COLORECTAL CANCER

Does a negative screening colonoscopy ever need to be repeated?

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Background and aims: Screening colonoscopy is thought to be a powerful and cost-effective tool to reduce colorectal cancer incidence and mortality. Whether and when colonoscopy with negative findings has to be repeated is not well defined. The aim of this study was to assess the long term risk of clinically manifest colorectal cancer among subjects with negative findings at colonoscopy.

Patients: 380 cases and 485 controls participating in a population based case-control study in Germany.

Methods: Detailed history and results of previous colonoscopies were obtained by interview and from medical records. Adjusted relative risks of colorectal cancer among subjects with a previous negative colonoscopy compared with those without previous colonoscopy were estimated according to time since colonoscopy.

Results: Subjects with previous negative colonoscopy had a 74% lower risk of colorectal cancer than those without previous colonoscopy (adjusted odds ratio (aOR)=0.26 (95% confidence interval, 0.16 to 0.40)). This low risk was seen even if the colonoscopy had been done up to 20 or more years previously. Particularly low risks were seen for sigma cancer (aOR=0.13 (0.04 to 0.43)) and for rectal cancer (aOR=0.19 (0.09 to 0.39)), and after a negative screening colonoscopy at ages 55 to 64 (aOR=0.17 (0.08 to 0.39)) and older (aOR=0.21 (0.10 to 0.41)).

Conclusions: Subjects with negative findings at colonoscopy are at very low risk of colorectal cancer and might not need to undergo repeat colonoscopy for 20 years or more, if at all. The possibility of extending screening intervals to 20 years or more might reduce complications and increase the feasibility and cost-effectiveness of colonoscopy based screening programmes.

Colonoscopy is generally considered to be the gold standard for the detection of colorectal cancer and its precursor lesions. Even though direct evidence is still limited to a few observational studies,^{1,2} and results from pertinent randomised trials are not yet available, it appears most likely that screening for colorectal cancer by colonoscopy with removal of precancerous lesions is a powerful and cost-effective approach to reducing colorectal cancer incidence and mortality.^{3,4} Colonoscopy has been recommended as a primary screening tool in expert panel recommendations for colorectal cancer prevention from various countries,^{5–8} and it was introduced nationwide as a primary screening tool in Germany in 2002.

Regarding required resources, complications, compliance, costs (and hence cost-effectiveness) of a colonoscopy based screening programme, the necessary time interval for repeating colonoscopy represents a critical variable. The majority of screenees have negative findings at screening colonoscopy—that is, no polyps are detected. The time interval for repeat screening colonoscopy most commonly recommended by expert panels for this group is 10 years. However, the empirical basis for choosing the optimal time intervals is quite sparse, and there have been conflicting suggestions in recent years to either increase or decrease the recommended time intervals after negative results at endoscopy.^{9,10}

Our aim in this study was to estimate the risk of clinically manifest colorectal cancer according to time since negative colonoscopy (compared with subjects who never underwent colonoscopy) in a population based case-control study from Germany.

METHODS

Study design and study population

We conducted a population based case-control study in the Rhine-Neckar region located in the southwest of Germany

and covering a population of about two million people. Patients with a first diagnosis of primary invasive colorectal cancer aged 30 or older between January 2003 and June 2004 were eligible for recruitment. However, only patients whose cancer was detected because of symptoms or incidentally (rather than by screening) were included in this analysis. Furthermore, we excluded subjects with a history of inflammatory bowel disease. The study area included 22 hospitals where patients with colorectal cancer were treated, and all of them agreed to participate in the study. Community based control subjects were randomly selected from population registers, employing frequency matching with respect to age, sex, and county of residence. The study was approved by the ethics committees of the Medical Faculty at the University of Heidelberg and of the Medical Chambers of Baden-Württemberg and Rhineland-Palatinate. Written informed consent was obtained from each participant.

