Incidence of rectosigmoid adenomatous polyps in subjects without prior colorectal adenoma or cancer: a prospective cohort study

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Abstract

Background—Subjects without known colorectal adenomas or cancer constitute a large majority of the population where 85% of all cases of colorectal cancer are thought to occur. Consequently these people should be considered for screening to decrease mortality from colorectal cancer in the general population.
Aims—To estimate the incidence rate of rectosigmoid adenomas in these subjects.
Methods—Subjects without adenomas or cancer at a previous examination which had visualised the rectosigmoid underwent a fibre endoscopy every three years. Endoscopic data and population characteristics were collected prospectively.
Results—A total of 450 subjects fulfilled the selection criteria; 287 (64%) underwent at least two examinations, and 163 had three or more. At the second examination, with a mean delay of 39 months, the incidence rate of rectosigmoïd adenomas was 1.50% per patient year. The rate was 1.75% per patient year (95% CI 0.80–3.33) at the third endoscopy with an additional mean delay of 38 months. The cumulative incidence rate at six years was 7.3% (95% CI 4.3–10.3), representing a mean of 1.2% per patient year. This rate increased with age and was higher for men than for women after age adjustment (p< 0.03).
Conclusions—The incidence rates are very low compared with those of patients with prior adenomas. These results should be considered in establishing rectosigmoid adenoma screening strategies.
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Keywords: adenomatous polyps; epidemiology; incidence; colonic polyps; rectal neoplasms; sigmoid neoplasms

Colorectal cancer is one of the main causes of death from cancer in Western countries.[1 2] Most colonic and rectal cancers are thought to arise from benign adenomatous polyps,[3] a sequence supported by morphological data, molecular biology results, animal studies, epidemiological evidence, and clinical observations[4–8] and whose duration was estimated at 10–15 years.[9] Colonoscopy with polypectomy is associated with a reduced mortality from colorectal cancer.[10 11] The prevalence of colorectal adenomas and some risk factors are known.[12] The rate of adenoma recurrence has already been estimated[12] and an effective interval between endoscopic examinations has been evaluated in a large group of patients with previous colorectal adenomas.[13] Although guidelines for the prevention of colorectal cancer have been published,[14 15] there are few data concerning the incidence of colorectal adenomas in populations without previously diagnosed adenomas,[16–19] although this group represents the majority of the population. Indeed, approximately 85% of all cases of colorectal cancer are thought to arise in people without (or without previously) diagnosed adenomas. That is the reason why this low risk, but large group should obviously not be excluded from screening, if a decrease in mortality from colorectal cancer is to be expected in the general population. An estimate of the incidence rate of colorectal adenomatous polyps in this population is thus necessary to help define an effective prevention strategy. The aim of this study was to estimate the incidence rate of rectosigmoid adenomas in subjects without prior rectosigmoid adenomas or cancer.

Methods

PATIENTS

Since July 1979 our Cancer Centre has carried out a prevention and screening programme for colorectal cancer based on endoscopy. This programme was proposed to 1745 subjects who had a previous colonic endoscopy in our hospital and whose life expectancy was not hypothetically shortened, particularly by an evolutive cancer, or cardiac, renal, hepatic, or pulmonary failure. The first endoscopy could have already been done for screening or for any other reason. Therefore, 677 subjects (mean (SD) age 55.2 (11.1) years, 60.3% women) had at least two rectocolic fibre endoscopies between July 1979 and July 1992. There could be several reasons for performing the initial examination: macroscopic (29.1%) or occult (6.2%) rectal bleeding, intestinal symptoms (28.1%), a personal history of rectocolic polyp (7.4%) or cancer (7.1%), breast cancer (8.6%), uterine cancer (9.9%), miscellaneous cancer (5.3%), or a first degree family history of colorectal polyp (3.2%) or cancer (14.2%); the most frequent reason was screening (72.1%), and the main aim of the endoscopist was to look for neoplastic lesions. In this group, subjects without previous colorectal polyp or cancer and whose initial endoscopy did not show any adenoma or cancer entered this prospective cohort study.

SREENING PROGRAMME DESIGN

Based on an estimated average of 10–15 years of growth from an adenoma to a cancer, our programme proposed a total colonoscopy every six years. As rectosigmoid is the main site of the adenomas, an additional flexible sigmoidoscopy was proposed in the interval of two colonoscopies, in an attempt to improve efficacy. Thus, a flexible sigmoidoscopy or a complete colonoscopy was alternatively proposed every three years. Three years after the previous endoscopy, each subject was contacted by mail a few weeks before each examination which was performed following written consent. Although the interval between two examinations was intended to be three years, it may have been shorter or longer at the request of the subject, or due to delay.

