Feasibility of family based screening for colorectal neoplasia: experience in one general surgical practice

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Abstract

Relatives of patients with colorectal cancer have on average a two to threefold increased risk for developing bowel neoplasia although in some families the risk is much higher. This study examined the compliance for endoscopic screening and faecal occult blood testing among first degree relatives of patients with colorectal cancer to determine the feasibility of offering a screening service in a surgical practice. The endoscopic method (flexible sigmoidoscopy or colonoscopy) offered depended upon the extent of family history. Spouses of patients were offered flexible sigmoidoscopy as a group for comparison. Compliance in first degree relatives was significantly higher than in spouses (69% *v* 47%, $p < 0.01$) and among those relatives of patients who had died recently from colorectal cancer but time since diagnosis in the index case had no effect. Adenomas were found in 14 of 92 (15%) relatives and three of 30 (10%) spouses. It is estimated that, under our screening guidelines, every 100 patients with colorectal cancer would generate a list of 35-40 relatives who would be screened once by flexible sigmoidoscopy and perhaps 75, who because of their young age, might be screened twice in their lifetime. Also, from this same 100 patients, about 12-15 relatives would merit entry in a colonoscopic screening programme because of their more extensive family history. These results indicate that endoscopic screening of relatives of patients with colorectal cancer is feasible within a practice.

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In 1988, in England and Wales, there were approximately 17 000 deaths from colorectal cancer.¹ The natural history of colorectal cancer suggests that this common disease is amenable to intervention through screening.² Population screening studies using faecal occult blood tests (FOBTs) show a higher proportion of cancers at an early pathological stage (Dukes's A) in groups offered screening than in unscreened controls.³⁻⁵ Furthermore, in one study about 25% of cancers identified by positive FOBT were managed by polypectomy alone.⁵ Population screening by FOBT is time consuming, however, both for the participant and medical personnel as biennial testing is recommended. In addition, positive FOBTs require subsequent endoscopy to rule out significant disease.

Apart from age, a family history of colorectal cancer represents the single most important risk factor for developing colorectal neoplasia, with first degree relatives of patients with colorectal cancer having a two or threefold increased risk of the disease.⁶ Also the relatives of subjects with

large adenomas have a similarly increased family history of colorectal cancer.⁶ In addition, adenomatous polyps are found more frequently in the relatives of patients with colorectal cancer than in controls.⁷⁻⁹ This evidence plus other molecular and pathological findings have further strengthened belief in the concept that most colorectal cancers evolve from benign pre-existing adenomas.^{10,11} Thus for subjects with a family history of colorectal cancer endoscopic screening may be more appropriate both because of the higher incidence of colorectal cancer in this group and also the increased prevalence of adenomas, recognition of which would allow prophylactic intervention. Furthermore, these subjects might provide a group who could be more easily targeted for screening. Compliance is likely to be higher and more invasive screening techniques acceptable. Various protocols for screening have been suggested, ranging from annual FOBT with flexible sigmoidoscopy every three to five years⁷ to regular colonoscopy.¹²

We have previously reported¹³ on the families of a series of 100 patients with colorectal cancer and found the first degree relatives had a fourfold increased risk of death from colorectal cancer over and above that of the general population, consistent with the results described above. Briefly, 23 of the patients had a family history of colorectal cancer in one or more first degree relatives and there was no evidence of increased risk of death from other malignancies. We have extended this study and now report the results of offering screening to the relatives of the resulting set of patients. The method of endoscopic screening offered was determined by risk estimates based on the family history.^{14,15}

Methods

Ethical approach for this study was received from the United Leeds Teaching Hospitals NHS Trust.

PATIENTS

Relatives of patients treated for colorectal cancer between January 1987 and January 1991 by one author (PJF) were eligible for inclusion in the study. Patients (termed the 'index cases' throughout) were asked to supply the name, age, address (if living in this country) of first degree relatives (parents, siblings, children), and their cause of death if deceased. The family history of a deceased index case was obtained from the spouse and confirmed by contacting a first degree relative before inclusion in the study. The ages and causes of death of the first degree relatives of these index cases were verified, where possible, by reference to hospital pathology records, death certificates, and Regional

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Cancer Registries. Within these families, 96% of the colorectal cancer diagnoses reported by family members could be verified by one of the above methods.¹³

SCREENING POLICY

Subjects with only one relative affected with colorectal cancer (– that is, the index case) were offered screening by FOBT (Haemoccult® Rohm Pharma, Germany) and flexible sigmoidoscopy. This offer was made only to subjects aged 50–75 years. The lower age was chosen to correspond to the age at which colorectal neoplasia should be present if colorectal cancer is to develop in the sixth decade, the median age of onset of colorectal cancer. Subjects aged 50–75 years with two or more affected relatives (– that is, the index case plus one or more other first degree relative) were offered screening by FOBTs and colonoscopy. If there were three or more affected members in the family (suggesting dominant inheritance) colonoscopic screening was offered from age 35. Subjects with a positive FOBT, irrespective of the family history, underwent colonoscopy as the first investigation. Colonoscopic screening was also offered to the relatives of index cases diagnosed below the age of 45 as this may also be indicative of dominant inheritance. In addition, subjects with histologically proved adenomatous polyps on flexible sigmoidoscopy underwent subsequent colonoscopy to exclude more proximal synchronous neoplasia.