Data collection

Patients were informed about the study by their caring physicians, in most cases during their hospital stay a few days after surgery. They were notified to the study centre upon receipt of informed consent. Personal interviews were conducted by trained interviewers, who visited the patients during their hospital stay, or, if they had already left hospital, at their homes. The standardised interviews, which lasted for about one hour, included a detailed medical and family history, as well as a lifetime history of sociodemographic and lifestyle factors. In addition, a blood sample was taken by the

Abbreviations: FOBT, faecal occult blood test; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; UICC, Union Internationale Contre Cancer

Table 1 Numbers of cases and controls recruited and numbers included in this analysis (bold figures)

	Cases		Controls	
Total numbers of recruited cases and controls	540		614	
After exclusion of cases detected by screening	432		614	
After exclusion of cases of IBD	432		613	
	Determination of history of colonoscopy		Controls	
	Cases		Controls	
Self reported endoscopy of large bowel	Yes	No	Yes	No
	84	346	271	342
After correction of subjects with misreport of endoscopy of large bowel (eg, gastroscopy) according to validation	80	350	262	351
After exclusion of subjects with endoscopy <1 year ago	74		226	
Written report of endoscopy of large bowel available	Yes	No	Yes	No
	49	25	169	57
After exclusion of subjects with sigmoidoscopy or rectoscopy according to medical charts where available, or according to self report otherwise	42	19	142	47
No detection of polyps according to charts where available, or according to self report otherwise	21	9	103	31
Total numbers of cases and controls included in analysis	380		485	

IBD, inflammatory bowel disease.

hospital doctors, or, if patients had left the hospital, by their general practitioner.

Controls were contacted by the study centre through mail and follow up calls, and interviews were scheduled at their homes. Blood samples were obtained in the same way as from the cases.

Information on previous endoscopic examinations of the large bowel (colonoscopy, sigmoidoscopy, or rectoscopy) was obtained in great detail during the interview. Whenever a previous endoscopic examination (that is, an endoscopic

examination that was not part of the diagnostic process leading to the current diagnosis) with or without polypectomy was reported by cases or controls, we sought to validate this information by pertinent medical records from the subjects' physicians.

Statistical analysis

This analysis was restricted to cases and controls with negative findings at the last colonoscopy or without any previous colonoscopy. Negative findings at colonoscopy were

Table 2 Distribution of sociodemographic factors and known or suspected risk factors or protective factors for colorectal cancer among 380 cases and 485 controls included in the analysis

Characteristic	Level	Cases		Controls	
		n	%	n	%
Age (years)	30–49	17	4.5	30	6.2
	50–59	55	14.5	87	18.0
	60–69	153	40.3	182	37.5
	70–79	103	27.1	133	27.4
	80+	52	13.7	53	10.9
Sex	Female	170	44.7	214	44.1
	Male	210	55.3	271	55.9
Education	≤ 9 years	272	71.6	311	64.1
	10–11 years	61	16.1	89	18.4
	≥ 12 years	47	12.4	85	17.5
Participation in general health screening examination	Ever	276	73.4	414	85.5
Family history	First degree relative*	41	10.8	51	10.5
Smoking	Never	177	46.8	239	49.3
	Current	61	16.1	73	15.0
	Former	140	37.0	173	35.7
Body mass index	<20.0 kg/m ²	24	6.4	12	2.5
	20.0–24.9 kg/m ²	132	35.4	166	34.2
	25.0–29.9 kg/m ²	139	37.3	224	46.2
	≥ 30.0 kg/m ²	78	20.9	83	17.1
NSAID use	Ever regular†	114	30.0	176	36.3
HRT use	Ever regular‡	49	29.5	112	52.3

*History of colorectal cancer in first degree relative.

†Ever regular use of aspirin or NSAID (at least once a month for one year).

‡Ever use of hormonal replacement therapy (women only).

HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

assumed if there was no indication of polyps in colonoscopy records. Among the minority of subjects for whom such records could not be located (see below), the criterion was a negative response to a question in the interview specifically addressing polypectomy. We first described patients and controls according to basic sociodemographic factors and known or suspected risk factors or protective factors for colorectal cancer.