ENDOSCOPIC PROCEDURES

Fibre sigmoidoscopies were performed without anaesthesia after one Normacol enema. Complete colonoscopies were performed with sedation and after intestinal cleaning by a polyethyleneglycol solution. If a neoplastic lesion was discovered on sigmoidoscopy, a total colonoscopy to examine the rest of the colon was performed. Only sigmoidoscopies which visualised more than 35 cm from the anal margin (as measured when pulling back the colonoscope) were selected. When a total colonoscopy was performed, only the data concerning the rectosigmoid were taken into account for this study.

STATISTICAL METHODS

For each subject included in the programme each successive examination was registered and analysed. The first positive examination (diagnosis of a neoplastic lesion) or the last negative examination defined the end point of follow up for statistical analysis. Data for age, sex, indications of the first examination, and past personal and first degree relatives' history of cancer and/or colorectal polyps were prospectively collected from each subject using a standardised questionnaire. The cumulative incidence rate and 95% confidence intervals (95% CI) of rectosigmoid adenomas was estimated for men and women, and for each age group at each successive examination (whatever the real date), and at six years of follow up (whatever the real number of examinations performed at that time). The size of each polyp (or the largest when several polyps were diagnosed) was recorded. The influence of age, sex, history of first degree relatives' colorectal cancer or adenomas, and intestinal symptoms, on the occurrence of colorectal adenomas was tested using the log rank test. Finally, the influence of sex on the occurrence of adenomas, with adjustment for the confounding effect of age, was tested using the log rank test. All statistical tests were performed using BMDP software.[20]

Results

Between July 1979 and July 1992, 450 subjects fulfilled the inclusion critera and underwent 1638 endoscopies. Table 1 presents the popu-

Table 1   *Characteristics of 450 subjects free of previous adenomas or cancer at the first examination*

	n (%)
Sex	
Male	152 (33.8)
Female	298 (66.2)
Age (years)	
<50	170 (37.7)
50–59	163 (36.2)
60–69	89 (19.7)
⩾70	28 (6.2)
Personal history	
Breast cancer	40 (8.8)
Uterine cancer	54 (12.0)
Other cancers	22 (4.8)
First degree relative history	
Colorectal cancer	13 (2.8)
Colorectal polyp	61 (13.5)
Reasons for doing first examination*	
Intestinal symptoms	142 (31.5)
Rectal bleeding	131 (29.1)
Screening	345 (76.6)

*Several reasons per subject are possible.

lation characteristics. No differences were observed when comparison was made with the 677 subjects who joined the screening programme, except for age, this subgroup being two years younger. The mean duration of follow up was 54 months (range 6–161) with 154 subjects (34%) followed up for more than six years. In 188 cases (41.8%) the initial examination was a fibre sigmoidoscopy; for 262 subjects a colonoscopy was performed which was complete in only 111 cases (24.7%). During the study 287 subjects (64%) had only two examinations, 116 subjects (26%) had three, and 47 (10%) had four or more; 32 patients were diagnosed with one or several concomitant rectosigmoid adenomas. No rectosigmoid cancer was diagnosed during the study. None of the adenomas removed was dysplastic.

INCIDENCE RATE AT EACH SUCCESSIVE EXAMINATION

A total of 287 subjects (64%) underwent only two examinations with a mean delay of 39 months (but up to the seventh year) and one or more adenomas were found in 22 of them. The incidence rate at this second examination was 1.5 per 100 patient years (95% CI 0.94–2.27). The size of the adenomas (or the largest when there was more than one) was under 5 mm for six patients, between 5 and 9 mm for 11 patients, between 10 and 14 mm for two patients, and 15 mm or larger for three patients. A total of 116 subjects (26%) whose second endoscopy was negative underwent a third examination, after an additional mean delay of 38 months. In nine patients, one or more adenomas were found with an incidence rate of 1.75 per 100 patient years (95% CI 0.80–3.33). The size of the adenomas (or the largest when there was more than one) was under 5 mm for three patients, between 5 and 9 mm for two patients, between 10 and 14 mm for three patients, and 15 mm or larger for one patient.

