Research Article

Cancer Epidemiology, Biomarkers & Prevention

Smoking, Lower Gastrointestinal Endoscopy, and Risk for Colorectal Cancer

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Abstract

Background: Lower gastrointestinal endoscopy can decrease colorectal cancer risk strongly through detection and removal of adenomas. Thus, we aimed to investigate whether utilization of lower gastrointestinal endoscopy modifies the effect of lifetime smoking exposure on colorectal cancer risk in a population-based case–control study.

Methods: In this study from Southern Germany including 2,916 patients with colorectal cancer and 3,044 controls, information about lifetime smoking and other risk factors was obtained from standardized interviews. Self-reported endoscopies were validated by medical records. Multivariate logistic regression was performed to investigate associations of smoking with colorectal cancer risk after stratification by utilization of lower gastrointestinal endoscopy in the preceding 10 years.

Results: Median age of patients and controls was 69 and 70 years, respectively. Former regular smoking was associated with increased colorectal cancer risk in the group with no previous endoscopy [adjusted OR, 1.50; 95% confidence interval (CI), 1.28–1.75], whereas no association was found in the group with preceding endoscopy (OR, 1.05; CI, 0.83–1.33; P for interaction <0.01). Lower gastrointestinal endoscopy did not modify the association of smoking and colorectal cancer risk among current smokers and among the more recent quitters.

Conclusions: Our results suggest that the increased risk of colorectal cancer among former regular smokers is essentially overcome by detection and removal of adenomas at lower gastrointestinal endoscopy. However, risk of colorectal cancer was increased if smoking was continued into higher adult age.

Impact: The strong protective effect of lower gastrointestinal endoscopy may be compromised by continued smoking. Smoking cessation may increase the efficacy of lower gastrointestinal endoscopy. *Cancer Epidemiol Biomarkers Prev; 23(3); 525–33. ©2014 AACR.*

Introduction

Cigarette smoking is an established risk factor of both colorectal adenomas and colorectal cancer. In meta-analyses, pooled relative risks of colorectal adenomas and colorectal cancer were 1.8 and 1.2, respectively (1, 2). Because of the high proportion of current and former smokers among older adults, noteworthy fractions of advanced adenomas and cancers are attributable to smoking, and it has been suggested that recommendations for screening and surveillance for the prevention and early detection of colorectal cancer should address smokers specifically (3–5).

Lower gastrointestinal endoscopy, i.e., sigmoidoscopy or colonoscopy, with its potential to detect and remove adenomas and, thereby, to decrease colorectal cancer risk strongly (6, 7), has been used by an increasing proportion of older adults in the past two decades in the Western countries (8–11), particularly after expert committees started to recommend screening by sigmoidoscopy and colonoscopy (12–15).

As smoking increases colorectal cancer risk and, even more, adenoma risk, previous utilization of lower gastrointestinal endoscopy could attenuate smoking-associated colorectal cancer risk through removal of adenomas that may partly have developed into carcinomas (see Fig. 1 for an illustration). Studies on the association of smoking and colorectal cancer risk conducted during the late 1990s and after the year 2000 that were not accounting for preceding colorectal endoscopies might, therefore, have underestimated the true carcinogenic effect of smoking (2, 16, 17).

The aim of this study was to investigate whether previous utilization of lower gastrointestinal endoscopy

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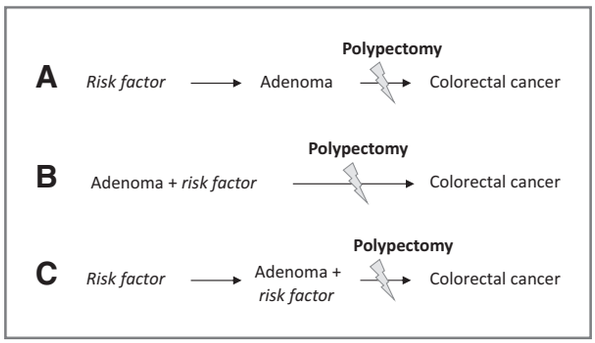

