Results of a pilot study of endoscopic screening of first degree relatives of colorectal cancer patients in Italy

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Abstract

Study objective—Screening recommendations for colorectal cancer include sigmoidoscopy in asymptomatic, average risk persons aged 50 and over and colonoscopy every three to five years in high risk groups. Little is known about the eligible population's compliance with endoscopic screening. This is the first Italian report of an endoscopic screening programme for colorectal cancer patients' relatives.

Design—In 1986, a pilot project for colorectal cancer screening by endoscopy in high risk subjects was started in the Desio (Milan, Italy) public health service region. The results obtained after seven years are described.

Setting—The names of 536 inhabitants with colorectal cancer diagnosed between January 1975 and December 1984 and their relatives' addresses were obtained from the Regione Lombardia Health System records and from the municipal registry offices respectively.

Participants—From October 1986 to October 1993, 778 first degree relatives aged 20–75 were offered colonoscopy.

Main results—After seven years, 233 (29.9%) had undergone endoscopic examination, mostly up to the splenic flexure. Being >60 in age at the start of the programme negatively affected participation (p<0.05). Two cancers were detected and adenomatous polyps were found in another 24 of those screened (frequencies: 0.9% and 10.3% respectively). Male gender (p<0.05), increasing age in males (p<0.01), and two or more affected relatives in females (p<0.01) positively affected the frequency of polyps detection.

Conclusion—These results suggest that about 30% of the eligible population would comply at least with sigmoidoscopic screening. The collaboration of family doctors and more widespread public information about the ability to cure colorectal cancer are necessary for better compliance.

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About 14 000 people die from colorectal cancer every year in Italy,[1] and about 56 000 in the United States.[2] Among the four high mortality cancers (that is, lung, colorectal, breast, and prostate), colorectal cancer is the only one that has become more curable in the past 25 years and the progressive stages of this cancer are now biologically known.[3 4]

It has been shown that annual faecal occult blood testing can decrease colorectal cancer mortality by 33%,[5] while sigmoidoscopic screening can lead to a reduction in mortality of at least 30–40% [6 7] and colonoscopy every three to five years in the high risk population might result in a reduction of approximately 60–75 %.[8] Every year in Italy, therefore, 4000–6000 people could, in theory, survive if screening strategies were successfully applied.

Current screening guidelines for colorectal cancer[9 10] include stool blood testing performed annually and flexible sigmoidoscopy every three to five years in asymptomatic people over the age of 50 who are at average risk for colorectal cancer. Colonoscopy is recommended for high risk groups,[2 10] such as siblings of colorectal cancer patients, who are three times more likely to develop the disease and may account for 12–25% of all colorectal cancers.[8 11]

Faecal occult blood testing is the only screening method whose effectiveness has been proved by a randomised trial.[5] It was suggested, however, that part of the benefit might be due to a random selection for endoscopic examination caused by the low specificity of the method used,[12] since 38% of the annually screened participants underwent at least one colonoscopy during the study.[5]

Greenberg and Baron suggested that faecal occult blood testing should be bypassed and endoscopy should be used directly as a screening tool.[13] Colonoscopy can detect both colorectal cancer and adenomatous polyps with high accuracy,[14] and colonoscopic removal of polyps decreased the expected incidence of colorectal cancer by 76–90%, as reported by Winawer *et al.*[15] Flexible sigmoidoscopy permits a 50–60% theoretical detection of colorectal cancers and the removal of small polyps in the rectum and the distal part of the large bowel, usually reaching a distance of 40–50 cm from the anus.[16] The procedure is simple enough to be performed by nurses, which reduces costs.[17 18] Besides the expense, disadvantages of endoscopic screening include patient discomfort and the risk of bowel perforation (about 1.4 per 10 000 sigmoidoscopies and 2 per 1000 colonoscopies).[19 20]

There have been few reports of the feasibility of endoscopic screening for colorectal cancer

to date.[21 22] The Desio screening programme is the first Italian report of colorectal cancer screening based on endoscopy. We report the results obtained in a group of first degree relatives of patients affected by colorectal cancer who were offered screening, including a complete colonoscopic examination, from October 1986 on. The aim of the programme was prevention of colorectal cancer by locating and removing adenomatous polyps in subjects at high risk because of a positive family history, including those who might belong to families affected by familial adenomatous polyposis and hereditary non-polyposis cancer, whose presence in the group could not be excluded on the basis of available information. For that reason, although the age at which screening should be started, in absence of a genetic syndrome, is 5–10 years younger than the youngest cancer relative or age 40 years, 20 and 75 years of age were chosen respectively as the lowest and highest entry age limit.

