commonly encountered with colorectal adenomas.

One might question, on theoretical grounds, the relevance of the findings of this clinical series to asymptomatic individuals, although it is unlikely that the presence of unrelated symptoms would influence the relative risks asscociated with the presence of adenomas. However, as a precaution the all-cause mortality was compared with that of the general population and found not to be significantly different (Section 5.3.1). Furthermore, the incidence and characteristics of the adenomas detected in this cohort were found to be similar to those in other published series of both symptomatic and asymptomatic individuals.

The incidence of adenomas within reach of the rigid sigmoidoscope during the period of recruitment of patients to this study was 1.9% (Table 4), a figure very similar to the 2.3% observed by Colvert & Brown (1948) and 2.4% by Castro et al., (1951) in more than 10,000 subjects undergoing routine proctosigmoidoscopy. It is lower than the figures quoted by Neugat & Pita (1988) in their survey of the literature which ranged up to 20%. However, they did not make a distinction between the 25 cm rigid and the longer flexible sigmoidoscope. Furthermore, in very few of these mostly early studies was a distinction made between adenomas and other non-neoplastic types of polyp. As a consequence, their rates should be regarded as an overestimate. It must be stressed that the present study included only patients with adenomas. Goligher (1980) noted in his textbook that American surgeons discovered polyps on sigmoidoscopy with much greater frequency than he did and that, in his experience, lesions in this region are far less common than is stated in many studies. In one study he quoted (Enquist, 1957), nearly half of the 2366 polyps seen on proctosigmoidoscopy were less than 3 mm. According to Goligher, these tiny polyps disappear spontaneously and are not visible at a subsequent examination. More recent studies have reported that 60% of small polyps in the distal colon and rectum are non-neoplastic (Church et al., 1988; Waye et al., 1988)

In two very large series (Jackman & Mayo, 1951; Rider et al., 1954), there was no difference in the prevalence of adenomas detected by proctosigmoidoscopy between symptomatic and asymptomatic patients. This is in accordance with the experience of several investigators that, apart from very large pedunculated adenomas which may bleed intermittently and villous adenomas which may produce mucus or pus, the vast majority of adenomas are asymptomatic. Moreover, about one quarter of the general public aged between 45 and 74 have some symptoms which could be associated with bowel neoplasia (Farrands & Hardcastle, 1984). Rectal bleeding is the most common reason for referral to hospital, but in the majority of cases the cause of the rectal bleeding is haemorrhoids. An association between the presence of haemorrhoids and adenomas was observed in a single autopsy study (Marigo et al., 1978), but the odds ratio for the joint association was only 1.5 and was not statistically significant.

There were twice as many men (1061) as women (557) in this study. A similar male: female ratio of patients with colorectal polyps has been observed in

other series (Castro & Brown, 1948; Prager et al., 1974; Spencer et al., 1984). There were approximately twice the number of men as women attending the outpatient clinics at St Mark's Hospital between 1957 and 1980 (Table 4) so the overall incidence of adenomas was similar in the men and women (1.9% vs 1.8%) in this series.

More than 85% of patients in the present study had only a single adenoma (Table 7). Comparison with other centres is not possible since an important methodological aspect of this study was the inclusion of patients with adenomas removed from the rectum and distal sigmoid colon only. Almost all previous studies included a proportion with adenomas removed from the proximal colon. More extensive examination would naturally increase the likelihood of finding multiple adenomas.

In the present study, 40% of adenomas were 1 cm or larger and 9% larger than 2 cm (Table 7). In most comparable series only the largest lesions were examined histologically and the smaller lesions undoubtedly included metaplastic polyps which rarely grow beyond 5mm (Ekelund & Lindstom, 1974). In a large series from Detroit, 55% of polyps were 5mm or smaller, but only 40% of the polyps of this size were biopsied (Wilson et al., 1955). Comparisons with more recent colonoscopy series may not be valid since the largest lesions in the rectum and distal sigmoid colon tend to be removed surgically prior to colonoscopy. Autopsy series may also be biased since very large lesions in the rectum are more likely to produce symptoms and be treated during life. The results of a few autopsy studies in which the size of adenomas have been related to the segment from which they were removed, suggest that the St Mark's figures may be rather high and possibly no more than 20% of individuals with adenomas in the general population have lesions 1 cm or larger (Arminski & Maclean, 1964; Eide & Stalsberg, 1978; Rickert et al., 1979; Williams et al., 1982; Clark et al., 1985).

In the current study, 63% of the adenomas removed at entry were classified as tubular, 27% as tubulovillous and 10% as villous (Table 7). The difficulties of comparisons with other series mentioned above are compounded by differences in definition. This study used criteria defined by Konishi and Morson (1982) in which adenomas comprising more than 80% of villous components were classified as villous, less than 20% as tubular and between 20% and 80% as tubulovillous. The National Polyp Study uses similar criteria

(O'Brien et al., 1990), and have reported that 40% of adenomas removed by colonoscopy at presentation have a tubulovillous or villous histology. These results relate to the whole colon, although the authors have stressed that most large villous lesions at entry are found in the rectum or sigmoid colon (Winawer et al., unpublished). Only a tiny proportion of adenomas found at autopsy are tubulovillous or villous (Rickert et al., 1979; Williams et al., 1982; Clark et al., 1985) suggesting perhaps that these are more likely to develop into cancers and produce symptoms during life.

The reporting of the grade of dysplasia is not only highly subjective, but also subject to differences in terminology and nomenclature. Severe dyplasia, also called carcinoma in situ or high grade dysplasia, occurred in 9% of the patients in the current series (Table 7); precisely the same proportion as reported by the National Polyp Study (O'Brien et al., 1990). The grade of dysplasia was not reported in any of the previous proctosigmoidoscopic or autopsy studies, therefore comparisons of the present series with the general population or with other series are not possible.

The findings from the study would appear, therefore, to be generally applicable to patients with adenomas in the rectum or distal sigmoid colon. It is important to realise, however, that they are relevent only to patients who have adenomas within reach of the rigid sigmoidoscope; they are not applicable to patients examined by colonoscopy who are found to have no adenomas in the colorectum or to those who have adenomas only in regions beyond the reach of the sigmoidoscope.

6.1.2 Ascertainment Bias

There are several other potential sources of bias inherent in the design of this study which could, theoretically, affect the validity of the findings. The most important relates to possible differences in the ascertainment of cancers in the the study group and the referent population. Most of the patients in the study group lived in the region covered by the North-East Thames Cancer Registry. This registry was started in 1950, but it was not until 1985, when the South Thames Cancer Registry assumed overall responsibility, that registration became anything like complete. That this study's data was more accurate than that of the North-East Thames Cancer Registry was emphasised by the finding that four of the colorectal cancers

diagnosed at St Mark's were not recorded in the Registry. Because of this discrepancy, rates for the South Thames region were used for comparison since accurate records have been maintained since 1950. It is unlikely that the two inner city populations differed substantially in their actual rates for the disease at that time, since the age-standardized incidence rates for 1985 and 1987 (when registration rates for the North-East Thames region were considered complete) were similar to those in the South Thames region (Table 50). Furthermore, the standardized mortality ratios for the two regions, were similar (Registrar General's Statistical Review of England and Wales, 1968-1971; Cancer Mortality Statistics, OPCS, 1975-1979).