Figure 1. Simplified model illustrating three ways how utilization of lower gastrointestinal endoscopy with polypectomy could attenuate associations of a risk factor with colorectal cancer risk: A, risk factor predominantly increases risk of colorectal adenomas; B, risk factor predominantly increases risk of progression from adenoma to cancer; C, risk factor increases both, risk of colorectal adenomas and cancer. In all cases, the adenoma–carcinoma sequence is discontinued through removal of adenomas.

modifies the association of smoking and colorectal cancer risk.

Materials and Methods

Study design and study population

The analyses were conducted within the DACHS study, a population-based case–control study from Germany, including 3,148 cases and 3,274 controls recruited between 2003 and 2010. The DACHS study [DACHS is derived from the German study title "Darmkrebs: Chancen der Verhütung durch Screening" (Colorectal cancer: potentials of prevention by screening)] is conducted in the Rhine-Neckar region in the southwest of Germany in an area with approximately 2 million inhabitants. All 22 hospitals offering colorectal cancer surgery in the study region participate in the recruitment of patients with a first diagnosis of primary colorectal cancer for this study. Eligible controls were randomly selected from population registers and frequency-matched to cases by age, sex, and county of residence. Cases and controls were eligible for this study if they were able to speak German, were at least 30 years old (no upper age limit), and were physically and mentally able to participate in an interview of about 1 hour. Control individuals with a history of colorectal cancer were excluded. On the basis of hospital statistics, approximately 50% of eligible patients in the study area were recruited. The participation rate of controls was 51%. More details of the study design have been reported previously (18, 19). The study was approved by the ethical committees of the Medical Faculty of the University of Heidelberg and 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 treating physicians, mostly during hospital stay after surgery or by mail after discharge from hospital. If patients agreed to participate, a notification was sent to the study centre. The study center then informed one of the trained study interviewers to conduct the personal interview. Controls were contacted through mail and follow-up calls, and interviews were scheduled at their homes. A minority of control participants (23%) not willing to participate in a personal interview provided information in a self-administered questionnaire including key information. For all patients, pathology reports and discharge letters were requested, and all primary cases of colorectal cancer were histologically confirmed. All information in the questionnaires was truncated at the index date, which was the date of diagnosis among the cases and the date of interview among the controls.

Assessment of active smoking

Information on lifetime active smoking was based on self-reports. Subjects were asked whether they had ever smoked at least one cigarette per day for at least 3 months. An ever-regular smoker was defined as someone having smoked at least 100 cigarettes in lifetime. Former smoking was defined as having stopped smoking >2 years before the index date. Pack-years of smoking were calculated from the average number of cigarettes smoked daily, multiplied by the duration of smoking in years, divided by 20 (one pack-year is defined as e.g., 20 cigarettes per day for 1 year or 10 cigarettes per day for 2 years).

Assessment of previous lower gastrointestinal endoscopy utilization

Information about previous utilization of colorectal endoscopies was obtained in great detail during the interviews, not including endoscopies conducted during the diagnostic process of the colorectal cancer diagnosis. If prior utilization of lower gastrointestinal endoscopy was reported, we requested matching endoscopy reports from the participants' physicians and corrected self-reported information in case of obvious inconsistencies, which were found to be rare (20). According to endoscopy reports, more than 95% of lower gastrointestinal endoscopies were colonoscopies. They were conducted for various reasons, of which screening was the most common one (21).

Study exclusions

For this analysis, we excluded all individuals with endoscopies conducted more than 10 years ago (178 cases, 225 controls) to assess a potential modifying effect of colorectal endoscopies within the preceding 10 years. A 10-year period was selected because 10 years are the currently recommended maximum screening interval before lower gastrointestinal endoscopy should be repeated in older adults to prevent colorectal cancer (22, 23). Also, we excluded 41 patients whose last endoscopy was conducted less than 1 year before, to be sure that examinations that were part of the diagnostic process are excluded. We further excluded current or former smokers who started regular smoking within the preceding 10

years or whose information on smoking was missing (13 cases, 5 controls). Finally, 2,916 patients and 3,044 remained in the analyses.

