

## ORIGINAL ARTICLE

# Five-Year Risk of Colorectal Neoplasia after Negative Screening Colonoscopy

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## ABSTRACT

**BACKGROUND**

The appropriate interval for endoscopic rescreening after a negative colonoscopic examination is uncertain.

**METHODS**

We identified persons with no adenomas on baseline screening colonoscopy who returned at 5 years for follow-up colonoscopy. Findings were categorized according to the most advanced lesion present: no polyp, a hyperplastic polyp, a tubular adenoma less than 1 cm in diameter, an advanced adenoma (a tubular adenoma  $\geq 1$  cm in diameter or a polyp with villous histologic features or high-grade dysplasia), or a cancer.

**RESULTS**

Baseline screening colonoscopy had identified 2436 persons with no adenomas; 1256 of them (51.6%) were rescreened a mean ( $\pm$ SD) of  $5.34 \pm 1.34$  years later. The mean age of this group at baseline was 56.7 years; 56.7% of its members were men. No cancers were found on rescreening (95% confidence interval [CI] for the detection rate, 0 to 0.24%). One or more adenomas were found in 201 persons (16.0%). A total of 19 advanced adenomas, of which 10 (52.6%) were distal to the splenic flexure, were found in 16 persons (1.3%). The risk of an advanced adenoma did not differ significantly between persons with no polyps at baseline and those with hyperplastic polyps at baseline (1.1% [12 of 1057] and 2.0% [4 of 199], respectively;  $P=0.30$ ). Men were more likely than women to have any adenoma (tubular less than 1 cm in diameter or advanced) (relative risk, 1.88; 95% CI, 1.42 to 2.51) and to have an advanced adenoma (relative risk, 3.31; 95% CI, 1.02 to 10.8).

**CONCLUSIONS**

Among persons with no colorectal neoplasia on initial screening colonoscopy, the 5-year risk of colorectal cancer is extremely low. The risk of advanced adenoma is also low, although it is higher among men than among women. Our findings support a rescreening interval of 5 years or longer after a normal colonoscopic examination.

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COLONOSCOPY HAS GAINED WIDESPREAD acceptance and even some preference as the primary screening method for the detection of colorectal cancer and precancerous polyps.<sup>1-4</sup> There is concern about whether adequate resources exist to satisfy the demand for colonoscopy,<sup>5-7</sup> and some data suggest that colonoscopy may be performed too frequently and for inappropriate indications.<sup>8,9</sup> Determination of the appropriate frequency of rescreening for persons with normal findings on initial screening colonoscopy could have a substantial effect on the cost of colonoscopy and the capacity to provide it.

Guidelines for colorectal cancer screening from the U.S. Multisociety Task Force on Colorectal Cancer and the American Cancer Society include, among other strategies, sigmoidoscopy every 5 years and colonoscopy every 10 years.<sup>3,4</sup> The U.S. Preventive Services Task Force also recommends colonoscopy as a screening test but does not specify a test interval.<sup>1</sup> Evidence supporting the 10-year interval comes largely from case-control studies that suggest that screening by sigmoidoscopy reduces mortality from distal colorectal cancer for up to 10 years.<sup>10,11</sup> However, there are no direct data with which to assess the validity of this recommendation. To provide direct data that can be used to inform decision making about an appropriate rescreening interval, we determined the incidence of any neoplasia and of advanced neoplasia on 5-year rescreening colonoscopy among persons who had no neoplasia on baseline screening colonoscopy.

## METHODS

### STUDY DESIGN

This study consisted of a retrospective examination of data obtained as part of routine clinical care of persons in the Lilly Colorectal Cancer Prevention Program; identifying information was removed from all data. A total of 36 gastroenterologists and gastrointestinal surgeons at seven sites in central Indiana participate in the program. The protocol was approved by the institutional review board of Indiana University. In September 1995, Eli Lilly began providing screening colonoscopy as a health benefit for employees, retirees, and dependents 40 years of age or older who had no personal history of colorectal cancer, adenomatous polyps, or inflammatory bowel disease and who were asymptomatic (i.e., reported no recent visible rectal bleeding, no change in bowel habits,

and no recent or current lower abdominal pain). Until October 2004, it was the program's policy to rescreen persons with negative results of colonoscopy (i.e., no adenomatous polyps) 5 years after the initial colonoscopy.

