

RESULTS OF SCREENING COLONOSCOPY AMONG PERSONS
40 TO 49 YEARS OF AGETHOMAS F. IMPERIALE, M.D., DAVID R. WAGNER, M.S., CHING Y. LIN, B.S., GREGORY N. LARKIN, M.D.,
JAMES D. ROGGE, M.D., AND DAVID F. RANSOHOFF, M.D.**ABSTRACT**

Background The prevalence of colorectal lesions in persons 40 to 49 years of age, as identified on colonoscopy, has not been determined.

Methods We reviewed the procedure and pathology reports for 906 consecutive persons 40 to 49 years of age who voluntarily participated in an employer-based screening-colonoscopy program. The histologic features of lesions that were identified and removed on endoscopy were categorized according to those of the most advanced lesion removed proximally (up to the junction of the splenic flexure and the descending colon) and the most advanced lesion removed distally. An advanced lesion was defined as an adenoma at least 1 cm in diameter, a polyp with villous histologic features or severe dysplasia, or a cancer.

Results Among those who underwent colonoscopic screening, 78.9 percent had no detected lesions, 10.0 percent had hyperplastic polyps, 8.7 percent had tubular adenomas, and 3.5 percent had advanced neoplasms, none of which were cancerous (95 percent confidence interval for cancer, 0 to 0.4 percent). Eighteen of 33 advanced neoplasms (55 percent) were located distally and were potentially within reach of a sigmoidoscope. If these results are applicable to the general population, at least 250 persons, and perhaps 1000 or more, would need to be screened to detect one cancer in this age group.

Conclusions Colonoscopic detection of colorectal cancer is uncommon in asymptomatic persons 40 to 49 years of age. The noncancerous lesions are equally distributed proximally and distally. The low yield of screening colonoscopy in this age group is consistent with current recommendations about the age at which to begin screening in persons at average risk. (N Engl J Med 2002;346:1781-5.)

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SCREENING for colorectal cancer among adults at average risk is recommended to begin at the age of 50 years. This age threshold was established in part because of a dramatic increase in the incidence of disease during the sixth decade of life. Between the ages of 45 and 49 years, the annual incidence of colorectal cancer is 24 cases per 100,000 persons, whereas between the ages of 50 and 54, the incidence is 48 per 100,000.^{1,2} However, nearly 7 percent of cases of colorectal cancer occur in persons under 50 years of age, many of whom have no risk factors that were recognized before diagnosis.² In some studies, such younger persons present

with more advanced disease and have a less favorable prognosis than older persons with newly diagnosed cancer.³

Although screening for colorectal cancer with colonoscopy among those 50 years of age or older has been shown to be cost effective,^{4,7} the yield from screening of persons in younger age groups is less certain. Data on the prevalence of neoplasia in persons below the age of 50 are lacking. This information would be useful for estimating the yield of screening before the age of 50 and for refining estimates of cost effectiveness for persons in this age group. The objective of this study was to measure the yield of screening colonoscopy for cancer and polyps among persons 40 to 49 years of age.

METHODS**Study Design**

We performed a retrospective, cross-sectional analysis of data on consecutive asymptomatic adults 40 to 49 years of age who underwent colonoscopic screening for the first time between September 1995 and April 2000. The study was approved by the institutional review board of Indiana University at Indianapolis; because this was a retrospective analysis of an existing data set, written informed consent was not obtained from the participating subjects.

Screening Program

In September 1995, Eli Lilly began providing colonoscopic screening as a fully reimbursable health benefit. Employees 40 years of age or older received written information about the screening program, including a toll-free telephone number to call to obtain more information about the program or to schedule an appointment for screening. A telephone interview was used to establish that persons who called to make an appointment for screening were asymptomatic (i.e., reported no visible rectal bleeding, no recent change in bowel habits, and no recent or current lower abdominal pain) and had no personal history of colorectal cancer, colorectal polyps, or inflammatory bowel disease. Persons with symptoms or such conditions were not eligible for the screening program, but they were urged to seek medical care from their usual provider. Information on the family history with respect to colorectal cancer and the results of prior screening or diagnostic colorectal evaluations was not routinely requested or recorded. Qualified gastroenterologists and colorectal surgeons practicing in central Indiana participated in the screening program.

