

Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic

R S Houlston, V Murday, C Harocopos, C B Williams, J Slack

Abstract

Objective—To introduce and monitor a screening programme for first degree relatives of patients with colorectal cancer based on their calculated lifetime risk.

Design—Lifetime risks were calculated for first degree relatives of patients with colorectal cancer and used to offer screening based on estimated risk.

Setting—A family cancer clinic was set up as part of the North East Thames Regional Genetic Service for relatives of patients who had developed colorectal cancer before the age of 45 and members of families in which multiple cancer had occurred.

Patients—Self referrals as well as patients referred by general and hospital practitioners.

Intervention—Relatives with a lifetime risk of 1 in 10 or greater (high risk group) were offered screening five yearly by colonoscopy, and those whose risk was between 1 in 10 and 1 in 17 were offered yearly screening for faecal occult blood. Women with family histories compatible with Lynch type II cancer family syndrome were offered screening for breast and pelvic tumours.

Results—In four years 715 patients were seen. Acceptance of screening was 90% (644 patients). Of 151 patients screened for faecal occult blood, two were found to have polyps. This screening test was unsatisfactory for the high risk group, having a negative predictive value of 78% in 59 patients tested. Regular screening by colonoscopy was offered to 382 high risk patients; 62 patients with polyps and five with colonic cancer were found. One hundred and ten pedigrees were identified with the Lynch type II cancer family syndrome, and four of 35 women screened were found to have breast cancer. Of 14 relatives aged over 65 with a 1 in 2 risk of site specific colonic cancer or Lynch type II cancer family syndrome, seven were found to have polyps, one of whom had carcinoma in situ.

Conclusions—Family history can be used to identify those at risk of colonic cancer and to target appropriate screening. Colonoscopy detected a high number of premalignant colonic polyps, but faecal occult blood testing was unsatisfactory for those at high risk of colorectal cancer.

Introduction

The lifetime risk of death from colorectal cancer in England and Wales is approximately 1 in 50 and increases rapidly from age 50. Unfortunately, the results of treatment are disappointing with an acknowledged survival rate of 50% in patients undergoing surgery with a view to cure. In 1974 Morson pointed out that most colorectal carcinomas arise in pre-existing adenomatous polyps and this hypothesis of the adenoma-carcinoma sequence offers an opportunity for early diagnosis and treatment if polyps can be identified.¹

Population screening using faecal occult blood tests, though low in cost, has so far been found to have a disappointing uptake and poor yield.² A screening

programme targeted at people at high risk should be more efficient. Furthermore, compliance is likely to be high among those who perceive themselves to be at increased risk and have a good understanding of the reasons for screening.

Family studies have shown that the risk of colorectal cancer in the first degree relatives of affected individuals is two to four times the risk in the general population.^{3,6} Furthermore, a number of dominantly inherited syndromes associated with colorectal cancer are now recognised. Adenomatous polyposis coli is the best known and is recognised as the condition with the highest risk of bowel cancer. Other dominant conditions associated with a high risk of colorectal malignancy include site specific colonic cancer⁷ and a cancer family syndrome^{8,9} that is associated with an increased risk of uterine, breast, and other extracolonic cancers in addition to an increased risk of colonic cancer. These two non-polyposis cancer family syndromes have been classified as Lynch types I and II respectively.¹⁰ Neither is associated with such florid polyposis of the bowel as is found in adenomatous polyposis coli, but adenomas occur and are recognised to be the premalignant lesion.

A family cancer clinic was opened to provide genetic counselling and screening for patients at risk. In four years 715 patients have been seen, and we report the results of screening.

Patients and methods

PATIENTS

In 1986 a family cancer clinic was opened at St Mark's Hospital as part of the North East Thames Regional Genetic Service for relatives of patients with colorectal cancer. The clinic was supported by the Imperial Cancer Research Fund and publicised in the national press. Clear guidance was given that screening was available for first degree relatives of patients who had developed colorectal cancer before the age of 45 and members of families in which multiple cancers had occurred. A decision was made to accept self referrals as well as people referred by general practitioners and hospital consultants.