There remained the potential problem, however, of the possible underdiagnosis of cases in the study group. There were 3 sources from which incident cases were collected: (i) diagnosis at St Mark's Hospital, (ii) death certificate via OPCS, (iii) cancer registration via OPCS. Of the 50 cases of colorectal cancer, 14 were diagnosed at St Mark's Hospital and 25 were reported by OPCS as a cause of death only. Fifteen cases were initially reported as cancer registrations of which 7 died and the colorectal cancer was mentioned as a cause of death on the death certificate. Thus there are 8 cases for which the source of information was the cancer registry only. It is this group which is likely to have been underestimated due to the inadequacy of the cancer registry data. The degree of underascertainment was assessed by comparing the standardized registration ratios (SRRs) for the two regions (Donnan, 1982; Swerdlow, 1986). For the period under study, the SRRs for the North-East Thames region were of the order of 30% lower than for the South Thames region (Cancer Statistics Registrations, OPCS, 1971-1982). Since the true incidence rates for the two regions were probably similar (see above), the differences in the SRRs reflect the extent of under-reporting in the North-East Thames region. Underestimation of the 8 cancer cases by 30% represents a loss of only 3 cases out of the total of 50 observed colorectal cancers in the study group. Since there is no reason to suppose that the accuracy of reporting of cases was related to the type of adenoma at entry, it is unlikely that this small discrepancy of 6% had a significant effect on the conclusions of this study.

Table 50. Age-Standardized Incidence Rates for Colorectal Cancer in the North-East and South Thames Regions, London for 1985 and 1987 (per 100,000 Population)

	North-East Thames	South Thames
1985		
Men	39.4	41.5
Women	41.0	46.4
1987		
Men	40.6	40.4
Women	42.3	42.0

6.1.3 Differential Censoring

Another potential source of bias, which was not problematic in this study, was the differential rate of censoring in the study group compared with the standard referent population. Almost half of the patients died during the 30 years of follow-up, but the death-rates throughout the study were similar to the general population (Table 20). Patients undergoing colonoscopy at follow-up were censored but no bias should have resulted since the decision to refer patients for colonoscopy was unrelated to the characteristics of the adenomas found at entry (Table 21). Only one cancer was diagnosed in this way and this was included as an endpoint in the study.

Bias due to loss to follow-up was not a problem since follow-up was passive via the OPCS. In many cases, especially those from the early years of the study, the NHS number was not known and was traced via OPCS from the patient's name, birth-date and address. Some of the patients were temporary residents in the area and so their addresses could not be used for tracing their NHS number. Patients who were not traceable could obviously not be followed up, but the majority of such patients were from outside the area, so they may have been a biased group and not comparable with the referent population.

Patients undergoing colonoscopy at entry were excluded because the risk of subsequent colon cancer after excision of adenomas from the colon was quite different from the group under study who only had adenomas excised from the distal colon and rectum. A further 64 cases were excluded at entry because they had large adenomas beyond the reach of the rigid sigmoidoscope treated by colotomy excision. Forty of these patients had no adenomas in the rectum or sigmoid colon and the large adenomas would have been missed by screening proctosigmoidoscopy. Among the remaining 24 cases, all but 6 cases had either a tubulovillous, villous or large ($\geq$ 1cm) adenoma within reach of the rigid sigmoidoscope which would have put them at high risk of colon cancer. Of the 6 cases with only small tubular adenomas, three had multiple adenomas in the rectosigmoid and two had a single adenoma with moderate dysplasia.

6.1.4 Errors of Measurement

Bias due to errors of measurement were minimised since all pathology specimens were examined by a single observer (Dr B. C. Morson) on a single occasion in a blind manner, that is without the pathologist knowing the ultimate status of the patient.

6.2 DISCUSSION OF RESULTS

This study was undertaken with the aim of providing a rational scientific basis for the investigation and follow-up of patients with colorectal adenomas. Whilst there is general agreement by all (Fruhmorgen et al., 1979; Waye & Braunfeld, 1982; Winawer et al., 1986) but a minority (Matek et al., 1985) of practitioners that all adenomas detected should be excised, there is no consensus as to the strategy for treating such patients thereafter. Should they undergo subsequent colonoscopy or would proctosigmoidoscopy of the rectum suffice? Alternatively is there a subgroup which requires no follow-up examinations at all?

To answer all of these questions, it is necessary to know the natural history of the disease, that is, the risk in the absence of surveillance. At St Mark's Hospital, a cohort of patients existed in whom a histological diagnosis of colorectal adenomas was made at a time when surveillance had not become routine practice. This cohort was and remains unique for several reasons. Firstly, biopsy of all colorectal polyps became mandatory at St Mark's Hospital from 1957. At other institutions, routine biopsy of colorectal polyps is a relatively recent phenomenon, most small polyps being removed in the past without a histological diagnosis (Wilson et al., 1955; Brahme et al., 1974; Spencer et al., 1984). Further, in this group it was possible to follow all but 3% of the patients until their death. Finally, there existed for England and Wales during the entire period of the study, a comprehensive system for notifying researchers of the development of colorectal cancer in study subjects as a result of cooperation between regional Cancer Registries and the National Health Services Central Register. Therefore, it was possible to be informed of cancers developing in the study subjects even if they moved away from the locality of the Hospital, although there were problems of ascertainment that have already been discussed.

Risks for rectal and colon cancer were examined separately. This was because after the initial examination and polypectomy, the rectum was considered to be essentially free of adenomas or cancers and at a low baseline risk at the time of entry compared with the general population. The colon, on the other hand, was essentially uninterfered with, since the rigid sigmoidoscope, even when inserted to its full extent, only reaches to the most distal part of the sigmoid colon leaving the majority of the colon unexamined. Risk of subsequent colon cancer was assumed, therefore, to be at least as high as that of the general population.

6.2.1 Risk of Rectal Cancer

Overall, the risk of subsequent rectal cancer was similar to that in the general population. There were 14 cases, only slightly higher than the 11.3 expected for the general population (SIR= 1.24; 95% CI: 0.7-2.1). It seemed, therefore, that the initial high risk of rectal cancer in these patients prior to adenoma-removal was reduced by polypectomy to the level of that in the general population

An indication of the possible number of rectal cancers prevented by adenoma-removal in this series can be estimated from the expected number of cases of a similar age and sex in the general population. If the prevalence of adenomas within reach of the rigid sigmoidoscope observed in this study, that is 2%, also pertained in an age and sex-matched cohort of 1618 men and women from the general population, then it can be assumed that adenomas were present in 34 individuals. There were 11.3 rectal cancers expected in this age and sex standardized population. If all the rectal cancers arose from adenomas present at start of follow-up, then the occurrence of 11.3 rectal cancers in only 34 patients, suggests that 32% of people with adenomas will develop rectal cancer.