Subjects were eligible for inclusion in the study if they were 50 years of age or older, were asymptomatic, and had undergone first-time screening colonoscopy between September 1995 and June 2000, with no adenomatous polyps identified. The study group consisted of persons who underwent follow-up colonoscopy at 5 years, between October 2000 and July 2005. The methods of bowel preparation and of determining the location, size, and histologic features of a polyp are described elsewhere.<sup>12,13</sup> An advanced adenoma was defined as a tubular adenoma 1 cm or larger in diameter, a polyp with a villous component of at least 25%, or a polyp with high-grade dysplasia. Persons with more than one polyp in any segment of the colon were categorized according to the most histologically advanced lesion proximally and distally.

If persons who had undergone an initial screening colonoscopy did not return for follow-up colonoscopy at 5 years, the screening program sent a reminder letter; if there was no response, we attempted to obtain follow-up information about subsequent colorectal-cancer screening and findings by sending a questionnaire. Endoscopy and pathology reports were obtained for persons who permitted examination of their medical records. For persons reported to be deceased, we obtained follow-up information on the cause of death from the National Death Index ([www.cdc.gov/nchs/ndi.htm](http://www.cdc.gov/nchs/ndi.htm)).

### STATISTICAL ANALYSIS

Demographic features of the rescreened group were compared with those of the group that was not rescreened. Descriptive statistics were used to express the risk (or 5-year incidence) of any neoplasia and of advanced neoplasia (advanced adenoma and adenocarcinoma) overall and stratified according to baseline features. Student's t-test and either the chi-square test or Fisher's exact test were used to compare means and proportions, respectively, between the groups. We used multiple logistic regression to adjust for differences in age, sex, and baseline findings (no polyps vs. hyperplastic polyps).

We used absolute risks to calculate the number needed to screen for the outcome of advanced neoplasia. Adapted from the number needed to

treat,<sup>14</sup> the number needed to screen is the number of persons who would need to undergo 5-year rescreening colonoscopy in order for one advanced neoplasm to be detected. Data were managed with Microsoft Excel 2003, version 11 (Microsoft), and analyzed with SPSS software, version 15.0 (SPSS). Exact methods were used to calculate 95% confidence intervals for all proportions.

Because of the large percentage of people who did not undergo follow-up colonoscopy and the resulting potential for biased risk estimates, we performed a sensitivity analysis. We assumed that among subjects who did not undergo follow-up colonoscopy, the detection rates for any adenoma and for an advanced adenoma ranged from half to twice the rates among subjects who underwent follow-up colonoscopy.

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## RESULTS

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### CHARACTERISTICS OF THE STUDY GROUP

From September 1995 through June 2000, a total of 2983 persons 50 years of age or older underwent screening colonoscopy for the first time; 2436 (81.7%) had no adenomas. Of those who had no adenomas on baseline colonoscopy, 1256 (51.6%) underwent follow-up colonoscopy at 5 years; 544 (43.3%) were women, and 712 (56.7%) were men. The mean ( $\pm$ SD) age at the baseline screening colonoscopy was  $56.7\pm 7.5$  years; the men were slightly younger than the women ( $56.4\pm 7.3$  years and  $57.1\pm 7.7$  years, respectively;  $P=0.43$ ). The mean time to rescreening was  $5.3\pm 1.3$  years (median, 5.4; interquartile range, 5.0 to 6.0). The group of people who underwent rescreening was younger at the time of the baseline colonoscopy than the group of 1180 persons who did not undergo rescreening ( $56.7\pm 7.5$  years vs.  $58.3\pm 8.9$  years,  $P<0.001$ ) but included a similar proportion of women (43.3% and 46.9%, respectively). Among those who were rescreened, 1057 persons had had no polyps and 199 had had hyperplastic polyps on baseline colonoscopy. Characteristics of these subgroups are shown in Table 1. Colonoscopy to the cecum was documented for 1186 persons (94.4%) at the baseline examination and for 1213 (96.6%) at the follow-up examination. No serious complications were reported, at either the baseline or the follow-up examination.

