

Low adherence to colonoscopy in the screening of first-degree relatives of patients with colorectal cancer

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Background: Colonoscopy is one of the methods of choice for screening relatives of patients with colorectal cancer.

Objective: To evaluate the rate of adherence to colonoscopy in first-degree relatives of patients with colorectal cancer and describe the lesions found.

Methods: A prospective, cross-sectional, multicentre, nationwide study was conducted. The study population was composed of first-degree relatives of patients with colorectal cancer selected randomly from the EPICOLON study. Seventy-four index patients were included. These had 342 living first-degree relatives (parents, siblings and children), of whom 281 were interviewed.

Results: The adherence rate was 38% (107/281). Adherence was greater in families with a higher degree of familial aggregation for colorectal cancer (88.9% for Amsterdam vs 33.3% for Bethesda and sporadic cancer; $p < 0.05$), an index patient aged under 65 years (60% for patients < 65 years vs 32.9% for patients ≥ 65 years; $p < 0.05$) and an index patient who was female (46.2% for women vs 31% for men; $p = 0.28$). Adherence was also greater in relatives under 65 years (54% in patients < 65 years vs 18% in patients ≥ 65 years; $p = 0.05$), in female relatives (49% in female relatives vs 27.3% in male relatives; $p < 0.05$) and in siblings and children (40% in siblings and children vs 13% in parents; $p < 0.05$). Lesions were found in 26% (28/107) of the study population. Nine (8.4%) individuals had a total of 18 advanced lesions.

Conclusions: These results indicate that adherence to colonoscopy in our population of first-degree relatives was low. The adherence was more frequently associated with a higher degree of familial aggregation, a relative age of under 65 years, a sibling or offspring relationship, and female sex.

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Colorectal cancer is the second most common form of cancer and the second leading cause of death from cancer in both men and women in the majority of developed countries. Death from colorectal cancer is also very high in Spain, where it is the second leading cause of death from cancer in men and women. Mortality has increased by an annual average of 2.6% for men and 0.8% for women since 1975, without variations.¹ It is estimated that colorectal cancer caused 11 900 deaths in Spain in 2000, which represents 11% of the total deaths from cancer in men and 15% of those in women.¹

One of the main risk factors for colorectal cancer is a family history of the disease. First-degree relatives (parents, siblings and children) of patients with colorectal cancer have a two- to threefold increased risk of developing the disease compared with the general population. Risk also depends on the age at which the neoplasm is detected, the number of relatives affected and the degree of kinship. Screening for colorectal cancer in first-degree relatives serves to detect neoplastic lesions in their early stages. Although the majority of international organisations recommend screening for colorectal cancer in first-degree relatives of affected patients,^{2–5} this practice is not widespread in the majority of regions in Spain.

Four strategies are currently used to screen for colorectal cancer in people at average risk or people with one first-degree relative affected at age ≥ 60 years: faecal occult blood testing; sigmoidoscopy; faecal occult blood testing combined with sigmoidoscopy; and colonoscopy. People with two or more first-degree relatives affected or one first-degree relative affected at age < 60 years should be advised to have screening

colonoscopy.^{2–5} Potential adherence rates, however, need to be evaluated before a new strategy is added to a screening programme targeting at-risk groups.

The purpose of this study was to test the rate of adherence to colonoscopy in first-degree relatives of patients with colorectal cancer, to identify associated factors and to study the characteristics associated with lesion detection.

METHODS

Screening programmes

We conducted a prospective, cross-sectional, multicentre, nationwide study that covered four regions in Spain (Basque Country, Galicia, Valencia and Catalonia). The study population was composed of first-degree relatives of patients with colorectal cancer selected randomly from the EPICOLON study. The following hospitals participated in the study: Hospital Clinic in Barcelona, Hospital Esperit Sant in Santa Coloma de Gramanet, Hospital Trias i Pujol in Badalona, Hospital General Universitario in Valencia, Hospital General in Alicante, Hospital Dexeus in Barcelona, Hospital San Eloy in Baracaldo and Hospital Meixoeiro in Vigo.