KEY POINTS

● Screening of first degree relatives of colorectal cancer patients should include colonoscopy every three to five years starting at the age of 40 years.

● About 30% of the eligible population in that high risk group would comply with sigmoidoscopic screening at least.

● Compliance was lower in those over 60 years at the start of screening, probably due to fear of a cancer diagnosis and lack of education about prevention.

Methods

RECRUITMENT

The names of 536 colorectal cancer patients diagnosed between January 1975 and December 1984 in the public health service region of Desio (Unità Socio Sanitaria Locale 63, Desio, Milan, Italy), which has about 130 000 inhabitants, were obtained from the official records of the Regione Lombardia Health System, which comprehensively registers all hospital diagnoses and causes of death. Each patient's identity and cancer diagnosis were verified by examining his/her hospital records.

The names and addresses of family members were obtained from the municipal registry offices and a file was created, consisting of 802 first degree relatives, aged between 20 and 75 years, belonging to 355 families.

Between October 1986 and October 1993 the relatives were repeatedly invited to undergo a screening protocol that included the collection of a personal and family history, faecal occult blood testing, and colonoscopy. The protocol also included a dietary interview with a dietician, measurement of anthropometrical parameters, and 12 blood analyses (results not included in the present report).

The project was presented to and discussed at different meetings with the 110 family practitioners of the public health service region. Their names were obtained from the official records of the Unità Socio Sanitaria Locale 63. They were given literature, material for faecal occult blood testing, and a list of their patients who had been included in the screening programme and whose participation they were requested to solicit.

In addition to the invitations extended by family practitioners, beginning in 1989, the target subjects were also invited to participate by a letter that stressed the increased risk of disease in consanguineous relatives. These letters were sent out three times over a five year period (almost every second year). Moreover, the 355 families were contacted once by phone and, at their consent, were visited by trained

personnel who explained the aim of the screening programme. Participants were requested to make an appointment by phone.

The family practitioners were kept informed periodically on the progress of the programme.

PROCEDURE

Personal and family history

The personal and family history of each participant were collected by trained medical personnel, who filled out a questionnaire. Family history investigation included information concerning stomach, breast, lung, endometrium, ovary, and urinary tract cancers.

Endoscopy

After receiving their informed consent, colonoscopy was performed. The participants were supplied with full bowel preparation instructions according to the standard procedure in use at the Desio Endoscopy Unit. In 1987–90, this required a residue-free diet in the 48 hours before the examination, together with saline purgatives and voiding enemas. From 1991 on, however, a polyethylene glycol electrolyte lavage solution was used. Patients received 20 mg of butylscopolamine bromide by intravenous injection before the examination. Analgesic premedication before colonoscopy was not in use at the Desio Endoscopy Unit during the years of the screening programme. The equipment used was a standard Pentax (160 cm) fiberoptic instrument in the years 1987–90 (Pentax -API SpA, Milan, Italy) and an apparatus for video-endoscopy (C 3800 and C 3810, Pentax-API SpA, Milan, Italy) subsequently. The examinations were performed by the same two endoscopists in turn. When a colonoscopy was incomplete and the subject was over 50 in age, a double contrast barium enema was recommended.

Statistical analysis

Results were processed by a *SPSS/PC+* package. The χ^2 test (with the appropriate degrees of freedom) was used to assess the differences between groups; Fisher's exact test (two tailed) was used when the minimum expected frequency was less than 5. A p value <0.05 was regarded as significant.
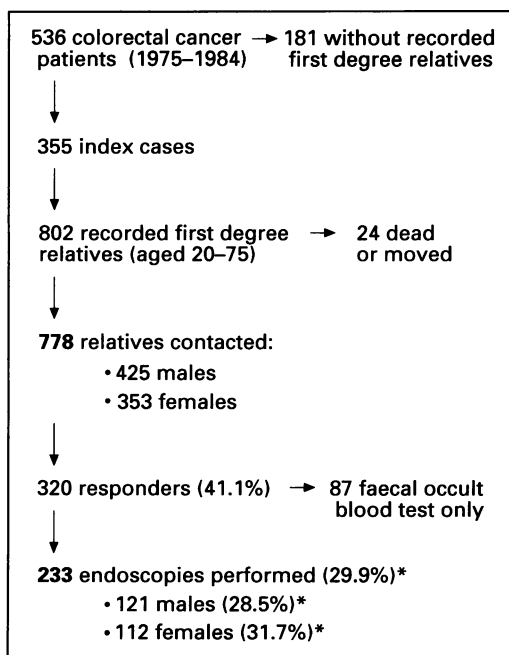
Figure 1   Compliance with endoscopic screening for colorectal cancer in Desio, Italy.