The present study group comprised only patients who had adenomas. If in the absence of adenoma-removal, 32% of the 1681 study patients would have developed rectal cancer, then 518 rectal cancers should have occurred. This compares with only 14 observed cases suggesting that 504 cancers were prevented. Thus, it appears that 97% of the expected number of rectal

cancers in the study group were prevented by removing adenomas in the rectum. This may be a slight overestimate since it makes the unproven assumption that all the rectal cancers diagnosed in the general population arose in patients with adenomas and that the adenomas in which the cancers developed were present at entry.

Most of the published studies on the subsequent risk of rectal cancer after excision of adenomas by proctosigmoidoscopy relate to patients treated in the late 1950's and most do not specify the histology of the removed polyps. In the current study, the histopathology of all of the polyps was examined by a single pathologist on a single occasion at the start of the study, so inter-observer variation or periodic changes in nomenclature were eliminated. Follow-up times tended to be very short in most comparable studies and the subsite of the subsequent cancers were often not reported. Nevertheless, the findings of others are in general agreement with those in this study.

The earliest study (Colvert & Brown, 1948) compared the development of cancer in 117 patients with polyps which had been excised and 43 patients with polyps which had not. Rectal cancer developed in 2% of the treated group compared with 7% of the untreated group within 5 years. More recently, Brahme et al., (1974) invited 115 patients with polyps diagnosed by double contrast barium enema and 115 controls without polyps to return for another examination at a mean of 10 years later. Only one patient developed rectal cancer and this was at the site of a previous villous adenoma. None of the controls developed cancer.

The relatively low risk of rectal cancer observed in these early studies has been confirmed in two large series from the Mayo Clinic. Together these included all the men and women who had had a diagnosis of colorectal polyps between 1950 and 1969. Patients with polyps smaller than 1 cm which had been treated without a histological diagnosis were the subject of one paper (Spencer et al., 1984). Patients with polyps larger than 1 cm or smaller than 1 cm, but with a histological diagnosis were described in the other (Lotfi et al., 1986). The follow-up times were similar to this present study (mean 13 years) and 43% of their cohort, the same proportion as in this series were followed until their death. In the first study, rectal cancer developed in 6 of 323 patients with large polyps, although 4 cancers developed within 1 year and would have been considered to have been present at entry in the current

study. The expected number of cases was not reported specifically for rectal cancer, but was given for the distal bowel (rectum, sigmoid and descending colon). There were 9 cases which developed more than 2 years after entry compared with 6.2 expected (SIR=1.3; 95% CI: 0.6-2.4). In the study of patients with small polyps (< 1 cm), there were ony 7 cases of distal bowel cancer compared with an expected 9.3 (SIR=0.7; 95% CI: 0.3-1.5). Thus in neither study was the risk of subsequent rectal cancer significantly higher or lower than in the general population.

Gilbertson and Nelm (1970) have reported briefly the results of their study of repeated screening by proctosigmoidoscopy. All polyps found were removed and only 13 rectal cancers were detected in 21,150 men and women during 92,650 patient-years of follow-up. Gilbertson and Nelm estimated from incidence rates for a similarly-aged group in the Minnesota population that 90 cases would have been expected. Thus, they concluded that 85% of cases had been prevented. Their methodology has been criticised on several counts (Miller, 1987; Neugat & Pita, 1988). Miller questioned the calculation of the expected number of cases and, using the Seer incidence data (Young et al., 1981) and assuming a median age of 54 years, he estimated that only 38 cases should have been expected, equivalent to a reduction of 66%. It is also possible that the reported low risk was the result of the short follow-up times after what was effectively a screening examination for cancer. Patients had an average of only 5.4 annual examinations, equivalent to only 4.4 years of follow-up. In the present study, patients were not considered to be at risk until 2 years after entry and most of the rectal cancers did not develop until at least 9 years after entry. Furthermore, in a significant departure from the methodology in the present study, annual proctosigmoidoscopic examinations were undertaken and all polyps detected were removed. By contrast, the present work is a study of the natural history of the risk of subsequent rectal cancer after adenoma-removal without surveillance and 97% of adenomas were removed at the first visit. Finally, the proportion of patients in Gilbertson's study who had adenomas detected in the rectosigmoid was not stated, whereas in the present study *all* patients had at least one adenoma diagnosed and were therefore a priori at high risk.

The results of the present study are complicated by the different risks observed in the men and women. Only 3 cases were observed compared with 8.3 expected in the 1061 men, 50% of whom were followed for at least 14 years

(RR=0.36; 95% CI: 0.07-1.1). Furthermore, there is evidence that in all 3 cases the original adenomas were merely biopsied and not actually excised. Had the original adenomas been fully excised at entry, it is possible that the risk in the men may have been reduced even further.

The findings in the women appear to contradict this conclusion, since there were 11 cases of rectal cancer compared with only 3.0 expected (SIR=3.6; 95% CI: 1.8-6.5). The adenomas in the women in the present study were larger, more villous and more severely dysplastic than in the men (Table 7), a finding which has been observed by others (Potet & Soullard, 1971; Vatn & Stalsberg, 1982; Clark et al., 1985). It has been suggested that although fewer in number, adenomas in women have a higher malignant potential (Hill et al., 1978). This is not merely an age effect since, in the present study, the proportion of women with large, tubulovillous or villous adenomas exceeded that in men throughout life. However, the observed differences in the size, histology and grade of dysplasia between the men and women were not of sufficient magnitude to account for the ten-fold difference in relative risks. Furthermore men with large, tubulovillous, villous or severely dysplastic adenomas were not at increased risk, while the women with similar adenomas were.

It appeared from the findings of a case-control study using matched controls (see Appendix), that the high risk in the women was due primarily to inadequate excision of sessile adenomas, combined with a lack of follow-up to monitor for local recurrence. All but 3 of the female cases were treated before 1965. Several surgeons have, since that time, stressed the importance of careful follow-up after removal of sessile, tubulovillous or villous adenomas to watch for recurrences which occur in about 10% to 30% of cases (Quan & Castro, 1971; Nivatvongs et al., 1973; Thomson, 1977; Christiansen et al., 1979; Galandiuk et al., 1987). According to Thomson (1977), the high risk of recurrence after local excision of these types of adenoma was not generally appreciated until the end of the 1960s.

Thus, in both men and women, excess risk of subsequent rectal cancer was confined to patients with large (≥ 1cm), tubulovillous, villous or severely dysplastic adenomas who did not have follow-up examinations. There was no excess risk in patients with similar adenomas who underwent follow-up examinations or in patients with only small, mildly or moderately dysplastic,

tubular adenomas whether or not they had subsequent rectal examinations (Table 35). In the latter patients, the risk of rectal cancer in men and women was only one third of that of the general population (2 observed vs 5.4 expected; SIR= 0.37; 95% CI: 0.04-1.3) (Table 34). The reduction in risk of rectal cancer that this represents depends on the risk that they were at prior to excision of their adenomas. An estimate of the overall risk in the cohort was made at the beginning of this section, but the risk in this specific low-risk group is not known; nor by inference, therefore, is the benefit of adenoma-excision at entry in this group.