Next, we assessed the risk of colorectal cancer according to the time since the last negative colonoscopy (categories 1–2, 3–4, 5–9, 10–14, 15–19, 20+ years), using subjects without any previous colonoscopy as the reference group. Odds ratios (OR) and 95% confidence intervals (CI) for the association between time since negative colonoscopy and colorectal cancer risk were estimated from multiple logistic regression models, adjusting for the matching factors age and sex (adjustment for county of residence did not alter the odds ratios to any relevant degree and was therefore omitted), as well as the following factors, which are known or have been suggested to be related to risk of colorectal cancer: level of school education (categories: ≤ 9 years, 10–11 years, 12+ years), history of colorectal cancer among first degree relatives, smoking (never, ever, current), ever regular use (at least once a month for at least one year) of non-steroidal anti-inflammatory drugs (NSAIDs), any hormone replacement therapy (HRT), and body mass index (categories: < 20 , 20–24.9, 25–29.9, 30+ kg/m²). To avoid confounding by general health behaviour, we additionally controlled for participation in a general health screening examination, offered to adults aged 36 and older every two years in the German health care system (categories: ever, never).

Because repeat colonoscopies may be done as surveillance colonoscopies in subjects at high risk of colorectal cancer or in those with detection of polyps at a preceding colonoscopy, additional specific analyses were carried out in subjects with only one previous colonoscopy, and in those with more than one previous colonoscopy. Specific analyses were also carried out according to age at colonoscopy (< 55 , 55–64, 65+ years), tumour stage (UICC stages 1 or 2, UICC stages 3 or 4), and location (caecum and ascending colon, other parts of colon, sigmoid, rectum).

All analyses were done using the SAS statistical software package, version 8.2.

RESULTS

Overall, 1154 persons (540 cases and 614 controls) were recruited. Based on the best available estimates of cancer incidence in southern Germany from the nearby population based Saarland Cancer Registry, and of the proportions of eligible patients from the hospitals, recruited patients constituted about 50% of the expected total number of eligible patients in the study area. The participation rate among eligible controls ($n = 1391$) was 44.4%, but another 350 subjects (25.2%) who did not agree to full participation were willing to provide information on key variables, including history of colonoscopy, in a short questionnaire.

For this analysis, we excluded 108 cases whose cancer was detected by screening, and one control with a history of inflammatory bowel disease (table 1). Among the remaining cases and controls, 84 and 271 reported having had one or more than one previous endoscopic examinations of the large bowel, respectively. Thirteen (3.7%) of the self reported examinations were found upon validation to be misreports of other examinations, such as gastroscopy, and were corrected accordingly. Of the remaining 80 cases and 262 controls with previous endoscopic examination of the large bowel, six cases reported an endoscopy less than one year ago. These were excluded from the analysis to avoid consideration of any endoscopies that might have been part of the diagnostic

process leading to the current cancer diagnosis. To ensure comparability, 36 controls with an endoscopy of the large bowel less than one year ago were also excluded. For 49 (66%) and 169 (75%) of the remaining cases and controls with a history of large bowel endoscopy, pertinent medical records could be obtained. Main reasons for failure to obtain written reports were that they had been destroyed ($n = 52$) or could not be located ($n = 24$) by the caring physicians.

According to self reports (88%) and to the endoscopy reports (85%), the majority of endoscopies were colonoscopies, followed by rectoscopy (11% and 11%, respectively) and sigmoidoscopy ($< 4\%$ according to both data sources). Both data sources agreed on the type of single or most recent endoscopy in 84% of the examinations. In cases of disagreement, self reports were corrected in line with the endoscopy reports, but self reports were assumed to be correct when a written endoscopy report was not available. To allow an “uncontaminated” comparison of subjects with and without previous colonoscopy, we excluded those whose previous endoscopy of the large bowel was a sigmoidoscopy or rectoscopy, as the latter may also have an impact on colorectal cancer risk, albeit to a lesser degree.

Among participants with a history of colonoscopy for whom both self reports and medical records were available, both data sources agreed in 79% of the examinations over whether or not polyps were detected and removed. In this analysis, the risk of colorectal cancer was compared among subjects with no detection of polyps at colonoscopy according to the case notes, where available, or according to self reports otherwise (21+9 cases, 103+31 controls), and among subjects who had never undergone a colonoscopy in the past (350 cases, 351 controls) (overall numbers of subjects: 380 cases, 485 controls).

