ORIGINAL ARTICLE

Interval cancers after negative colonoscopy: population-based case-control study

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ABSTRACT

Objective The risk of colorectal cancer after a previous negative colonoscopy is very low. Nevertheless, interval cancers occur. We aimed to assess the characteristics and predictors of interval cancers after negative colonoscopy.

Methods A population-based case-control study was conducted in Southern Germany in 2003–7. Sociodemographic and tumour characteristics were compared among 78 patients with interval cancers occurring 1–10 years after a negative colonoscopy and 433 colorectal cancers detected at screening. In addition, the indication for the preceding negative colonoscopy and its completeness were compared between patients with interval cancers and 515 controls with a preceding negative colonoscopy.

Results 56.4% of interval cancers occurred among women compared with 33.7% of cases detected by screening (p=0.0001). After adjustment for covariates, female sex (OR 2.28, 95% CI 1.35 to 3.83) and location in the caecum or ascending colon (OR 1.98, 95% CI 1.17 to 3.35) were independently associated with occurrence of interval cancers. The preceding negative colonoscopy was more commonly conducted because of a positive faecal occult blood test (26.0% vs 12.9%, p=0.009) and was more often incomplete (caecum not reached: 18.1% vs 6.7%, p=0.001) among interval cancer cases than among controls. Characteristics of the preceding negative colonoscopy strongly and independently associated with occurrence of interval cancers were follow-up of a positive faecal occult blood test among men (OR 5.49, 95% CI 2.10 to 14.35) and incompleteness among women (OR 4.38, 95% CI 1.69 to 11.30).

Conclusions The observed patterns suggest that a substantial proportion of interval cancers are due to neoplasms missed at colonoscopy and are potentially preventable by enhanced performance of colonoscopy.

Significance of this study

What is already known about this subject?

- The risk of colorectal cancer after a previous negative colonoscopy is very low. Nevertheless, interval cancers occur.
- Interval cancers may result from missed neoplasms or de novo development after colonoscopy.

What are the new findings?

- Interval cancers occurred more often among women, in the caecum and ascending colon.
- Interval cancers occurred more often after a negative colonoscopy following a positive faecal occult blood test, particularly among men.
- Interval cancers occurred more often after an incomplete negative colonoscopy (caecum not reached), particularly among women.

How might it impact on clinical practice in the foreseeable future?

- The observed patterns suggest that a substantial proportion of interval cancers are due to neoplasms missed at colonoscopy and should motivate further efforts to enhance the performance of colonoscopy.

INTRODUCTION

A number of observational studies have shown the risk of colorectal cancer (CRC) to be low within the 10-year screening interval commonly recommended after a negative colonoscopy.[1–4] Nevertheless, interval cancers occur, especially in the right colon,[2] and, given limited empirical evidence, it is uncertain to what degree they result from neoplasms missed at the preceding negative colonoscopy or represent cancers that have developed since. A recent study from Canada, which was based on physicians' billing claims, hospital discharge and cancer registry databases, suggested that a deficiency in colonoscopy quality rather than accelerated tumour biology was the cause of the majority of interval cancers occurring within 3 years after a negative colonoscopy.[5 6] Furthermore, female sex and older age of the patients and performance of the colonoscopy by a non-gastroenterologist were identified as predictors of missed/early CRC after negative colonoscopy.

However, most previous studies on interval cancers after colonoscopy relied on registry and administrative data,[5–9] were restricted to the initial 3–5 years after colonoscopy,[6–10] did not specifically focus on interval cancers occurring after a negative colonoscopy (ie, a colonoscopy with no detection of adenomatous polyps)[8–12] and provided limited information on possible predictors of interval cancers. Furthermore, most previous reports came from Canada or the USA.[5–9] The quality of colonoscopies might differ between countries. For example, recent evidence suggests that, compared with Canada,[13 14] the risk of CRC after preceding colonoscopy may be more substantially reduced,

even in the right colon, in Germany where the nationwide introduction of screening colonoscopy in 2002 was accompanied by major efforts of quality assurance.[15] We aimed to assess characteristics and predictors of interval cancers occurring within 10 years after a negative colonoscopy in a large population-based case-control study from Germany.