APPROACH TO RELATIVES

Details of the relatives’ general practitioners (if not supplied by the index case) were obtained from local Family Practitioner Committees. Each

general practitioner was informed of the study and of our intention to offer his patient screening by one of the methods outlined above. None refused permission to contact their patients. Two weeks later a letter was sent to the relative describing the study and inviting them to attend for screening. One week later they were contacted by telephone. Relatives who declined were contacted only once unless they had more than two affected relatives when they were telephoned twice. The test packs were posted with a stamped addressed envelope for their return and developed unhydrated by one author (BMS). Spouses were invited for screening as a comparison group as they were not blood relatives of patients with colorectal cancer.

ENDOSCOPY

All endoscopic examinations were performed by one investigator (BMS). Flexible sigmoidoscopy was performed using a 60 cm Olympus CF-P20S after two disposable phosphate enemas. Colonoscopy was performed after full bowel preparation using an Olympus CF-20HL instrument. If colonoscopy was incomplete a double contrast barium enema was performed. All polyps identified were biopsied or snare excised and subjected to full histological examination by senior pathologists who were blinded to the relationship of the individual to the index case (– that is, relative or spouse). Only histologically proved adenomatous polyps were considered an indication for subsequent colonoscopy.

STATISTICAL ANALYSIS

The significance of differences between groups was assessed with the appropriate χ^2 test and 95% confidence intervals given for the difference in proportions.

Results

PATIENTS AND RELATIVES

Two hundred and one patients with colorectal cancer were treated during this four year period. For 36 of these index cases, no contact could be made with either the patient or any of their relatives. Seventeen of the remaining 165 (10%) patients refused to give a family history. For the 148 patients we identified 935 first degree relatives, of whom 477 were alive. Of these, 77 were too old and 199 too young to be offered screening and we did not contact another 47 for a variety of reasons (Figure). Therefore, 154 first degree relatives were eligible for screening by our protocol. Most relatives (74%) were contacted over a year after the diagnosis in the index case.

COMPLIANCE

One hundred and seven first degree relatives accepted the invitation for screening (compliance 69%) and 30 of 64 spouses (47%) ($\chi^2=9.89$, $p<0.01$, 95% confidence interval for difference in compliance 8 to 37%). The method of endoscopic screening did not affect compliance

Figure: Breakdown of patients/relatives

* These relatives were overseas, had lost touch with the index case, or we were asked not to make contact.

† The ages of these individuals were outside the screening protocol.

TABLE I Compliance for endoscopic screening among the relatives and spouses. Data are shown as number (percentage) of subjects

	Relatives (n=154)	Spouses (n=64)	
Overall	107 (69)	30 (47)	(p<0.01)
Sex			
Men	43 (65)	8 (44)	(NS)
Women	64 (73)	22 (48)	(p<0.01)
Age (years)			
<50 years	10 (100)	6 (100)	
50-59 years	58 (80)	7 (44)	(p<0.01)
60 or more years	39 (54)	17 (40)	(NS)
Index case			
Alive	(66)		
Deceased	(83)		(p<0.05)

($\chi^2=0.02$, $p>0.5$). Older relatives and spouses were less likely to comply as were men compared with women (Table I). Relatives of deceased index cases were more likely to comply with screening (83%) than those of index cases still alive (66%) ($\chi^2=4.4$, $p<0.05$. 95% confidence interval 1 to 33%).

FAECAL OCCULT BLOOD TESTING

FOBTs were completed in all screened subjects. Three were positive; one in a female relative aged 73 and two in female spouses aged 60 and 67.

ENDOSCOPY AND PATHOLOGY

Fifteen of the 107 relatives were screened at their local hospital, 92 at our hospital. Seventy one subjects (mean age 58, range 50 to 74) with a single affected relative and 28 spouses (mean age 56, range 43 to 74) underwent flexible sigmoidoscopy and one relative and two spouses were examined by colonoscopy because of positive FOBTs. Flexible sigmoidoscopy was completed to the junction of the sigmoid and descending colon in all patients. The upper descending colon was reached in 79% of patients and the splenic flexure or distal transverse colon in 58% (Table II). Twelve (17%) first degree relatives (mean age 58 years) and three (10%) spouses (mean age 63 years) had adenomatous polyps ($\chi^2=1.5$ for difference in proportions, $p>0.10$). The mean size of the adenomas was 0.9 cm (range, 0.5-2.5, $n>1$ cm=6) in relatives and 0.7 cm in spouses (range 0.5-1). Three relatives had two or more adenomas on sigmoidoscopy. For three spouses results of subsequent colonoscopies were normal, whereas one relative had a further adenomatous polyp (1 cm) in the mid-transverse colon.