EPICOLON was a prospective, multicentre, nationwide study that was set up to record consecutive cases of colorectal cancer in 25 hospitals in Spain in 2001. The initial aim of the study was to determine the incidence and characteristics of familial forms of colorectal cancer in Spain.^{6,7} Eight of the 25 hospitals that

Abbreviation: CT, computed tomography

participated in EPICOLON took part in our study. The other hospitals did not participate due to the implied workload.

Study procedures

We randomly chose 88 of the 433 colorectal cancer patients identified by the eight hospitals during the EPICOLON study for our study. The number of index patients per hospital was as follows: 22 from Hospital Clinic in Barcelona, 15 from Hospital San Eloy in Baracaldo, 14 from Hospital General Universitario in Valencia, 12 from Hospital Trias i Pujol in Badalona, seven from Hospital de Meixoeiro in Vigo, 14 from Hospital General in Alicante, two from Hospital Esperit Sant in Santa Coloma de Gramanet and two from Hospital Dexeus in Barcelona.

Fourteen of the 88 index patients were finally excluded from the study: eight because they could not be contacted and six because there were no records of their having relatives. The final number of index patients was therefore 74. These were divided into three groups according to their degree of familial aggregation for colorectal cancer: those who fulfilled Amsterdam criteria II, those who fulfilled revised Bethesda guidelines and those had a family history of a first-degree relative with sporadic colorectal cancer.

All first-degree relatives aged over 25 years of age were included in the study. Excluded were relatives who had been diagnosed with familial adenomatous polyposis or inflammatory bowel disease.

With the help of the index patients, we collected data on their first-degree relatives (number, age, sex and place of residence) and contacted these directly. Relatives were contacted within 2 years of diagnosis of the index case. A letter was sent to those who could not be contacted by telephone asking them to contact the investigator. Personal interviews were conducted by the gastroenterologist who had participated in the EPICOLON study. During the interview, relatives were informed of the purpose of the study and the risks and benefits associated with colonoscopy. Those who refused to undergo the procedure were offered the option of barium enema screening. The colonoscopy and preparation of the colon were free of charge, and flexible arrangements were offered. Written informed consent to undergo colonoscopy and participate in the study was obtained from all participants.

The colonoscopies were performed by the participating hospitals' regular endoscopists. Conscious sedation, induced mostly by midazolam or dolantin, was used in all cases. Anaesthesia was not used. The colon was prepared according to the procedures in place at each of the hospitals (oral phosphosoda in most cases).

Data were collected on the length of colon explored and the lesions detected during each procedure. Lesions were analysed for number, location, size, morphology, histology (villous component, grade of dysplasia) and staging in cases of cancer. The lesions were classified in three groups: hyperplastic polyps, advanced neoplasia and non-advanced neoplasia.

Advanced neoplasia was defined as a carcinoma or adenoma ≥ 1 cm or a villous component or high-grade dysplasia.

Non-advanced neoplasia was defined when it was neither a hyperplastic polyp nor an advanced neoplasia. All are adenomas.

Colonoscopy adherence was defined as the percentage of first-degree relatives interviewed that agreed to do undergo colonoscopy (number of relatives that accepted/number of relatives interviewed $\times 100$).

Screening compliance was defined as the percentage of the total number of first-degree relatives that agreed to undergo colonoscopy (number of relatives that accepted/total number of relatives $\times 100$).

The study was approved by the clinical research ethics committees at the respective hospitals.

Statistical analysis

Means and standard deviations were used to describe continuous variables and percentages to describe qualitative variables. Percentages were compared using the χ^2 test or Fisher's exact test, and means were compared using the t test or analysis of variance. A binary logistic regression model was adjusted to determine which variables were independently associated with potential colonoscopy adherence. The statistical analysis was performed using the SPSS statistical package (version 13.0).