The finding that neither age nor the number of adenomas removed at entry were predictive of subsequent risk of rectal cancer in a multivariate Cox model analysis contrasts with colonoscopy series where these factors are the strongest predictors of risk of metachronous adenomas (Waye & Braunfeld, 1982; Holtzman et al., 1987). In a previous study from St Mark's Hospital (Muto et al., 1975), the probability of finding a focus of malignancy within an adenoma increased with increasing size, villousness and severity of dysplasia of the lesion. That size, histology and severity of dysplasia were also univariate risk factors for risk of future rectal cancer in the present study rather than a tendency to produce further adenomas in that region, emphasises that the malignant potential of the adenoma removed at entry is the most predictive of subsequent risk. This observation combined with the differential effects of the risk factors in the men and women reinforced the idea that the risk in the women was due to recurrence of the original adenomas rather than to development of new adenomas. These results confirm the importance of not only completely excising all adenomas detected via the rigid sigmoidoscope, but also of careful surveillance of patients with large, sessile, tubulovillous or villous adenomas or adenomas with severe dysplasia. If, however, it can be ensured that all adenomas in the rectum have been completely removed, that area may be at a lower risk of subsequent rectal cancer, than the general population.

6.2.2 Risk of Colon Cancer

The risk of subsequent cancer in the largely unexamined colon was approximately twice that in the general population (SIR=1.89; 95% CI: 1.35-2.70) and the relative risks in men and women were similar (SIR=1.7 and 2.3 respectively). Risk increased with age at entry with an approximate doubling of rates with each decade, but the relative risks showed no trend.

An approximate doubling of risk of colon cancer compared with either standard rates or a control group without polyps has been observed in several other similar series. In a 15-year follow-up of 283 patients (Prager et al., 1974), there were 12 cases of colon cancer beyond the reach of the rigid sigmoidoscope compared with 6.5 expected giving a relative risk of 1.85 (95% CI: 0.95-3.2). In a case-control study from Malmo, Sweden (Brahme et al., 1974) there were 2 colon cancers in 115 patients with adenomas after 10 years follow-up and none in 115 age, sex-matched controls without adenomas. In another study of 9669 patients examined by proctosigmoidoscopy, 537 patients with polyps were followed up and re-examined on a single occasion 5 to 9 years later (Rider et al., 1959). As a result cancer was detected in 3% compared with 2% in the remaining 9132 patients initally not found to have adenomas. These controls were not strictly comparable, however, as they were not subjected to the same follow-up examinations as the other patients.

The two studies from the Mayo Clinic (Spencer et al., 1984; Lotfi et al., 1986) are the most similar in design to the present study. The first study concerned small polyps (< 1cm) treated without a diagnosis and the second mainly large polyps which were biopsied. Thus, it is not known what proportion of their small polyps were adenomas. Risk of cancer of the whole colon was not reported, but for cancer proximal to the splenic flexure in the two studies combined the relative risk was 2.7 (95% CI: 1.7-4.1). This compares with a relative risk of 2.30 (95% CI: 1.3-3.7) in the present study for cancer of the colon proximal to the sigmoid.

It would seem, therefore, that the presence of adenomas in the rectum or sigmoid colon is a marker for risk of cancer in the colon particularly in proximal parts beyond the reach of the rigid sigmoidoscope. This would

appear to be confirmatory evidence in favour of the current practice of regular surveillance by colonoscopy of all patients with adenomas, a daunting task given the high proportion of the population theoretically at risk. However, in the present study, a raised risk was confined to patients with tubulovillous, villous or large (≥1 cm) adenomas (SIR=3.6; 95% CI: 2.3-4.8). All but 4 of the 35 colon cancers occurred in this group which was designated the 'High-Risk$_{colon}$' group.

This observation has not been made before, possibly because previous studies have not defined the histopathology of the index adenomas so carefully. There have been a few anecdotal reports of increased risk of colon cancer in patients with villous adenomas or papillary polyps as they were once called. There were 13 such patients in the study by Prager et al., (1974) and one (7.7%) developed a cancer in the colon (caecum), which was twice the proportion in the group overall. A high rate of occurrence of simultaneous colorectal adenomas or carcinomas in patients with tubulovillous or villous adenomas has also been noted in several surgical series (Southwood, 1962; Quan & Castro, 1971; Thomson, 1977).

Among the group of 323 Mayo Clinic patients (Lotfi et al., 1986) with a histological diagnosis of adenoma, the majority of whom were stated to have adenomas larger than 1 cm, the relative risk of colorectal cancer overall was 2.7 (95% CI: 1.7-4.2) and for proximal colon cancer, 4.2 (95% CI: 2.1-7.3). The risk was stated to be higher in patients with tubulovillous and villous adenomas, but the numbers were small. Furthermore, only 8% of the adenomas in their study were defined as tubulovillous or villous, a strikingly lower proportion than the 64% of adenomas larger than 1 cm in the present study. The differences may have resulted from a different classification of their adenomas which were examined between 1950 and 1969. The criteria used for their histological classification were not defined and no attempt was made to re-examine the pathology using WHO criteria (WHO, 1976). The histological classification of adenomas is subjective and misclassification is more likely to occur in large adenomas. This is because the histology of adenomas is heterogeneous and is defined according to the most villous histology seen in a specimen. Sampling errors are more likely to occur in large adenomas. When a series of pedunculated polyps removed at the Mount Sinai Hospital, New York, USA between 1948 and 1962, and previously classified as adenomatous polyps (tubular adenomas) were re-examined, one

third were found to contain a villous component and the likelihood of finding a villous component increased with increasing size (Kaneko, 1970). Fung and Goldman (1970) also showed that focal villous changes were much commoner than was previously supposed. They found such changes in 35% of adenomas overall and 75% of lesions larger than 1 cm. The raised risk of colon cancer in the Mayo Clinic patients with adenomas larger than 1 cm is confirmation that in situations where misclassification of the histology of adenomas is likely to occur, it is important also to consider the size.

While patients with tubulovillous, villous or large (≥ 1cm) adenomas were at an increased risk of colon cancer, patients with only small tubular adenoma(s) irrespective of the grade of dysplasia were at a low risk (Table 43). Only 4 of the total 35 cases occurred in this group and their risk was only half of that of the general population (SIR=0.51; 95% CI: 0.1-1.3). As a result they were designated the 'Low-Risk$_{colon}$' group.

In the Mayo Clinic Study, the relative risk of colorectal cancer in the patients with small polyps was not significantly higher than age and sex-matched members of the general population, (SIR=1.2; 95% CI: 0.7-1.9). This finding was used as a basis for their argument that removal of small colorectal polyps without biopsy is not associated with an increased risk of subsequent cancer. However, there were twice the expected number of cases of cancer in the proximal colon, beyond the splenic flexure (11 versus an expected 5.6) which almost reached statistical significance (95% CI: 0.98-3.5). Furthermore, of the 227 patients with small polyps examined histologically at entry, 3% were found to have a carcinoma demonstrating that not all small adenomas are innocent, as has been previously demonstrated (Muto et al., 1975; Enterline et al., 1962; Grinnel & Lane, 1958). In the present study, 18% of adenomas smaller than 1 cm had a tubulovillous or villous histology (Table 13). Since the majority of tubulovillous and villous adenomas were larger than 1 cm (62% and 92% respectively), it can be assumed that most small, tubulovillous or villous adenomas are destined to become large. The great majority (83%) of tubular adenomas are, however, smaller than 1 cm, suggesting that they are growing more slowly and may not become large. Thus, size alone in the absence of histopathology is not a reliable indicator of the malignant potential of a polyp.

