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ORIGINAL CONTRIBUTIONS

Colonoscopic Screening for Neoplasms in Asymptomatic First-Degree Relatives of Colon Cancer Patients

A Controlled, Prospective Study

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Individuals with a family history of colorectal cancer are believed to be at an increased risk of developing colorectal neoplasia. To estimate this risk and the potential yield of screening colonoscopy in this population, we recruited and prospectively colonoscoped 181 asymptomatic first-degree relatives (FDR) of colorectal cancer patients and 83 asymptomatic controls (without a family history of colorectal cancer). The mean ages for the FDR and control groups were 48.2 ± 12.5 and 54.8 ± 11.0, respectively. Adenomatous polyps were detected in 14.4 percent of FDRs and 8.4 percent of controls. Although 92 percent of our FDRs had only one FDR afflicted with colon cancer, those subjects with two or more afflicted FDRs had an even higher risk of developing colonic adenomas (23.8 percent) than those with only one afflicted FDR (13.1 percent). A greater proportion of adenomas was found to be beyond the reach of flexible sigmoidoscopy in the FDR group than in the controls (48 percent *vs.* 25 percent, respectively). Logistic regression analysis revealed that age, male sex, and FDR status were independent risk factors for the presence of colonic adenomatous polyps (RR = 2.32, 2.86, and 3.49, respectively; $P < 0.001$). Those at greatest risk for harboring an asymptomatic colonic adenoma are male FDRs over the age of 50 (40 percent *vs.* 20 percent for age-matched male controls). Based on probability curves, males with one FDR afflicted with colon cancer appear to have an increased risk of developing a colonic adenoma beginning at 40 years of age. Our results document, for the first time, an increased prevalence of colonoscopically detectable adenomas in asymptomatic first-degree relatives of colon cancer patients, as compared with asymptomatic controls, and support the use of colonoscopy as a routine screening tool in this high-risk group. [Key words: Colonoscopy; Asymptomatic; Adenomas; Familial; Prospective; Controlled study]

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Despite advances in multimodality therapy, the colorectal cancer (CRC) mortality rate remains essentially unchanged from 40 years ago, while the incidence of this disease continues to

rise.[1,2] Strategies to reduce colon cancer mortality have therefore focused on the early detection and treatment of cancers and adenomatous polyps, the known precursor lesion for most cases of CRC.[3] We and others have demonstrated the value of colonoscopy in the detection of early-stage neoplasms in individuals with rectal bleeding.[4-6] The current recommendations of the American Cancer Society for screening asymptomatic individuals include annual fecal occult blood testing as well as sigmoidoscopy every three to five years starting at age 50 years. For individuals at elevated risk for developing CRC, more intensive surveillance has been recommended.[7-9]

While relatives of patients with certain rare genetic syndromes, such as familial adenomatous polyposis, Gardner's syndrome, and cancer family syndrome,[10] would almost certainly benefit from an intensive screening program, the majority of "familial" colon cancer is seen in first-degree relatives of patients with CRC. Autopsy and retrospective studies[11-15] have demonstrated a two- to threefold increased risk of CRC and adenomatous polyp development in this population. Three case-control studies, based upon hospital records or registry data,[16-18] also demonstrated an increased prevalence of adenomatous polyps and cancers among first-degree relatives of patients with colorectal cancer. However, these studies were limited since they included only symptomatic patients.

Because of the paucity of prevalence data on adenomas in asymptomatic individuals, the exact guidelines for screening this large population have yet to be defined. Several endoscopic studies, including our own, have documented a high prevalence of adenomatous polyps in asymptomatic first-degree relatives of CRC patients.[19-25] Most were retrospective and without a control population.[19-22] Four of the studies were prospective but did not have a control population[23-26] or used flexible sigmoidoscopy for screening.[27] Others dealt with kindreds and limited their evaluation to a flexible sigmoidoscopy, thereby missing the right colon.[28] With a recent right-sided shift in colon neoplasms among the general population[29] as well as a propensity for proximally located CRC in the cancer family syndrome,[30] the screening of first-degree relatives of colon cancer patients should include the entire colon.

In the present study, we compared the colonoscopic detection rate of neoplasms in asymptomatic first-degree relatives of CRC patients with that in asymptomatic individuals without a family history of colorectal cancer.