CUMULATIVE INCIDENCE RATE OF RECTOSIGMOID ADENOMAS AT SIX YEARS

Table 2 shows the cumulative incidence rate of rectosigmoid adenomas at six years. With 22 cases of rectosigmoid adenomas diagnosed

Table 2 Cumulative incidence rate at six years of rectosigmoid adenomas in 450 subjects free of previous adenomas or cancer

	n	Patients with adenomas (n)	Cumulative rate (%)	95% CI	p Value
All subjects	450	22	7.3	4.3–10.3	
Sex					
Male	152	13	12.9	6.1–19.7	
Female	298	9	4.5	1.5–7.5	0.03
Age at first endoscopy (years)					
<50	170	5	4.2	0.5–7.9	
50–59	163	9	8.1	2.9–13.4	
⩾60	117	8	10.9	3.4–18.4	0.02*

*Overall test: a significant difference was only observed between <50 and ⩾60 years.
CI, confidence interval.

during this period the cumulative incidence rate of rectosigmoid adenomas at six years was 7.3% (95% CI 4.3–10.3%) which corresponds to a mean incidence rate of 1.2% per year (95% CI 0.7–1.7%). Ten additional subjects were diagnosed after six years. The cumulative incidence rate increased with age from 4.2% (95% CI 0.5–7.9%) for subjects under 50 years of age to 10.9% (95% CI 3.4–18.4%) for subjects aged 60 and over (p<0.02). The impact of age was observed for both men and women. The rate was higher in men (12.9% (95% CI 6.1–19.7%)) than in women (4.5% (95% CI 1.5–7.5%)) even after adjustment for age (p<0.03). Intestinal symptoms, rectal bleeding, or first degree relative history of colorectal polyps or cancer as the reasons for performing the first endoscopy were not statistically associated with the occurrence of rectosigmoid adenomas.

Discussion

To our knowledge only four studies have investigated the incidence of colorectal adenomas in subjects without a prior colorectal polyp or cancer.[16–19] The size of the population in the present study, the duration of follow up, and the number of examinations done makes this study the most extensive investigation performed on this topic. The present work, as did that of Rex *et al*,[17] focused on the rectosigmoid.

Our results show a very low incidence of rectosigmoid adenomas in this cohort. Lewis *et al* screened a group of 94 American male polypropylene manufacturing workers without polyps at their first examination compared with 72 matched controls.[16] The purpose of that study was to test polypropylene exposure as a risk factor for the occurrence of colorectal adenomas. Therefore, those results were only expressed in terms of the incidence rate ratio compared with the control group. However, adenomatous polyps occurred in 19 of 90 subjects (21%) with at least three years between examinations for 97% of the workers. This suggests a high incidence rate in this specific group. More recently, Neugut *et al* reported that by the end of the follow up period (mean 34 months) 24 of 99 patients with negative initial colonoscopy results had developed an adenoma, which was expressed as "a cumulative incidence of approximately 16% after three years", also suggesting a rather high incidence rate.[18] It is important to note that these two series were small. Rex *et al* had a very similar approach to that of the present study.[17] Their aim was to evaluate the results of flexible sigmoidoscopy three years after a negative examination in an average risk person (asymptomatic, and without first degree relatives with colorectal polyps or cancer, inflammatory bowel disease, a personal history of colorectal polyps or cancer, breast or uterine cancer, or Peutz-Jeghers syndrome). With a mean interval of 41 months between examinations, among 259 persons who were rescreened, 15 (6%) had one or more adenomas, and none had cancer. This study and the present one were both performed in average or low risk groups from Western countries. These results support the hypothesis that the annual incidence rate of rectosigmoid adenomas for subjects 50 years and older is approximately 1–2%.

Another recent study from the same group, evaluating the five year incidence of adenomas in the same asymptomatic average risk persons, and based on total colonoscopy, reported quite similar results.[19] Of 154 persons who underwent a second screening, a mean of 66 months after the initial negative colonoscopy, 41 (27%) were found to have at least one adenoma, 61% of which were located proximal to the splenic flexure. These rates are more than twice lower than the 32.0% reported by the US national polyp study group[13] in patients rescreened three years after an initial polypectomy. It is also important to note that in the study by Rex *et al* and in our investigation no cancer was detected, even after five years.

It is well known that some polyps, especially small ones, may be missed at a first examination and obviously this fact cannot be excluded in our cohort. These polyps, only diagnosed at a further examination, may falsely increase the apparent incidence of new polyps. Some of our subjects had symptoms at their first examination and that too may be associated with an increased risk of neoplastic lesions. However, small polyps which could be missed are usually asymptomatic. It is also noteworthy that the second and following examinations were never diagnostic but screening ones. All these facts reinforce the significance of the low incidence rate in our cohort.