Results

COMPLIANCE WITH COLONOSCOPIC SCREENING

As summarised in figure 1, 778 living, first degree relatives of the 355 colorectal neoplasm patients were contacted. Altogether 425 of them were males and 353 were females.

After seven years, 233 subjects from the group (29.9%) had complied with the screening programme and had undergone at least one endoscopy; 87 more persons (11.2%) had had a faecal occult blood test without endoscopy.

Consent was greatest in the first two years (1987–88), when 187 subjects took part in screening and 108 endoscopies were performed. It fell during subsequent recalls—there were 69 participants in 1989–90 (65 endoscopies) and 64 in 1991–93 (60 endoscopies). Gender did not affect participation. The mean age at the first endoscopy was 44.3 in males (range: 26–68; SD: 10.8) and 45.8 in females (range: 23–74; SD: 11.2).

Compliance with endoscopic screening in relation to the age at the beginning of the programme was evaluated. Thirty six out of 205 subjects aged 20–29 at 10/01/1986 (17.6%) underwent endoscopy. Significant differences in participation were observed in older subjects

(table 1), with the highest compliance in the age groups 30–39 and 40–49, lower compliance in the group 50–59, and a drop in people aged 60 or older.

Education level in the screened group was compared with that of the general population (about 4 000 000 people) in the province of Milan, as per the 1991 national census data.[23] No significant difference was seen when participants were stratified by age.

ANATOMICAL SITE REACHED BY ENDOSCOPY

Colonoscopy was performed up to the caecum in 48 of 223 subjects (20.6%), including those who were found positive for colorectal neoplasms. In the remaining 185 participants (79.4%), the examination was terminated at different bowel sites for the following reasons:

● Discomfort which negatively affected patient compliance (54%),

● Poor bowel preparation (40%),

● Risk of complications because of technical difficulties (6%).

The transverse colon was reached in 30 subjects (12.9%), the splenic flexure in 99 (42.5%) and the descending colon in 56 (24.0%).

FAECAL OCCULT BLOOD TESTING RESULTS

Among the 233 participants who underwent endoscopic screening, the faecal occult blood tests yielded 1 true positive (in a subject with a Dukes's A cancer of the transverse colon), 1 false positive (in a subject without neoplasms), 3 false negatives (in subjects whose endoscopy disclosed adenomatous polyps measuring 10 mm in diameter or more), and 228 true negatives. The subjects with polyps less than 10 mm in diameter were not regarded as false negatives, even though none of them tested positive, because their lesions were considered to be bleeding only intermittently.[24] Test sensitivity and specificity were 25% and 99% respectively.

Among the 87 subjects who agreed to undergo faecal occult blood testing but refused endoscopy, two tested positive with Haemoccult II. One of them underwent an operation for colon cancer two years later, the other one was lost to follow up.

THE NEOPLASTIC FINDINGS AT SCREENING

Two subjects with cancer (frequency = 0.9%) and 24 with adenomatous polyps (frequency = 10.3%) were found among the 233 screened participants. Twenty seven adenomatous polyps were found (more than 1 finding per subject). The anatomical site and pathology of the neoplastic findings are shown in table 2.

A Dukes's A cancer of the transverse colon was found in a subject who also had two tubular polyps. The polyps were found in the sigma and descending colon respectively. Carcinoma "in situ" was seen in a 2.5 cm large, villotubular adenoma.