### SUBJECTS WHO WERE NOT RESCREENED

Contact information was available for 1042 of the 1180 persons (88.3%) who did not undergo follow-

up colonoscopy at 5 years through the screening program. The response rate for the survey was 30.2%. Of the 315 persons who responded, 101 (32.1%) indicated that they had undergone subsequent colonoscopy outside the screening program (24 because of the development of symptoms and 77 for screening), and 71 (22.5%) indicated that they had not undergone subsequent colorectal cancer screening; the remaining 143 persons (45.4%) did not respond to the question. Among the 143 persons who did not respond to the question about colonoscopy, 23 were reported to be deceased, with the cause of death not given. With the use of the National Death Index, we ascertained the cause of death for 21 of these 23 persons; none had died from colorectal cancer. Of the 101 persons who had undergone subsequent colonoscopy outside the screening program, 26 indicated that the findings were normal (i.e., no polyps); the remaining 75 indicated either that they had polyps or that they were uncertain of the findings. Pathology reports for 44 of the 75 (58.7%) were obtained; 29 persons had normal findings, 9 had hyperplastic polyps, and 6 had neoplasia (4 had small tubular adenomas, 1 had a 1-cm tubular adenoma, and 1 had a 4-mm villous adenoma). Because of incomplete follow-up, these findings were not included in our analyses.

### COLONOSCOPIC FINDINGS IN RESCREENED SUBJECTS

Among the 1256 persons who were rescreened as part of the screening program, no cancers were discovered (upper 95% confidence limit for the detection rate, 0.24%). One or more neoplastic polyps were found in 201 persons (16.0%), of whom 67 (33.3%) had only distal neoplastic polyps, 80 (39.8%) had only proximal neoplastic polyps, and 54 (26.9%) had both proximal and distal neoplastic polyps. A total of 19 advanced neoplasms were found in 16 persons (1.3%; 95% confidence interval [CI], 0.73 to 2.1); the characteristics of the advanced neoplasms that were found are shown in Table 2.

At least one adenomatous polyp was present in 47 of 199 persons (23.6%) who had had hyperplastic polyps on baseline colonoscopy, as compared with 154 of 1057 persons (14.6%) who had had no polyps on baseline colonoscopy (relative risk, 1.62; 95% CI, 1.21 to 2.15). The 5-year risk of any neoplasia was greater for men than for women (Table 3). Male sex and the presence of hyperplastic polyps at baseline were independent risk factors for any adenoma on follow-up colonoscopy.

**Table 1. Baseline Characteristics of 1256 Subjects Who Underwent Follow-up Colonoscopy at 5 Years, According to Findings on Baseline Colonoscopy.\***

Characteristic	No Polyps on Baseline Colonoscopy (N=1057)	Hyperplastic Polyps on Baseline Colonoscopy (N=199)	P Value
Age — yr	56.6±7.5	57.2±8.5	0.34
Male sex — no. (%)	584 (55.3)	128 (64.3)	0.02
Follow-up interval — yr	5.44±1.3	4.73±1.6	<0.001

\* Plus-minus values are means ±SD.

Advanced adenomas were found in 4 of 199 persons (2.0%) who had had hyperplastic polyps on baseline colonoscopy, as compared with 12 of 1057 (1.1%) who had had no polyps at baseline (relative risk, 1.77; 95% CI, 0.61 to 5.14). Men had a higher incidence of advanced adenomas than women (Table 4).