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Study Procedures and Definitions

Polyethylene glycol lavage solution was used for bowel preparation. Fecal occult-blood testing was not performed before colonoscopy. During colonoscopy, the location and size of all polyps were determined before their removal from the colon. The pathological specimens were evaluated by one of three pathologists, who classified polyps according to the criteria established by the World Health Organization.⁸ The histologic findings were reported as normal mucosa, hyperplastic polyps, tubular adenomas, tubulovillous polyps, or villous polyps.

For purposes of the analysis, the junction of the splenic flexure and the descending colon, as determined by the endoscopist, defined the border between the proximal and the distal colon. Patients with more than one polyp in either the proximal or the distal segment of the colon were categorized according to the most advanced lesion in that segment. The size of the polyp was estimated with the use of open-biopsy forceps or on the basis of clinical judgment.

The endoscopic and pathological evaluations recorded whether the mucosa was normal or had evidence of hyperplastic polyps, tubular adenomas, or advanced neoplasms. An advanced neoplasm was defined primarily as a large tubular adenoma (at least 1 cm in maximal diameter), a polyp with villous features, a polyp with high-grade dysplasia, or a cancer. A secondary definition of advanced neoplasm included only adenomas with villous features or high-grade dysplasia and cancers, and it excluded tubular adenomas 1 cm or more in diameter. Findings such as lipomas, lymphoid aggregates, chronic nonspecific inflammation, and inflammatory or juvenile polyps were categorized as indicating normal mucosa. When these diagnostic categories were used, no specimen was considered to be nondiagnostic.

Statistical Analysis

Descriptive statistics were used for basic demographic features and the prevalence of overall findings with stratification according to the location within the bowel. The prevalence of cancer was compared with that in the cohort of screened persons 50 years of age or older, with published data from other studies of screening colonoscopy,^{9,11} and with three autopsy series.^{12,14} Ninety-five percent confidence intervals were calculated by the exact binomial method. The prevalence of findings according to sex was compared by the chi-square statistic. For detection of advanced neoplasms, the "number needed to screen" was calculated as the number of persons with a particular finding who would have to undergo colonoscopy for one advanced neoplasm to be detected.¹⁵ Point estimates for the number needed to screen were derived from the inverse of the point estimates for the prevalence of the type of polyp. The confidence intervals for the numbers needed to screen were derived by inverting the 95 percent confidence intervals for the risk proportions. Analyses were performed with SPSS for Windows software (version 10.0). All P values and confidence limits were two-sided.

RESULTS

Screening of 3421 persons by colonoscopy took place from September 1995 through April 2000. The analysis was stratified according to age; 2515 persons were older than 49 years, and 906 were 40 to 49 years of age. The mean (\pm SD) age of the cohort from 40 to 49 years of age was 44.8 ± 7.8 years; 61 percent were men (mean age, 44.8 ± 8.0 years). Colonoscopy to the cecum was performed in 99 percent of patients.

Prevalence of Cancer

No cancers were detected among the 906 persons 40 to 49 years of age (0 percent; 95 percent confi-

dence interval, 0 to 0.4 percent). In contrast, 13 cancers (9 invasive cancers and 4 carcinomas in situ) were detected among screened persons 50 years of age or older (mean age, 60.0 ± 8.1 years), for a prevalence of 0.5 percent (95 percent confidence interval, 0.3 to 0.9 percent). The difference in the prevalence of cancer between the two age groups was statistically significant ($P=0.03$). Cancer was present in 3 of 1533 persons 50 to 59 years of age (0.2 percent), 2 of 625 persons 60 to 69 years of age (0.3 percent), and 8 of 357 persons 70 years of age or older (2.2 percent) (P for trend <0.001).

