ORIGINAL RESEARCH | Annals of Internal Medicine

Protection From Colorectal Cancer After Colonoscopy

A Population-Based, Case–Control Study

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Background: Colonoscopy with detection and removal of adenomas is considered a powerful tool to reduce colorectal cancer (CRC) incidence. However, the degree of protection achievable in a population setting with high-quality colonoscopy resources remains to be quantified.

Objective: To assess the association between previous colonoscopy and risk for CRC.

Design: Population-based case–control study.

Setting: Rhine-Neckar region of Germany.

Patients: A total of 1688 case patients with colorectal cancer and 1932 control participants aged 50 years or older.

Measurements: A detailed lifetime history of CRC risk factors and preventive factors, including history and results of previous colonoscopies, and of medical data obtained by self-reports and medical records. Odds ratios of CRC associated with colonoscopy in the preceding 10 years were estimated, after adjustment for sex, age, education level, participation in a general health screening examination, family history of CRC, smoking status, body mass index, and use of nonsteroidal anti-inflammatory drugs or hormone replacement therapy.

Results: Overall, colonoscopy in the preceding 10 years was associated with 77% lower risk for CRC. Adjusted odds ratios for any CRC, right-sided CRC, and left-sided CRC were 0.23 (95% CI, 0.19 to 0.27), 0.44 (CI, 0.35 to 0.55), and 0.16 (CI, 0.12 to 0.20), respectively. Strong risk reduction was observed for all cancer stages and all ages, except for right-sided cancer in persons aged 50 to 59 years. Risk reduction increased over the years in both the right and the left colon.

Limitation: The study was observational, with potential for residual confounding and selection bias.

Conclusion: Colonoscopy with polypectomy can be associated with strongly reduced risk for CRC in the population setting. Aside from strong risk reduction with respect to left-sided CRC, risk reduction of more than 50% was also seen for right-sided colon cancer.

Primary Funding Source: German Research Council and German Federal Ministry of Education and Research.

Ann Intern Med. 2011;154:22-30. www.annals.org

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Colorectal cancer (CRC) is the fourth most common cancer in men and the third most common cancer in women worldwide, accounting for more than 1 million new diagnoses and more than 500 000 deaths each year (1). Colonoscopy enables detection and removal of precancerous lesions and may thereby effectively prevent CRC. The National Polyp Study (2) demonstrated colonoscopy to be associated with a 76% to 90% risk reduction for CRC among persons with colorectal polyps under highly standardized conditions. The effectiveness of colonoscopy in preventing CRC is less clear in the community setting. Observational studies conducted in the community setting (and not restricted to specialized centers) have indicated a reduction of CRC incidence and mortality after colonoscopy, albeit to a much lesser extent (3–9), possibly because colorectal adenomas may be missed more frequently in such settings (10–13). Furthermore, recent studies suggest that risk reduction mainly affects or may even be restricted to the left colon and rectum, whereas risk reduction in the right colon remains uncertain (14, 15). However, previous studies were limited by small sample size or reliance on administrative claims data, or they were carried out in populations or periods with limited establishment of high-quality colonoscopy resources.

We sought to assess the association between previous colonoscopy and risk for cancer in the right and left colon in a large case–control study in Germany, where colonoscopy was introduced as a primary screening offer for women and men aged 55 years or older in 2002 and introduction of screening colonoscopy was accompanied by major efforts in terms of training and measures of quality assurance (15–17).

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METHODS

Study Design and Population

We conducted a population-based, case–control study in the Rhine-Neckar region, located in southwestern Germany and covering a population of about 2 million persons. Details of the study design, as well as preliminary results pertaining to case patients and control participants recruited from January 2003 to June 2004, are reported elsewhere (18–20). In brief, patients with a first diagnosis

of invasive primary CRC who were aged 30 years or older, were physically and mentally able to participate, and were able to communicate in German were eligible for recruitment. Our report is based on much larger numbers of case patients ($n = 1945$) and control participants ($n = 2399$) recruited from January 2003 to December 2007. All 22 hospitals in the study area in which patients with CRC received treatment were involved in recruitment. Community-based control participants were frequency matched with respect to age, sex, and county of residence and randomly selected from population registers. We excluded persons with a history of CRC; otherwise, inclusion and exclusion criteria were the same as in case patients. The ethical committees of the Medical Faculty at the University of Heidelberg and the Medical Chambers of Baden-Württemberg and Rhineland-Palatinate approved this study. We obtained written informed consent from each participant.

