CLINICAL—ALIMENTARY TRACT

Low Risk of Colorectal Cancer and Advanced Adenomas More Than 10 Years After Negative Colonoscopy

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See related article, Rabeneck L et al, on page 275 in *CGH*.

BACKGROUND & AIMS: Screening colonoscopy is an effective method to reduce the incidence of and mortality from colorectal cancer (CRC). There is little empirical evidence available about the optimal interval for screening, making this a subject of debate. We associated the prevalence of advanced colorectal neoplasms with time since negative colonoscopies. **METHODS:** In a study of participants in the German colonoscopy screening program, we determined the prevalence of colorectal neoplasias detected at screening colonoscopy among subjects who had undergone a previous colonoscopy without detection of polyps (negative colonoscopy). Data were compared with that from subjects who had not received colonoscopies. **RESULTS:** No CRCs were detected in participants who had a previous negative colonoscopy an average of 11.9 years previously (n = 553), compared with the 8.4 CRC cases expected based on age- and gender-specific prevalences among participants who had not received a colonoscopy (n = 2701; standardized prevalence ratio [SPR] = 0.00; 95% confidence interval [CI]: 0.00−0.55). Prevalence of advanced adenoma was also much lower among subjects who had previous colonoscopies (SPR = 0.42; 95% CI: 0.25−0.68). Adjusted prevalence ratios (95% CIs) for detecting an advanced adenoma were 0.38 (95% CI: 0.16−0.90), 0.34 (95% CI: 0.15−0.74), 0.38 (95% CI: 0.16−0.90), and 0.53 (95% CI: 0.27−1.04) among participants with a negative colonoscopy conducted 1−5, 6−10, 11−15, and >16 years ago, respectively, compared to participants with no previous colonoscopy. **CONCLUSIONS: The low risk of CRC and advanced adenomas after a negative colonoscopy supports suggestions that screening intervals be extended to ≥10 years.**

Keywords: Colonoscopy; Colorectal Cancer; Screening.

With >1 million new cases and >500,000 deaths each year, colorectal cancer (CRC) is the 3rd most common cancer and the 4th most common cancer cause of death globally.[1] Colonoscopy, which enables detection and removal of precancerous lesions, is an effective method for CRC prevention. The National Polyp Study demonstrated a 76%−90% risk reduction of CRC among carriers of colorectal polyps.[2] On the basis of this and other accumulating evidence, colonoscopy is recommended for early detection and prevention of CRC by expert committees in various countries.[3,4] However, there still remains uncertainty with respect to necessary screening intervals, mainly because of the sparseness of pertinent empirical evidence.

Recently, a large prospective study among 1256 screening participants has shown that the prevalence of CRC and of advanced adenomas 5 years after a negative colonoscopy (ie, a colonoscopy without detection of polyps) is extremely small, which led to the conclusion that a negative colonoscopy does not need to be repeated within 5 years.[5] How far the surveillance interval can be extended beyond 5 years is much less clear.[6] Several case-control studies have suggested that risk of CRC remains very low for up to 20 years or longer,[7–9] but pertinent data with respect to advanced adenomas, the primary target for preventive colonoscopy, are lacking.[6]

To provide additional data on optimal colonoscopy screening intervals, we assessed prevalence of CRC, advanced colorectal adenomas, and other adenomas, according to time since prior negative colonoscopy in a large population of participants of screening colonoscopy in Germany.

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; SPR, standardized prevalence ratio.

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Methods

Setting

In Germany, screening colonoscopy has been offered free of charge for women and men aged 55 or older by the statutory health insurance system since October 2002. Up to 2 screening colonoscopies ≥10 years apart are offered. Annual participation is about 3% of eligible people (corresponding to an expected 30% participation rate within a 10-year time interval). Screening is almost exclusively done in practices of gastroenterology or internal medicine. Only experienced endoscopists, having conducted at least 200 colonoscopies and at least 50 polypectomies under supervision in the preceding 2 calendar years are eligible to conduct screening colonoscopies. Requirements for maintenance of eligibility in subsequent years include performance of at least 200 colonoscopies and at least 10 polypectomies per year. Histopathological examination is performed locally by certified pathological laboratories. The offer of screening colonoscopy is complementary to the offer of colonoscopy for diagnostic purposes. Both are free of charge in the German health insurance system.