The finding in the present study that the risk of cancer in patients with only small tubular adenomas was less than that of the general population is intriguing. If small tubular adenomas are not a marker for risk of colon cancer, one would expect the risk to be no higher, but certainly no lower either. The reduction in risk was not statistically significant, but only half the expected cases developed. There are two possible explanations for this finding:

1) Most of the adenomas likely to become malignant in these patients occurred within reach of the rigid sigmoidoscope and were removed at entry. This is theoretically feasible since adenomas and cancers tend to cluster in the same segments of the bowel (Eide & Schweder, 1984; Capell & Forde, 1989). Multiple adenomas are distributed evenly throughout the bowel, but solitary adenomas tended to be concentrated in the most proximal or distal ends of the bowel: the distal end in younger patients and at the proximal end in older patients (Williams et al., 1979; Ekelund, 1963).

2) An alternative possibility is that patients with only a small tubular adenoma when first seen tend to produce adenomas with a low malignant potential that are not destined to develop into cancer.

Evidence in support of the latter hypothesis was obtained from findings in 192 patients who underwent colonoscopy at a mean of 7 years after entry. The risk of development of metachronous adenomas of any size or type did not differ significantly between the 'High-Risk$_{colon}$' and the 'Low-Risk$_{colon}$' groups (35% vs 46% respectively; p=0.13). However, an 'at-risk' adenoma (either large, tubulovillous, villous or severely dysplastic) was detected in 19% of the 'High-Risk$_{colon}$' compared with only 8% of the 'Low-Risk$_{colon}$' group. In a similar study by Grossman et al. (1988), metachronous adenomas occurred in 29% of patients whose index lesion in the rectum or sigmoid colon was only a single small (<1cm) tubular adenoma with mild or moderate dysplasia, but only 3% had an 'at risk' adenoma and there were no cases of cancer. This compared with a risk in the remaining patients of metachronous adenomas of any size of 42% and a 13% rate of 'at-risk' adenomas. So it seems that patients with small tubular adenomas may be just as prone to develop metachronous adenomas as the patients with tubulovillous, villous or large adenomas, but these are of low malignant potential.

This would confirm another observation in this study, that the number of adenomas was a relatively unimportant risk factor for colon cancer after taking size and histology into consideration. The presence of multiple adenomas, in addition to at least one tubulovillous, villous or large adenoma, was associated with a profound increase in risk (SIR=6.6) and 10% of such patients developed colon cancer. However, risk was also raised in patients with a single large, tubulovillous or villous adenoma (SIR=2.9). Very similar findings were observed in the Mayo Clinic study of patients with adenomas larger than 1 cm where the relative risk was 2.7 in patients with single adenomas and 5.3 in patients with multiple adenomas. It should be noted that, in the present study, the increased risk associated with multiple adenomas among patients in the 'High-Risk$_{colon}$' group was confined only to the men (Table 43); women with single adenomas were at a higher risk than those with multiple adenomas.

Among patients in the 'Low-Risk$_{colon}$' group, the presence of multiple adenomas did not confer any increased risk. There were only 64 patients with multiple small tubular adenomas, but not a single case of colon cancer occurred in this group. The results from the Mayo Clinic would again support this finding. In the study of polyps < 1cm in size (Spencer et al., 1984), the relative risk of colon cancer was 1.3 in patients with single polyps compared with 0.9 in patients with multiple polyps. Patients with small tubular adenomas would appear therefore to be at low risk of subsequent colon cancer even if multiple adenomas are present.

These observations confirm that it is the size and histology of adenomas rather than the multiplicity which is of importance in defining risk for subsequent colon cancer when only the rectosigmoid is examined.

This may not, however, be the case if the the whole colon is examined by colonoscopy. Kronberg (personal communication) has shown that the risk of developing new adenomas after colonoscopy increases with the villousness of the adenomas found at entry. The rate of recurrence in patients with only tubular adenomas was 15% compared with 25% and 50% in patients with tubulovillous or villous adenomas. It seems therefore that when only the rectum and distal sigmoid colon are examined, the presence of a large or tubulovillous or villous adenoma may be a marker for multiple adenomas throughout the colon and an indication for colonoscopy. Alternatively since

patients with multiple adenomas usually have one which is large, tubulovillous or villous (Table 17), the presence of these adenomas in the rectosigmoid may be a surrogate measure for multiplicity when only the distal bowel is seen.

6.3 IMPLICATIONS

6.3.1 Colonoscopic Surveillance

The findings in this study have important implications. At present, the 25 cm rigid sigmoidoscope is the most common means by which adenomas in the colorectum are diagnosed. Because of the high rate of recurrence of adenomas in the colon beyond the reach of the sigmoidoscope, it is currently recommended that patients with adenomas in the rectosigmoid undergo regular surveillance by colonoscopy at 1 to 5 yearly intervals for life. The results of this study would suggest that this recommendation may be of benefit to patients with tubulovillous, villous or large adenomas because the risk of colon cancer is increased by a factor of more than three-fold. However, the results also suggest that such a policy would have no justification in patients with only small tubular adenomas, since their risk of colon cancer is no higher than that of the general population (unless surveillance by colonoscopy is to be applied to the entire population above 50 years of age). It would appear that at present endoscopists may be engaged in a time consuming process, removing small colonic polyps which are detected at follow-up in approximately 30% of these patients, while offering little benefit in terms of cancer prevention. It is reasonable to suggest therefore that patients with only small tubular adenomas in the rectosigmoid may require no surveillance after adenoma-removal at initial presentation.

There are however three provisos to this proposal:

(i) The majority of patients with small tubular adenomas had just a single adenoma. There were only 64 patients with multiple small tubular adenomas. Although none of these patients developed colon cancer and although the low risk observed in this study was also seen in the Mayo Clinic study, the numbers of patients involved in either study are too small to be confident that risk is indeed low in patients with multiple small tubular adenomas. Further confirmation is essential before defining these patients as a low-risk group in whom further colonoscopic surveillance may not be required.

(ii) Only patients free of colorectal cancer were entered into this study. To ensure that end, patients with cancers detected within 2 years were excluded, since it was assumed that the cancers were probably present at entry.

Therefore, the results of this study give no indication of the likelihood of finding a synchronous cancer at the time of entry, although, it is unlikely that adenomas with a high malignant potential were present in the unexamined colon at that time, since the risk of subsequent colon cancer was low.