On the basis of 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 control participants ($n = 4769$) was 50.3%, but another 1151 persons (24.1%) who did not agree to full participation provided some information about former endoscopies of the large bowel.

Data Collection

Eligible patients were identified prospectively in the cooperating hospitals and informed about the study by the physicians in charge of their treatment, in most cases during their hospital stay and after surgery. Trained interviewers conducted personal interviews during hospitalization or, if patients had already left the hospital, at their homes. Interviews were conducted in a strictly standardized manner by using a questionnaire, along with clear-cut instructions for interviewers to ensure the maximum possible degree of standardization in its application in case patients and control participants. To enhance completeness of recruitment, eligible patients who had not been approached during the hospital stay were retrospectively identified by the clinical partners and invited for participation by mail approximately every 6 months. The standardized interviews included a detailed medical and family history, as well as a lifetime history of sociodemographic and lifestyle factors. The study center contacted control participants by mail and through follow-up calls, and interviews were scheduled at their homes. A self-administered questionnaire that included key information was obtained from a minority of control participants who were not willing to participate in an interview.

Information on previous endoscopies of the large bowel done for any reason was obtained in detail during the interview. Whenever a previous endoscopy (an endoscopy other than the one leading to the current cancer diagnosis) was reported, we sought to validate this information by medical records. Medical records could be obtained for 84% of reported single or last previous endoscopies within the preceding 10 years. As reported in detail elsewhere, validity of self-reports with respect to history of endoscopies was very high, and self-reports of not having had a preceding colonoscopy were confirmed by physicians in all 84 cases in a validation study conducted in a subsample of the study sample (21). According to self-reports, 91%, 5%, and 1% of endoscopies were colonoscopies, rectoscopies, and sigmoidoscopies, respectively. The type of endoscopy was unknown in 3% of cases. According to medical records, 94%, 4%, and 1% of examinations could be classified as colonoscopy, rectoscopy, and sigmoidoscopy, respectively. Medical records were used for classification where available; otherwise, self-reports were used. According to colonoscopy records, the cecum was reached in 91% of colonoscopies, and polyps were detected and removed in 26% of colonoscopies.

Context

Under highly standardized conditions, colonoscopy has been associated with a reduction in colorectal cancer (CRC), although its overall effectiveness in community practice and its ability to reduce the risk for right-sided colon cancer are less clear.

Contribution

This population-based study in Germany compared rates of colonoscopy in the preceding 10 years among patients with CRC and community control participants. Colonoscopy was associated with significant reductions in the risk for both left- and right-sided CRC.

Caution

Residual confounding cannot be excluded in this observational study.

Implication

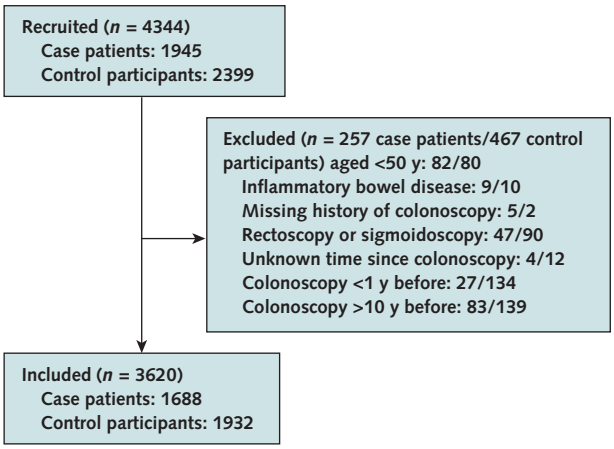
Significant reductions in the incidence of both left- and right-sided CRC seem to be achievable with colonoscopy in the community setting.