Table 5 shows the numbers of persons who would need to be rescreened in order for one advanced adenoma to be detected. Among all 1256 persons, 79 would need to be rescreened at 5 years to detect one advanced adenoma (95% CI, 49 to 137). Among men, 55 would need to be rescreened, whereas among women, 182 would need to be rescreened. For persons with hyperplastic polyps at baseline, the number who would need to be rescreened is 50, whereas among those with no polyps at baseline, the number is 88.

Assuming, in the sensitivity analysis, that the detection rates for any adenoma and for advanced adenoma among the 1180 subjects who did not undergo follow-up colonoscopy through the screening program were two times as high as the rates among the subjects who did, the 5-year risks for the entire group of 2436 persons would be 23.8% (95% CI, 22.1 to 25.5) for any adenoma (detected in 579 of the 2436 subjects), and 1.9% (95% CI, 1.4 to 2.5) for an advanced adenoma (detected in 46 subjects). The number of subjects who would need to be rescreened to detect one advanced adenoma is 53 (95% CI, 40 to 72). Assuming that the detection rates among the 1180 persons who did not undergo follow-up colonoscopy through the screening program were half as high as the rates among the persons who did, the 5-year risks would be 12.1% (95% CI, 10.8 to 13.5) for any adenoma (detected in 295 of 2436 subjects) and 1.0% (95% CI, 0.6 to 1.5) for an advanced adenoma (detected in 24 subjects). The number who would need to be rescreened in order to detect one advanced adenoma is 101 (95% CI, 68 to 159).

## DISCUSSION

Our data provide information on the 5-year risk of colorectal neoplasia among persons with an average risk of colorectal cancer who had no neoplasia on baseline screening colonoscopy. No cancers were discovered on rescreening colonoscopy. However, at least one adenomatous polyp was found in nearly 16% of the subjects, more frequently in men than in women (19.5% vs. 11.0%). Advanced adenomas, which were present in 1.3% of the persons overall, were also more prevalent in men.

The low rates of cancer and of advanced adenomas 5 years after an initial colonoscopic examination showing no abnormal findings provide support for rescreening after an interval of 5 years or longer. Our study did not assess a 10-year rescreening interval, which is the interval that is recommended in some guidelines for colorectal-cancer screening.<sup>3,4</sup> Recommendation of the 10-year interval is based on retrospective case-control data stratified according to the time from the screening examination to the discovery of cancer among the cases.<sup>10,11</sup> There are no data from prospective studies of sufficient size and duration to permit a direct assessment of the recommendation. However, at least two studies<sup>15,16</sup> provide strong indirect support. One was a retrospective cohort study in which the investigators used billing-claims data to calculate standardized incidence ratios for the incidence of colorectal cancer in a group of 32,203 persons with no neoplasia on colonoscopy, as compared with the incidence in the general population. The standardized incidence ratios were 0.66 at 1 year, 0.55 at 5 years, and 0.28 at 10 years.<sup>16</sup> In that study, 33% of the subjects were younger than 50 years of age when they underwent colonoscopy, a fact that may limit the generalizability of the findings. The second study was a population-based case-control study

**Table 2. Characteristics of 19 Advanced Adenomas in 16 Subjects on Rescreening Colonoscopy.**

Characteristic	Value
Maximal diameter — mm	
Mean $\pm$ SD	8.0 $\pm$ 5.5
Median (range)	8.0 (2–20)
Villous histologic features — no. (%)	18 (94.7)
Distal colon and rectum — no. (%)	10 (52.6)

in which control subjects without colorectal cancer were 3.5 times as likely to have had normal findings on previous colonoscopy as were case subjects with colorectal cancer.<sup>15</sup> The adjusted odds ratio for colorectal cancer developing in control subjects was 0.26 (95% CI, 0.16 to 0.40); previous colonoscopy was protective for up to 20 years.