Study Design and Study Population

A statewide cohort study was initiated in 2005 in Saarland, a small state (1 million inhabitants) located in the Southwest of Germany, with the primary aim of monitoring long-term reduction in CRC incidence and mortality among participants of screening colonoscopy. To be eligible, patients have to be residents of Saarland aged 55 or older and to undergo screening colonoscopy in one of the participating practices. The study was approved by ethics committees of the University of Heidelberg and of the Medical Association of Saarland. Almost all practices conducting screening colonoscopies in Saarland agreed to recruit patients for the cohort. The current cross-sectional analysis is based on baseline data of participants recruited in 33 gastroenterology practices in Saarland between May 2005 and December 2007. Informed consent was obtained from each participant.

Data Collection

Upon consenting and before screening colonoscopy, patients were asked to fill out a standardized questionnaire on personal and family medical history, sociodemographic factors, and potential CRC risk factors. In particular, participants were asked if they ever had a previous colonoscopy for any reason and, if so, whether polyps had ever been detected, and in which year the last colonoscopy had been conducted. We did not ask for other endoscopic large bowel examinations, such as flexible sigmoidoscopy, which are rarely done in Germany.[9] Patients were asked to return the completed questionnaire before colonoscopy. However, a minority of participants returned their questionnaires later by mail, as did another minority of participants who could not be recruited prior to colonoscopy because of practices' work overload and were invited to participate by mail shortly after colonoscopy.

Results of screening colonoscopy were independently abstracted and transferred to a standardized form from colonoscopy and histology reports by 2 trained investigators who were blinded with respect to questionnaire data. Items recorded included number, location, and size of polyps and their histological classification. Records from the 2 investigators were compared and any initial discrepancy was resolved by review and discussion. Participants were classified according to occurrence of the most advanced of the following findings: CRC, advanced adenoma (defined as presence of at least 1 adenoma with at least 1 of the following features: >1 cm in size, tubulovillous or villous components, high-grade dysplasia), other adenoma, hyperplastic or unspecified polyp, none of the aforementioned.[10,11]

Statistical Analysis

For this analysis, we selected participants with one or several previous negative colonoscopies (and no previous positive colonoscopy), and compared them to participants with no previous colonoscopy. To avoid any possible impact on questionnaire responses of knowing the current screening colonoscopy result, we excluded participants who were recruited or returned their questionnaire after screening colonoscopy. We further excluded patients with a history of inflammatory bowel disease, participants with missing information on the year of the prior colonoscopy, and participants who reported a prior colonoscopy within the same (current) year.

We first described participants without previous colonoscopy (group I), and those with one or more prior negative colonoscopies (group II) with respect to sociodemographic characteristics and potential CRC risk factors. Next, we assessed the prevalence of the most advanced colorectal lesion in both groups. For group II, further stratification was made according to the time since the prior colonoscopy (1−5, 6−10, 11−15, and 16+ years).

We then looked at the observed numbers of cases with CRC or with any "advanced neoplasm" (advanced adenoma or CRC) as the most severe finding at colonoscopy in group II, and we compared these numbers with the numbers of cases expected if the same age- and gender-specific prevalence rates were observed in this group as in participants without previous colonoscopy. Standardized prevalence ratios (SPRs) were calculated as the ratio of observed and expected numbers, and their exact 95% confidence intervals (CI) (taking error in expected numbers into account) were obtained using Simple Interactive Statistical Analysis.[12] Additional SPR analyses were carried out according to number of prior colonoscopies in group II, according to location of neoplasms (proximal: proximal to the splenic flexure, distal: splenic flexure to

rectum), and after exclusion of the minority of participants who indicated any symptoms potentially related to colorectal neoplasms as a motivation to undergo screening colonoscopy.