Pedigrees were obtained from those attending, risks were estimated and explained, and a screening programme was offered.

CALCULATION OF RISKS TO FIRST DEGREE RELATIVES

Before the clinic was opened the risks to relatives of patients with colorectal cancer had been estimated from Lovett's pedigrees⁶ of families ascertained through a consecutive series of patients with colorectal cancer by life table methods.¹¹ For first degree relatives of index patients—that is, parents, siblings, and children aged 45 and under—there were 1665 years at risk, and the relative risk was 6.4 (95% confidence interval 1.9 to 10.9). For first degree relatives aged over 45 there were 54 856 years at risk and the relative risk was 2.7 (2.3 to 3.1). Relative risks were used to estimate lifetime risks to relatives of index patients with colorectal cancer; because of the large confidence

Department of Clinical Genetics, Royal Free Hospital and School of Medicine, London NW3 2QG

R S Houlston, MRCPATH, lecturer
V Murday, MRCP, lecturer
J Slack, DM, senior lecturer

St Mark's Hospital, London EC1V 2PS
C Harocopos, SRN, genetic pedigree nurse
C B Williams, FRCP, consultant

Correspondence to: Dr Slack.

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intervals rounded figures were used for clinical practice (table I).

SCREENING POLICY

From the calculated risks a practical policy for screening relatives was devised. Those with risks between 1 in 10 and 1 in 17 were offered annual screening by faecal occult blood testing (Haemoccult test). For those whose risks were 1 in 10 or greater colonoscopy was chosen for two reasons: firstly, large bowel lesions in high risk families tend to be right sided, with only 26% being detectable by sigmoidoscopy,^{10,12} and, secondly, colonoscopy allows the removal of small adenomas at the time of screening. Among affected members of high risk families the mean age for developing colonic cancer is 40 years, and 77% of the risk of having colorectal cancer is past by the age of 69.¹²

Follow up studies of adenoma suggest that examinations at three year intervals are adequate for those with

TABLE I—Lifetime risks of colorectal cancer in first degree relatives of patients with colonic cancer (based on the Lovett series⁹)

Population risk	1 in 50
One relative affected	1 in 17
One first degree relative and one second degree relative affected	1 in 12*
One relative aged under 45 affected	1 in 10
Two first degree relatives affected	1 in 6
Dominant pedigree	1 in 2

*Estimated from polygenic model.

TABLE II—Screening policy for colonic, breast, and pelvic cancer at a family cancer clinic

Colonic cancer:	
Risk <1 in 10	Faecal occult blood test
Risk ≥1 in 10	Colonoscopy five yearly, three yearly if polyps found
Breast cancer:	
Age 25-	Baseline mammography, yearly ultrasonography
Age 40-	Yearly mammography
Age ≥50	Participation in national breast screening programme
Pelvic cancer:	
From age 25	Yearly pelvic ultrasonography

TABLE III—Sources of referrals to family cancer clinic. Values are numbers (percentages)

Type of referral	First 20 months (n=411)	Next 28 months (n=304)	All four years (n=715)
By patient	252 (61)	174 (57)	426 (60)
Self referral	196 (48)	166 (55)	362 (51)
Through general practitioner	56 (14)	8 (3)	64 (9)
By medical practitioner	158 (38)	131 (43)	289 (40)
General practitioner	102 (25)	57 (19)	159 (22)
Hospital consultant	52 (13)	68 (22)	120 (17)
Other (screening programmes)	4 (1)	6 (2)	10 (1)

TABLE IV—Results of screening by colonoscopy in relatives at high risk of colorectal cancer