Twenty subjects (mean age 56, range 38 to 71) with two or more affected relatives or an affected relative diagnosed before age 45 underwent

colonoscopy as their primary investigation. Examination was complete to the caecum in 12 patients. Three of the eight remaining patients refused barium enemas, and normal results were obtained for the other five. In 17 of these relatives, flexible sigmoidoscopy was performed after sedation and before colonoscopy to estimate the false negative rate if only flexible sigmoidoscopy had been used. Two relatives (10%), both aged 42, had two adenomatous polyps (1 and 1.5 cm), one of which was caecal and would have been missed by flexible sigmoidoscopy (Table III). In addition, one further relative had a large (2 cm) hamartomatous polyp in the distal transverse colon but had no evidence of Peutz-Jeghers syndrome or juvenile polyposis.¹⁶

A further 20 relatives (mean 46 years, range 33-49) asked to be screened because of a concern about their family history. We screened these relatives even though their ages did not fit into our screening protocol. These relatives are, of course, not included in the compliance results reported above. All had only a single affected first degree relative. One man aged 45 with a positive FOBT underwent colonoscopy and was found to have a 1.5 cm moderately dysplastic adenoma at 20 cm. For the other 19 relatives results of sigmoidoscopies were normal.

FOBTs were unhelpful in predicting the presence of adenomas. Of those found at endoscopy only one was detected by faecal occult blood testing (positive predictive value 25%, negative predictive value 87%). In subjects to be screened by flexible sigmoidoscopy, the three positive FOBTs led to normal colonoscopy results. Two colorectal cancers are known to have occurred during the period of this study: one in a non-compliant subject with two affected first degree relatives, and one in a relative aged 76 whose daughter developed colorectal cancer at age 42. No cancers have occurred in the 64 spouses.

Discussion

Flexible sigmoidoscopy is a sensitive method of detecting colorectal neoplasia distal to the splenic flexure, an area which harbours over 75% of all adenomas and 90% of adenomas more than 1 cm in size.¹⁷ The examination is quickly and easily performed without the need for full bowel preparation and results in little discomfort for the patient.^{18 19} In contrast with biennial screening by FOBTs with an observed fall in compliance,⁵ examination by flexible sigmoidoscopy may need to be repeated only every 5-10 years as most adenomas are slow growing.^{20 21} This should be performed during the period of maximum age related risk aiming to reduce the incidence of left sided colorectal cancer. We performed this study to investigate whether a screening service for first degree relatives could feasibly be adapted into the clinical practice of any physician with an interest in gastroenterology. On the basis of our experiences, we conclude that such a service is indeed practical both in terms of compliance and workload. In particular, we have shown that relatives are willing to comply with endoscopic screening when approached on the basis of a family history.

TABLE II The yield of colorectal adenomas in the different risk groups

	No (%) of subjects with adenoma on flexible sigmoidoscopy or colonoscopy	Mean size (range) of adenoma (cm)	Mean (SD) age (years) (years) of relative with adenoma
One affected relative (n=72)	12 (17%)	0.9 (0.5-2.5)	57 (6.3)
Two or more affected relatives or relative aged <45 (n=20)	1 (5%)*	1.25	42 (NA)
Spouses (n=30)	3 (10%)	0.7 (0.5-1.0)	63 (8.3)

* Subsequent colonoscopy led to the detection of one further patient with an adenoma.

TABLE III The percentage of first degree relatives of patients with colorectal cancer with endoscopically detected adenomas in controlled endoscopic screening studies

			Age (years)		
			<50	50-60	>60
Tel Aviv, Israel ^f	Overall				
	Controls	4	2	3	5
Utah, USA ^a	Relatives	8	5	11	16
	Controls	12	6	9	13
New York, USA ^a	Relatives	19	14	27	29
	Controls	8	0	13	
Present study	Relatives	12	3	24	
	Controls	10	0	10	13
	Relatives	15	11*	15	13

*28% when relatives who requested screening but who were not eligible for the study on the basis of age were included.