More direct evidence for this supposition was obtained from patients undergoing colonoscopic examinations at entry and excluded from the main analysis. Only 5% of patients with small tubular adenoma(s) in the rectosigmoid had an 'at-risk' adenoma (≥1cm, tubulovillous or villous or severely dysplastic) in the colon beyond the reach of the rigid sigmoidoscope compared with 23% in patients with large, tubulovillous or villous adenomas (Table 46). Tripp et al., (1987) reported similar findings: of 32 cases with diminutive colonic polyps (DCP's) (<5mm) in the rectum or sigmoid colon, 11 (34%) had synchronous lesions in the proximal colon, but in only 4(12%) was the adenoma larger than 5mm and there were no cases of cancer. They concluded that colonoscopic investigation of patients with only small adenomas in the rectosigmoid is unnecessary. However, a different conclusion was reached by Ryan et al. (1989): of 73 patients with DCP's identified by flexible sigmoidoscopy who subsequently underwent colonoscopy, synchronous lesions were found in 57.5% and in 10 patients (14%) the lesions were of 'significance' (carcinoma, adenomas larger than 8mm or severely dysplastic). They concluded that colonoscopic examination of the colon is essential even for patients with small adenomas in the rectosigmoid. It should be noted that there were 8 tubulovillous adenomas and one villous adenoma among the DCP's at entry and whether the 'significant' synchronous lesions occurred in patients in this group was not mentioned.

However, in the absence of more consistent evidence from larger numbers of patients, it would be premature to suggest that patients with only small tubular adenomas do not require an initial screening colonoscopy to eliminate the possibility of synchronous cancer. Thus it is suggested that, where facilities exist, a single screening colonoscopy be performed.

(iii) The presence of adenomas of tubulovillous or villous histology or large size (≥1cm) were shown in this study to be the major risk factors for cancer in both the rectum and colon. In a Cox model, severe dysplasia was an extra

risk factor specifically for rectal cancer and multiplicity of adenomas, a minor extra risk factor for colon cancer. In formulating a policy for the management of patients who are found on examination with the rigid sigmoidoscope to have one or more adenomas, it might be safer to narrow the 'Low Risk' group for colorectal cancer overall to those with only a single small, mildly or moderately dysplastic, tubular adenoma. The implications of this study are that this group, which comprised 43% of this series, are at very low risk of subsequent rectal or colon cancer and may not require any further investigation or surveillance by colonoscopy.

The remaining patients with either multiple, large (≥1cm), tubulovillous, villous or severely dysplastic adenomas comprise a group among whom depending upon the completeness of the initial treatment of the adenoma, some patients may be at increased risk of subsequent rectal cancer and also of colon cancer. These patients may possibly benefit from colonoscopic surveillance, but determination of the degree of benefit or of appropriate intervals between examinations is beyond the scope of this study and is being investigated in the 'Neoplastic Polyp Follow-up Study' (Macrae et al.,1990).

6.3.2 Prevention of Rectal Cancer

The findings in the men indicate that if all adenomas detected via the rigid sigmoidoscope at entry are completely removed and if follow-up is instituted for patients with tubulovillous, villous, large (≥ 1cm) or severely dysplastic adenomas, then the risk of subsequent rectal cancer becomes lower than that of the general population.

In this study, not only was the risk of rectal cancer low, but also the probability of developing new adenomas in the rectum. Of 697 patients re-examined by proctosigmoidscopy, only 28 (4%) had new adenomas in the rectum. It has been shown in several autopsy studies that adenomas tend to be located in the distal bowel in younger patients and are more prevalent in the proximal bowel at older ages (Vatn & Stalsberg, 1982; Clark et al., 1985). These changes in the distribution of adenomas with age parallel changes in the location of cancers. It is possible that once adenomas have been removed from the distal bowel on initial examination, that area may remain

essentially free of adenomas. Early results from the National Polyp Study indicate that adenomas found on initial colonoscopy tend to be concentrated in the distal bowel, while new adenomas develop subsequently in the proximal colon (O'Brien et al., 1990). This would imply that repeated examination of the rectum after adenoma-removal is unnecessary. Gilbertson found that there were no cases of rectal cancer within 7 years of two negative proctosigmoidoscopic examinations. Using mathematical modelling, Eddy (1980) suggested screening at intervals of 3-5 years, and based on this, the American Cancer Society (1980) currently recommends screening sigmoidoscopy at 3-5 yearly intervals after two negative sigmoidoscopies. Frame and Carlson (1975) have suggested that only a single proctosigmoidoscopic examination at age 55 years is required and that further examinations are uneconomic. The present study would support that suggestion to some extent in that after adenoma-removal (on a single occasion in all but 3% of cases), risk of cancer was very low. The current study offers little information regarding the optimum age at which to perform this single examination. The median age of the patients in the present study was 59 years with an interquartile range of 50 to 66 years, therefore age 55 years seems a reasonable option.

However, to accept the proposition that a single examination is sufficient, it is necessary to assume that the adenomas destined to develop into cancer are already present by age 55 years (or whatever age is chosen). It would be important to avoid length-time bias, that is the detection mainly of slowly growing lesions of low malignant potential which do not constitute a significant risk of cancer. However, this may not be a problem in practice since in the present study, 50% of patients in this series had tubulovillous, villous or large ($\geq$ 1cm) adenomas which if left in-situ are known to have a high malignant potential (Muto et al., 1975). It is proposed to repeat the current study in patients who have been found on proctosigmoidoscopy to have no adenomas in the rectosigmoid. A low risk of subsequent rectal cancer in these patients would be powerful evidence in support of a single examination for average-risk asymptomatic individuals.

This method would enable the detection of patients with large tubulovillous or villous or severely dysplastic (and possibly multiple) adenomas who would require regular surveillance. The remainder with only a single, small tubular mildly or moderately dysplastic adenoma would (after adenoma-

removal) be considered to be at the same risk as the patients who were initially polyp-free.

6.3.3 Prevention of Colon Cancer

Approximately 55% of colorectal cancers occur in the rectum or sigmoid colon (Thames Registry data). Assuming that these cancers arise from pre-existing benign adenomas, the majority should be, at least theoretically, amenable to prevention by polypectomy via the rigid sigmoidoscope. In practice, however only the most distal 17 cm of the bowel are consistently examined using the rigid sigmoidoscope (Nivatvongs & Fryd, 1980; Winnan et al., 1980; Marks et al., 1979). This is because it can be difficult to negotiate the rectosigmoid bend. Therefore, adenomas and adenocarcinomas of the colon occurring in the sigmoid colon just beyond the rectosigmoid region may be missed using the 25 cm rigid sigmoidoscope. Flexible sigmoidoscopes which are similar to, but shorter than, the colonoscope are now available and allow passage of the instrument higher into the bowel with less discomfort to the patient. Flexible sigmoidoscopes have been shown to increase the yield of neoplasms four-fold (Bohlman et al.,1977; Marks et al.,1979; Winnan et al., 1980; Weissman et al., 1987). Also patients report less discomfort with the flexible scope than with the rigid sigmoidoscope and were more willing to return for repeat examinations (Winawer et al., 1987).

Thirty percent of cancers occur in the region of the colon proximal to the splenic flexure and would not be detected by the 60 cm flexible sigmoidoscope. It has therefore been suggested that screening by complete colonoscopy is necessary (Reasbeck, 1987; Neugat & Forde, 1988). This study has shown that the presence of either a large, tubulovillous or villous adenoma in the rectosigmoid is predictive of increased risk of cancer in the proximal colon; therefore there is scope for prevention of such cancers if patients with large tubulovillous or villous adenomas are referred for colonoscopy. The proportion of proximal colon cancers which could be prevented in this way is not known. Examination of the distal bowel will not, of course, identify patients at risk of proximal colon cancer in the absence of any rectosigmoid adenomas. It is proposed to determine what proportion of patients with cancer in the proximal colon cancer have index adenomas in the rectosigmoid, with a view to determining the likely impact of sigmoidoscopy on prevention of colon cancer.