—The Editors

Statistical Analysis

For statistical analysis, we excluded persons who were younger than 50 years (screening colonoscopy is not recommended for the average-risk population at that age); had a history of inflammatory bowel disease (frequent surveillance colonoscopy owing to increased risk for CRC [22]); had missing information on history of colonoscopy; had a self-reported last endoscopy other than colonoscopy (specifically, rectoscopy or sigmoidoscopy); had missing information for time since single or last previous colonoscopy or single or last previous colonoscopy was less than 1 year before (to prevent potential bias by erroneous reporting of colonoscopy done as part of the diagnostic process);

Figure 1. **Study flow diagram.**



and had a single or last previous colonoscopy more than 10 years before (10 years is the most commonly recommended interval for screening colonoscopy [23, 24]). **Figure 1** provides specific numbers for exclusions. After these exclusions, 1688 case patients and 1932 control participants remained for the main analysis. To explore the effect of the last 2 exclusion criteria, additional sensitivity analyses were carried out without these exclusions.

We first described case patients and control participants according to age, sex, and covariates (ascertained during the interviews) known or have been suggested to be related to CRC risk (25–28): education level (<9 years, 10 to 11 years, or ≥12 years [standard categories of education levels in Germany]), history of CRC in a first-degree relative, smoking status (never, current, or former), body mass index (<20, 20 to 24.9, 25 to 29.9, or ≥30 kg/m^2), ever use (regular use at least twice per week for ≥1 year) of nonsteroidal anti-inflammatory drugs, ever use of hormone replacement therapy, and ever participation in a general health screening examination. The last criterion was considered as a potential indicator of general health behavior. It focuses on diabetes and cardiovascular and renal disease and is offered every 2 years to adults aged 36 years or older in Germany.

Next, we assessed the risk for CRC according to history of single or last colonoscopy in the past 1 to 10 years, using persons without any previous endoscopy as the reference group. Odds ratios (ORs) and their 95% CIs for the association between history of colonoscopy and CRC risk were estimated from several logistic regression models, after adjustment for age and sex and the aforementioned covariates. In addition to estimates for all CRCs, estimates were derived by cancer site, stage, and mode of detection. Stage was categorized according to the classification of the Union Internationale Contre le Cancer. The mode of detection was classified as screening or other (that is, by symptoms or incidentally). In the German health care system, screening includes fecal occult blood testing, which has been offered as primary screening tool since 1977. Screening by fecal occult blood test was offered annually from age 45 years from 1977 to 2002. Since October 2002, it has been offered annually for persons aged 50 to 54 years, and every 2 years from age 55 years. In addition, screening colonoscopy has been offered as an alternative screening tool from age 55 years (up to 2 colonoscopies 10 or more years apart) since October 2002.

To evaluate potential variation in risk reduction across population groups and over time, we derived estimates of relative risk for any, right-sided (cecum to transverse colon), and left-sided (splenic flexure to sigmoid colon) CRC in subgroup-specific analyses by sex, age, history of CRC in a first-degree relative, and year of diagnosis (case patients) or recruitment (control participants). We conducted specific analyses on the basis of the calendar years to evaluate potential trends in risk reduction over time.

All statistical analyses were done by using SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

The German Research Council and German Federal Ministry of Education and Research funded the study. The

Table 1. **Sociodemographic Factors and Known or Suspected Risk Factors or Protective Factors for CRC in the Study Sample**

Characteristic	Case Patients (*n* = 1688), *n* (%)	Control Participants (*n* = 1932), *n* (%)
Age		
50–59 y	267 (15.8)	293 (15.2)
60–69 y	604 (35.8)	596 (30.9)
70–79 y	553 (32.8)	655 (33.9)
≥80 y	264 (15.6)	388 (20.1)
Women	706 (41.8)	825 (42.7)
Men	982 (58.2)	1107 (57.3)
Education level		
≤9 y	1182 (70.2)	1186 (61.9)
10–11 y	259 (15.4)	365 (19.0)
≥12 y	244 (14.5)	366 (19.1)
Ever participated in a general health screening examination	1374 (81.9)	1630 (87.4)
Family history of CRC*	240 (14.7)	211 (11.2)
Smoking status		
Never	810 (48.2)	1051 (54.7)
Current	250 (14.9)	210 (10.9)
Former	621 (36.9)	661 (34.4)
Body mass index		
<20.0 kg/m^2	73 (4.4)	48 (2.5)
20.0–24.9 kg/m^2	568 (34.0)	608 (31.6)
25.0–29.9 kg/m^2	713 (42.7)	919 (47.8)
≥30.0 kg/m^2	317 (19.0)	347 (18.1)
Ever regular use of aspirin or NSAIDs†	393 (23.4)	576 (30.2)
Ever regular use of HRT‡	233 (33.2)	367 (44.9)

CRC = colorectal cancer; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug.
* History of CRC in a first-degree relative.
† At least twice weekly for 1 y.
‡ Women only.