A single tubular adenoma located in the ascending colon was found in a participant who

Table 1   Compliance with endoscopic screening for colorectal cancer in relation to age at the start of the programme

	Age (y) at start of screening*			
	30–39	40–49	50–59	60
Screened (no (%))	71 (39.4)	61 (36.3)	50 (33.1)	15 (20.3)
Contribution to χ^2 (3df)	1.34	0.18	0.07	4.28
Not screened (no (%))	109 (60.6)	107 (63.7)	101 (66.9)	59 (79.7)
Contribution to χ^2 (3df)	0.70	0.10	0.04	2.25
Total (no (%))	180 (100.0)	168 (100.0)	151 (100.0)	74 (100.0)
Contribution to χ^2 (3df)	2.04	0.28	0.11	6.53
	χ^2 (3df) = 8.96		$p < 0.05$	

* Age of first degree relatives at 10/01/1986. Among people aged 20–29, 36 out of 205 subjects (17.6%) took part in the screening.

Table 2 Anatomical site and pathology of the neoplastic findings* in 26 subjects

Pathology	Anatomical site				
	Rectum	Sigma	Descending colon	Transverse colon	Ascending colon
Cancer Dukes's A	–	–	–	1	–
Carcinoma in situ	1	–	–	–	–
Villo-tubular adenoma	–	5	2	–	–
Tubular adenoma	–	12	7	–	1
Total	1	17	9	1	1
No of screened subjects†	233	233	177	78	48
Frequency (%)	0.4	7.3	5.1	1.3	2.1

* More than 1 finding per subject.
† Number of subjects whose corresponding anatomical site was examined.

Table 3 Adenomatous polyps in relation to age and family history

Age (y)*	Positive versus screened subjects (%)		
	1 relative affected	2 relatives affected	Total
Males			
20–39	0/40	1/11 (9.1)	1/51 (2.0)
40–59	8/44 (18.2)	3/15 (20.0)	11/59 (18.6)
60	2/4 (50.0)	4/6 (66.7)	6/10 (60.0)
All ages	10/88 (11.4)	8/32 (25.0)	18/120 (15.0)
Females			
20–39	0/25	0/9	0/34
40–59	1/48 (2.1)	5/17 (29.4)	6/65 (9.2)
60	0/9	0/3	0/12
All ages	1/82 (1.2)	5/29 (17.2)	6/111 (5.4)

* Age of the participants at the time they underwent endoscopy.

had consented to undergo colonoscopy up to the caecum.

FREQUENCY OF POLYPS IN RELATION TO SEX, AGE, AND FAMILY HISTORY

The subject with Dukes's A cancer was a 56 year old man, while the in situ carcinoma was found in a 31 year old woman. They both had only one first degree relative with colorectal cancer.

The influence of gender, age, and family history on the frequency of adenomatous polyps in the group of participants was investigated (table 3), although the real prevalence of neoplastic findings could not be calculated because of the incompleteness of endoscopic examination.

No cases of familial adenomatous polyposis were encountered. All the subjects who had two or more colorectal cancer patients in their family history (n = 61) were grouped separately from those who had only one (n = 170). The kinship of 15 subjects included not only two or more members with colorectal cancer but also two or more members with cancers at other sites (stomach, breast, lung, or ovary). Their eight families did not strictly fulfil the requirements for the clinical diagnosis of hereditary nonpolyposis colorectal cancer, however,[25] so they were not grouped apart.

Polyps were found more frequently in men than in women (p<0.05). In male subjects a higher frequency of adenomatous polyps was associated with increasing age (p<0.01). Polyps were more frequently found in subjects with two or more relatives affected by colorectal cancer than in subjects who had only one, but the difference reached a statistical significance only for women (p<0.01).

Discussion

Although endoscopic screening begins to be taken into account as a promising tool for colorectal cancer prevention,[18 26 27] its implementation poses many problems including the cost benefit ratio, the availability of the required skill and technology, and a good level of compliance with the proposed procedure by the target population.

The present screening programme addressed high risk consanguineous relatives of colorectal cancer patients. The prevalence of adenomatous polyps found in this group agreed with that obtained by Rozen in a screening programme for colorectal neoplasm, where different screening methods (faecal occult blood testing, flexible sigmoidoscopy, colonoscopy) were used according to the degree of cancer risk.[28]

After 7 years of screening, the compliance of the target population was 41.1% for faecal occult-blood test and 29.9% for endoscopy. The percentages of participants are considerably lower than those reported by Stephenson et al,[22] who performed colonoscopy in 107 out of 154 (69%) first degree relatives of colorectal cancer patients and sigmoidoscopy in 30 out of 64 (47%) spouses. In their programme, a relatively short time had elapsed since the index cases' diagnosis of colorectal cancer had been established, a factor that could have favourably affected the outcome. Nevertheless, the level of compliance with endoscopy achieved in the present screening programme was close to that reported for sigmoidoscopy in two other studies—31% in the Kaiser multiphase evaluation study[21] and 24% reported by Dietrich et al.[29]