Finally, we compared the prevalences of the most severe colorectal findings in subgroups of group II defined by time since negative colonoscopy (1−5, 6−10, 11−15, and 16+ years) with the prevalences in participants without previous colonoscopy. Prevalence ratios and their 95% confidence intervals were calculated. In addition to crude prevalence ratios, prevalence ratios were adjusted for age and gender, and additionally adjusted for CRC risk factors found to be differentially distributed in the 2 groups compared ($P < .20$). Analyses were done using log-binomial regression with the SAS statistical software package (SAS Institute, Cary, NC) as described previously.[13] In contrast to the commonly employed logistic regression, log-binomial regression allows direct estimation of prevalence ratios, the parameter of primary interest in our analysis without the need of approximation by odds ratios.

Results

Overall, 5181 study participants aged 55 years or older were recruited during the study period. After application of the various exclusion criteria outlined here, 3224 participants were included in the analyses: 533 participants with ≥1 prior negative colonoscopies (and no prior positive colonoscopy) and 2701 participants with no prior colonoscopy (Figure 1). Colonoscopy to the cecum was documented for 3132 participants (96.9%). Three-quarters of participants with previous negative colonoscopies had just 1 previous colonoscopy, almost 20% had 2 previous colonoscopies, and only 5% had ≥3 previous colonoscopies (Table 1). Mean time since the last negative colonoscopy was 11.9 (median, 10) years.

Table 1 also shows sociodemographic characteristics and potential CRC risk factors of the 2 groups of partic-

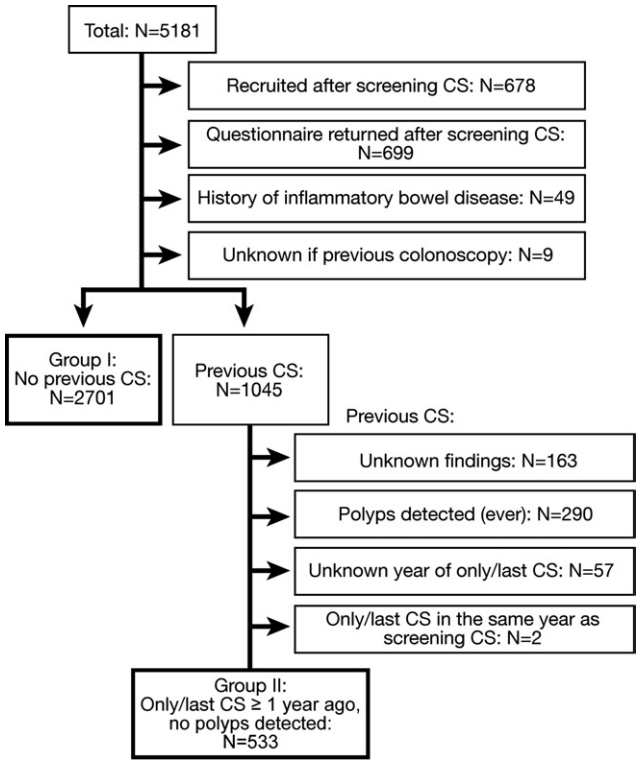

Figure 1. Flow diagram of patients included in the study (*bold framed boxes*) and of patients excluded from this analysis for various reasons. CS, colonoscopy.

Table 1. Characteristics of the Study Population

Characteristic	Previous colonoscopy: No (n = 2701) n[a]	%	Yes, no polyps detected (n = 533) n[a]	%	*P* value
No. of previous colonoscopies					
1	—	—	376	75.4	
2	—	—	97	19.4	
3	—	—	20	4.0	
>3	—	—	6	1.2	
Time since last colonoscopy (*y*)	—	—			
1−5	—	—	115	21.6	
6−10	—	—	166	31.1	
11−15	—	—	117	22.0	
16+	—	—	135	25.3	
Gender					
Male	1330	49.2	226	42.4	
Female	1371	50.8	307	57.6	.004
Age (*y*)					
55−59	888	32.9	128	24.0	
60−64	614	22.7	121	22.7	
65−69	666	24.7	149	28.0	
70−74	330	12.2	92	17.3	
75+	203	7.5	43	8.1	.0002
School education (*y*)					
<10	1836	68.7	354	67.2	
10+	837	31.3	173	32.8	.49
Family history of colorectal cancer					
No	2388	88.4	452	84.8	
Yes	313	11.6	81	15.2	.02
Smoking					
Never	1378	51.4	300	56.8	
Current	271	10.1	55	10.4	
Former	1032	38.5	173	32.8	.04
Body mass index[b]					
<25	858	32.2	164	31.2	
25−29.9	1249	46.9	257	48.9	
≥30	554	20.8	105	20.0	.72

[a]Numbers do not add up to the total numbers because of missing values for some variables (in parentheses: numbers of missing values for participants without/with previous colonoscopy): number of previous colonoscopies (0/34), school education (28/6), smoking (20/5), body mass index (40/7).
[b]Body mass index is calculated as kg/m^2.