Table 2. **Association of Previous Colonoscopy With Risk for CRC**

Group	Total Participants, *n*	Colonoscopy 1–10 y Before, *n* (%)	Odds Ratio (95% CI)*	
			Adjusted for Age and Sex	Adjusted for Multiple Covariates†
Control participants	1932	793 (41.1)	–	–
Case patients				
Overall	1688	230 (13.6)	0.23 (0.19–0.27)	0.23 (0.19–0.27)
By cancer location				
Cecum	181	41 (22.7)	0.42 (0.30–0.61)	0.42 (0.28–0.61)
Ascending colon	213	59 (27.7)	0.54 (0.40–0.74)	0.58 (0.42–0.80)
Hepatic flexure	81	16 (19.8)	0.34 (0.20–0.60)	0.31 (0.16–0.59)
Transverse colon	72	13 (18.1)	0.32 (0.17–0.59)	0.34 (0.18–0.65)
Right colon combined	537	125 (23.3)	0.43 (0.35–0.54)	0.44 (0.35–0.55)
Splenic flexure	43	8 (18.6)	0.33 (0.15–0.72)	0.33 (0.15–0.73)
Descending colon	71	16 (22.5)	0.42 (0.24–0.73)	0.44 (0.25–0.79)
Sigmoid colon	374	35 (9.4)	0.15 (0.10–0.21)	0.14 (0.10–0.20)
Rectum	585	45 (7.7)	0.12 (0.09–0.17)	0.13 (0.09–0.18)
Left colon and rectum combined	1060	101 (9.5)	0.15 (0.12–0.19)	0.16 (0.12–0.20)
By cancer stage‡				
I	408	68 (16.7)	0.29 (0.22–0.38)	0.27 (0.20–0.36)
II	521	67 (12.9)	0.21 (0.16–0.28)	0.23 (0.17–0.30)
III	522	71 (13.6)	0.23 (0.18–0.30)	0.22 (0.17–0.29)
IV	233	23 (9.9)	0.16 (0.10–0.24)	0.17 (0.11–0.27)
By mode of detection				
Screening	382	67 (17.5)	0.31 (0.23–0.41)	0.28 (0.21–0.37)
Other§	1305	163 (12.5)	0.21 (0.17–0.25)	0.21 (0.18–0.26)

CRC = colorectal cancer.
* Odds ratio for CRC or CRC subgroup, comparing persons who had had colonoscopy 1 to 10 y before with persons who had not had previous colonoscopy.
† Adjusted for age and sex in addition to education level, participation in general health screening examination, family history of CRC, smoking status, body mass index, ever regular use of nonsteroidal anti-inflammatory drugs, and ever regular use of hormone replacement therapy.
‡ According to Union Internationale Contre le Cancer.
§ Cases of cancer detected by symptoms or incidentally (e.g., in the context of medical examinations conducted for other reasons).

funding sources had no role in the design or conduct of the study; collection, analysis, and interpretation of the data; preparation or review of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Table 1 shows the distribution of sociodemographic factors and of known or suspected risk factors or protective factors of CRC among case patients and control participants included in the analysis. Mean age of case patients and control participants was 69 and 70 years, respectively; 58% of case patients and 57% of control participants were men. Case patients less often had higher levels of education than control participants ($P < 0.001$), and a higher proportion of case patients had never attended a general health screening examination ($P < 0.001$). A positive family history and having ever smoked regularly were more common among case patients than among control participants ($P = 0.002$). Most case patients and control participants were overweight or obese (mean body mass index, 26.5 kg/m^2 and 26.8 kg/m^2, respectively). Ever regular use of nonsteroidal anti-inflammatory drugs and hormone replacement therapy was less common among case patients than among control participants ($P < 0.001$ for both covariates).

A total of 1023 study participants had had at least 1 colonoscopy in the past 1 to 10 years. Of these, most reported to have had 1 (60%) or 2 colonoscopies (23%). Overall, 41.1% of control participants and only 13.6% of case patients had had a colonoscopy in the preceding 1 to 10 years, resulting in an OR of 0.23 after adjustment for age and sex (**Table 2**). Further adjustment for potential confounders did not change the estimate (OR, 0.23 [95% CI, 0.19 to 0.27]). Sensitivity analyses not excluding persons with a previous colonoscopy less than 1 year or more than 10 years before yielded very similar results (adjusted OR with neither exclusion, 0.25 [CI, 0.22 to 0.29]).