Our findings are similar to those in previous studies of interval rescreening colonoscopy among persons with normal findings on baseline colonoscopy.<sup>17–19</sup> Among three studies with 29 subjects,<sup>19</sup> 99 subjects,<sup>17</sup> and 154 subjects<sup>18</sup> and with a mean time to follow-up ranging from 5.4 to 5.7 years, no cancers were discovered. The incidence rates for any adenoma were 41%, 24%, and 27%, respectively. In one study, persons with hyperplastic polyps at baseline did not have an increased risk of subsequent adenomas.<sup>18</sup>

Our findings are also similar to those in studies that have measured incident findings after a negative sigmoidoscopic examination.<sup>20–22</sup> As compared with studies of repeat colonoscopy, the sigmoidoscopy studies have had larger samples, ranging from 250 subjects<sup>20</sup> to 9317 subjects,<sup>21</sup> and more variable follow-up times, ranging from 3 years<sup>21</sup> to between 5 and 6 years.<sup>22</sup> In one study, 6% of the subjects had adenomas on follow-up sigmoidoscopy; none of the adenomas were advanced.<sup>20</sup> Another study involved two cohorts: one underwent a follow-up examination at 3 to 4 years, and the other at 5 to 6 years. The respective risks of advanced neoplasia were 0.9% (detected in 12 of 1300 subjects) and 1.1% (in 30 of 2710), including two cancers (one in each group) among 4010 persons, representing a cancer risk of 0.05%.<sup>22</sup> In a 3-year follow-up study of 9317 persons in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 286 persons (3.1%) had any neoplasia, including 72 (0.8%) with advanced adenomas and 6 (0.06%) with cancer.<sup>21</sup> The interval detection rates in these studies are consistent with

those in the current study, and all the rates are extremely low. In the sigmoidoscopy studies, some of the interval cancers may be explained by variation in the insertion depth of the instrument if some of the cancers were present in a precursor lesion proximal to the farthest point of insertion at the initial examination.

This study has several limitations. First, the sample was small. Given the low 5-year incidence of advanced neoplasia, even a study with more than 1000 subjects has imprecise risk estimates. A study population an order of magnitude greater than that in our study would be needed for more precise risk estimates. Second, the follow-up information for persons who did not return for a 5-year follow-up examination is incomplete. The risk of neoplasia may differ between persons who returned for follow-up colonoscopy and those who did not, although the direction of risk (either higher or lower) and its magnitude are uncertain. In sensitivity analyses, we estimated that the risk of advanced neoplasia would increase from 1.3% to 1.9% if the rate in the group that did not return for a follow-up colonoscopy were twice the rate in the rescreened group and would decrease to 1.0% if the rate were half the rate in the rescreened group.

In addition, the generalizability of our findings is uncertain. The study cohort was composed primarily of compliant, middle-class to upper-middle-class whites; the extent to which the study findings apply to different groups is unknown. Furthermore, the Lilly Colorectal Cancer Prevention Program includes 36 experienced gastroenterologists and gastrointestinal surgeons who attain high cecal intubation rates. These results may not apply to less experienced groups.

As we have indicated previously,<sup>12,13</sup> there is uncertainty about the clinical importance of “advanced adenoma” and its appropriateness as a target in programs of screening and surveillance. In a study in which 226 persons were directly followed over time, large polyps (defined as  $\geq 1$  cm in diameter) that were left intact progressed to colorectal cancer at a rate of about 1% per year.<sup>23</sup> However, the histologic features of the polyps were not known; some may have already been cancerous at baseline, resulting in an overestimation of the rate of progression to cancer. On the other hand, length–time bias (unintentionally preferential detection of slow-growing lesions) may have resulted in an underestimation of this rate. For lesions smaller than 1 cm, it is unclear whether

**Table 3. Risk of Any Adenoma among Subjects Who Underwent Follow-up Colonoscopy at 5 Years.**

Group	Any Adenoma <i>no./total no. (%)</i>	Relative Risk (95% CI)	Adjusted Odds Ratio (95% CI)*
Subjects with hyperplastic polyps on baseline colonoscopy	47/199 (23.6)	1.62 (1.21–2.15)	1.98 (1.45–2.71)
Subjects with no polyps on baseline colonoscopy	154/1057 (14.6)		
Men	143/712 (20.1)	1.88 (1.42–2.51)	1.92 (1.49–2.47)
Women	58/544 (10.7)		

\* The logistic-regression model included age, sex, and baseline findings as independent variables.