RESULTS

The 74 index patients had a total of 342 living first-degree relatives. Of these, 281 were contacted, interviewed and offered the option of undergoing colonoscopy. It was not possible to contact 61 of the 342 first-degree relatives, due to the fact that they lived in other states or countries, or that the relationship between the index case and the relative was poor or non-existent. One hundred and seven agreed to undergo the procedure, corresponding to an adherence rate of 38% (107 out of a total of 281). Screening compliance was 31.28% (107 out of a total of 342 first-degree relatives). When we compared the adherence including all relatives >25 years old with those who meet the criteria recommended by various official bodies^{2,3} (sifted from 25 years in first-degree relatives with Amsterdam II criteria and from 40 or 10 years earlier than the youngest diagnosis in their family in the remaining groups), we did not find any differences. There was therefore an adherence of 38% (107/281) when all the first-degree relatives >25 years old were included, and of 40% (102/254) when only those first-degree relatives who met the recommended criteria were included.

Only four (3.7%) first-degree relatives had undergone a colonoscopy, indicated by other physicians, following diagnosis of their relative. The colonoscopy was completed in 101 subjects (94.4%). The six incomplete colonoscopies (5.6%) were all in women ($p = 0.05$). In 31 (41.9%) families, none of the relatives agreed to undergo colonoscopy while in 14 (18.9%) families all of the relatives agreed. The adherence rate in the remaining 29 families ranged from 45% to 50%.

We found that factors such as an index patient age of under 65 years, a higher degree of familial aggregation and a sibling or offspring relationship were more likely to have a greater influence on adherence to colonoscopy. Adherence was also greater among relatives under 65 years of age and female relatives (see table 1). When we adjusted a binary logistic regression model for all the variables included in the above analysis, we found that the age of the relative (younger), sex of the relative (female), relationship (siblings or children vs parents), age of the index patient and form of colorectal cancer (Amsterdam criteria vs sporadic cancer) had an independent and statistically significant influence on greater adherence to colonoscopy (table 2).

Twenty-eight (26.2%) of the subjects who underwent colonoscopy had lesions. A total of 54 lesions were found. The mean (SD) age was 51 (13.6) years for subjects with lesions and 45.2 (13) years for subjects without lesions. These differences were statistically different. The majority of lesions were sessile (85.2%) and 66.7% were 5 mm or smaller. According to the type of lesions, 20 (37%) were non-advanced neoplasia, 16 (30%) were hyperplastic polyps and 18 (33%) were advanced neoplasia.

Forty-eight percent of the lesions were proximal to the splenic flexure. Specifically, 25% of the carcinomas, 33% of the dysplasias, 58% of the tubular adenomas and 50% of the villous tubular adenomas were proximal to the splenic flexure.

Advanced neoplasia was identified in nine patients (8.4%). Seven dysplastic lesions were found, all with high-grade dysplasia, and four first-degree relatives (7.4%) had five

Table 1 Characteristics of relatives and index cases associated with adherence rate

Characteristics	Results (%)	p Value
Age of index patient (%)		
<65 years	60	0.027
≥65 years	32.9	
Sex of index patient (%)		
Male	42.3	0.28
Female	34.1	
Hereditary type (%)*		
1	88.9	0.005
2	34.1	
3	32.5	
Family relationship† (%)		
Sibling/child	40.7	0.16
Parent	14.3	
Age of first-degree relative (%)		
<65 years	53.7	0.000
≥65 years	17.9	
Sex of first-degree relative (%)		
Male	27.3	0.026
Female	49	

*Type 1 are those who fulfilled Amsterdam criteria II, type 2 those who fulfilled revised Bethesda guidelines and type 3 those had a family history of a first-degree relative with sporadic colorectal cancer.

†Family relationship refers to the relationship of the relatives to the index case; this may be as a parent, sibling or offspring.

carcinomas. One subject had two synchronous colorectal cancers. Twenty-eight percent of the advanced neoplasias were distal to the splenic flexure and 38.5% were proximal. The mean age for carcinoma and polyps >1 cm was 67 and 61 years, respectively. Table 3 shows the association between the presence of lesions and the characteristics of the relatives. The mean age of individuals with lesions was higher than that of those without lesions, and the percentage of men with lesions was statistically significantly higher than the percentage of women with lesions ($p < 0.05$). No significant differences were found for the age of the index patient. There was a higher prevalence of lesions in relatives with a higher degree of familial aggregation, but this was not statistically significant.