CHAPTER SEVEN

CONCLUSIONS

After removal of adenomas from the rectum and distal sigmoid colon via the rigid sigmoidoscope, the risk of subsequent rectal cancer in the 1618 men and women in this study followed for a mean of 14.2 years was no higher than that of the general population. There were however significant sex differences in risks. The men were at only one third of the risk of the general population, while the women were at a more than three-fold increased risk.

The women were significantly older than the men and their adenomas were significantly larger, more villous and more dysplastic, but none of these factors accounted for the ten-fold difference in relative risks between the sexes. A case-control study indicated that the main difference between the sexes was in the proportion of sessile and inadequately excised adenomas. Thus the increased risk in the women appeared to be a consequence of the inadequate excision of large, sessile adenomas at entry, combined with an absence of follow-up to monitor for local recurrence.

It may be concluded from these findings that if **all** adenomas detected via the rigid sigmoidoscope are removed at entry, and if patients are monitored for local recurrences when the adenomas are large ($\geq$ 1cm), tubulovillous, villous or severely dysplastic, then the risk of subsequent rectal cancer is lower than that of the general population. In this study, 97% of adenomas were detected at the first visit and very few patients developed new (metachronous) adenomas in the rectum, suggesting that complete removal of adenomas on a single occasion may be sufficient to prevent the majority of rectal cancers.

Risk of subsequent cancer of the largely unexamined colon was twice that of the general population and was similar in men and women. However, increased risk was confined to patients with tubulovillous, villous or large ($\geq$ 1cm) adenomas regardless of the number of adenomas present. Thirty one of the 35 colon cancers occurred in this group. These patients were, therefore, designated a 'High-Risk$_{colon}$' group.

The remaining 776 patients with only small tubular adenoma(s) were at only half the risk of the general population and were designated the 'Low-Risk$_{colon}$' group. Although this group comprised 48% of the cohort, only 4 of the 35 cancers occurred therein.

The number of adenomas detected in the rectosigmoid region did not influence the division into 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' groups. Patients with small tubular adenomas were at low risk whether or not adenomas there were multiple adenomas present (SIRs= 0.6 for single versus 0.0 for multiple adenomas). While patients with tubulovillous, villous or large ($\geq$ 1cm) adenomas were at high-risk even if there was only a single adenoma (SIR=2.9). If, however, multiple adenomas were present, risk was particularly high (SIR=6.6) and almost 10% of this group developed colon cancer.

It was shown that the risk of development of synchronous and metachronous adenomas in the colon was of the order of 20% to 40% in both the 'Low-Risk$_{colon}$' and 'High-Risk$_{colon}$' patients, but the adenomas in the 'Low-Risk$_{colon}$' group were mainly small and of low malignant potential. This finding together with the observation that the risk of colon cancer is low in the 'Low-Risk$_{colon}$' group would suggest that removal of small adenomas from the colon may not be of benefit to patients.

In conclusion, the results of this study indicate that colonoscopic surveillance may be warranted for patients found to have tubulovillous, villous or large ($\geq$ 1cm) adenomas in the rectosigmoid. On the other hand, it would appear that it may be unrewarding as a cancer prevention measure in patients with only small tubular adenomas in the rectosigmoid, since their risk is so low.

In formulating a surveillance policy, it may be advisable to limit a 'No Follow-Up' group to those with only a single, small (< 1cm), mildly or moderately dysplastic, tubular adenoma. It may also be advisable to perform a single screening colonoscopy at entry to exclude synchronous colonic carcinomas, but the finding of small tubular adenomas in the colon need not necessarily be considered an indication for further surveillance. These occur in approximately one third of patients and do not appear to be associated with excess risk of colon cancer. This finding would have a

considerable impact on the work-load of colonoscopists, since 43% of patients of this series fell into this 'No Follow-Up' category.

APPENDIX

CASE-CONTROL STUDY OF RISK FACTORS FOR RECTAL CANCER

AIMS

1) To determine whether the incomplete excision of adenomas at entry or the lack of local surveillance after excision were additional risk factors for the development of subsequent rectal cancer in the main cohort.

2) To determine whether these factors account for the observed differences in risk of rectal cancer between the men and women in the main cohort.

BACKGROUND

The treatment of colorectal adenomas is largely dependent on the size of the adenoma and whether the lesion is sessile or pedunculated. Pedunculated lesions present few problems in their management. Sessile adenomas are difficult to treat, particularly if they are large or situated in the lower rectum. The aim of treatment is to preserve the anal sphincters. Diathermy excision is the least invasive and most commonly used technique. However, complete excision is difficult to achieve with local excision and there is a high rate of recurrence, a fact that was not generally appreciated until the late 1960s (Thomson, 1977). It is important, therefore, to provide follow-up for all sessile lesions particularly if it is suspected that the lesion is incompletely excised.

Since the high risk in the women in the cohort study was confined to those treated before 1965, it was decided to investigate whether differences between the sexes in the management of their adenomas at entry were responsible. Rather than examining the hospital notes for the whole of the original cohort, the additional information was collected on all of the cases and a suitable subset of the controls.

METHODS

For each case, up to 10 controls were selected from among the remaining patients in the study, based on the following matching criteria: age at entry (± 5 years), the number, size, histology and grade of dysplasia of the adenomas removed at entry and the year of entry into the study (± 5 years). They were not matched on sex. The controls must have been at risk after adenoma-treatment for at least as long as the matching case. When more than 10 controls met the matching specification, those controls that most closely matched the case were selected.

The patients' hospital notes were examined and the following additional information was extracted wherever possible.

1. The morphology of the initial adenoma(s): sessile, pedunculated or presence of a stalk not recorded.
2. The type of excision: local (diathermy, snare), segmental resection (including submucosal excision).
3. The completeness of excision according to the pathology report (this was rarely recorded during the 1960s when the majority of these cases entered the study.
4. The number of years of follow-up.
5. Removal of metachronous adenomas and, if appropriate, their subsites.
6. Recurrence and further excision of the original adenoma (prior to development of cancer in the cases).

A new variable, "adequacy of excision" was created combining the information above:
An adenoma was to be considered to be "adequately excised" if it was
(i) pedunculated and excised (not just biopsied)
(ii) "completely excised" according to the pathology report
(iii) sessile, but treated by segmental resection or submucosal excision
The remainder were considered to be "inadequately excised".

STATISTICAL METHODS

Initially, each case was individually matched to one or more controls. Cases with identical matching criteria were placed in the same stratum, so that the number of cases and controls varied from set to set.

The statistical package, PECAN, was used to estimate the:

1) Odds ratio from the conditional likelihood, OR=exp (β), where β is the regression coefficient for each variable in the logit linear model
2) Standard error for each variable in the equation
3) Score statistic for the test of the null hypothesis that the most recently added variable does not affect risk, H_0: OR=1.

