Improving the ascertainment of families at high risk of colorectal cancer: a prospective GP register study

Peter W Rose, Michael Murphy, Marcus Munafo, Cyril Chapman, Neil Mortensen and Anneke Lucassen

SUMMARY

Background: *Screening for colorectal cancer is effective in family members with a high risk of this condition, owing to single gene mutations. However, it is not known which is the most effective method of ascertaining these families at high risk.*

Aims: *To investigate whether a case-finding approach using computerised general practitioner (GP) registers would improve the ascertainment of families at high risk of colorectal cancer due to family history.*

Design of study: *Prospective GP register study.*

Setting: *General practices in Oxfordshire.*

Method: *Identification of patients with colorectal cancer using GP registers, followed by a family history questionnaire survey to identify those at high risk.*

Results: *Using GP registers, 758 patients with a diagnosis of colorectal cancer were identified; a prevalence of 172 cases per 100 000 (95% confidence interval = 159 to 184). Of these, 305 patients, diagnosed under the age of 65 years, were sent a family history questionnaire. Two hundred and one (66%) patients responded to the survey; 10 (5%) patients were assessed as having high-risk families and 47 (23%) patients were assessed as having families at moderate risk. Eight of the high-risk patients had 34 first degree relatives who would benefit from routine disease surveillance, and 37 moderate-risk patients had 153 first degree relatives. Only two high-risk and six moderate-risk patients identified were previously known to the local Clinical Genetics Department.*

Conclusion: *A case-finding approach using GP records and a family history questionnaire is an effective way of identifying families at high risk of developing colorectal cancer, who can then be offered disease surveillance.*

Keywords: *colorectal cancer; colorectal neoplasms, hereditary nonpolyposis; medical records; primary health care.*

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Introduction

ADVANCES in genetic medicine have begun to alter clinical practice in primary care.[1] There is debate about the correct use of the family history as a screening tool in primary care,[2] but many general practitioners (GPs) are already collecting family history data at the time of registration,[3] and two practices have reported screening their entire adult population for increased genetic risk of cancer using a postal questionnaire.[4,5] One study identified 3.2% of the adult population as having a significant family history of colorectal cancer,[4] and the other identified 4.4% of patients with a high risk of either colorectal cancer or breast cancer.[5] Colorectal cancer is the third most common cancer in the United Kingdom,[6] and it has a significant hereditary element, including some single gene disorders, such as hereditary non-polyposis colon cancer, which result in a high risk of developing colorectal cancer. The National Screening Committee recently concluded that there was no case to offer population screening for inherited colorectal cancer, and that limited resources should be spent on identifying patients with hereditary non-polyposis colon cancer.[7] The value of disease surveillance for families at high risk of developing cancer owing to their family history is unproven, but a parallel cohort study showed likely benefits in families with hereditary non-polyposis colon cancer.[8]

The Department of Clinical Genetics, at the Churchill Hospital in Oxford, holds a database of families at high risk of cancer owing to their family history, and this department provides services to all patients registered with Oxfordshire GPs. In 1997 it was noted that the database underascertained, by approximately 60%, the number of families with autosomal dominant conditions, compared with the numbers predicted on the basis of known prevalence. Similarly, another autosomal dominant disease, familial hypercholesterolaemia, is underdiagnosed in routine practice[9] and an analysis of different methods of screening for this condition demonstrated that the most cost-effective way of identifying cases was by cascade screening of family members.[10]

Applying such cascade screening to the detection of individuals at risk of colorectal cancer would involve the identification of patients with both a diagnosis of colorectal cancer and a significant family history. This might then allow their relatives to benefit from disease surveillance and genetic testing, where appropriate. We tested the feasibility of a case-finding approach using general practice records, as the initial step in this process.

Method

The Department of Colorectal Surgery, at the John Radcliffe Hospital in Oxford, holds a database of information about

HOW THIS FITS IN

What do we know?

Taking a family history can identify people at higher risk of inherited colorectal cancer. Those identified as high-risk patients benefit from regular disease surveillance using colonoscopy, which results in reduced mortality.

What does this paper add?

General practitioner computerised registers can be used effectively to identify prevalent cases of colorectal cancer. A case-finding approach produces a greater yield of higher-risk families than other screening methods in primary care.

patients with colorectal cancer, dating from 1992. This database was used at the outset of this study to undertake an audit of the hundred most recent cases. The audit showed that 75% had a family history recorded, but many were incomplete. A separate audit of all the GP practices in Oxfordshire showed that 65% of all patients had computerised medical records.