METHODS

Study design and study population

Our analysis is based on data from the "Darmkrebs: Chancen der Verhütung durch Screening" (DACHS) study, a population-based case-control study conducted in the Rhine-Neckar region located in the south-west of Germany and covering a population of about 2 million people. Details of the study design have been reported elsewhere.[2 15] Briefly, the study area includes 22 hospitals where patients with CRC are treated, and all of them agreed to participate in the study. Patients with a first diagnosis of primary invasive CRC aged 30 or older living in the study area are eligible for recruitment. Control subjects are randomly selected from population registers using frequency matching with respect to age, sex and county of residence. We excluded subjects with a history of inflammatory bowel disease who are typically under frequent colonoscopic surveillance. The study was approved by the ethical committees of the Medical Faculty of the University of Heidelberg and of the Medical Chambers of Baden-Württemberg and Rhineland-Palatinate. Recruitment for this study is ongoing. The current analysis is based on cases and controls recruited between January 2003 and December 2007. Overall, 4344 persons (1945 cases and 2399 controls) were recruited. Based on the statistics of patients with CRC treated in the hospitals, recruited patients constitute about 50% of the expected total number of eligible patients in the study area. The participation rate among eligible controls (n=4769) was 50.3%. Written informed consent was obtained from each participant.

Data collection

Patients were informed about the study by their treating physicians, in most cases during 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 hospitalisation or, if they had already left the hospital, at their homes. The standardised interviews, which lasted for about 1 h, included a detailed medical and family history as well as a lifetime history of sociodemographic and lifestyle factors. Controls were contacted by the study centre by mail and follow-up calls, and interviews were scheduled at their homes among controls with no history of CRC. The interviews were conducted in the same way as for cases. A self-administered questionnaire that included key information was obtained from a minority of control participants who were not willing to participate in a personal interview.

Detailed information on any previous endoscopic examinations of the large bowel was obtained during the interview. Whenever a previous endoscopy (ie, an endoscopy 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 subject's physician.

Statistical analysis

From 1945 cases of CRC we identified 78 interval cancer cases with a validated negative colonoscopy within 10 years prior to diagnosis, as shown in figure 1. In case of multiple preceding endoscopies, only the most recent one was considered.

In a first set of analyses we compared patients with interval cancers with 433 cases whose cancer was detected at screening (figure 1, left side) with respect to the distribution of sex, age, cancer site, stage and grade. Differences between patients with interval cancers and cases detected by screening were tested for statistical significance using χ^2 tests. In addition to showing results for all interval cancers, interval cancers were stratified according to time since negative colonoscopy (<3 years, 3–10 years). Multiple logistic regression was used to identify independent associations (ORs and 95% CIs) of sex, age, tumour location and grade with the occurrence of interval cancers.

In a second set of analyses we compared the 78 patients with interval cancers with 515 controls with a validated negative colonoscopy within 10 years prior to recruitment, who were selected in the same way as the cases with a history of negative colonoscopy (figure 1, right side). Cases and controls with a preceding negative colonoscopy were compared with respect to indication (as reported by the study participants) as well as