Prevalence of Polyps

Table 1 shows the prevalence of hyperplastic polyps, tubular adenomas, and advanced neoplasms throughout the colon, as well as according to location (proximal or distal), among persons 40 to 49 years of age. Advanced neoplasms were found in 3.5 percent of the cohort (2.3 percent when large tubular adenomas were excluded). One subject had advanced neoplasms in both the proximal and the distal colonic segments. Within this age group, there were no differences in the mean ages among subgroups defined according to the most advanced findings. In comparison, advanced neoplasia was present in 63 of 1533 persons 50 to 59 years of age (4.1 percent), 49 of 625 persons 60 to 69 years of age (7.8 percent), and 42 of 357 persons 70 years of age or older (11.8 percent) (P for trend <0.001).

Women were less likely to have a polyp of any type (16 percent, vs. 24 percent for men; relative risk, 0.67; 95 percent confidence interval, 0.43 to 0.86) or a neoplasm of any type (8 percent, vs. 12 percent for men; relative risk, 0.66; 95 percent confidence interval, 0.40 to 0.99). No sex differences were apparent in the distribution of polyps between the proximal and distal segments or in the frequency of advanced neoplasms.

Advanced Neoplasms

There were 33 advanced neoplasms in 32 persons, 18 (55 percent) of which were located distally. Of the 15 advanced proximal neoplasms, 4 (27 percent) had a distal sentinel lesion. When advanced neoplasia was defined by histologic findings alone, there were 22 polyps in 21 persons, 14 (64 percent) of which were distal. Of the eight advanced proximal neoplasms among those defined by histologic findings alone, only two (25 percent) had a distal sentinel lesion.

Number Needed to Screen

On the basis of the upper confidence limit of 0.4 percent for the prevalence of colorectal cancer, the smallest number of persons 40 to 49 years of age who would need to be screened to detect one cancer

RESULTS OF SCREENING COLONOSCOPY

TABLE 1. FINDINGS IN 906 PERSONS 40 TO 49 YEARS OF AGE WHO WERE SCREENED BY COLONOSCOPY.

FINDING	OVERALL	DISTAL COLON	PROXIMAL COLON	number of persons (percent)			
No polyp	715 (78.9)	767 (84.7)	821 (90.6)				
Hyperplastic polyp	91 (10.0)	76 (8.4)	35 (3.9)				
Tubular adenoma	79 (8.7)	49 (5.4)	42 (4.6)				
Any advanced neoplasm*	32 (3.5)	18 (2.0)	15 (1.7)				
Neoplasm with advanced histologic findings*†	21 (2.3)	14 (1.5)	8 (0.9)				

*One patient had two lesions.

†Data are for persons with an advanced neoplasm other than a large tubular adenoma.

is 250. If the middle and lower parts of the confidence interval are used, the numbers needed to screen are much higher: 500 for a prevalence of 0.2 percent, and 1000 for a prevalence of 0.1 percent. The numbers needed to screen to detect an advanced neoplasm anywhere in the colon or in the proximal part only are shown in Table 2. Among all persons 40 to 49 years of age, the number needed to screen with colonoscopy to detect one advanced neoplasm anywhere in the colon is 28 (95 percent confidence interval, 20 to 41). For histologically advanced neoplasms only, the number needed to screen is 43 (95 percent confidence interval, 28 to 69). Among persons with no distal polyps (such as might be identified by screening sigmoidoscopy), the number needed to screen with colonoscopy to detect one advanced neoplasm is 70 (95 percent confidence interval, 44 to 138). For histologically advanced neoplasms only, the number needed to screen is 128 (95 percent confidence interval, 60 to 345).