Eighty-eight practices in Oxfordshire were invited to participate by letter. Those that agreed produced a register of all patients with a previous diagnosis of colorectal cancer retrieved from computerised medical records. Subsequently, patients whose colorectal cancer was diagnosed under the age of 65 years were sent a letter from their GP inviting them to participate in the study. A second letter was sent to non-responders after 4 weeks. People who consented to enter the study were sent a family history questionnaire based on a previous study,[4] and a reminder was sent to those who had not returned their questionnaires after 4 weeks.

The responders were treated as the index cases and their families were categorised into high, moderate or low additional risk according to the family history information supplied (Box 1). Families fulfilling modified Amsterdam criteria were labelled high risk,[11] and moderate and low risk were defined using local guidelines based on published evidence.[12] (Moderate risk was defined as one person in the family diagnosed with colorectal cancer under the age of 45 years, two first degree relatives on the same side of the family at any age, or two close relatives with the average age of diagnosis less than 60 years). Index case patients in whom the risk was uncertain were telephoned by a research nurse to elicit more information, and their risk categorisation was assigned by a consultant clinical geneticist. The index case patients were informed of their family's risk category, and of the possible implications for their close relatives, 4 weeks after returning the questionnaire. Index case patients at low additional risk were reassured and those at high or moderate risk were invited to discuss this with their GP, with a view to referral to a clinical geneticist. They were also given information to pass on to close relatives. Information was also sent to their GPs. Referrals of index case patients or their relatives to the local clinical genetics clinic were monitored, but it was not possible to systematically monitor referrals to other centres. Patients at high or moderate risk were also asked to report on how many first degree relatives they had (excluding parents), to assess numbers of people potentially eligible for disease surveillance.

High risk
Families that fulfil modified Amsterdam criteria:
- There should be at least three relatives with a hereditary non-polyposis colon cancer-associated tumour (colorectal cancer, endometrium, small bowel, ureter, or renal pelvis)
- One relative should be a first degree relative of the other two
- At least two successive generations should be affected
- The diagnosis of colorectal cancer should be made before the age of 50 years in at least one individual
- Familial adenomatous polyposis coli should be excluded
- Tumours should be verified by histological examination

Moderate risk[a]
- One person in the family diagnosed with colorectal cancer under the age of 45 years

or

- Two first degree relatives on the same side of the family diagnosed at any age

or

- Two close[b] relatives with the average age of diagnosis less than 60 years

Low risk[a]
All other families

[a]Those not exactly fulfilling criteria, individually assessed by a clinical geneticist. [b]Close relatives are parents, children, siblings, grandparents, aunts, uncles, nephews, and nieces.

Box 1. Categorisation of risk: families were categorised according to the number and ages of all family members diagnosed with colorectal cancer.

The psychological impact of this intervention was assessed using the short form of the Spielberger state-trait anxiety inventory (STAI)[13] and the impact of event scale (IES)[14] (using the assessment of family history by the subject as the event). The STAI was sent to all participants with the original family history questionnaire. The STAI and IES questionnaires were then sent to all participants at 4 weeks with the result of the family history questionnaire. Subjects assessed as moderate or high risk were sent both psychological questionnaires again 6 months later.

Data were analysed using SPSS version 10. The distributions of the psychological measures (STAI and IES) were normalised prior to analysis by applying a square root transformation where appropriate. STAI and IES data were compared between the moderate- and high-risk groups, and between time points, using a repeated measures analysis of variance. A *P*-value of 0.05 was regarded as statistically significant.

The study was approved by the Applied and Qualitative Research Ethics Committee, Oxford.

Results

Fifty-five (63%) practices agreed to take part in the study and 758 patients with colorectal cancer were identified from these practices. Figure 1 shows a flow chart of the uptake and the risk assignment of each case. Three hundred and forty-one patients were diagnosed with colorectal cancer under the age of 65 years, but the patients' GPs decided that 36 of

these were unsuitable to invite. Three hundred and forty-one patients were sent questionnaires, of whom 201 (66%) replied. The survey identified 10 (5%) high-risk and 47 (23%) moderate-risk families. The prevalence rate of all cases of colorectal cancer identified by this study, irrespective of age of diagnosis, was 172/100 000 patients (95% confidence interval = 159 to 184).

Three responders out of 201 did not complete the part of the questionnaire regarding previous discussions with family or health professionals about their risk. Table 1 shows that, prior to the study 113/198 (57.1%) patients had discussed the chances of getting bowel cancer with other family members and 51 (25.8%) had discussed the risk of their family developing bowel cancer with a doctor or nurse; 15 with a GP and 24 with one or more health professionals in secondary care. Twenty-three (11.6%) of these said that screening had been recommended for relatives, nine of whom were assessed as low risk, 13 as moderate and one as high.