Table 2. Findings at Screening Colonoscopy According to History of Previous Colonoscopy

	Most advanced finding at screening colonoscopy											
	Colorectal cancer		Advanced adenoma[a]		Other adenoma		Hyperplastic polyp		Unspecified polyp		None	
Previous colonoscopy	n	%	n	%	n	%	n	%	n	%	n	%
No (n = 2701)	41	1.5	267	9.9	494	18.3	281	10.4	54	2.0	1564	57.9
Yes, no polyps detected												
1+ y ago (n = 533)	0	0.0	25	4.7	86	16.1	33	6.2	5	0.9	384	72.0
1−5 y ago (n = 115)	0	0.0	5	4.4	13	11.3	9	7.8	1	0.9	87	75.7
6−10 y ago (n = 166)	0	0.0	6	3.6	31	18.7	6	3.6	1	0.6	122	73.5
11−15 y ago (n = 117)	0	0.0	5	4.3	23	19.7	9	7.7	0	0.0	80	68.4
16+ y ago (n = 135)	0	0.0	9	6.7	19	14.1	9	6.7	3	2.2	95	70.4

[a]Defined as presence of at least 1 adenoma with at least 1 of the following features: >1 cm in size, tubulovillous or villous components, high-grade dysplasia.

ipants. Gender distribution was almost equal and mean age was 63.8 years in participants without previous colonoscopy, whereas women were overrepresented and mean age was slightly higher (65.1 years) in participants with previous negative colonoscopies. A history of CRC in a first-degree relative was more common and ever-smoking was less common in participants with previous negative colonoscopies compared to those without previous colonoscopy. There was no difference between both groups with respect to school education and body mass index.

Among participants without a previous colonoscopy, the most advanced finding at screening colonoscopy was colorectal cancer in 41 cases (1.5%), advanced adenoma in 267 cases (9.9%), and other adenoma in 494 cases (18.3%) (Table 2). No colorectal cancer and much lower proportions of advanced adenomas were detected in participants with previous negative colonoscopies, even if the prior negative colonoscopy had been conducted many years ago. By contrast, the proportion of participants with other adenomas as the most advanced finding was similar among those with a previous negative colonoscopy and those without previous colonoscopy.

Overall, colorectal cancer and advanced neoplasm were observed in 0 and 25 participants with previous negative colonoscopies (Table 3). These numbers are far and significantly below the numbers that would have been expected based on the age- and gender-specific prevalences in participants undergoing first-time colonoscopy. The standardized prevalence ratios are 0.00 (95% CI: 0.00−0.55) and 0.42 (95% CI: 0.25−0.68) for these 2 outcomes, respectively. Very similar results were obtained in additional analyses for participants with only 1 previous colonoscopy. SPRs for this group were 0.00 (95% CI: 0.00−0.89) and 0.47 (95% CI: 0.26−0.82), respectively. Likewise, SPRs did not differ between women and men in additional gender-specific analyses: SPRs were 0.42 (95% CI: 0.18−0.87) and 0.43 (95% CI: 0.21−0.82) for advanced neoplasms in women and men, respectively. Furthermore, prevalence reduction remained unchanged after exclusion of the minority of participants who indicated any symptoms potentially related to colorectal neoplasms as a motivation to undergo screening colonoscopy (SPR 0.42; 95% CI: 0.21−0.80). However, risk reduction was more pronounced for distal than for proximal neoplasms: SPRs were 0.28 (95% CI: 0.14−0.52) and 0.82 (95% CI: 0.35−1.89) for advanced distal neoplasms and advanced proximal neoplasms, respectively.