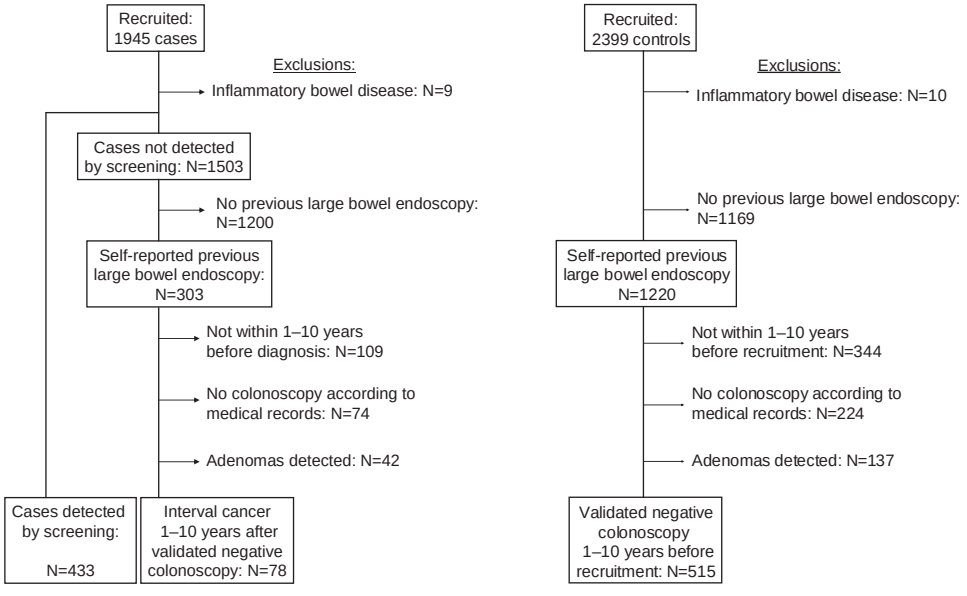

Figure 1 Flow chart of selection of study participants.

Table 1 Characteristics of interval cases after a negative colonoscopy during the preceding 1–10 years compared with cases with no previous colonoscopy during the same time interval

Characteristic	Cases with interval cancer			Cases detected by screening, N (%)	p Value*
	Within <3 years, N (%)	Within 3–10 years, N (%)	Total, N (%)		
Sex					
Men	16 (45.7)	18 (41.9)	34 (43.6)	287 (66.3)	
Women	19 (54.3)	25 (58.1)	44 (56.4)	146 (33.7)	0.0001
Age					
<60 years	6 (17.1)	5 (11.6)	11 (14.1)	71 (16.4)	
60–69 years	14 (40.0)	20 (46.5)	34 (43.6)	167 (38.6)	
70–79 years	9 (25.7)	13 (30.2)	22 (28.2)	149 (34.4)	
80+ years	6 (17.1)	5 (11.6)	11 (14.1)	46 (10.6)	0.55
Cancer site					
Caecum	4 (12.1)	8 (18.6)	12 (15.8)	45 (11.0)	
Ascending colon	14 (42.4)	10 (23.3)	24 (31.6)	74 (18.1)	
Right flexure, transverse colon	2 (6.1)	6 (14.0)	8 (10.5)	48 (11.7)	
Left flexure to sigmoid colon	4 (12.1)	11 (25.6)	15 (19.7)	139 (33.9)	
Rectum	9 (27.3)	8 (18.6)	17 (22.4)	104 (25.4)	0.02
Stage†					
I	5 (14.3)	7 (16.3)	12 (15.4)	178 (41.3)	
II	13 (37.1)	14 (32.6)	27 (34.6)	104 (24.1)	
III	10 (28.6)	19 (44.2)	29 (37.2)	127 (29.5)	
IV	7 (20.0)	3 (7.0)	10 (12.8)	22 (5.1)	<0.0001
Grade‡					
G1and G2	21 (61.8)	29 (72.5)	50 (67.6)	312 (79.2)	
G3 and G4	13 (38.2)	11 (27.5)	24 (32.4)	82 (20.8)	0.03

Numbers of cases with missing data: sex: 0 (0%), age: 0 (0%), cancer site: 25 (4.9%), stage: 2 (0.4%), grade: 43 (8.4%).
*For difference between all cases with interval cancer and cases detected by screening.
†According to Union Internationale Contre le Cancer (I=T1/T2 N0 M0; II=T3/T4 N0 M0; III=any T N1/N2 M0; IV=any T any N M1).
‡G1=well differentiated, G2=moderately differentiated, G3=poorly differentiated, G4=undifferentiated.

completeness (caecum reached: yes/no, taken from medical records) of that colonoscopy. Again, differences between the groups were assessed for statistical significance by χ^2 tests, and multiple logistic regression was employed to assess independent associations of indication and completeness of the preceding colonoscopy with the occurrence of interval cancers, quantified by sex and age-adjusted ORs and their 95% CIs. In addition to analyses for all cases and controls meeting the inclusion criteria, analyses were carried out for subgroups defined by sex, age (<70 and ≥70 years), time since preceding negative colonoscopy (<3 and 3–10 years) and location of cancer (proximal: caecum or ascending colon, distal: other).