Table 2 shows that 13 moderate- or high-risk patients were referred to the Oxford Clinical Genetics Department as a result of this study, but by the end of the study, five high-risk patients had still not been referred to this department.

Thirty-seven out of forty-seven moderate-risk index case patients reported having 153 first degree relatives (excluding parents) and 8/10 high-risk index case patients reported having 34 first degree relatives (excluding parents) and these relatives would be eligible for consideration of regular surveillance by colonoscopy.

A 2 ∞ 3 mixed model repeated measures ANOVA of STAI data, with assessed risk as a between-subjects factor (low, moderate, high) and time as a within-subjects factor (baseline, 4 weeks) indicated no significant main effect of time (*F*-score <1) or interaction effect of assessed risk and time ($F<1.6$). There was marginal evidence for a significant main effect of assessed risk on anxiety, F (2, 188) = 3.85, $P<0.025$, although this test did not reach statistical significance when corrected for multiple testing using Bonferroni's method. State anxiety (untransformed scores) increased across the three diagnostic groups of low risk (mean = 31.86, standard deviation [SD] = 11.35), moderate risk (mean = 34.90, SD = 13.55) and high risk (mean = 43.83, SD = 4.92). Post-hoc tests indicated that at 6 months this difference was no longer significant ($F<1$).

Mean STAI and IES scores by risk group and time point are shown in Table 3. A score of 26 or above on the IES is taken as clinically significant.

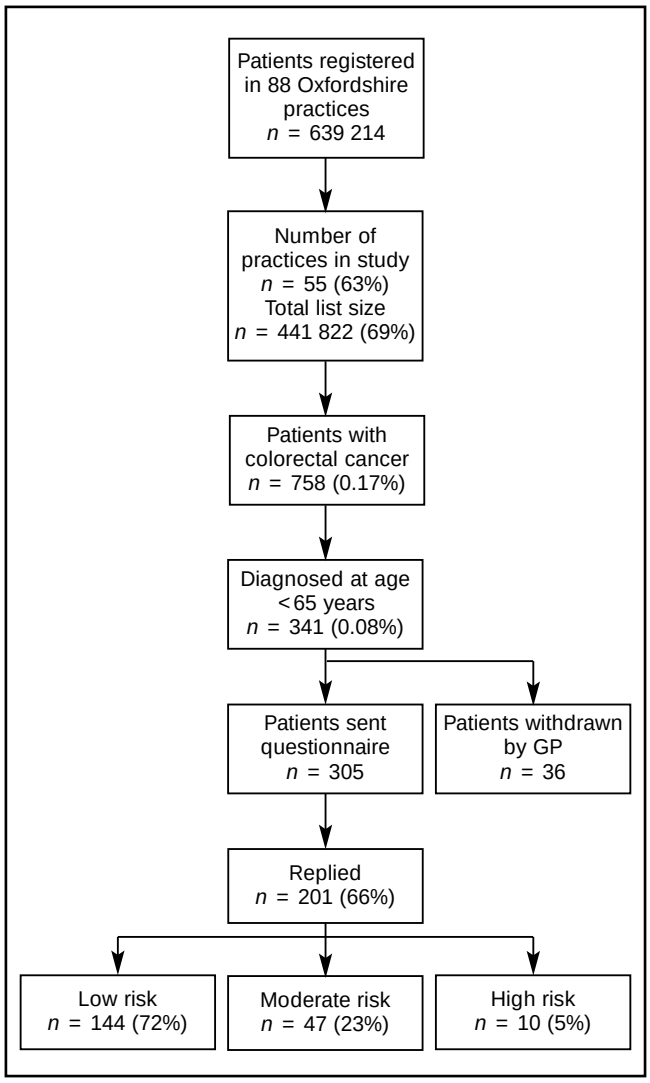

Figure 1. Flow chart of study.

Discussion

The study has shown that it is feasible to identify a substantial number of patients with colorectal cancer from primary care databases, and subsequently use a family history questionnaire to identify families at increased risk of carrying a genetic mutation for colorectal cancer. These families can

*Table 1. Patient actions concerning family risk of bowel cancer prior to this study (*n *= 198).*

	Assessed risk			
	Low *n*	Moderate *n*	High *n*	Total *n* (%)
Discussed chances of getting bowel cancer with other family members	70	35	8	113 (57)
Discussed risk of family developing cancer with any doctor or nurse	24	21	6	51 (26)
Discussed with GP	7	7	1	15
Discussed with a clinical geneticist	0	3	4	7
Discussed with a surgeon/colorectal cancer nurse specialist	6	4	1	11
Discussed with other consultant	4	4	0	8
Did not discuss with family or health professional	70	12	2	84 (42)

then be considered for gene testing and disease surveillance. This intervention did not cause any lasting psychological harm to the participants.