The exact location was known for 1582 cases of cancer (93.7%). A preceding colonoscopy was associated with strong and statistically significant risk reduction of cancer at any single subsite assessed, even though risk reductions were somewhat less pronounced for types of cancer located at subsites from the cecum to the descending colon (adjusted ORs from 0.31 to 0.58) than for sigmoid colon cancer and rectal cancer (adjusted OR, 0.14 and 0.13, respectively). Adjusted ORs for right-sided (cecum to transverse colon) and left-sided (splenic flexure to rectum) cancer combined were 0.44 (CI, 0.35 to 0.55) and 0.16 (CI, 0.12 to 0.20), respectively.

Information on stage was available for all but 4 types of cancer (99.8%). Most case patients had stage II or stage III cancer (31% each). Preceding colonoscopy was associated with strong reduction of CRC risk at all stages. There

Table 3. **Association Between Previous Colonoscopy and Risk for CRC in Various Subgroups**

Group	Control Participants		Case Patients		Adjusted Odds Ratio (95% CI)*
	Total Participants, *n*	Colonoscopy 1–10 y Before, *n (%)*	Total Patients, *n*	Colonoscopy 1–10 y Before, *n (%)*	
Women	825	320 (38.8)	706	94 (13.3)	0.24 (0.18–0.32)
Men	1107	473 (42.7)	982	136 (13.9)	0.22 (0.18–0.28)
Age					
50–59 y	293	79 (27.0)	267	24 (9.0)	0.26 (0.15–0.43)
60–69 y	596	256 (43.0)	604	83 (13.7)	0.22 (0.16–0.29)
70–79 y	655	305 (46.6)	553	87 (15.7)	0.22 (0.16–0.29)
≥80 y	388	153 (39.4)	264	36 (13.6)	0.23 (0.15–0.36)
Family history†					
No	1668	665 (39.9)	1395	185 (13.3)	0.23 (0.19–0.28)
Yes	211	111 (52.6)	240	40 (16.7)	0.20 (0.13–0.32)
Year of recruitment					
2003–2004	469	143 (30.5)	797	103 (12.9)	0.37 (0.27–0.50)
2005	415	163 (39.3)	331	46 (13.9)	0.24 (0.16–0.36)
2006–2007	1022	470 (46.0)	558	80 (14.3)	0.18 (0.14–0.25)

CRC = colorectal cancer.
* Adjusted for age and sex in addition to education level, participation in general health screening examination, family history of CRC, smoking status, body mass index, ever regular use of nonsteroidal anti-inflammatory drugs, and ever regular use of hormone replacement therapy.
† History of CRC in a first-degree relative.

was a trend toward stronger risk reduction for more advanced cancer, but the differences between stages were not very large, and the CIs of OR estimates overlapped. No major difference was seen for cancer that was detected by screening and for cancer that was detected on the basis of symptoms or incidentally.

Risk reduction associated with a preceding colonoscopy was very strong and essentially the same among women and men and among those with and without a family history of CRC (**Table 3**). Sensitivity analyses additionally controlling for history of mammography (women) and prostate-specific antigen testing (men) as further indicators of health-seeking behavior did not alter the results (data not shown). Likewise, risk reduction was similar across age groups. From 2003 to 2004 and 2006 to 2007, the proportion of control participants with a preceding colonoscopy increased from 30.5% to 46.0%. By contrast, this proportion remained at low levels of 13% to 14% among case patients. As a result, estimated risk reduction increased over time ($P = 0.001$).

Table 4 shows results of more detailed analyses of risk reduction of right- and left-sided cancer in the various subgroups. In each subgroup, risk reduction was substantially stronger for left-sided cancer than for right-sided cancer. Risk reduction did not vary by sex and family history of CRC, neither for right-sided cancer nor for left-sided cancer. Risk reduction became more pronounced in later years, with ORs decreasing from 2003–2004 to 2006–2007 from 0.63 to 0.38 for right-sided cancer and from 0.27 to 0.11 for left-sided cancer, although this trend was statistically significant for left-sided cancer only (P values for interaction of previous colonoscopy with period of recruitment were 0.14 and 0.001 for right- and left-sided cancer, respectively). An age gradient, with more pronounced risk reduction among persons aged 70 years or older than among younger persons was seen for right-sided cancer ($P = 0.05$ for interaction of previous colonoscopy with age), but not for left-sided cancer. In the youngest age group (50 to 59 years), risk reduction for right-sided cancer was only moderate and not statistically significant.