The distribution of major sociodemographic factors and of known or suspected risk factors or protective factors for colorectal cancer among cases and controls is shown in table 2. About two thirds of subjects were between 60 and 79 years of age (mean age 67 years), and somewhat more than half were men. The proportion of subjects who ever participated in general health screening examinations, and who reported ever regular use of NSAIDs or HRT, was somewhat greater among the controls than among the cases.

A previous negative colonoscopy was about 3.5 times as common among controls (27.6%) than among cases (7.9%) (see table 3). Previous negative colonoscopies included colonoscopies conducted as primary screening examinations (28%), as follow up examinations for a positive result of a faecal occult blood test (FOBT) (24%), or for other reasons (48%), such as gastrointestinal symptoms. After adjustment for the matching factors age and sex and other potential confounding variables, a previous negative colonoscopy was associated with a strongly reduced risk of colorectal cancer (adjusted odds ratio (aOR) = 0.26 (95% CI, 0.16 to 0.40)), and this risk reduction persisted throughout 20 years. A strong risk reduction was even apparent (though not statistically significant) more than 20 years after negative colonoscopy. Even lower odds ratios were observed among subjects who had undergone more than one previous colonoscopy. Overall odds ratios were furthermore particularly low among subjects who had had a negative colonoscopy at ages 55–64 or at ages 65+ years.

Strong risk reductions were observed with respect to both colorectal cancer detected at early stages (UICC 1 or 2) and colorectal cancer detected at late stages (UICC 3 or 4) (table 4). With adjusted odds ratios of 0.13 and 0.19, overall risk reduction was most pronounced for sigmoid and rectal cancer. Albeit less pronounced, risk reductions were still strong and statistically significant for proximal colon cancer. Risks were though not as low for cancers of the caecum and

Table 3 Risk of colorectal cancer according to time since single or most recent negative colonoscopy

History of screening colonoscopy	Cases (n = 380)	Controls (n = 485)	Odds ratio (95% CI)	
			Adjusted for age and sex	Adjusted for multiple covariates*
No previous colonoscopy	350 (92.1%)	351 (72.4%)	1.00 Reference	1.00 Reference
Single or multiple colonoscopies, last negative colonoscopy, any age				
Any time ago	30 (7.9%)	134 (27.6%)	0.22 (0.14 to 0.34)	0.26 (0.16 to 0.40)
1–2 years ago	7 (1.8%)	50 (10.3%)	0.13 (0.06 to 0.30)	0.16 (0.07 to 0.36)
3–4 years ago	8 (2.1%)	31 (6.4%)	0.26 (0.12 to 0.58)	0.29 (0.13 to 0.68)
5–9 years ago	5 (1.3%)	23 (4.7%)	0.21 (0.08 to 0.57)	0.25 (0.09 to 0.69)
10–19 years ago	5 (1.3%)	17 (3.5%)	0.29 (0.11 to 0.80)	0.33 (0.12 to 0.91)
20+ years ago	5 (1.3%)	13 (2.7%)	0.38 (0.13 to 1.09)	0.46 (0.16 to 1.32)
Single negative colonoscopy, any age				
Any time ago	22 (5.8%)	83 (17.1%)	0.27 (0.16 to 0.43)	0.30 (0.18 to 0.50)
1–4 years ago	8 (2.1%)	41 (8.5%)	0.19 (0.09 to 0.42)	0.21 (0.09 to 0.47)
5+ years ago	14 (3.7%)	42 (8.7%)	0.33 (0.18 to 0.62)	0.39 (0.21 to 0.73)
Multiple colonoscopies, last negative colonoscopy, any age				
Any time ago	7 (1.8%)	50 (10.3%)	0.14 (0.06 to 0.31)	0.16 (0.07 to 0.37)
1–4 years ago	6 (1.6%)	39 (8.0%)	0.15 (0.06 to 0.36)	0.18 (0.07 to 0.44)
5+ years ago	1 (0.3%)	11 (2.3%)	0.09 (0.01 to 0.69)	0.11 (0.01 to 0.84)
Single or multiple colonoscopies, last negative colonoscopy <55 years				
Any time ago	13 (3.4%)	38 (7.8%)	0.35 (0.18 to 0.66)	0.45 (0.23 to 0.88)
1–4 years ago	4 (1.1%)	10 (2.1%)	0.51 (0.16 to 1.66)	0.58 (0.17 to 1.93)
5+ years ago	9 (2.4%)	28 (5.8%)	0.34 (0.16 to 0.73)	0.41 (0.19 to 0.90)
Single or multiple colonoscopies, last negative colonoscopy 55–64 years				
Any time ago	7 (1.8%)	49 (10.1%)	0.14 (0.06 to 0.32)	0.17 (0.08 to 0.39)
1–4 years ago	4 (1.1%)	29 (6.0%)	0.15 (0.05 to 0.42)	0.18 (0.06 to 0.51)
5+ years ago	3 (0.8%)	20 (4.1%)	0.14 (0.04 to 0.49)	0.17 (0.05 to 0.58)
Single or multiple colonoscopies, last negative colonoscopy 65+ years				
Any time ago	10 (2.6%)	47 (9.7%)	0.21 (0.11 to 0.42)	0.21 (0.10 to 0.44)
1–4 years ago	7 (1.8%)	42 (8.7%)	0.14 (0.06 to 0.33)	0.16 (0.07 to 0.39)
5+ years ago	3 (0.8%)	5 (1.0%)	0.46 (0.11 to 1.99)	0.51 (0.12 to 2.21)