All analyses were carried out using the SAS statistical software package Version 9.2. All statistical tests were two-sided at an α level of 0.05.

RESULTS

A comparison of the characteristics of patients with interval cancers and those whose cancer was detected at screening is shown in table 1. More than half (56.4%) of the patients with interval cancer were women compared with only 33.7% of screening detected cases (p=0.0001). There were no significant age differences between the two groups of patients. Almost half

Table 2 Crude and adjusted associations of sociodemographic factors and tumour characteristics with the occurrence of interval cancers

	Interval cancers <3 years				Interval cancers 3–10 years				Interval cancers 1–10 years			
	Crude analysis		Adjusted analysis*		Crude analysis		Adjusted analysis*		Crude analysis		Adjusted analysis*	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sex												
Men	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Women	2.33	1.17 to 4.67	1.98	0.94 to 4.15	2.73	1.44 to 5.17	2.50	1.28 to 4.87	2.54	1.56 to 4.15	2.28	1.35 to 3.83
Age												
<70 years	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
≥70 years	0.92	0.46 to 1.84	0.77	0.37 to 1.64	0.88	0.47 to 1.66	0.77	0.39 to 1.50	0.90	0.55 to 1.46	0.78	0.46 to 1.31
Location†												
Distal	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Proximal	2.94	1.43 to 6.02	2.54	1.20 to 5.35	1.76	0.93 to 3.35	1.68	0.86 to 3.30	2.20	1.34 to 3.62	1.98	1.17 to 3.35
Grade‡												
G1 and G2	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
G3 and G4	2.36	1.13 to 4.90	2.04	0.94 to 4.43	1.44	0.69 to 3.01	1.36	0.64 to 2.90	1.83	1.06 to 3.15	1.62	0.91 to 2.88

*Adjusted for other variables listed in the table.
†Proximal: caecum to ascending colon; distal: other.
‡G1=well differentiated, G2=moderately differentiated, G3=poorly differentiated, G4=undifferentiated.

(47.4%) of the interval cancers were located in the caecum or ascending colon compared with 29.1% of screening detected cancers. This proportion was particularly high (54.5%) among interval cancers occurring <3 years after a negative colonoscopy. The proportions of stage I cancers and of low-grade cancers (G1 or G2) were much higher among screening detected cancers (41.3% and 79.2%, respectively) than among interval cancers (15.4% and 67.6%, respectively), especially interval cancers occurring <3 years after a negative colonoscopy (14.3% and 61.8%, respectively).

The results of multiple logistic regression are shown in table 2. Female sex and location of cancer in the caecum or ascending colon were strongly and independently associated with occurrence of interval cancers (adjusted OR 2.28 (95% CI 1.35 to 3.83) and 1.98 (95% CI 1.17 to 3.35), respectively). For cancer location, the association was stronger and statistically significant only for interval cancers occurring <3 years after a negative colonoscopy.

Comparison of patients with interval cancer and controls with a preceding negative colonoscopy (table 3) showed that the preceding negative colonoscopy was less often conducted as a primary screening examination (39.0% vs 50.9%) and more often conducted as a follow-up examination for a positive faecal occult blood test (FOBT, 26.0% vs 12.9%) in patients with interval cancers (p=0.009). Furthermore, the colonoscopy had been more often incomplete (ie, the caecum had not been reached) among patients with interval cancers (18.1% vs 6.7%, p=0.001). Differences in incompleteness of the preceding colonoscopy between patients with interval cancers and controls were particularly pronounced among women (25.0% vs 8.3%, p=0.002), whereas differences in the indication for the preceding colonoscopy were most pronounced among men. Among men with interval cancers, the preceding colonoscopy had been conducted to follow up a positive FOBT in 35.3% of cases compared with only 10.6% among male controls with a preceding negative colonoscopy (p=0.0001). Differences in indication and completeness of the preceding negative colonoscopy between patients with interval cancers and controls were more pronounced among participants aged <70 years.