Risk	No (%) of relatives			Mean (SD) age (years) of relatives with polyps
	Screened	With adenomatous polyps	With cancer	
1:2	202	36 (18)	3	46.4 (9.9)
<1:2 to 1:10	132	14 (11)		48.7 (9.8)
Affected	30	9 (30)	2	45.2 (7.0)
<1:10 with symptoms	18	3 (17)		43.7 (11.1)

TABLE V—Number of patients at risk of colorectal cancer who had colorectal polyps

Risk	Polyps in proximal colon* (n=12)	Polyps in middle colon† (n=16)	Polyps in distal colon‡ (n=36)
1:2	7	8	22
<1:2 to 1:10	2	4	8
Affected	2	3	4
<1:10 with symptoms	1	1	2

*Caecum and ascending colon.

†Hepatic flexure to splenic flexure, including transverse colon.

‡Descending and sigmoid colon and rectum.

pre-existing polyps (unpublished data). It was therefore decided to offer colonoscopy every three years between the ages of 25 and 65 if polyps were detected on initial examination, but every five years if no polyps were detected. In clinical practice, when there was evidence of dominant inheritance those family members over 65 who had a 1 in 2 risk of inheriting the liability were offered one colonoscopic examination but were not included in the regular screening programme.

Women from families with pedigrees compatible with the Lynch type II cancer family syndrome were offered additional screening for breast, uterine, and ovarian cancers, starting at age 25. Table II shows the screening strategy for colonic, breast, and pelvic cancers.

Results

Sixty one per cent of the patients in the first two years (252/411) were self referrals; subsequently a greater proportion of patients were referred by medical practitioners. Table III shows in detail the sources of referrals. Of the 715 patients, 461 had a lifetime risk of 1 in 10 or greater, 103 had a risk between 1 in 10 and 1 in 17, and 42 were themselves affected but required further screening. In all, 608 (85% of those who attended the clinic) required screening and 508 (71%) were at high risk, requiring colonoscopy.

One hundred and fifty one patients with lifetime risks less than 1 in 10 were offered screening by faecal occult blood test. Compliance rates were 136 of 151 patients (90%) for the first screen and 69 of 79 (87%) for the second screen. Three patients with positive occult blood tests proceeded to colonoscopy. Two were found to have polyps, one in association with enterocolitis, and the third had ulcerative colitis. Faecal occult blood tests were also performed on 59 high risk patients before colonoscopy. Two were positive due to bleeding from ulcerative colitis. Of the 57 patients with negative results, however, 13 had adenomatous polyps, one of whom had carcinoma in situ, giving a negative predictive value for polyps of 78%.

So far, 382 relatives have undergone the first of their regular screenings by colonoscopy. Table IV shows the number of relatives with varying risks, their ages, and the number in whom polyps or colorectal cancers were detected. In two relatives with a risk of 1 in 2 polyps were too numerous for control through colonoscopy and colectomy was performed. There was no evidence of adenomatous polyposis coli in either of these patients. Polyps were detected in nine relatives who were already known to have colonic cancer; two had metachronous colonic cancer. Eighteen relatives were screened by colonoscopy because, although their risks were less than 1 in 10, they reported rectal bleeding or had positive results on occult blood tests; three had polyps.

Table V shows the anatomical distribution of adenomatous polyps. Twice the expected number of polyps were found in the proximal and middle colon: the St Mark's series of 1181 adenomas had found 8.2% and 13.6% respectively¹³; in 64 adenomas we found 12 (19%) and 16 (25%) respectively.

Of the 715 patients seen, 83 had pedigrees compatible with site specific colonic cancer (table VI); 19 were found to have polyps at the first screen, and three had colonic cancer. Of 110 patients with evidence of the Lynch type II cancer family syndrome in their pedigrees, 16 were found to have polyps and one to have colonic cancer. Thirty five women with Lynch type II cancer family syndrome were offered breast and pelvic screening, of whom four were found to have breast cancer.