*Adjusted for age, sex, education, participation in general health screening examination, family history of colorectal cancer, smoking, body mass index, ever regular use of NSAIDs, ever regular use of HRT.
CI, confidence interval; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

the ascending colon (aOR = 0.50) as for cancers located at other parts of the proximal colon (aOR = 0.24), suggesting that some polyps located in the caecum or ascending colon

may have remained undetected in incomplete colonoscopies. We therefore repeated the analysis after excluding subjects with colonoscopies that were recorded as being incomplete in

Table 4 Risk reduction according to stage and location of cancers

Stage/location of cancer	History of screening colonoscopy		Cancers*	Adjusted odds ratios (95% CI)†
UICC stages 1 or 2	No colonoscopy Colonoscopy	Any 1–4 years ago 5+ years ago	160 (94.1%)	1.00 Reference
			10 (5.9%)	0.20 (0.10 to 0.40)
			4 (2.4%)	0.14 (0.05 to 0.38)
			6 (3.5%)	0.30 (0.12 to 0.72)
UICC stages 3 or 4	No colonoscopy Colonoscopy	Any 1–4 years ago 5+ years ago	155 (90.6%)	1.00 Reference
			16 (9.4%)	0.28 (0.16 to 0.50)
			9 (5.3%)	0.25 (0.12 to 0.52)
			7 (4.1%)	0.33 (0.14 to 0.75)
Proximal colon cancer	No colonoscopy Colonoscopy	Any 1–4 years ago 5+ years ago	125 (89.3%)	1.00 Reference
			15 (10.7%)	0.40 (0.21 to 0.72)
			9 (6.4%)	0.41 (0.20 to 0.87)
			6 (4.3%)	0.38 (0.16 to 0.92)
Caecum and ascending colon	No colonoscopy Any colonoscopy	Any	66 (85.7%)	1.00 Reference
			11 (14.3%)	0.50 (0.25 to 1.00)
Other proximal colon cancer	No colonoscopy Any colonoscopy	Any	60 (93.8%)	1.00 Reference
			4 (6.3%)	0.24 (0.08 to 0.68)
Distal cancer (sigmoid or rectum)	No colonoscopy Colonoscopy	Any 1–4 years ago 5+ years ago	208 (94.1%)	1.00 Reference
			13 (5.9%)	0.17 (0.09 to 0.32)
			6 (2.7%)	0.12 (0.05 to 0.30)
			7 (3.2%)	0.25 (0.11 to 0.57)
Sigmoid	No colonoscopy Any colonoscopy	Any	64 (94.1%)	1.00 Reference
			4 (5.9%)	0.13 (0.04 to 0.43)
Rectum	No colonoscopy Any colonoscopy	Any	144 (94.1%)	1.00 Reference
			9 (5.9%)	0.19 (0.09 to 0.39)

*For numbers and proportion of controls in respective categories, see table 3.