More detailed analyses are shown in Table 4 for the detection of advanced neoplasms (advanced adenomas and cancer combined) at screening colonoscopy according to time since negative colonoscopy. Among participants with a prior negative colonoscopy within the past 1−5, 6−10, or 11−15 years, prevalence of advanced neoplasms was >60% lower compared to those without previous colonoscopy, and prevalence ratios were only marginally affected by adjustment for age, gender, family history, and smoking. Among those with a negative colonoscopy >15 years ago, prevalence was still >40% lower than among those with no previous colonoscopy, even though this difference failed to reach statistical significance.

Table 3. Observed and Expected Numbers, and Standardized Prevalence Ratio of Colorectal Cancer or Advanced Adenoma at Screening Colonoscopy Among Participants With Prior Negative Colonoscopy

Most advanced finding at screening colonoscopy	Observed	Expected[a]	SPR	95% CI
Cancer	0	8.4	0.00	0.00−0.55
Advanced adenoma or cancer ("advanced neoplasm")	25	59.4	0.42	0.25−0.68

CI, confidence interval; SPR, standardized prevalence ratio.
[a]Expected based on the age and gender-specific prevalences observed among 2701 participants with no previous colonoscopy.

Table 4. Prevalence of Advanced Neoplasm (Advanced Adenoma or Cancer) at Screening Colonoscopy According to Time Since Previous Negative Colonoscopy

Previous colonoscopy	n	Prevalence		Prevalence ratio (95% confidence interval)		
		n	%	Crude	Adjusted for age and gender	Adjusted for multiple covariates[a]
No	2701	308	11.4	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes, no polyps detected						
1–5 y ago	115	5	4.4	0.38 (0.16–0.90)	0.38 (0.16–0.91)	0.38 (0.16–0.90)
6–10 y ago	166	6	3.6	0.32 (0.14–0.70)	0.33 (0.15–0.73)	0.34 (0.15–0.74)
11–15 y ago	117	5	4.3	0.37 (0.16–0.89)	0.37 (0.16–0.89)	0.38 (0.16–0.90)
16+ y ago	135	9	6.7	0.58 (0.31–1.11)	0.59 (0.31–1.12)	0.53 (0.27–1.04)

[a]Adjusted for age, gender, history of colorectal cancer in a first-degree relative, and smoking.

Discussion

In this large colonoscopy-based screening study, no single colorectal cancer was detected (compared to 8.4 expected cases) among 533 participants with a previous negative colonoscopy conducted on average 11.9 years ago. Within 15 years after a negative colonoscopy, prevalence of advanced neoplasms was >60% lower than among people without previous colonoscopy, and prevalence was still about 50% lower even after ≥16 years.

That prevalence of advanced colorectal neoplasms is very low within 5 years after a negative colonoscopy has been well-established.[5,14,15] However, only few studies have addressed prevalence after longer time intervals. A retrospective cohort study from Canada found a strongly and significantly lower risk of CRC within 10 years after a negative colonoscopy.[16] In a previous case-control study from Germany, a significant 67% lower risk and a non-significant 54% lower risk of CRC was found among people who had a negative colonoscopy 10–19 or ≥20 years ago, respectively.[9] However, these studies had been restricted to colorectal cancer only. The current study provides evidence that a similarly very low risk is also seen if advanced colorectal adenomas are included in a combined end point of advanced neoplasms. Taken together, these patterns support suggestions that a very low risk of clinically relevant colorectal neoplasms prevails far beyond 5 or 10 years after a negative colonoscopy, the most commonly recommended intervals for endoscopic screening examination of the large bowel.

Advanced adenomas or cancers detected at a repeated colonoscopy may represent either cases that were missed at the prior colonoscopy or incident cases since the prior colonoscopy.[17,18] Because colonoscopy itself is considered the standard for detection of colorectal neoplasms, estimation of missed proportions of neoplasms at colonoscopy is difficult. Under highly standardized conditions in special study settings, estimated proportions of missed adenomas ranged from 0% for adenomas ≥1 cm to up to 27% for adenomas ≤0.5 cm.[19–21] However, these proportions could be substantially higher in routine practice in the community setting.[22–24] In the context of our study, neoplasms detected at screening colonoscopy that may have been already present at a prior colonoscopy most likely have been much smaller and much more difficult to detect at the time of the prior colonoscopy. Also, our finding of a smaller difference in the right colon than in the left colon and rectum after a negative colonoscopy, which is consistent with previous observations for colorectal cancer[9,16] could, apart from suggested biological differences,[25,26] be indicative of a higher miss rate of colonoscopies in the right colon. However, given that prior colonoscopies were conducted on average >10 years earlier, incident cases of colorectal neoplasms also probably account for a substantial proportion of neoplasms detected after such long time intervals.[17] Also, in contrast to the Canadian study,[16] the risk of advanced colorectal neoplasms was equally low within 1–5 and 6–10 years after a negative colonoscopy, suggesting that miss rates might be less relevant in our setting.