PATIENTS AND METHODS

Subjects

The office records of four Columbia-Presbyterian Medical Center (CPMC) surgeons were reviewed for the years 1980 to 1990 to identify all patients with a diagnosis of CRC. All living, pathologically confirmed CRC patients were contacted to obtain the name, age, sex, relationship, and address of all their first-degree relatives (FDRs; FDR = parent, sibling, or offspring). FDRs were then contacted and recruited for participation. The majority (92 percent) of FDR subjects were recruited in this manner. The remaining 8 percent of FDRs were referred to us by other members of the CPMC community.

Criteria for inclusion into the study as an FDR were: a) pathologic proof of CRC in the index case; b) age >21 years; c) no signs or symptoms suggestive of CRC or other gastrointestinal pathology; d) no prior history of CRC or colonic polyps; e) no history of inflammatory bowel disease, familial polyposis, Gardner's syndrome, or cancer family syndrome; and f) no previous history of colonoscopy.

Controls

Criteria for inclusion into the study as a control were parameters b, c, d, e, and f, as shown above, as well as absence of a family history of CRC. The controls came from two sources. Twenty-five (30 percent) were spouses of our FDR subjects. An additional 58 were actively recruited from members or friends of the CPMC community. To reduce selection bias, no volunteer controls were accepted.

Methods

Individuals recruited for colonoscopy were carefully screened *via* phone conversation for any evidence of gastrointestinal symptomatology. With controls, great care was also taken to screen for a personal or family history of CRC or colonic polyps. Furthermore, all subjects submitted a detailed personal and family medical history report (including second-degree relatives), in order to identify and exclude possible cases of Lynch syndrome. After bowel preparation with GoLYTELY® (courtesy of

Braintree Laboratories Inc., Braintree, MA), the colonoscopies were performed by one of three experienced endoscopists (K.A.F., J.G.G., and M.R.T.), who were blinded to the status (FDR or control) of the subject. For all lesions encountered, biopsy specimens were obtained and anatomic location recorded. The histopathology of the lesion was determined by the study pathologist (K.M.O.), without knowledge of the status of the subject. Lesions determined to be a hyperplastic polyp on histology were excluded from analysis. No complications were encountered during the performance of the 181 colonoscopies.

Statistical Methods

Logistic regression analysis was used to identify risk factors for the occurrence of colonic adenomatous polyps.[31] Age, sex, and relationship of an individual (FDR or control) were used as explanatory factors in this model. Wald chi-squares were used to determine statistical significance.[31]

RESULTS

A total of 438 CRC index cases was identified and successfully contacted. Of these, 206 (47 percent) consented to participate. *Via* this mechanism, a group of 459 FDRs was identified and contacted, of whom 191 (42 percent) consented to participate in the study. A group of 225 controls was also identified and contacted, of whom 90 (38 percent) participated in the study. Seventeen subjects (10 FDRs and 7 controls) were subsequently eliminated from analysis for a variety of reasons, including the presence of gastrointestinal symptoms (5), family history of CRC in controls (7), incomplete colonoscopy (2), and no biopsy performed (3).

The results of our study are therefore based on the colonoscopic findings in 181 FDRs and 83 controls. The mean age and range, as well as sex distribution for both the FDR and control groups, are shown in Table 1. The mean age of the control group was slightly higher than that of the FDR group. Furthermore, the percentage of men in the control group was greater than that in the FDR group—55 percent *vs.* 43 percent, respectively.

The overall detection rates of adenomatous polyps in the FDR and control groups were 14.4 percent and 8.4 percent, respectively. This difference was not statistically significant. When the prevalence of polyps is determined as a function of age, sex, and familial risk, it is clear, as shown in Table 2, that FDRs develop colonic adenomas at an earlier age than do controls. In the 30- to 39-year age group, 2.1 percent of the FDRs had an adenoma detected, whereas none were detected in 7 controls. Similarly, in the 40- to 49-year age group, 8.3 percent of the FDRs had an adenoma detected, whereas none were detected in 24 controls. With the exception of the 50- to 59-year age group, in all other age and sex categories the prevalence of adenomas was greater in the FDRs than in controls. This difference was most striking for men. As noted, for men over the age of 50, the prevalence

Table 1.
Characteristics of FDRs and Control Group

	FDR	Control
Number	181	83
Age range (yr)	25–83	31–78
Age mean (yr)	48.2 ± 12.5	54.8 ± 11.0
Age median (yr)	46	57
Male (%)	43	55

FDR = first-degree relative of CRC patients.