Multiple imputation of missing data

The self-administered questionnaire that was offered to control participants who denied a full interview included no information about former weight in its early version and thus no information on former body mass index (BMI) was available ($N = 482$, 16% of controls). As former BMI [mean time before diagnosis (cases) or interview (controls): 10 years] is more relevant in investigations of colorectal cancer risk than current BMI, and because additional missing data in the other covariates in multivariate analyses (ranging from 0.2% to 3%) can sum up to a considerable proportion of excluded subjects in complete-case analyses, we performed multiple imputation using the Markov Chain Monte Carlo method to fill in missing data ($N = 5$ imputed datasets; SAS procedure PROC MI). The variables in the imputation model included all covariates of the multivariate logistic regression model (see below) plus the additional explanatory variables height and current BMI. Thereby, data from 5,960 instead of 5,077 participants (85%) could be analyzed.

Statistical analyses

We compared the distribution of potential risk factors and protective factors among patients and controls, and assessed differences between the two groups by χ^2 tests (see Table 1). Unconditional multiple logistic regression was used to estimate adjusted ORs and their 95% confidence intervals (95% CI) for the association of smoking and colorectal cancer risk among cases and controls with no previous lower gastrointestinal endoscopy and with a previous lower gastrointestinal endoscopy in the preceding 10 years, respectively. ORs for regular smoking were adjusted for age and sex, and for the following additional potential confounders: school education ($\leq$9/10–11/12+ years), previous general health screening examination (yes/no), history of colorectal cancer in a first-degree relative (yes/no), former BMI (based on weight 10 years ago on average, per increment of 5 kg/m^2), regular use of nonsteroidal anti-inflammatory drugs (2 + times per week for at least 1 year, ever/never), ever use of hormone replacement therapy (ever/never), previous diagnosis of diabetes (yes/no), physical activity (average metabolic equivalent hours per week in past 12 months), and alcohol consumption (average ethanol intake per week in last 12 months). Interaction of regular smoking and utilization of lower gastrointestinal endoscopy in the preceding 10 years regarding colorectal cancer risk was evaluated after inclusion of a multiplicative term into the model. More specific analyses addressed timing of smoking (current, former), time since smoking cessation, location (colon, rectum), and stage of colorectal cancer (stage I–II, stage III–IV).

Restricted cubic spline analyses were conducted on the association of pack-years of smoking and colorectal cancer risk to illustrate dose–response associations for (i) current smoking with no previous endoscopy, (ii) current smoking with endoscopy in the preceding 10 years, (iii) former smoking with no previous endoscopy, and (iv) former smoking with endoscopy in the preceding 10 years. The 25th, 50th, and 75th percentiles of pack-years of smoking among the controls were used to define the spline knots for each group (bullet points). Adjusted ORs and 95% CI were calculated (same covariates as listed above) for associations of colorectal cancer risk with 10, 20, 30, and 40 pack-years of smoking.

All analyses were carried out with SAS statistical software package, version 9.2 (SAS Institute Inc). Statistical tests were two-sided using a α level of 0.05. For descriptive analyses of the study population, we used the dataset containing all five imputed datasets, rounded imputed information to the next higher or lower category wherever necessary, and assigned a weight inverse to the number of imputed datasets (weight = 0.2) to obtain averaged results. SAS procedures PROC LOGISTIC and PROC MIANALYZE were used for logistic regression analyses across the imputed datasets. Dose–response analyses by restricted cubic spline functions were calculated using the SAS macro by Desquilbet and Mariotti (24).