DISCUSSION

Colonoscopy is recommended by numerous national and international organisations as the most effective screening method for colorectal cancer in first-degree relatives of affected individuals.³⁻⁵ It has been estimated that one-time colonoscopy is the most cost-effective method of screening for colorectal cancer and the most effective method of reducing mortality.⁸ A study by Lieberman and colleagues¹ found that an adherence rate of 44% for one-time colonoscopy could reduce death from colorectal cancer by 35%. The efficacy of any colorectal cancer screening programme is largely dependent on adherence. Lieberman and colleagues, for example, calculated that the cost per death prevented would increase from US\$225 000 to US\$331 000 if faecal occult blood test adherence decreased from 100% to 50%, and from US\$274 000 to US\$337 000 if colonoscopy adherence decreased by the same proportion. They also concluded that faecal occult blood testing would need an adherence rate of 80% to produce the same decrease in mortality as colonoscopy with an adherence rate of 50%. The adherence rate to faecal occult blood testing is lower in clinical practice than in controlled studies (15–63% vs 53–78%), and adherence is lower still when the test is repeated annually.⁹

Our study, which was conducted in a high-risk population for colorectal cancer, found low adherence to colonoscopy, even lower than that reported by previous retrospective studies,^{10 11} and lower than theoretical calculations showing colonoscopy to be the best screening method.⁹ Ladabaum and colleagues,¹² for

Table 2 Independent variables associated with colonoscopy adherence

Characteristics	Odds ratio (95% CI)
Age of index patient	
<65 years vs ≥65 years	17.3 (2.5 to 117.04)
Sex of index patient	
Female vs male	4.3 (1.2 to 15.3)
Family relationship*	
Sibling/child vs parent	33.1 (1.3 to 811)
Hereditary type†	
1 vs 2	181 (11 to 2999)
2 vs 3	1.3 (0.2 to 7.7)
Age of first-degree relative	
<65 years vs ≥65 years	13.6 (3 to 61.7)
Sex of first-degree relative	
Female vs male	4.3 (1.2 to 15.3)

*Family relationship refers to the relationship of the relatives with the index case; this may be as a parent, sibling or offspring.

†Type 1 are those who fulfilled Amsterdam criteria II, type 2 those who fulfilled revised Bethesda guidelines and type 3 those had a family history of a first-degree relative with sporadic colorectal cancer.

example, modelling optimal screening practices, estimated that screening 75% of the population aged over 50 years would reduce colorectal cancer incidence by 17–54% and death by 28–60%. Our findings are particularly intriguing if we consider that testing was free, and flexible arrangements were offered. Possible factors that might have influenced our results are the delay in contacting relatives (0–2 years after diagnosis of the index case), the inclusion of all the index patients' first-degree relatives (many lived in other cities or countries) and the age of the relatives (many were parents or siblings over 70 years). We found that adherence was lower among parents than among siblings or children, probably due to their advanced age. Other studies have found that elderly patients are reluctant to undergo screening due to cost, discomfort and fear of lesion detection.¹³ In our study, the age of 25 years was added as a cut-off point for inclusion of first-degree relatives, due to the fact that it was the lowest recommended age for performing sifting with colonoscopy in one of the risk groups (Amsterdam II criteria). In addition, with this cut-off point we were able to analyse the influence of age on adherence to colonoscopy in this group of individuals. However, when we compared the adherence including all relatives >25 years old with those who meet the criteria recommended by various official organisations^{2 3} (sifted from 25 years in first-degree relatives with Amsterdam II criteria and from 40 or 10 years earlier than the youngest diagnosis in their family in the remaining groups), we did not find any differences.