The overall prevalence rate of colorectal cancer identified by this study was 172/100 000 patients, and it is comparable to recently reported prevalence figures of 260/100 000 for English cancer registries.[15] The yield of higher-risk patients in this study of 28% compares favourably with the yields of 3.2% and 4.4% from studies using a population-screening approach.[4,5] According to our local audit, most patients newly diagnosed with colorectal cancer currently have a family history assessment in hospital, but this may not have been routine practice in the past. It may take a long time before new incident cases result in the ascertainment of all high-risk families; the use of cancer registers would enable GPs to implement this method immediately. The formal assessment of family history could also prevent the offer of disease surveillance to members of lower additional-risk families, which was apparent in our study (and carries attendant risks such as perforation).

There are problems with collecting family histories in primary care owing to recall bias,[16] and with contacting relatives not registered with the practice. Even an accurate family history is not sensitive enough to identify all higher-risk families.[17] However, the alternative of offering gene testing to all patients with colorectal cancer has a low yield, which makes this approach impractical at present.[18] Until there are proven effective methods of screening whole populations for hereditary non-polyposis colon cancer and other significant mutations, either by family history or gene testing, it would be most efficient for GPs to identify and assess the family history of existing cases of colorectal cancer. This should supersede the current practice of screening the population of newly registered patients by family history, the value of which is uncertain.

The modest response rate to the questionnaire survey has implications for the interpretation of the results. It may show that a significant group of patients may not wish to consider disease screening or may find it too difficult to contemplate the discussion of this information within their family; the index case patients were already diagnosed with cancer and may feel that they are no longer at risk. These factors may affect the overall effectiveness of this method of case finding.

At least 6 months after being told of their high-risk status, five people had still not been referred to the Clinical Genetics Department. We do not know the reasons for this, but we are aware of two patients who were referred to surgeons outside the catchment area. It is possible that patients, or more likely their relatives, chose to be referred elsewhere. The rate of referral, assessment, and follow-up of at-risk families may therefore be higher than we report. However, there may still be underascertainment of high-risk families overall, owing to incomplete records or high-risk families with no currently surviving member with colorectal cancer. This case-finding method may not be so successful in areas with less comprehensive computerisation of GP notes, but computerisation is increasing rapidly everywhere, and the development of practice cancer registers forms part of the new GP contract.[19] Screening for genetic problems has been identified as a possible future role for GPs.[20] Before this additional service is adopted in primary care, it may be necessary to address the issues of increased workload and whether GPs have the skills to undertake these assessments.[21] However, a simple educational package sent to all GPs has been shown to be effective in improving GP assessment of family histories.[22]

Table 2. Referral to clinical genetics department and comparison of risk assessment by questionnaire and clinical geneticist.

	Risk assessment according to study questionnaire	
	Moderate *n*	High *n*
Total	47	10
Patients referred to clinical genetics department by the study end	16	5
Assessed risk by clinical geneticist		
High	2	5
Moderate	5	0
Low	1	0
Not yet seen	8	0
Referred as a result of this study	10	3

Table 3. Mean STAI and IES scores by risk group and time point.

	STAI			IES	
	Baseline (SD)	4 weeks (SD)	6 months (SD)	4 weeks (SD)	6 months (SD)
Low	34.19 (12.75)	31.86 (11.35)	n/a	10.68 (14.33)	n/a
Moderate	36.50 (12.63)	34.90 (13.55)	31.35 (10.81)	13.26 (17.55)	10.84 (14.46)
High	32.86 (10.00)	43.83 (4.92)	30.56 (7.12)	16.22 (13.78)	11.62 (14.05)

IES = impact of event scale; n/a = not applicable; SD = standard deviation; STAI = Spielberger state-trait anxiety inventory.

There is a concern that any form of screening or case finding may cause anxiety to people. This method of case finding possibly caused transient increases in anxiety in those found to be at increased risk, but this failed to reach statistical significance when corrected for multiple testing. This may have been a result of the small sample size and may be worthy of further testing. These findings are similar to findings in other studies where a family history has been taken proactively in primary care.[23,24]

This study has described the initial steps in a cascade-screening process to identify patients at high risk of colorectal cancer. Further research would need to ascertain the feasibility and cost-effectiveness of this approach in a range of primary care settings. Studies of the whole process would need to explore how information is circulated within families and how extended families who are not registered with a single practice can be managed. The psychological impact on both affected and unaffected individuals would need further study. If successful, this method of ascertainment could also be applied to other potentially inheritable diseases when effective interventions are available.

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