Results

Median age among cases and controls was 69 and 70 years, respectively (Table 1). The proportion of female participants was 41% among both cases and controls. Control subjects more often had a higher school education and a previous colonoscopy, whereas cases had more frequently first-degree relatives with colorectal cancer and a smoking history, and were more often obese ($P < 0.01$). Slightly more than half of the colorectal cancers were stage I or II, and two thirds were located in the distal colon or rectum. Among cases and controls, 54% and 47% were ever-regular smokers, respectively. According to endoscopy reports, most lower gastrointestinal endoscopies were colonoscopies (95%).

In multivariate analyses, ever smoking was associated with an increased risk of colorectal cancer in the total study population (with and without adjustment for a lower gastrointestinal endoscopy in the preceding 10 years: OR, 1.35; 95% CI, 1.20–1.53; and OR, 1.36; CI, 1.22–1.52, respectively).

Former smoking was associated with colorectal cancer risk in the group with no previous lower gastrointestinal endoscopy (OR, 1.50; CI, 1.28–1.75), but not in those with lower gastrointestinal endoscopy in the preceding 10 years (OR, 1.05; CI, 0.83–1.33; P for interaction < 0.01; Table 2). Among current smokers, risk of colorectal cancer was not attenuated by previous utilization of lower gastrointestinal endoscopy (OR, 1.85; CI, 1.25–2.65). Also, if smoking was stopped 3 to 9 or 10 to 19 years before, no reduction of the smoking-related excess risk could be observed (OR, 1.92; CI, 1.16–3.18; and OR, 1.53; CI, 1.02–2.28, respectively). No risk of colorectal cancer was observed with smoking, if smoking was stopped $\geq$20

Table 1. Characteristics of the study population

	Cases ($N = 2{,}916$)	Controls ($N = 3{,}044$)	
	N (%)	*N* (%)	*P*
Female	1,197 (41)	1,236 (41)	0.73
Age			
<60 years	592 (20)	515 (17)	
60–69 years	934 (32)	913 (35)	
70–79 years	938 (32)	1,058 (35)	<0.01
80+ years	452 (16)	558 (18)	
Median (range)	69 (30–96)	70 (34–99)	
School education			
≤9 years	1,991 (68)	1,821 (60)	
10–11 years	480 (17)	588 (20)	<0.01
12–13 years	440 (15)	609 (20)	
History of colorectal cancer in a first degree relative			
No/unknown	2,499 (86)	2,719 (89)	
Yes	417 (14)	325 (11)	<0.01
Previous lower gastrointestinal endoscopy			
No/unknown	2,422 (83)	1,536 (50)	
Yes	494 (17)	1,508 (50)	<0.01
Former BMI			
<25 kg/m^2	921 (32)	1,164 (38)	
25–<30 kg/m^2	1,369 (47)	1,437 (47)	<0.01
≥30 kg/m^2	626 (21)	443 (15)	
Cigarette smoking			
Never	1,338 (46)	1,596 (53)	
Former	1,119 (38)	1,108 (36)	<0.01
Current	456 (16)	333 (11)	
1–9 pack-years	510 (18)	521 (17)	
10–19 pack-years	374 (13)	321 (11)	
20–29 pack-years	275 (9)	259 (9)	<0.01
≥30 pack-years	404 (14)	306 (10)	
Cancer stage			
Stage I	667 (23)	—	—
Stage II	910 (31)	—	—
Stage III	910 (31)	—	—
Stage IV	417 (14)	—	—
Cancer location			
Proximal colon	927 (32)	—	—
Distal colon	795 (27)	—	—
Rectum	1,213 (42)	—	—

years ago in the group with previous lower gastrointestinal endoscopy. Findings were very similar without multiple imputation of missing data (data not shown).

Among current smokers, risk was similarly elevated for colon and rectum cancer, early-, and late-stage cancer in the group with previous lower gastrointestinal endoscopy (Table 3). Among former smokers, no significant differences were observed in the endoscopy group by colorectal cancer site and stage regarding the absence of a smoking-associated risk. Results for proximal and distal location within the colon were very similar (data not shown).