DISCUSSION

In our large, population-based, case–control study in Germany, colonoscopy in the preceding 10 years was associated with a 77% reduced risk for CRC. Risk reduction was particularly pronounced for cancer in the left colon and rectum, but a substantial risk reduction was also seen for cancer in the right colon. Strong risk reduction was observed for all cancer stages, in both women and men, and in all age groups, and risk reduction increased over time, reaching 82% overall in the most recent period (2006–2007). For right- but not left-sided cancer, an age gradient in risk reduction was observed, with only moderate (26%) and statistically nonsignificant risk reduction in persons younger than 60 years.

Colonoscopy is obviously not protective in and of itself; protection results from removal of adenomas at colonoscopy. Given that most cases of CRC are assumed to develop from advanced adenomas, most advanced adenomas can be detected and removed at colonoscopy (29), and risk for recurrence during commonly recommended

screening intervals (23, 24) is low, the estimates of risk reduction of the magnitude observed in our study seem plausible.

Our results are consistent with and extend previous findings of risk reduction of CRC after colonoscopy, which were either based on much smaller numbers of case patients (3, 8, 9, 20) or relied on administrative claims (14). In particular, our results corroborate the evidence that colonoscopy may also substantially reduce CRC incidence in the community setting, and they suggest that this risk reduction may be stronger than shown by previous studies. Several reasons may contribute to the stronger risk reduction found in our study. Previous studies pertained to case patients who received a diagnosis in earlier periods, such as 1988 to 1993 (6), 1996 to 1998 (3), 1996 to 2001 (14), and 1996 to 2005 (9), and technology and training in colonoscopy have improved since then. Furthermore, differences in quality of colonoscopy between populations might play a role (30). In Germany, major efforts of training and quality assurance were made along with introduction of screening colonoscopy in 2002 (16, 17). The finding that more than 90% of colonoscopies reached the cecum and the finding of increasing protection in recent years, with respect to cancer in the right and the left colon, suggest that, under such conditions, major protection may also be possible for right-sided colon cancer.

Fundamental differences in the setting of our study compared with a recent study from Canada, which was based on administrative claims and did not find protection from deaths from right-sided cancer (14), are also reflected in the proportions of control participants who had previous colonoscopy. In our study, this proportion was 41.1% and increased over time, compared with 9.8% in the Canadian study. The persisting (albeit strongly reduced) differences in risk reduction for right- and left-sided cancer might reflect a remaining higher percentage of missed adenomas in the right colon (12, 13, 31) or differences in the biology of right- and left-sided cancer (31–34). The age gradient with less pronounced risk reduction of right-sided cancer at younger ages might be a possible indication of the importance of the latter.

The risk reduction for CRC after colonoscopy in the preceding 1 to 10 years found in our study was substantially larger than the reduction in prevalence of advanced colorectal neoplasm (either advanced adenoma or CRC) found in our recent study among participants in the German screening colonoscopy program from 2005 to 2007 (15). In the latter study, prevalence was reduced by 48% overall, and it was restricted to the left colon and rectum, in which a 67% prevalence reduction was found. Because both studies were done during a similar period in the same health care system (albeit in different regions of Germany), quality of preceding colonoscopies is unlikely to explain the differences. A more plausible explanation could be that development of advanced adenomas, either de novo or from small adenomas missed at the preceding colonoscopy, takes much less time than development of CRC, keeping in mind that 10-year progression rates from advanced adenomas to CRC are estimated to be less than 50% (35). With CRC, the current study had a much stronger end

Table 4. **Association Between Previous Colonoscopy and Risk for Right-Sided and Left-Sided CRC in Various Subgroups**