†Adjusted for age, sex, education, participation in general health screening examination, family history of colorectal cancer, smoking, body mass index, ever regular use of NSAIDs, ever regular use of HRT.

CI, confidence interval; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; UICC, Union Internationale Contre Cancer.

Table 5 Risk reduction of proximal colorectal cancer according to location and recorded completeness of colonoscopy

	Adjusted odds ratio (95% CI)*	
	Any colonoscopy	After exclusion of colonoscopies without documented completeness
Any proximal colorectal cancer	0.40 (0.21 to 0.72)	0.39 (0.18 to 0.81)
Caecum and ascending colon	0.50 (0.25 to 1.00)	0.44 (0.18 to 1.08)
Other proximal colon cancer	0.24 (0.08 to 0.68)	0.29 (0.09 to 0.98)

*Adjusted for age, sex, education, participation in general health screening examination, family history of colorectal cancer, smoking, body mass index, ever regular use of NSAIDs, ever regular use of HRT.
CI, confidence interval; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

the case notes (12%) or where the completeness was not documented by medical reports. These analyses showed only slightly lower risks for cancers of the caecum and ascending colon (table 5).

In a sensitivity analysis to address potential selection bias by overrepresentation of controls with previous colonoscopy—as these might be more interested in the study question and hence in participation—we repeated our analyses with the inclusion of eligible controls who provided only limited information on the main study variables. Additional inclusion of these subjects (resulting in inclusion of 69% of all eligible controls) led to slightly higher but still strongly reduced odds ratios. The age and sex adjusted odds ratio for a previous negative colonoscopy at any time increased from 0.22 to 0.26, and the pattern regarding time since last colonoscopy essentially remained unchanged.

DISCUSSION

In this large case-control study, subjects with negative findings at colonoscopy had a strongly reduced risk for at least 20 years compared with people who never underwent colonoscopy. Particularly low risks were seen for sigmoid cancer and for rectal cancer, and after a negative screening colonoscopy at ages 55–64 and older.

Our results are in agreement with recent findings of persistence of a very low incidence of distal colorectal cancer for at least five years following negative sigmoidoscopy.¹¹ They are also in good agreement with two previous case-control studies from Germany and the USA which had addressed long term risk after colonoscopy or sigmoidoscopy.^{12–13} However, both studies had relied on self reports of endoscopic examinations only and did not take the finding of polyps into account; both of these are crucial with respect to the need for and time intervals of repeat colonoscopy.

Clearly, colonoscopy is not a preventive measure by itself. The strongly reduced risk among subjects who underwent colonoscopy without polypectomy is therefore not a “result” of colonoscopy, but rather reflects the inherently low risk of subjects free of endoscopically visible precancerous lesions. Among these, the occurrence of colorectal cancer within 20 years and probably beyond appears to be very unlikely, a finding that is consistent with observations of a very slow development of colorectal cancer from its precancerous lesions.^{1–14} Despite not being preventive by itself, our results suggest that a negative colonoscopy is of great clinical value, as the people with such a result can be assured of being at very low risk of colorectal cancer for a very long time. Furthermore, the finding of a sustained very low risk for at least 20 years suggests that a screening colonoscopy might not need to be repeated within 20 years in case of negative findings. In fact, colonoscopy might not need to be repeated at all, at least among subjects aged 55 or older, among whom risk reduction was found to be particularly strong in our analysis, and among whom a very low risk might prevail throughout their remaining life expectancy.

In our study, the risk was even lower among subjects with multiple colonoscopies than among subjects with a single negative colonoscopy. This result was somewhat unexpected, as repeat colonoscopies may include those done for surveillance among subjects at increased risk—for example, in people with a positive family history or with previous polyp detection. However, less than 20% of subjects with repeat colonoscopy reported polypectomy at the preceding colonoscopy. The even lower probability of overlooking a polyp in repeat colonoscopy compared with a single colonoscopy might provide an additional explanation for the observed findings.