With adjusted ORs of 2.26 (95% CI 1.16 to 4.42) and 2.63 (95% CI 1.25 to 5.0), respectively, indication by positive FOBT and incompleteness of a preceding negative colonoscopy remained strong and independent predictors of interval cancers after controlling for each other as well as for age and sex (table 4). With adjusted ORs of 2.93 (95% CI 1.13 to 7.61) and 7.24 (95% CI 1.78 to 29.34), respectively, associations were particularly strong with interval cancers occurring <3 years after a negative colonoscopy. Positive associations were also observed with interval cancers occurring 3–10 years after a negative colonoscopy, but they were much weaker and did not reach statistical significance in stratum-specific analysis. Although age and sex were adjusted for in the multiple regression models, estimation of the association of these covariates with occurrence of interval cancers in the case-control analyses would not be meaningful, given that these factors were matched for in recruitment of controls.

Stratified analyses by sex showed very distinct patterns of covariate adjusted associations with indication and completeness of the preceding negative colonoscopy (table 5). Among men, the risk of interval cancers was more than fivefold increased when the preceding colonoscopy had been performed because of a positive FOBT, whereas no significant association was seen with completeness of the colonoscopy. By contrast, incompleteness of the preceding negative colonoscopy was associated with a more than fourfold increase in the risk of interval cancers among women, for whom no association was seen with indication. Differences by age were much less pronounced even though associations with indication and completeness were somewhat stronger in participants aged <70 years and did not reach statistical significance in those aged ≥70 years. Somewhat unexpectedly, the association of incompleteness of the preceding colonoscopy was slightly weaker for interval cancers located in the caecum and ascending colon than for those located in more distal parts of the colon and rectum. The latter interval cancers also showed a much stronger association with a positive FOBT prior to the preceding negative colonoscopy.

Table 3 Comparison of cases with interval cancers and controls with a negative result at a preceding colonoscopy with respect to indication and completeness of colonoscopy

Group	Indication and completeness of colonoscopy	Cases with interval cancer, N (%)	Controls, N (%)	p Value
Total	Indication			
	Screening	30 (39.0)	218 (50.9)	
	Positive FOBT	20 (26.0)	55 (12.9)	
	Other	27 (35.1)	155 (36.2)	0.009
	Complete			
	Yes	59 (81.9)	447 (93.3)	
	No	13 (18.1)	32 (6.7)	0.001
Men	Indication			
	Screening	10 (29.4)	148 (58.0)	
	Positive FOBT	12 (35.3)	27 (10.6)	
	Other	12 (35.3)	80 (31.4)	0.0001
	Complete			
	Yes	29 (90.6)	258 (94.5)	
	No	3 (9.4)	15 (5.5)	0.37
Women	Indication			
	Screening	20 (46.5)	70 (40.5)	
	Positive FOBT	8 (18.6)	28 (16.2)	
	Other	15 (34.9)	75 (43.4)	0.60
	Complete			
	Yes	30 (75.0)	189 (91.8)	
	No	10 (25.0)	17 (8.3)	0.002
<70 years	Indication			
	Screening	18 (40.9)	91 (49.2)	
	Positive FOBT	13 (29.6)	24 (13.0)	
	Other	13 (29.6)	70 (37.8)	0.03
	Complete			
	Yes	34 (79.1)	195 (92.4)	
	No	9 (20.9)	16 (7.6)	0.007
≥70 years	Indication			
	Screening	12 (36.4)	127 (52.3)	
	Positive FOBT	7 (21.2)	31 (12.8)	
	Other	14 (42.4)	85 (35.0)	0.18
	Complete			
	Yes	25 (86.2)	252 (94.0)	
	No	4 (13.8)	16 (6.0)	0.11

Numbers of cancers with missing data: sex: 0 (0%), age: 0 (0%), indication: 1 (1.3%), completeness: 6 (7.7%); numbers of controls with missing data: sex: 0 (0%), age: 0 (0%), indication: 87 (16.9%), completeness: 36 (7.0%).
FOBT, faecal occult blood test.