Table 2.
Stratification of Adenomas by Age, Sex, and Risk

Age Range (yr)	FDRs (No. of Polyps/No. of Subjects)*			Controls (No. of Polyps/No. of Subjects)*		
	Total	Females	Males	Total	Females	Males
20–29	0/5	0/1	0/4	0/0	0/0	0/0
30–39	1/49	1/29	0/20	0/7	0/3	0/4
40–49	4/48	2/30	2/18	0/24	0/12	0/12
50–59	7/41	2/24	5/17	3/18	1/7	2/11
60–69	10/31	4/18	6/13	3/27	0/13	3/14
70–79	4/6	1/2	3/4	1/7	0/2	1/5
80–89	0/1	0/0	0/1	0/0	0/0	0/0
Total	26/181	10/104	16/77	7/83	1/37	7/46
(%)	(14.4)	(9.6)	(20.8)	(8.4)	(2.7)	(15.4)

FDR = first-degree relative.
* Ratio refers to number of subjects with an adenomatous polyp over total number of subjects colonoscoped.

Table 3.
Results of Logistic Regression Model

Predictor	Parameter Estimate	Standard Error	Wald Chi-Square	Relative Risk	95% C.I.*
Male sex	1.05	0.42	6.31†	2.86	1.26–6.51
Age‡	0.84	0.02	19.56§	2.32	0.45–2.41
FDR status	1.25	0.49	6.54†	3.49	1.33–9.12

* Confidence intervals.
† $P < 0.05$.
‡ Ten-year age intervals.
§ $P < 0.001$.

of adenomas was 40 percent for FDRs compared with only 20 percent for controls. Furthermore, this differential appeared to increase with each succeeding 10-year period.

Logistic regression analyses revealed that age, male sex, and FDR status were independent risk factors for the presence of colonic adenomatous polyps. The statistical significance of the overall model, as determined by the chi-squared test for covariates, was 32.9 with 3 DF ($P = 0.0001$). The relative risk ratios for age, male sex, and FDR status were 2.32, 2.86, and 3.49, respectively (Table 3). Probability curves generated from our logistic regression model (Figs. 1 and 2) revealed an increased risk for FDRs. This elevated risk, found in both men and women, increases with age. Of note is that the risk of developing a colonic adenoma is greatest for male FDRs and least for female controls. Of particular interest is the superimposability of the probability curves for the male control group and the female FDR group, suggesting a similar risk.

Anatomic and pathologic analyses revealed a greater proportion of polyps proximal to the splenic flexure in the FDRs than in the controls—48 percent *vs.* 25 percent, respectively. This was, however, not statistically significant. Although no cases of invasive carcinoma were detected, the proportion of polyps with marked cytologic atypia (intraepithelial carcinoma) appears to be greater in FDRs than in controls—18 percent *vs.* 13 percent, respectively. Polyps were classified as tubular, tubulovillous, or villous. As shown in Table 4, there was no significant difference in the histopathologic features of the adenomas detected in the FDR and control groups.

Although 92 percent of our FDRs had only one first-degree relative afflicted with CRC, those FDRs with two or more first-degree relatives afflicted with CRC had a higher risk of developing a colonic adenoma (23.8 percent) than those with only one first-degree relative with CRC (13.1 percent) (Table 5). Because of the paucity (N = 21) of patients with two or more first-degree relatives afflicted with CRC, the difference was not statistically significant ($P < 0.1$), although the trend was in the right direction.

The exact relationship of the index case to the FDR had a significant influence on the likelihood of finding an adenoma in the FDR. For those individuals whose only known family member with CRC was a sibling, the probability of having a colonoscopically detectable adenoma was 24 percent, compared with 9 percent for those having a parent afflicted with CRC. The odds ratio for this relationship was 0.325, with 95 percent confidence limits of 0.127 and 0.834 ($P < 0.05$; Fisher's exact test). An increased frequency of CRC among subjects whose FDR was a sibling, as opposed to a parent, has previously been noted in a registry-based study.[18] Our study is the first to demonstrate this pattern for adenomas.