DISCUSSION

Our data provide information on the prevalence of colorectal neoplasia in asymptomatic persons less than 50 years of age. Colorectal cancer is infrequent in this age group; no cancers were discovered by colonoscopy in 906 persons screened. Given the cohort size, as few as 250 or as many as 1000 people in this age range would have to be screened to detect one cancer. In spite of the low prevalence of cancer detected by screening in persons under 50 years of age, about 7 percent of colorectal cancers are known to occur in this age group. If 7 percent of the 13 cancers detected in the entire screened cohort (including persons from 40 to 49 years of age and those 50 or

TABLE 2. NUMBER OF 40-TO-49-YEAR-OLDS WHO WOULD NEED TO BE SCREENED BY COLONOSCOPY TO DETECT AN ADVANCED NEOPLASM.

PATIENT GROUP	LOCATION	LESIONS TO BE DETECTED BY COLONOSCOPY	
		ANY ADVANCED NEOPLASM	NEOPLASM WITH ADVANCED HISTOLOGIC FINDINGS
		no. (95% CI)*	
All patients	Anywhere in colon	28 (20–41)	43 (28–69)
Patients with no distal polyps	Proximal colon	70 (44–138)	128 (60–345)

*CI denotes confidence interval.

older) occurred in persons under the age of 50, only 1 cancer would be expected in this group. Therefore, our finding of no cancers in the younger age group within this cohort is not unexpected.

Table 3 compares the prevalence of cancer among several cohorts, including the persons aged 40 to 49 years who were screened in our study, older persons in the same colonoscopy-screening program, and subjects in other studies. The prevalence of cancer in subjects 40 to 49 years of age was significantly lower than that in nearly all the other groups shown in Table 3. The only exceptions are those in the two studies by Rex and colleagues,^{10,11} in which a small sample necessarily resulted in imprecision in the estimates of prevalence.

Three studies listed in Table 3 were autopsy series, which provide another source of data to assess the prevalence of colorectal cancer and polyps. In these series,¹²⁻¹⁴ which excluded patients with known colorectal cancer, the estimated mean age ranged from 65 to 67 years, and the prevalence of colorectal cancer ranged from 1.3 percent to 2.1 percent. The higher mean age and the possibility that not all persons were asymptomatic at the time of death are consistent with the view that younger age was the main reason for the lower prevalence of neoplasia found in our study.

Nearly 90 percent of the subjects in our cohort who were 40 to 49 years of age had no neoplastic polyps anywhere in the colon or rectum. Nearly 93 percent of participants had no distal neoplastic polyps, and nearly 95 percent had no proximal neoplastic polyps. Nearly two thirds of advanced neoplasms characterized by villous histologic findings or severe dysplasia were located distal to the splenic flexure.

TABLE 3. PREVALENCE OF COLORECTAL CANCER ACCORDING TO AGE IN SELECTED STUDIES.

STUDY	MEAN AGE	MALE SEX	NO. OF SUBJECTS	CASES OF CANCER	
	yr	%		no.	% (95% CI)*
Current study					
40–49 yr	45	61	906	0	0 (0–0.4)
≥50 yr	60	59	2515	13	0.5 (0.3–0.9)
Lieberman et al. ⁹	63	97	3121	30	1.0 (0.6–1.4)
Rex et al. ¹⁰	60	61	496	3	0.6 (0.1–1.8)
Rex et al. ¹¹	60	43	121	0	0 (0–0.3)
Vatn and Stalsberg ^{12†}	67‡	59	445	6	1.3 (0.5–2.9)
Rickert et al. ^{13†}	65‡	59	518	11	2.1 (1.1–3.8)
Williams et al. ^{14†}	66‡	54	365	6	1.6 (0.6–3.5)

*CI denotes confidence interval.

†Data are from an autopsy series.

‡The mean age was estimated.