In our population, colonoscopy adherence was higher among female relatives, relatives of index patients under 65 years and relatives with a higher degree of familial aggregation for colorectal cancer. We believe that the disease has a greater impact on awareness of risk in families in which the index patient is young and/or in families in which several members of the family are affected. In accordance with the findings of other studies,¹⁴⁻²² we also believe that the perception that colonoscopy and/or the preparation of the colon are uncomfortable or painful has a considerable influence on adherence. This is supported by findings that subjects prefer less uncomfortable screening methods such as faecal occult blood tests.² Other reasons reported for low adherence are lack of time to visit the doctor, low economic and educational levels, lack of interest, the perception of colorectal cancer as a minor problem and, in the case of women, the fact that the endoscopist is a man.^{20 21 23-28} If the effectiveness and cost-effectiveness of new diagnostic methods such as faecal DNA or imaging techniques such as virtual colonoscopy, also known as computed tomography (CT)

Table 3 Variables associated with the presence of lesions

Variables	Advanced lesions	Non-advanced lesions	Hyperplastic polyps	No lesions	p Value
Mean age of index patient (years)	55.4	59.4	53.2	61	0.3
Mean age of first-degree relative (years)	51.8	50.3	44.9	45	0.03
Sex of index patient (%)					
Male	16.3	29.1	14	54.7	0.1
Female	8.5	23.4	8.5	68.1	
Sex of first-degree relative (%)					
Male	16.7	39.4	18.2	43.9	0.000
Female	10.4	14.9	6	74.6	
Hereditary type (%)					
Amsterdam II	26.7	33.3	13.3	40	0.2
Bethesda	14.7	22.7	17.3	62.7	
Sporadic	7	32.6	2.3	60.5	

colonography, improve with time, they might provide a viable alternative to colonoscopy.^{29–30}

We believe that Spain will need to implement several measures to counter reluctance to undergo colonoscopy if it eventually decides to implement this procedure as its screening method of choice. Specifically, it needs to raise awareness among the general population of the health problems associated with colorectal cancer, reduce the level of discomfort caused by bowel preparation, inform the population of the few risks associated with the procedure and “guarantee” minor discomfort by using conscious or deep sedation. It has been shown that individuals who believe in the screening programme and who are properly informed of the risks posed by colorectal cancer are more likely to comply.³¹ It has also been seen that using a celebrity to promote awareness among the general population can increase adherence rates.³²

Our findings are also consistent with the literature in that we detected a high frequency of lesions in our population, which confirms the value of screening for disease in high-risk groups.^{33–34} We also found that lesions were more common in men than in women,^{33–34} and that approximately half of all severe lesions were located in the proximal region,^{33–37} which justifies exploring the full length of the colon. Like Hampel and colleagues,³⁸ we found that the mean age of patients with severe lesions was higher than expected, which suggests that the current recommended age for beginning screening may be too conservative.^{2–3} In our population, the number of lesions increased with degree of familial aggregation for colorectal cancer, although this correlation was not statistically significant, perhaps due to a lack of statistical power.

Recent research has called attention to the existence of some variants of hyperplastic polyp which are potentially malignant.³⁹ In our study, we observed a high prevalence of hyperplastic polyps in first-degree relatives (29.6%), data similar to those obtained by Dove-Edwin *et al*³⁵ in individuals with a family history of colorectal cancer (28%) and lower than those obtained by Regula *et al*³⁴ in 2006 (35.4% of hyperplastic polyps in the age group of 50–66 years and 43.9% in the age group of 40–49 years). In the latter study, 79% did not have a family history of colorectal cancer.

In view of the low adherence to colonoscopy among the first-degree relatives we studied, we believe that it is necessary to implement measures to increase adherence rates. We detected a high number of lesions, many of them in the ascending colon, and many in patients with a higher mean age than that described by colorectal cancer screening guidelines. Further studies are needed to assess potential adherence to colonoscopy in Spain and to analyse the age at which first-degree relatives of patients with colorectal cancer should first be screened.

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Competing interests: None.

Principal investigators in the EPICOLON Group are listed in the Appendix.

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APPENDIX 1 STUDY ORGANISATION AND INVESTIGATORS FROM THE GASTROINTESTINAL ONCOLOGY GROUP OF THE SPANISH GASTROENTEROLOGICAL ASSOCIATION WHO PARTICIPATED IN THE STUDY

All participants listed below were fully involved in the study:

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