The age of the index case (parent) at the time of the diagnosis of CRC was lower for those whose FDR had a detectable adenoma than for those who had a normal colonoscopy—61 years and 73 years, respectively.

DISCUSSION

Present recommendations for the screening of asymptomatic individuals with an average or high risk for colorectal neoplasia have been based, in part, on data obtained from population, kindred, or autopsy studies. Prior screening studies have been limited by small sample size, sigmoidoscopy only, partly symptomatic individuals, or lack of a comparison group.[19–28] The significance of the present study is that it documents, for the first time, the colonoscopic detection rate and spatial distribution of colonic adenomas in asymptomatic first-degree relatives of CRC patients as compared with asymptomatic average-risk individuals.

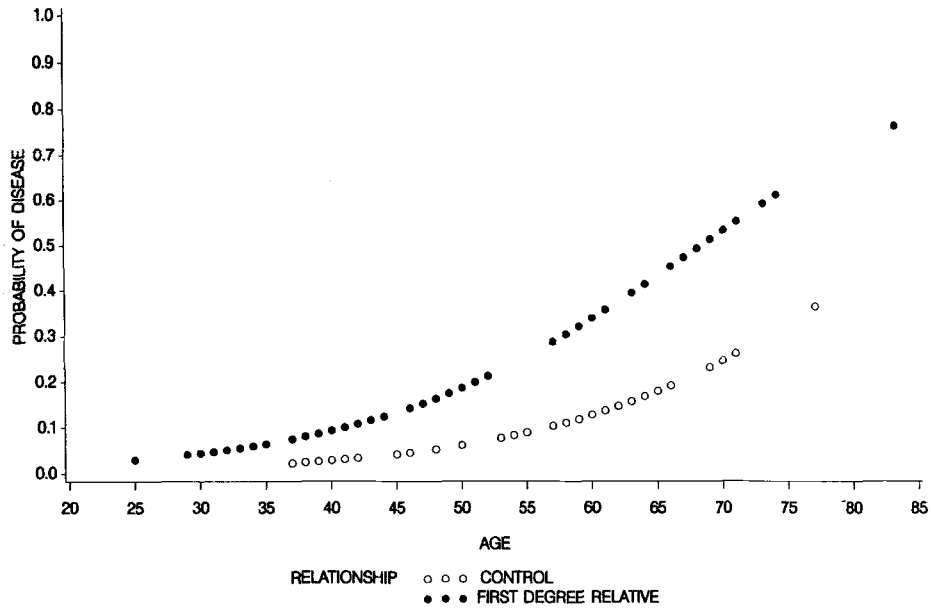

Figure 1. Probability of the occurrence of colonic adenomatous polyps by age for males.