DISCUSSION

Using data from a large population-based case-control study from Germany, we provide a detailed comparison of patients with interval CRC occurring within 10 years after a negative colonoscopy both with patients whose CRC was detected at screening colonoscopy and with controls who had a negative colonoscopy within the previous 10 years and no diagnosis of

Table 4 Crude and adjusted associations of indication and completeness with the occurrence of interval cancers

	Interval cancers <3 years				Interval cancers 3–10 years				Interval cancers 1–10 years			
	Crude analysis		Adjusted analysis*		Crude analysis		Adjusted analysis*		Crude analysis		Adjusted analysis*	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Indication												
Screening	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive FOBT	2.97	1.20 to 7.36	2.93	1.13 to 7.61	2.35	0.95 to 5.77	1.79	0.69 to 4.65	2.64	1.40 to 5.00	2.26	1.16 to 4.42
Other	1.17	0.50 to 2.76	0.75	0.27 to 2.04	1.30	0.61 to 2.75	1.08	0.49 to 2.38	1.27	0.72 to 2.21	0.97	0.53 to 1.78
Complete												
Yes	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
No	9.08	2.46 to 33.44	7.24	1.78 to 29.34	1.90	0.79 to 4.52	1.72	0.69 to 4.27	3.08	1.53 to 6.20	2.63	1.25 to 5.50

*Adjusted for indication or completeness of previous colonoscopy, as well as for age and sex.
FOBT, faecal occult blood test.

CRC. The former comparison indicates strong over-representation of cancers in the caecum and ascending colon among patients with interval CRC, particularly when the interval cancer occurred <3 years after the negative colonoscopy. Furthermore, a more than twofold higher risk of interval cancers was observed in women than in men. The latter comparison indicates that, in men, a preceding positive FOBT and, in women, incompleteness of colonoscopy are strong predictors of the occurrence of CRC after a negative colonoscopy.

Our finding of over-representation of proximal colon cancer among interval cancers is consistent with a previous analysis in a much smaller subset of our study population (including cases and controls recruited in 2003 and the first half of 2004 only) which found that risk reduction after negative colonoscopy was less pronounced for proximal colon cancer, especially cancer in the caecum and ascending colon.[2] Likewise, over-representation of interval cancers in the right colon has been reported in colonoscopy cohorts from Canada,[1 3 6 9] where colonoscopy was also found to be associated with reduced mortality from left-sided but not right-sided CRC.[13 14]

In this context, the contribution of the quality of the colonoscopy and biological factors to the site differences are of major interest. In a previous study from New Zealand, nine of 17 interval cancers occurred after an incomplete colonoscopy.[11] Although this proportion was lower among the 78 interval cancers included in our study (18%), a clear association between interval cancers and completeness of the preceding negative colonoscopy (ie, whether the caecum was reached) emerged. This association was most pronounced among women, for whom the proportion of incomplete colonoscopies was much higher than for men, which is consistent with previous observations[16–19] and may explain the higher risk of interval cancers among women. Interestingly, incompleteness of colonoscopy was associated with proximal interval cancers, which may have occurred beyond the reach of incomplete colonoscopy, and also (and even to a slightly greater extent) with distal cancers. A possible explanation may be that incompleteness may be strongly associated with other aspects of the quality of colonoscopy including miss rates in the distal colon and rectum. This explanation would be consistent with previous studies that found the qualifications of endoscopists to be an important predictor of the occurrence of interval cancers.[5 6 9 12]

To our knowledge, our study is the first to document an association between interval cancers and the performance of the preceding colonoscopy due to a positive FOBT. Guaiac-based FOBT has been offered free of charge as a primary screening tool for CRC in Germany since 1977 (immunological FOBTs have also been available in more recent years but have been used much less often as they are not covered by health insurance). A positive FOBT prior to performing a negative colonoscopy could be an indication that a neoplasm had already been present but remained undetected at colonoscopy. Our finding of a stronger association with distal interval cancers is consistent with observations that most FOBT-detectable cancers seem to be located in the left colon and rectum.[20 21] Recent work has suggested that the sensitivity of FOBTs for detecting adenomas is higher in men than in women,[21 22] and is particularly high in men using low-dose aspirin for prevention of cardiovascular disease.[23] Although these findings pertained to immunological FOBTs, the observed patterns suggest that FOBTs may more often be positive in men even in the case of smaller adenomas which have a higher risk of being missed at colonoscopy and may explain the particularly strong association of interval cancers with a preceding positive FOBT in men.