Our overall compliance of nearly 70% in first degree relatives of patients with newly diagnosed colorectal cancer shows that this method of screening is acceptable to this group and is reinforced by the fact that some relatives were willing to travel long distances to attend screening clinics. In previously reported controlled endoscopic screening studies compliance has been as high as 95%.⁸ These studies, however, recruited their screened subjects in various ways including volunteers,⁷ offering free screening,⁸ and simple 'recruitment'.⁹ Understandably, the true compliance is therefore either uncertain^{7,9} or not comparable.⁸ Sandler *et al*²² found that compliance for FOBTs was significantly higher in siblings of patients recently diagnosed with colorectal cancer than in controls (52% *v* 37%). Although our overall compliance was higher, we found a similar difference between first degree relatives and spouses when offered endoscopy (69% *v* 47%). In our study spouses cannot be regarded as a meaningful control group because they have recent experience with this disease. The difference in perceived risk between the two groups warrants further attention as it might imply that family members are concerned about potentially inherited tendencies. If this were true other screening programmes could take advantage of this awareness.

We found that the timing of the offer of screening did not affect compliance while having a deceased relative did, understandably, improve compliance. Interestingly, in both relatives and spouses below the age of 50 compliance was 100% and in relatives aged below 60 it was over 80%. This suggests that the idea of endoscopic screening is more acceptable to younger relatives when they perceive themselves at increased genetic risk, irrespective of its magnitude. The compliance in the spouses of our patients is similar to that attained in a population screening study using FOBTs in this country,⁵ suggesting that the 'case for screening' was presented in such a manner as to attract rather than deter the relatives at whom screening was targeted.

In agreement with other studies^{7,8} we found adenomatous polyps in 15% of first degree relatives. Although the difference in prevalence of adenomas failed to reach statistical significance because of our small numbers, the prevalence is in agreement with those larger studies which report an increased prevalence of adenomas in relatives than in controls at all ages (Table III).

If such a screening service were implemented we estimate that one clinician would initially be

offering in the range of 35-40 flexible sigmoidoscopies and 12-15 colonoscopies to the first degree relatives of every 100 patients treated for colorectal cancer. Of those subjects offered sigmoidoscopy, only the young ones would be encouraged to have a further examination, perhaps 5-10 years later, thus maintaining a high compliance. Those shown to be at higher risk and requiring colonoscopy, should be entered into standard three to five year follow up programmes. The vast majority of those subjects too young to be offered screening had only one affected relative. Assuming 70% compliance in this group, approximately 75 subjects (for every 100 patients with colorectal cancer) remain to be screened by flexible sigmoidoscopy at a later date. Once a screening service was established, 100 patients with colorectal cancer would generate in the order of 200 first degree relatives for sigmoidoscopic screening. When such a service was set up, family trees could be easily obtained from patients during postoperative follow up, removing the need to trace patients retrospectively. The relative's general practitioner would then be informed of the family history by a standard letter and asked to arrange the appropriate screening at their local hospital. In this way, the diagnosis of colorectal cancer is established without doubt in the index case and this avoids the need for verifying a reported family history of colorectal cancer which would otherwise be necessary if details of relatives were accrued in other ways. In this study the pathology in families reporting an additional affected relative was confirmed in all cases. With the knowledge that at least one relative has colorectal cancer, this extra administrative exercise is therefore probably unnecessary in clinical practice.

Opinion from prospective studies about the most appropriate screening method is divided. Some suggest that flexible sigmoidoscopy would suffice^{7,23,24} with others endorsing colonoscopy.^{9,12} Screening subjects with only one affected relative by colonoscopy would impose an unmanageable burden on the resources currently available in many countries and would almost certainly deter most clinicians from offering routine screening. As about 7% of first degree relatives undergoing screening colonoscopy had isolated neoplasia beyond the reach of the 60 cm flexible sigmoidoscope,¹³ we estimate that a further three first degree relatives might have been found to have adenomas. This extra yield, however, would have required a substantial increase in workload (58 colonoscopies), in addition to the inconvenience caused to those subjects, including time off work. Moreover, compliance might have been adversely affected.²⁵ In essence, a compromise must be reached. Furthermore, cost benefit analyses have suggested that colonoscopy would be best reserved for individuals with at least two affected relatives.^{26,27}

We found the Haemocult[®] test unhelpful as there was a negative predictive value of 87% for adenomatous polyps. For those additional relatives requesting screening outside the age range, FOBTs could be offered at little extra expense. More recently, newer guaiac

(HaemoccultSENSA®) and haemagglutination immunochemical (HaemSelect®) FOBTs have been developed. With these more sensitive tests, the number of adenomas detected^{28, 29} in combination with, but out of range of flexible sigmoidoscopy, may be sufficiently increased to dissuade those who suggest that screening should only be by colonoscopy.

In summary, screening first degree relatives of patients with colorectal cancer by this protocol is feasible and the workload manageable. Compliance is high and endoscopic screening readily accepted. Further study is needed to identify the factors that affect compliance although it is clear that a family history of colorectal cancer is strong motivation.

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