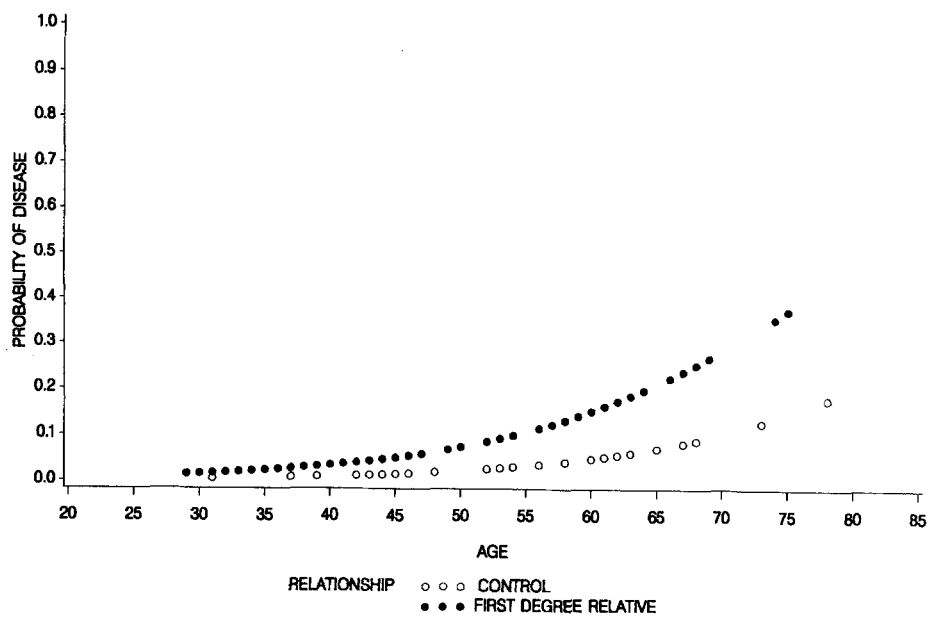

Figure 2. Probability of the occurrence of colonic adenomatous polyps by age for females.

Our data demonstrate that male sex, increasing age, and having as few as one first-degree relative with CRC are independent, statistically significant risk factors for the development of colonoscopically detectable colon adenomas.

Prior uncontrolled studies[21, 24] as well as mathematical models[32] suggested that the risk for FDRs was "significant" only when two or more index cases with CRC existed. Our results demonstrate that having one FDR with CRC increases the risk of developing colonic adenomas in a statistically significant manner. Therefore, although there appears to be a linear relationship between the number of FDRs afflicted with CRC and the development of colon adenomas, the risks exist with as few as one afflicted FDR.

Since CRC in members of cancer family syndromes tends to develop in the proximal colon, a similar distribution would be anticipated in FDRs. Our results confirm this notion by demonstrating that 48 percent of the adenomas detected in FDRs were proximal to the splenic flexure, compared with only 25 percent for controls. This proximal distribution has clinical significance since these lesions would not be detected if flexible sigmoidoscopy were utilized for screening.

Table 4.
Characteristics of Adenomas in FDR and Controls

	FDR	Control
Proximal	16/33 (48.5%)	2/8 (25%)
Atypia	6/33 (18.2%)	1/8 (12.5%)
Histology pattern		
Tubular	10/33 (30.3%)	2/8 (25%)
Tubulovillous	16/33 (48.5%)	3/8 (37.5%)
Villous	7/33 (21.2%)	3/8 (37.5%)

Proximal—refers to cecum, ascending, hepatic flexure, and transverse colon up to, but not including, the splenic flexure.

Atypia (marked)—refers to cytologic features including pleomorphism, nuclear enlargement, and hyperchromasia, sufficient to justify a diagnosis of intraepithelial carcinoma.

Tubular/tubulovillous/villous—describe the predominant architecture of the adenoma.

Table 5.
Prevalence of Asymptomatic Adenomas as a Function of Familial Risk

Afflicted FDR	Subjects with Adenomas/Total No. of Subjects (%)
0	7/83 (8.4%)
1	21/160 (13.1%)
≥2*	5/21 (25.0%)

FDR = first-degree relative with histologically proven CRC.

* Of 21 subjects with ≥2 FDRs afflicted with CRC, 20 had 2 and 1 had 3 afflicted FDRs.

$\pi^2 = 3.768$ ($P < 0.1$).

Although our data clearly identify increasing age, male sex, and the presence of as few as one FDR with CRC as independent, statistically significant risk factors for colonoscopically detectable adenomas, we are unable to comment on the detection rate of CRC, since none was detected in either group. This is perhaps due to the relatively young age of our study population. However, we did identify significant cytologic atypia in a greater proportion of the adenomas detected in the FDR group than in controls.

Our data offer an objective assessment of the potential yield of screening colonoscopy in asymptomatic first-degree relatives of CRC patients as well as average-risk, asymptomatic individuals. It is beyond the scope of this paper to provide a definitive cost-benefit analysis of screening colonoscopy in first-degree relatives of CRC patients. However, as Figures 1 and 2 suggest, there is an increasing divergence in colon neoplasm risk, between FDR and control groups, as age increases. These data suggest that the risk of harboring a colonic neoplasm in a FDR may outweigh the costs and risks of screening colonoscopy and justify its use in certain subsets. We feel that first-degree relatives of colon cancer patients over the age of 40, particularly males, should be offered a screening colonoscopy.

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