Two other important findings in the present study are the increased incidence rate with age and in men. An increased prevalence of adenomatous polyps with age has been well established,[12 21 22] and has recently been confirmed[23–25] and reviewed.[26] The influence of age on incidence has also been identified by Neugut *et al* for their entire population (with or without abnormalities on index colonoscopy)[17] and by Winawer *et al* in patients with previous colorectal adenomas.[13]

Sex is also an important characteristic when considering the risk of colorectal neoplasias. Although it remains controversial,[12] the higher prevalence of adenomas in men has been extensively documented in necropsy series,[22] in clinical data,[21] and especially with multivariate analysis[23 25] in asymptomatic patients with a family history of colorectal cancer[27 28] as well as in patients with prior colorectal adenomas.[13] The present study of the incidence rate is the

only one to document a significantly higher risk in men than in women. In fact, all the workers studied by Lewis *et al*,[16] and 90% of the population studied by Rex and colleagues[17] were men, which obviously makes a comparison impossible. These results have only been previously reported in subjects without prior colorectal neoplasias by Neugut *et al*, but due to the size of their sample, those results were not statistically significant.[18]

Based on the inclusion criteria, the patients in this study did not have prior colorectal adenomas or cancer, but some did have a prior history of other cancers, or a family history of colorectal cancer. A personal history of cancer was noted in 25.8% of the subjects, including 8.8% with previous breast cancer and 12% with uterine cancer. Furthermore 16.3% had a first degree relative with a history of colorectal cancer or polyps (table 1). These conditions could be associated with a risk of colorectal neoplastic lesions different to that in the general population. Many studies have shown that a history of adematous polyps or colorectal cancer in a family member is associated with a high risk of adenomatous polyps of the rectum or colon.[28 29] These data suggest that the population studied here could have been at a slightly higher risk for colorectal adenomas than the general population. This would enhance the low rate that we have observed. On the other hand, it should be kept in mind that two recent reports revealed no increased prevalence in adenomas in women with breast cancer screened with colonoscopy[30 31] and, to our knowledge, there is no proved association between endometrial cancer and adenomatous colorectal polyps.

Our cohort was not intended to be representative of the general French population and may differ particularly for age and personal or family history. The mean age of our subjects was 53 years at their first examination. This is quite close to the mean age of 56.4 in the study by Rex *et al*, and may explain the similar results.[17] In our series, 66% of the subjects were women while in the general French population over 50 years old 58% were women.[32] The possible differences between the characteristics of the population in this study and the general population in Western countries will probably not affect our main results which are highly significant. Thus, only small differences in the evaluation of the incidence rates are expected. Once again, the similarities with the Indianapolis study[18] are important and the characteristics of our patients are probably those of potentially compliant individuals in a preventive programme in a Western country.

While cancer seems to occur most frequently in the rectum and distal colon,[33] the segmental distribution of adenomas within the large bowel is controversial and may be influenced by age and methodology. However, there is a certain consensus that large adenomas and/or adenomas with dysplasia are found more often in the rectum and the sigmoid colon,[12 21 22] thus justifying focusing on the rectosigmoid in the present work and

the study by Rex *et al*. This is also a strong argument for screening programmes based on sigmoidoscopy.

These results could help to develop more effective rectosigmoid adenoma screening strategies. The findings, as well as the duration of the polyp-cancer sequence, contribute to support the proposals of a sigmoidoscopy every six to 10 years[10] or even "once only",[34] not only in the high risk population or in patients with positive faecal occult blood tests, but also in the average or low risk population over 50 years of age, in order to decrease the overall mortality from colorectal cancer.