However, when all advanced neoplasms were considered, including large tubular adenomas, the proportion located distal to the splenic flexure decreased to 55 percent. This distribution suggests that, if detecting advanced neoplasms was a desirable goal, sigmoidoscopy alone would find just over half of such neoplasms under ideal circumstances.

The term “advanced neoplasia” deserves comment. Neoplasms are classified as advanced on the basis of size and histologic findings, but there are virtually no data to confirm or refute the appropriateness of the label “advanced.” The term has come into use in part because colorectal cancer has such a low incidence and prevalence in studies of screening.^{9,16–18} Although advanced neoplasia may be considered a convenient proxy for colorectal cancer, its use as an outcome measure may be misleading in screening studies, because the natural history of this lesion is unknown. Stryker and colleagues reported that large polyps (more than 1 cm in diameter), when left intact, progressed to colorectal cancer at a rate of about 1 percent per year¹⁹; however, no histologic data were available in that study. It is unclear whether small polyps with the histologic features of advanced neoplasia have an ominous natural history. Although the size of a polyp may be used in the definition of “advanced neoplasm,” some studies indicate that in vivo measurement of polyp size may be inaccurate.^{20,21} For this reason, we analyzed our data using two different definitions of advanced neoplasm (i.e., including or not including large tubular adenomas), and found that the overall results were similar. As expect-

ed, the yield of screening colonoscopy was higher with the more inclusive definition of advanced neoplasm; however, whether the difference has any clinical relevance is still unknown.

The prevalence of advanced neoplasms of 3.5 percent in this study may seem high, and the number of persons needed to screen to detect one advanced neoplasm may seem low at 28 (depending on the definition of “advanced” and on whether the entire colon or just the proximal colon is considered). However, these numbers alone do not necessarily suggest that the results of screening to detect advanced neoplasms (presumably with colonoscopy) justify the effort, risk, and cost it entails. It is not possible to estimate how many of the advanced neoplasms detected in this study might have progressed to incurable cancer before being detected by screening beginning at the age of 50 years.

The limitations of this study require comment. First, despite the colonoscopic screening of 906 persons, the number of advanced neoplasms detected was small, resulting in imprecise estimates of risk, as reflected in the wide confidence intervals for the numbers needed to screen. Second, the analysis did not include clinical information about known risk factors for colorectal cancer, such as family history, race, and body-mass index. Third, it is unclear to what extent the results of this analysis apply to populations of similar age but with different sociodemographic characteristics. Our cohort was largely white and middle-to-upper-middle class. Fourth, a cross-sectional study of screening such as this necessarily involves a survival cohort that does not include persons who had symptomatic or fatal cancer and who might have benefited from a program of screening. Finally, the results of this analysis do not apply to persons at higher risk for colorectal cancer, including those with a known history of a hereditary polyposis syndrome or a clinically significant family history of sporadic colorectal cancer. For persons in these and other higher-risk groups, earlier and more intensive screening has been recommended.^{22,23}

A cost–utility analysis has suggested that one-time colonoscopic screening of asymptomatic persons 45 to 49 years of age is less effective and more costly than one-time screening of older persons.⁵ The prevalence rates of colorectal cancer used in that analysis, 155 in 100,000 for men and 124 in 100,000 for women,⁵ fall within the confidence interval of our findings.

Despite the low yield of colonoscopic screening for cancer in this study, the discovery of advanced colorectal cancer in young persons is particularly tragic and creates tension with our findings. Decisions about whether and how to screen persons under the age of 50 years require consideration of factors beyond the

scope of this study, including life expectancy, cost, the natural history of nonmalignant advanced neoplasia, and individual risk. With identification of phenotypic — and eventually genotypic — factors affecting risk, the ability to stratify risk may make it possible to target subgroups more likely to benefit from screening before the age of 50. In the meantime, our results suggest that the overall prevalence of colorectal cancer is low in persons 40 to 49 years of age; these results are compatible with the current strategy of starting to screen for colorectal cancer at the age of 50 among persons at average risk.

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