Group	Control Participants		Patients With Right-Sided CRC			Patients With Left-Sided CRC		
	Total Participants, *n*	Colonoscopy 1–10 y Before, *n* (%)	Total Patients, *n*	Colonoscopy 1–10 y Before, *n* (%)	Adjusted Odds Ratio (95% CI)*	Total Patients, *n*	Colonoscopy 1–10 y Before, *n* (%)	Adjusted Odds Ratio (95% CI)*
Women	825	320 (38.8)	259	56 (21.6)	0.45 (0.32–0.65)	407	36 (8.9)	0.15 (0.10–0.22)
Men	1107	473 (42.7)	278	69 (24.8)	0.43 (0.31–0.58)	653	65 (10.0)	0.16 (0.12–0.22)
Age								
50–59 y	293	79 (27.0)	62	14 (22.6)	0.74 (0.37–1.46)	184	9 (4.9)	0.13 (0.06–0.29)
60–69 y	596	256 (43.0)	171	47 (27.5)	0.52 (0.35–0.78)	400	34 (8.5)	0.13 (0.09–0.20)
70–79 y	655	305 (46.6)	180	40 (22.2)	0.32 (0.21–0.49)	343	45 (12.9)	0.17 (0.12–0.25)
≥80 y	388	153 (39.4)	124	24 (19.4)	0.37 (0.21–0.63)	133	13 (9.8)	0.15 (0.08–0.29)
Family history†								
No	1668	665 (39.9)	448	101 (22.5)	0.44 (0.34–0.57)	871	80 (9.2)	0.16 (0.12–0.20)
Yes	211	111 (52.6)	72	21 (29.2)	0.41 (0.22–0.76)	153	19 (12.4)	0.14 (0.08–0.26)
Year of recruitment								
2003–2004	469	143 (30.5)	274	54 (19.7)	0.63 (0.42–0.94)	490	48 (9.8)	0.27 (0.18–0.39)
2005	415	163 (39.3)	96	26 (27.1)	0.51 (0.30–0.86)	219	21 (9.6)	0.17 (0.10–0.29)
2006–2007	1022	470 (46.0)	167	45 (27.0)	0.38 (0.25–0.57)	350	31 (8.9)	0.11 (0.07–0.17)

CRC = colorectal cancer.
* Adjusted for age and sex in addition to education level, participation in general health screening examination, family history of CRC, smoking status, body mass index, ever regular use of nonsteroidal anti-inflammatory drugs, and ever regular use of hormone replacement therapy.
† History of CRC in a first-degree relative.

point. Finally, the number of patients with right-sided advanced neoplasms in our previous study was much smaller ($n = 73$) than that of patients with right-sided CRC in the current study ($n = 537$). As a result, CIs around effect estimates in our previous study were wider and still compatible with a moderate protective effect of previous colonoscopy.

Absence of an association of preceding colonoscopy with advanced neoplasms (most of which were advanced adenomas) in the right colon in our previous study (15) may have suggested flexible sigmoidoscopy to be as effective for CRC prevention as colonoscopy. However, the finding of a major protective effect for cancer—a clinically more relevant end point in the current study—suggests that colonoscopy may prevent additional types of cancer in the right colon. A relevant question, to be addressed in careful cost-effectiveness analyses, is the extent to which the incremental effect of colonoscopy compared with sigmoidoscopy is worth the additional costs, risks, and inconvenience (36–39). Sigmoidoscopy could be a valuable tool to provide strong protection from CRC to persons not ready or willing to undergo screening colonoscopy (20), as recently demonstrated by a large randomized trial (40).

The effect of colonoscopy on CRC incidence and mortality has not been evaluated in a randomized, controlled trial. Evidence for a protective effect is entirely based on observational studies and may therefore be affected by confounding factors related to utilization of colonoscopy. On the one hand, utilization of colonoscopy may be more common among persons at increased risk for CRC. On the other hand, it may also be higher among more health-conscious persons who may be at reduced risk for CRC. In our study, we aimed to minimize potential confounding by excluding persons with a history of inflammatory bowel disease and by careful ascertainment of and adjustment for potential confounding factors. Although several of these factors were differentially distributed among case patients and control participants, simultaneous adjustment for them had only a very small effect on estimated ORs. We cannot rule out residual confounding by imperfect measurement of confounders or by additional confounders not included in the analysis, but it seems unlikely that such residual confounding could account for the strong inverse associations between history of colonoscopy and CRC risk found in our study.