Nine patients from three previously undiagnosed

TABLE VI—*Syndromes identified in 715 patients at risk of colorectal cancer*

Syndromes	No of patients at risk	No with polyps
Lynch type I syndrome (site specific colonic cancer)	83	19
Lynch type II cancer family syndrome	110	16
Adenomatous polyposis coli	9	2
Other syndromes (Cowden's, Torres's, Gorlin's, multiple lipomas)	25	1

families with adenomatous polyposis coli attended the clinic. Two had multiple polyps requiring colectomy. Twenty five patients had stigmata compatible with other syndromes known to be associated with colonic cancer, and other cancers, including Cowden's, Torres's and Gorlin's syndromes.¹⁴ Two patients were seen to have multiple lipomas in association with colorectal cancer, and eight first degree relatives at risk were found to have lipomas. (Multiple lipomas are common in the population at large and these observations could be fortuitous.)

Discussion

In a family cancer clinic obtaining risk estimates for first degree relatives of patients with colorectal cancer from family histories enabled screening to be offered to relatives based on their probability of developing colorectal cancer. We decided to talk to patients and their relatives frankly about their risks. Contact with other family members at risk was made only through the patients who attended the clinic. We were aware that anxieties might be heightened in this vulnerable population by discussing numerical risks and the possibility of malignancy, but in practice patients from high risk families attending the clinic seemed relieved to discuss their risks and take responsibility for their screening. Indeed, a remarkable feature of the patients who had referred themselves was the accuracy with which they had estimated their risk: 237 of 365 (65%) were in the high risk category. Of all 606 patients, 545 (90%) took up the offer of screening including examinations by colonoscopy, which involved time and discomfort.

Screening by faecal occult blood tests seems to be unsuitable for high risk patients as it has a poor negative predictive value, and this supports the observations of Rozen *et al.*¹⁵ Colonoscopy, however, is an efficient method of detecting malignant polyps. In our series polyps were detected and removed through the regular screening programme in 62 of 382 (16%) patients in the high risk groups. The young age of the patients and the right sided distribution of the polyps were consistent with the observations of other workers^{10 12 13 16} and support the view that colonoscopy is an appropriate screening method for this high risk group.^{15 16}

The high proportion of patients with family histories compatible with the Lynch types I and II cancer family syndrome was not wholly unexpected; their contribution to the overall incidence of colonic cancer has been estimated as 6-10%.¹⁰ Twenty seven per cent of the patients who presented to the family cancer clinic because they had recognised the high frequency of bowel cancer in their family had pedigrees compatible with these Lynch cancer family syndromes. Any strategy targeting patients at high risk of colorectal cancer for screening must recognise that screening of the breasts and pelvis should be available to patients from families with Lynch type II cancer family syndrome.

Seven out of 14 patients over 65 with a risk of 1 in 2 who were screened were found to have colonic polyps on colonoscopy, contrasting with an estimate from the results of postmortem examination of 37-70%.^{17 18} One patient, however, had a carcinoma in situ. These patients were not included in a regular screening programme because they were over 65, but they were offered colonoscopy for clinical management because their risk was high and the result would contribute to the genetic information relevant to other family members. The numbers are too small to draw any conclusion about the possible benefits of screening older relatives, but the question may merit further consideration.

We conclude that by taking a careful family history it is possible to identify people at increased risk of colorectal cancer and that screening by colonoscopy to detect premalignant polyps is appropriate for high risk patients. Furthermore, targeting such high risk patients may make better economic use of available screening facilities than large scale population screening.

The economic benefits of screening the high risk groups cannot be estimated until long term follow up has shown the effects on mortality or morbidity. In 1985 in England and Wales, however, 323 people under 45 died from colorectal cancer,¹⁹ and twice that number would be expected to develop the disorder. These people would have 2445 first degree relatives (1438 parents and 1007 siblings) who could be identified as having a life time risk of 1 in 10, offering an opportunity to detect 244 cases of colorectal cancer at an early stage.

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