Obviously, the long-lasting lower risk of colorectal neoplasia after a negative colonoscopy is not to be interpreted as a protective effect of colonoscopy because no polyps were removed. Rather, it indicates the inherently lower risk of participants who were found to be free of polyps at a previous colonoscopy. Nevertheless, our results suggest that a negative colonoscopy may also have an important beneficial effect by itself, through alleviating unnecessary anxiety of patients who have had a negative colonoscopy.

A strength of our study is the very large number of participants who were recruited into this statewide study in the screening setting. Our results, therefore, pertain to mostly asymptomatic people. However, prior colonoscopies were conducted in the diagnostic rather than the screening setting, as the latter was established, along with its strict measures of quality assurance, in late 2002 only. Most likely, adenoma miss rates might be further reduced in the setting of an organized screening program.

Our study is limited by the fact that information on previous colonoscopy (including the year performed and whether or not polyps were detected) was based on self-reports only. In a previous validation study from Germany in which self-reported colonoscopies were validated by medical records, we found that a previous endoscopy

of the large bowel (which was a colonoscopy in the vast majority of cases) is almost always correctly recalled.[27] Furthermore, in about 95% of self-reported negative colonoscopies, lack of polypectomy was confirmed by medical records. Nevertheless, the remaining misclassification of polyp detection may have led to erroneous inclusion of some people with previous polyp detection in the group of patients with a negative history of colonoscopy in our study. As people with previous polyp detection would be expected to be at higher risk than those with previous negative colonoscopy, the true risks among the latter may even be lower than observed in our study.

Because of the observational nature of our study, the possibility of confounding requires attention. In particular, people undergoing repeat colonoscopy might be more health conscious than those with no prior colonoscopy. However, both groups did not differ with respect to school education, which tends to be strongly related to health consciousness. Although ever-smoking was less common among participants with previous negative colonoscopy than in those without previous colonoscopy, the difference was small, and adjustment for smoking in multivariable analysis did not have any appreciable impact on effect estimates. Nevertheless, the possibility of confounding by other, unmeasured covariates cannot be ruled out, but major confounding by other risk factors, such as diet and exercise, which have a modest impact on the risk of colorectal neoplasms, seems unlikely.

Other potential limitations are related to the fact that our results pertain to prevalent rather than incident colorectal neoplasms. By investigating colorectal neoplasms prevalent and detected at a screening colonoscopy, neoplasms that might have become clinically manifest before screening colonoscopy could not be considered. On the other hand, not all of the detected cancers, and only some proportion of the detected advanced adenomas, would have become clinically manifest during a lifetime. Nevertheless, inclusion of advanced colorectal adenomas may also be considered a strength of our study, as these are now considered to represent the primary target for preventive colonoscopy.[3]

In conclusion, our finding of a very low risk of advanced colorectal neoplasms after a negative colonoscopy even in the very long run may be helpful to define optimal colonoscopy screening intervals. The very low risk for distal CRC should be considered in screening recommendations for flexible sigmoidoscopy in particular, as 5-year screening intervals have been commonly recommended for this screening modality in the past.[3,4] Enhanced training and quality assurance, as well as new technology, may be crucial for further reducing adenoma miss rates at large bowel endoscopy and "interval neoplasms,"[28] especially in the right colon.[29,30] Our analysis suggests that possible extension of screening intervals, which could strongly enhance acceptance and cost-effectiveness of endoscopy-based screening and reduce its discomfort, might be achieved while maintaining high levels of safety.

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Conflicts of interest

The authors disclose no conflicts.

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