**Table 4. Risk of Advanced Adenoma among Subjects Who Underwent Follow-up Colonoscopy at 5 Years.**

Group	Advanced Adenoma <i>no./total no. (%)</i>	Relative Risk (95% CI)	Adjusted Odds Ratio (95% CI)*
Subjects with hyperplastic polyps on baseline colonoscopy	4/199 (2.0)	1.77 (0.61–5.14)	1.80 (0.56–5.74)
Subjects with no polyps on baseline colonoscopy	12/1057 (1.1)		
Men	13/712 (1.8)	3.31 (1.02–10.8)	3.17 (0.88–11.33)
Women	3/544 (0.6)		

\* The logistic-regression model included age, sex, and baseline findings as independent variables.

polyps with villous histologic features progress to cancer and, if so, at what rate. A recent registry-based study estimated the risk of progression of advanced adenomas to colorectal cancer by examining the prevalence of advanced adenoma and the incidence of cancer in groups stratified according to sex and 5-year age category.<sup>24</sup> Projected rates of transition from advanced adenoma to cancer increased with age, from 2.6% annually and 25% at 10 years among women 55 to 59 years of age to 5.1% and 39.7%, respectively, among men 80 years of age or older. However, this study did not follow persons directly, and it made assumptions that could have substantially affected the risk estimates. The appropriateness of advanced adenoma as a target outcome would be clearer if its natural history were known.

Although this study provides data for direct assessment of the risk of advanced neoplasia after a negative colonoscopic examination, the appropriate rescreening interval after a negative colonoscopic examination is uncertain. Given the low risk of advanced neoplasia, we believe that 5 years is probably the minimal duration of protection for nearly all persons who do not have a family his-

tory of colorectal cancer. However, the protective effect of a normal colonoscopic examination is likely to be a function of both the quality of the baseline colonoscopy and patient-specific features. Whether factors such as age,<sup>24</sup> diet, frequency and intensity of exercise, smoking status, and body-mass index affect the subsequent risk of advanced neoplasia and rate of transition to cancer among persons with a normal baseline colonoscopic examination is unknown. Finally, although it is important to have information on the risk of advanced neoplasia in a person with normal findings on screening colonoscopy, recommendations about the screening interval will also be affected by factors of safety, cost, access, infrastructure, and other considerations not addressed here.

We conclude that among persons previously screened with colonoscopy who have no colorectal neoplasia, the 5-year risk of colorectal cancer is extremely low. The risk of advanced neoplasia is low, and it is lower for women than for men. These findings suggest that among persons who are at average risk for colorectal cancer, rescreening colonoscopy need not be performed sooner than 5 years after an initial colonoscopic exami-

**Table 5. Number of Persons with Normal Findings on Baseline Screening Colonoscopy Who Would Need to Be Rescreened at 5 Years to Detect One Advanced Adenoma.**

Group	No. of Subjects	Subjects with Advanced Adenoma	No. Needed to Screen (95% CI)*
		%	
Overall	1256	1.3	79 (49–137)
Men	712	1.8	55 (32–102)
Women	544	0.6	182 (63–909)
Subjects with hyperplastic polyps at baseline	199	2.0	50 (20–182)
Subjects with no polyps at baseline	1057	1.1	88 (51–169)

\* The number needed to screen is the inverse of the percent with advanced adenoma.

nation with normal findings. However, the follow-up interval for this study was only 5 years; we did not assess the appropriateness of the recommended 10-year rescreening interval for colonoscopy.

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**CORRECTION**

**Five-Year Risk of Colorectal Neoplasia after Negative Screening Colonoscopy**

Five-Year Risk of Colorectal Neoplasia after Negative Screening Colonoscopy . In the References (page 1224), reference 24 should have read: "Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007;56:1585-9." The article has been corrected at NEJM.org.