Table 5 Risk of interval cancers with respect to indication and completeness of preceding negative colonoscopy in preceding 1–10 years in defined subgroups

	Location of interval cancer				Sex				Age			
	Caecum or ascending colon		Other		Men		Women		<70 years		≥70 years	
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Indication												
Screening	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive FOBT	1.41	0.47 to 4.26	3.31	1.47 to 7.44	5.49	2.10 to 14.35	0.95	0.35 to 2.53	2.41	1.00 to 5.81	2.00	0.67 to 5.98
Other	1.64	0.74 to 3.63	0.53	0.21 to 1.39	2.04	0.82 to 5.04	0.49	0.21 to 1.14	0.67	0.29 to 1.54	1.48	0.60 to 3.66
Complete												
Yes	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
No	2.51	0.94 to 6.70	3.46	1.30 to 9.24	1.32	0.33 to 5.25	4.38	1.69 to 11.30	2.98	1.15 to 7.73	1.99	0.56 to 7.03

*Adjusted for indication or completeness of previous colonoscopy, as well as for age and sex (as applicable).
FOBT, faecal occult blood test.

Taken together, the associations with a preceding positive FOBT and incompleteness of the previous negative colonoscopy support suggestions recently expressed based on model calculations that missed detection rather than biological factors may be the main cause for the occurrence of interval cancers after a negative colonoscopy.[24]

Nevertheless, biological factors undoubtedly contribute to the occurrence of interval cancers, particularly in the right colon. For example, microsatellite instability (MSI) and the CpG island methylator phenotype, which are more common among cancers in the right colon than in the left colorectum,[25 26] have been shown to be associated with interval cancers.[27 28] In our study, MSI and CpG island methylator phenotype status were not available. However, interval cancers—particularly those occurring <3 years after a negative colonoscopy—were more commonly grade 3 or 4 than cancers detected by screening, and this difference was even more pronounced among cancers located in the caecum and ascending colon (data not shown). Higher tumour grade is associated with advanced stage and worse prognosis,[29 30] and faster growth of these cancers may make their detection (or detection of their precursors) at colonoscopy less likely. Nevertheless, in multivariate analysis, cancer site and sex remained strong predictors of interval cancers even after control for tumour grade.

Our study has specific strengths and limitations. The strengths include its reliance on detailed data collected in a large population-based case-control study that enabled comparison of patients with interval cancers after negative colonoscopy with patients whose cancer was detected by screening and with controls who also had a previous negative colonoscopy but no cancer. All self-reported previous colonoscopies were validated by medical records, but we did not validate the absence of a previous colonoscopy in all participants. However, the self-reported absence of a previous large bowel endoscopy was confirmed by participants' physicians in all of the 84 cases in a validation study among a subsample of study participants.[31] The participation rate of both cases and controls was approximately 50%. Although this participation rate seems low, it is probably close to what is achievable in such a population-based study. Most of the participating 22 hospitals have no infrastructure to recruit and treat patients within studies. Almost half of our study population were aged ≥70 years (with no upper age limit). It is challenging to perform extensive data collection with personal interviews lasting about 1 h (conducted in home visits among controls) in elderly subjects. The possibility of selection bias, particularly for the oldest age groups who had the lowest participation rates, therefore has to be kept in mind. Despite the overall large size of our study, sample size limitations of interval cancers prevented more detailed analyses by, for example, tighter time intervals following a negative colonoscopy or by additional factors potentially related to the risk of interval cancers such as diet, exercise or use of non-steroidal anti-inflammatory drugs.

Notwithstanding these limitations and the undoubted role of biological factors in interval cancers, our study corroborates and extends the evidence that a substantial proportion of interval cancers after a negative colonoscopy are probably due to missed neoplasms at colonoscopy. A previous analysis from the DACHS study has demonstrated major protection from CRC by colonoscopy,[15] despite the likely occurrence of missed cases suggested by the current analysis. Our results suggest that even larger protection might be possible by further efforts to enhance the quality of colonoscopies—especially those conducted following a positive FOBT (for which less rigorous quality assurance standards have so far been implemented in Germany than for primary screening colonoscopies)—and completeness of colonoscopies, especially among women.

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Competing interests None.

Patient consent Obtained.

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Contributors All authors have contributed to the conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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