1 American Cancer Society. *Cancer facts and figures—1990.* Atlanta: American Cancer Society, 1990.
2 Ménégoz F, Black RJ, Arveux P, *et al*. Cancer incidence and mortality in France in 1975–95. *Eur J Cancer Prev* 1997;**6**:442–66.
3 Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;**36**:2251–70.
4 Madara JL, Harte P, Deasy J, *et al*. Evidence for an adenoma-carcinoma sequence in dimethylhydrazine-induced neoplasms of rat intestinal epithelium. *Am J Pathol* 1983;**110**:230–5.
5 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;**61**:759–67.
6 Simons BD, Morrison AS, Lev R, *et al*. Relationship of polyps to cancer of the large intestine. *J Natl Cancer Inst* 1992;**84**:962–6.
7 Stryker SJ, Wolf BG, Culp CE, *et al*. Natural history of untreated colonic polyps. *Gastroenterology* 1987;**93**:1009–13.
8 Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N Engl J Med* 1992;**326**:658–62.
9 Morson BC, Dawson IMP. *Gastro-intestinal pathology.* 2nd edn. London: Blackwell Scientific Publications, 1979:637.
10 Selby JV, Friedman GD, Quesenberry CP Jr, *et al*. A case control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;**326**:653–7.
11 Müller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32702 veterans. *Ann Intern Med* 1995;**123**:904–10.
12 Peipins LA, Sandler RS. Epidemiology of colorectal adenomas. *Epidemiol Rev* 1994;**16**:273–97.
13 Winawer SJ, Zauber AG, O'Brian MJ, *et al*. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N Engl J Med* 1993;**328**:901–6.
14 Conférence de consensus. Préventon, dépistage et prise en charge des cancers du colon. *Gastroenterol Clin Biol* 1998;**22**:205–18.
15 Winawer SJ, Fletcher RH, Miller L, *et al*. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997;**112**:594–642.
16 Lewis RJ, Lerman SE, Schnatter AR, *et al*. Colorectal polyp incidence among polypropylene manufacturing workers. *J Occup Med* 1994;**36**:174–81.
17 Rex DK, Lehman GA, Ulbright TM, *et al*. The yield of a second screening flexible sigmoidoscopy in average-risk persons after one negative examination. *Gastroenterology* 1994;**106**:593–5.
18 Neugut AI, Jacobson JS, Ahsan H, *et al*. Incidence and recurrence rates of colorectal adenomas: a prospective study. *Gastroenterology* 1995;**108**:402–8.
19 Rex DK, Cummings OW, Helper DJ, *et al*. 5-Year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons. *Gastroenterology* 1996;**111**:1178–81.
20 Dixon WJ (ed). *BMDP statistical software manual.* Berkeley: University of California Press, 1992.
21 Faivre J, Boutron MC, Bataillon P. Epidemiology of adenoma: clinical data. In: Faivre J, Hill MJ, eds. *Causation and prevention of colorectal cancer*. Amsterdam: Elsevier Science, 1977:29–37.
22 Vatn MH. Epidemiology of adenomas: autopsy data. In: Faivre J, Hill MJ, eds. *Causation and prevention of colorectal cancer*. Amsterdam: Elsevier Science, 1977:13–27.
23 Rex DK, Lehman GA, Ulbright TM, *et al*. Colonic neoplasia in asymptomatic persons with negative fecal blood tests: influence of age, gender, and family history. *Am J Gastroenterol* 1993;**88**:825–31.
24 Cannon-Albright LA, Bishop DT, Samowitz W, *et al*. Colonic polyps in an unselected population: prevalence, characteristics, and associations. *Am J Gaestroenterol* 1994;**89**:827–31.
25 Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zeland. *Gut* 1992;**33**:1508–14.

26 Rex DK. Colonoscopy: a review of its yield for cancers and adenomas by indication. *Am J Gastroenterol* 1995;**90**:353–65.

27 Burt RW, Bishop DT, Cannon LA. Dominant inheritance of adenomatous colonic polyps and colorectal cancer. *N Engl J Med* 1985;**312**:1540–4.

28 Gaglia P, Atkin WS, Whitelaw S, *et al*. Variables associated with the risk of colorectal adenomas in asymptomatic patients with a family history of colorectal cancer. *Gut* 1995;**36**:385–90.

29 Bonelli U, Martines H, Conio M. Family history of colorectal cancer as a risk factor for benign and malignant tumors of the large bowel: a case-control study. *Int J Cancer* 1988; **41**:513–17.

30 Murray TI, Neugut AI, Garbowski GC, *et al*. Relationship between breast cancer and colorectal adenomatous polyps. A case-control study. *Cancer* 1992;**69**:2232–4.

31 Rex DK, Sledge GW, Harper PA, *et al*. Colonic adenomas in asymptomatic women with a history of breast cancer. *Am J Gastroenterol* 1993;**88**:2009–14.

32 Ministère Français des Affaires Sociales. *Annuaire des statistiques sanitaires et sociales*. Paris: La documentation Française, 1993–1994.

33 Cooper GS, Yuan Z, Landefeld CS, *et al*. A national population-based study of incidence of colorectal cancer and age. *Cancer* 1995;**75**:775–81

34 Atkin WS, Hart A, Edwards R, *et al*. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. *Gut* 1998;**42**:560–5.