Gender did not affect the propensity to undergo screening in this study. However, significant differences in participation were seen in relation to age. The decrease in compliance recorded in subjects who were over 60 at the start of the screening programme is worrisome as colorectal cancer incidence rates rise with ageing.[30] Possible explanations for that finding could be, firstly, better education in maintaining healthy lifestyles in younger people and, secondly, the fear, which could increase with ageing, of getting an advanced diagnosis of a disease thought to be incurable.

The sensitivity of faecal occult blood testing by Haemoccult II (without rehydration) ranges from 80 to 31% for cancers,[5 19 24] and is thought to be about 10% for large adenomas.[19] The sensitivity obtained in the Desio screening programme was rather low, as expected in asymptomatic people, and it is improbable that the faecal occult blood test results exerted any positive influence on the participants' propensity to undergo endoscopic screening. It is remarkable that 2 of the 320 responders, who consented to undergo faecal occult blood testing but refused endoscopy, persisted in refusing it even though their tests turned out to be positive.

Difficulties in completing the endoscopic examination up to the caecum were encountered both in men and in women; it is probable that better results would have been achieved if

analgesic agents had been used, since most of the examinations were stopped when the patients judged the discomfort to be unbearable. Nonetheless, colonoscopy could be performed in subjects found positive for colorectal neoplasms, either immediately or at a second recall. That was certainly due to the propensity of endoscopists to complete exploration up to the caecum or not, taking into account that the risk of complications increases with the depth of exploration.[9 20] Nevertheless, it also suggests that being aware of personal risk can positively affect the compliance of participants.

During the seven years of the Desio screening programme, one Dukes's A carcinoma and one villo-tubular adenoma with carcinoma in situ were detected among 233 participants. Both the neoplasms were in the early stages, as would be expected in a screening programme of asymptomatic people. Bertazzi et al found 9 colorectal cancers per 31 384 person-years in average risk men and women aged 20–74 living in the area north of Milan that includes Desio,[31] while Ponz de Leon et al reported a total crude incidence of 52.8 colorectal cancer cases per 100 000 person-years in the northern Italy district of Modena.[32] On the basis of both authors' data and considering the increase in colorectal cancer risk associated with a family history, the expected number of carcinomas in the group that underwent endoscopic examination varied from 0 to 3. Owing to the incompleteness of colonic examination, the possibility that cancers proximal to the splenic flexure had gone undetected cannot be excluded (the continuing follow up of cancer diagnosis, for the moment, has reached the year 1990).

The frequency with which polyps were found in the Desio group is comparable to the prevalence reported by Rozen and by Stephenson et al[28 22] when corresponding age groups are taken into account. Other authors,[33 34] whose data were based on full bowel colonoscopy, reported higher prevalence rates for adenomatous polyps in subjects comparable to those of the present study for age, gender, and family history.

Although the real prevalence of adenomatous polyps in the Desio group could not be assessed, the findings of the screening programme seem to confirm the data of different authors,[28 32 33 35] who have reported an increasing prevalence with ageing, and a higher prevalence of adenomatous polyps in males than in females and in subjects with two or more colorectal cancer patients in their family history than among those with only one.[35]

The results of the Desio screening programme suggest that about 30% of the eligible population would consent to undergo colorectal cancer screening by endoscopic examination. In other words at least 1000–1500 deaths could be prevented in Italy in one year.

Nevertheless, the Desio endoscopic screening results suggest that before colorectal cancer screening by endoscopy can be successfully implemented in a large eligible population, widespread information must be supplied to the public about the ability to cure colorectal

cancer in its early stages and the benefit of detecting adenomatous polyps in order to improve the acceptability of such a screening method. An example among cancer prevention tools could be the publicity given to mammography in the USA, where the percentage of women who had undergone a mammogram at least once increased from 13–17% in 1978 to 74% in 1992.[36] As calculated by Ransohoff,[27] the cost per life saved by a one time colonoscopic screening is comparable with that of mammographic screening, and the higher curability of early colorectal cancer in comparison with breast cancer[3] prompts such an effort.

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