Our results could have been affected by recall bias if previous colonoscopy was differentially recalled by case patients and control participants who were recruited in different settings, according to the case–control design. However, as outlined in the Methods section, self-reported colonoscopies could be validated by medical records and were found to be highly accurate (21), making a major role of recall bias unlikely. Furthermore, we cannot rule out that some of the covariates, such as body mass index, might have been affected by disease status. Finally, some of the control participants might have had latent, undiagnosed CRC, but this proportion is probably very small, given that latent CRC is found in less than 1% of older adults at screening colonoscopy (41).

Another potential limitation is selection bias by incomplete and potentially differential participation rates of eligible case patients and control participants. In this population-based study, about 50% of eligible patients in a catchment area with about 2 million inhabitants could be recruited. As discussed in detail elsewhere (18), incomplete ascertainment of case patients was primarily due to work overload of physicians in charge of case notifications and, in cases of recruitment after discharge, limited adherence to home interviews, and is unlikely to be related to history of colonoscopy. Nevertheless, patients with more advanced disease or older patients, for whom participation can be difficult or impossible for health reasons, are somewhat underrepresented, as suggested by a lower proportion of case patients with stage IV cancer and a lower proportion of older patients compared with reports from population-based cancer registries in Germany (42). Because associations with colonoscopy were slightly stronger in older patients and those with more advanced disease, underrepresentation of these patients may have led to some underestimation of overall risk reduction. The response rate among control participants in this study population of elderly persons with no upper age limit was slightly greater than 50% overall, with substantially higher participation rates in the younger age groups than in the oldest age groups. It is conceivable that more health-conscious control participants who had had colonoscopy in the past would be more likely to participate. Limited data from a short questionnaire obtained from about one half of nonparticipating control participants indicated history of colonoscopy to be slightly less common overall than among participating control participants (but still much higher than among case patients), which could have led to slight overestimation of the protective effect of colonoscopy. However, the consistency of the inverse associations of history of colonoscopy with overall CRC risk across age groups does not support a major role of selection bias due to nonresponse among control participants.

Our results pertain to colonoscopy done for any reason, not specifically to screening colonoscopy, which was introduced in Germany only in October 2002. Furthermore, the final goal of CRC screening should be to reduce CRC mortality. Although that end point was not addressed in our study, it is closely related to the occurrence of advanced-stage CRC. Tentatively higher risk reduction for advanced-stage disease than for early-stage disease found in our analysis suggests that associated reduction of mortality might be of similar or even higher magnitude.

Despite its limitations, our study adds to the increasing evidence that colonoscopy, with removal of colorectal adenomas, may substantially reduce CRC incidence. Our results further suggest that major reduction may also be achieved for right-sided CRC, even in the community set-

ting, when widespread offer of colonoscopy is paired with major efforts in terms of training and quality assurance.

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Acknowledgment: The authors thank Ute Handte-Daub for her excellent technical assistance. They are grateful to the study participants and the interviewers who collected the data. The authors also thank the following hospitals and cooperating institutions that recruited patients for this study: Chirurgische Universitätsklinik Heidelberg, Klinik am Gesundbrunnen Heilbronn, Sankt Vincentiuskrankenhaus Speyer, Sankt Josefskrankenhaus Heidelberg, Chirurgische Universitätsklinik Mannheim, Diakonissenkrankenhaus Speyer, Krankenhaus Salem Heidelberg, Kreiskrankenhaus Schwetzingen, Sankt Marien- und Sankt Annastiftkrankenhaus Ludwigshafen, Klinikum Ludwigshafen, Stadtklinik Frankenthal, Diakoniekrankenhaus Mannheim, Kreiskrankenhaus Sinsheim, Klinikum am Plattenwald Bad Friedrichshall, Kreiskrankenhaus Weinheim, Kreiskrankenhaus Eberbach, Kreiskrankenhaus Buchen, Kreiskrankenhaus Mosbach, Enddarmzentrum Mannheim, Kreiskrankenhaus Brackenheim, and Cancer Registry of Rhineland-Palatinate in Mainz.

Grant Support: By the German Research Council (BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, and CH 117/1-1) and the German Federal Ministry of Education and Research (01KH0404 and 01ER0814).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1362.

Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code*: Available by request from and written agreement with Dr. Brenner (e-mail, h.brenner@Dkfz-Heidelberg.de).

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