The somewhat less pronounced risk reduction for proximal colon cancer, particularly of cancer of the caecum and the ascending colon, may also be explained in part by missed polyps in cases of incomplete colonoscopy. However, risk estimates for those cancers became only slightly lower when subjects with potentially or documented incomplete colonoscopy were excluded from the analysis, and still remained higher than the very low risk estimates for the sigmoid and rectum, suggesting that additional factors, such as potential differences in tumour biology,^{15–17} might also play a role.

Colonoscopy was introduced as a primary screening examination in Germany in late 2002 only, and some of the colonoscopies considered in this analysis were undertaken to follow up a positive faecal occult blood test, done because of symptoms or for other specific indications, rather than as primary screening examinations. This may limit the generalisability of our results to a primary screening setting. Although similar patterns of risk reduction according to time since negative colonoscopy might be expected in a primary screening setting, risks might even be somewhat lower in an unselected screening population.

Several studies have examined the cost-effectiveness of colonoscopy based screening for colorectal cancer. They consistently found it to be cost-effective, even with the commonly recommended 10 year interval for repeat colonoscopy after a negative result.^{18–23} If, as suggested by our study, this time interval could be extended to 20 years, or if repeat colonoscopies might not be needed at all, the cost-effectiveness would even be greater than previously assumed. At the same time, fewer resources would be needed, time and suffering of patients as well as cumulative risk for death and serious complications would be reduced,⁸ and population-wide, colonoscopy based screening may become feasible even in countries with limited resources for high quality colonoscopy.

In the interpretation of our study, various limitations have to be borne in mind. Though we included all hospitals treating patients with colorectal cancer in the study region, and despite major efforts to ensure continuous cooperation of these hospitals, only about 50% of the expected total number of incident eligible cases during the study period were recruited. Many of these were probably missed because they were not informed about the study by their physicians, who

often suffer from severe work overload in German hospitals. Few patients who were informed about the study refused to participate. Because of the very strict confidentiality rules in Germany, it is not possible for us to quantify the proportions involved, as patients may only be contacted through the doctors in charge of their treatment. However, a more detailed look at regional data showing large variations in coverage of expected numbers of eligible cases by subregion strongly supports the view that deficient recruitment by clinicians in some hospitals—which is unlikely to be a relevant source of selection bias—rather than patient characteristics was the limiting factor in recruitment.

The rate of full participation among potential control subjects was slightly less than 50% in this population based study, requiring personal interviews, access to medical case files, and blood sampling, and including cases and controls aged 80 or older, who are more difficult to recruit. Nevertheless, data on history of colonoscopies were obtained from 69% of eligible controls. A detailed sensitivity analysis including all of these controls indicated that potential selection bias is unlikely to have a major impact on the patterns observed in our study.

Despite our efforts to control for a variety of known or suspected risk factors or protective factors of colorectal cancer, potential “residual” confounding by imperfect measurement of confounding factors or by failure to include relevant confounding factors cannot be ruled out in this observational study.

Although the overall numbers of patients with colorectal cancer and of controls included in this study were large, the estimates of risk reduction according to time since colonoscopy were based on small numbers, and showed rather wide confidence intervals. Sample size limitations also hindered more detailed analyses of risks with respect to additional factors such as a family history of colorectal cancer, which may play a role in the decision about whether and when to repeat a screening colonoscopy with a negative result.

Despite its limitations, our study suggests a long lasting very low risk of colorectal cancer following a negative colonoscopy, which may have important implications for colonoscopy based screening regimens. Our results, which should be replicated in larger studies, suggest that average risk subjects with a negative colonoscopy might not need another screening colonoscopy for at least 20 years, if at all. With the possibility to extend screening intervals beyond 10 years, the cost-effectiveness of screening colonoscopy could even be substantially greater, and cumulative rates of serious complications as well as death could be lower than previous analyses have suggested. Thus population-wide colonoscopic screening might become feasible even in countries with limited resources for high quality colonoscopy.

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