A multivariate analysis was performed to determine which, if any, of the variables under study explained the differences in risk between the sexes. The variable sex was added to the model after each of the variables in turn.

RESULTS

UNIVARIATE ANALYSIS

CASES VS CONTROLS

There were 74 controls (43 men and 31 women) who met the matching criteria. For the purposes of matching, the 14 cases were divided into 11 matched sets (Table 51).

Sex: As expected from the multiple regression analysis of the full cohort, there was still a statistically significant relative risk associated with sex (OR after matching =4.7; 95% CI=1.2-19; p=0.02).

Morphology: 71% of the cases had sessile adenomas compared with only 20% of the controls (OR after matching=14.6; 95% CI=3-72; p<0.001). Thus most of the cases had sessile adenomas while most of the adenomas in the controls were pedunculated.

Table 51. Morphology, Method and Completeness of Excision and Clinical Follow-up in Cases with Rectal Cancer and Controls.

	Number (%) of Patients	
	Cases n=14	Controls n=74
Morphology		
Sessile	10 (71.4)	15 (20.3)
Pedunculated	3 (21.4)	57 (77.0)
Not known	1 (7.1)	2 (2.7)
Method of Excision*		
Not excised	6 (42.9)	2 (2.7)
Local excision	8 (57.1)	66 (89.2)
Resection	0 (0.0)	6 (8.1)
Follow-up (years)		
0	13 (92.9)	39 (52.7)
1-4	1 (7.1)	9 (12.2)
5-9	0 (0.0)	8 (10.8)
10 or more	0 (0.0)	18 (24.3)
Inadequate Excision**	11 (78.6)	21 (28.4)
Inadequate Excision without Follow-up	10 (71.4)	8 (10.8)

* Local: diathermy +snare if pedunculated;
Resection: segmental resection or submucosal excision

** Biopsied only, sessile treated by diathermy or "incompletely excised"

Method and Completeness of Excision: The adenomas in almost half of the cases (6/14) were merely biopsied and, for various reasons (mainly patient refusal), the adenomas were not excised. The remaining 8 cases were treated by local excision methods only.

In only 2 of the 74 controls were the adenomas merely biopsied and not excised. Of the remaining patients, 90% were treated by local excision methods. However, 77% of the controls had pedunculated adenomas that were easily treated by snaring the stalk and diathermy of the base. Of the 10 controls with sessile adenomas, 6 were treated by segmental resection which ensured complete excision.

The adenomas were reported to be "completely excised" in 22% of the controls and in none of the cases.

Adequacy of Excision: Three quarters of the controls compared with only one third of the cases had their adenomas "adequately excised" according to previously defined criteria (OR after matching =7.8, 95% CI=2-30 $p<0.001$).

Follow-up: Only one of the cases had any clinical follow-up and this was for just 18 months. By contrast, more than half of the controls were followed for up to 30 years and, as a result, 6 were treated for recurrences. The odds ratio for follow-up (0 vs 1 or more years) after matching was 10.8 (95%CI=1-88; $p=0.006$).

Adequacy of Excision and Follow-up: 71% of the cases had inadequately excised adenomas and no follow-up compared with 11% of the controls (OR after matching =26.2; 95% CI=5-139; $p<0.001$).

MEN VS WOMEN

There were a total of 46 men (3 cases, 43 controls) and 42 women (11 cases, 31 controls). The simple proportions of men and women with sessile adenomas, "inadequate excision" and no follow-up provide some indication of the confounding (Table 52). However, in order to take account of the

Table 52. Morphology, Method and Completeness of Excision, and Clinical Follow-up in Male and Female Cases and Controls*.

	Number (%) of Patients	
	Men n=46	Women n=42
Morphology		
Sessile	9 (19.6)	16 (38.1)
Pedunculated	36 (78.3)	24 (57.1)
Not known	1 (2.2)	2 (4.8)
Method of Excision**		
Not excised	5 (10.9)	3 (7.2)
Local excision	36 (78.3)	38 (90.5)
Resection	5 (10.9)	1 (2.4)
Follow-up (years)		
0	27 (58.7)	25 (59.5)
1-4	5 (10.9)	5 (11.9)
5-9	3 (6.5)	5 (11.9)
10 or more	11 (23.9)	7 (16.7)
Inadequate Excision***	12 (26.1)	20 (47.6)
Inadequate Excision without Follow-up	7 (15.2)	11 (26.2)

* Men: 3 cases, 43 controls; Women: 11 cases, 31 controls

** Local: diathermy +snare if pedunculated;
Resection: segmental resection or submucosal excision

*** Biopsied only, sessile treated by diathermy or "incompletely excised"

stratified sampling, odds ratios estimated from the conditional likelihood are also presented as a measure of association. This is a purely descriptive statistic and has no interpretation as a population value.

Morphology: The proportion of women with sessile adenomas was almost double that of the men (38% vs 20% respectively, OR after matching = 2.5; 95% CI=1-7).

Method and Completeness of Excision: Methods of excision did not differ significantly in men and women, although 11% of men compared with only 2% of women were treated by methods other than local excision. Adenomas were biopsied only and not excised in a similar proportion of men and women (7% vs 11% respectively).

The proportion of patients with adenomas reported as "completely excised' did not differ significantly between the sexes.

Adequacy of Excision: The proportion of women with inadequately excised was almost double that in men (48% vs 26%) although the differences were not significant (OR after matching=2.3 95% CI=0.9-1.8; p=0.06).

Follow-up: The proportion of men and women with no follow-up at all was very similar (59% of men vs 60% of women).

Inadequate Excision and No follow-up: The proportion of women with "inadequately excised" adenomas among the patients with no follow-up was also about double that in the men (26% vs 15% respectively), but because of small numbers, the differences were not significant (OR after matching=2.3 95% CI=0.6-5.7; p=0.2).

MULTIVARIATE ANALYSIS

The single variables that accounted for most of the variability in the data were morphology and "adequacy of excision". When sex was was added (in a forward stepwise manner) to a regression model with either of these factors the score statistic was not significant (p=0.09). Thus it seems that the higher proportion of sessile and inadequately excised adenomas in the women at least partially explained the increased risk of rectal cancer in the women.

Although absence of follow-up was a significant univariate risk factor for rectal cancer, it did not explain the differences in risks between the sexes. This suggests that both men and women were followed inadequately, but to a similar degree. This mattered less in the men because their adenomas were more often pedunculated, or if sessile treated by segmental resection and, as as a result, they were more adequately excised.

CONCLUSION

The morphology of the adenomas, the adequacy of excision and the follow-up after excision were all shown to be important additional risk factors for rectal cancer. Only one case had any follow-up and this was only for 18 months. However absence of follow-up did not account for differences in risk between the sexes because a similarly large proportion (60%) of both men and women had no follow-up. The main differences between the sexes was in the proportion of sessile and "inadequately" excised adenomas which was approximately double in the women. It appears that the higher risk observed in the women in the cohort resulted from the inadequate excision of sessile adenomas which were either large, tubulovillous, villous or severely dysplastic. This problem was compounded by a lack of follow-up to monitor for local recurrence.

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