An additional analysis using never smokers without lower gastrointestinal endoscopy as a reference yielded adjusted ORs of 1.43 (CI, 1.16–1.76), 0.75 (CI, 0.67–0.84), and 0.49 (CI, 0.45–0.54) for current smokers without lower gastrointestinal endoscopy, current smokers with lower gastrointestinal endoscopy, and never smokers with lower gastrointestinal endoscopy in the preceding 10 years, respectively.

In dose–response analyses, the ORs of colorectal cancer risk increased steadily from 10 to 40 pack-years of smoking (and beyond) among current smokers whether or not a previous lower gastrointestinal endoscopy had been performed (no endoscopy group: OR, 1.16–1.73; endoscopy group: OR, 1.27–2.24; Fig. 2). Among former smokers, ORs were only slightly but nonsignificantly elevated, and did

Table 2. Association of regular smoking and colorectal cancer risk among cases and controls with no previous lower gastrointestinal endoscopy and among cases and controls with utilization of lower gastrointestinal endoscopy in the preceding 10 years

	No previous lower gastrointestinal endoscopy ($N = 3,958$: 2,422 cases, 1,536 controls)			Lower gastrointestinal endoscopy in the preceding 10 years ($N = 2,002$: 494 cases, 1,508 controls)			
	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]	*P* for interaction[b]
Nonsmokers	1,093 (45)	824 (54)	1.00	245 (50)	772 (51)	1.00	
Ever smokers	1,329 (55)	712 (46)	1.45 (1.26–1.67)	249 (50)	736 (49)	1.15 (0.92–1.44)	0.02
Current smokers	395 (16)	219 (14)	1.42 (1.15–1.75)	61 (12)	114 (8)	1.82 (1.25–2.65)	0.28
Former smokers	932 (39)	490 (32)	1.50 (1.28–1.75)	187 (38)	618 (41)	1.05 (0.83–1.33)	<0.01
Time since smoking cessation							
3–9 years	138 (6)	73 (4)	1.45 (1.06–1.98)	29 (6)	50 (3)	1.92 (1.16–3.18)	0.49
10–19 years	228 (9)	97 (6)	1.82 (1.39–2.38)	47 (10)	100 (7)	1.53 (1.02–2.28)	0.38
20–29 years	223 (9)	102 (7)	1.64 (1.26–2.14)	34 (7)	153 (10)	0.73 (0.48–1.11)	<0.01
≥30 years	341 (14)	217 (14)	1.23 (0.99–1.53)	77 (16)	315 (21)	0.83 (0.60–1.14)	0.02
P for trend			0.27			0.01	

[a]ORs are adjusted for matching factors age and sex, and additionally, for school education, participation in health screening examinations, history of colorectal cancer in a first-degree relative, former BMI, ever regular use of nonsteroidal anti-inflammatory drugs, ever use of hormone replacement therapy, diabetes, physical activity, and alcohol consumption.
[b]*P* value for interaction of ever regular smoking and utilization of lower gastrointestinal endoscopy in preceding 10 years.

not increase with higher number of pack-years in the group with preceding lower gastrointestinal endoscopy. If no endoscopy had been performed before, risk of colorectal cancer increased with numbers of pack-years, but did not further increase above 20 pack-years. Restricted cubic spline analyses yielded similar results if duration of smoking in years was used instead of pack-years of smoking (figures not shown). In Supplementary Table S1,

Table 3. Association of regular smoking and type of colorectal cancer among cases and controls with no previous lower gastrointestinal endoscopy and among cases and controls with utilization of lower gastrointestinal endoscopy in the preceding 10 years

	No previous lower gastrointestinal endoscopy			Lower gastrointestinal endoscopy in the preceding 10 years		
	Smokers (%)	Nonsmokers (%)	OR (95% CI)[a]	Smokers (%)	Nonsmokers (%)	OR (95% CI)[a]
Current smokers						
Controls	219 (14)	824 (54)	1.00	114 (8)	772 (51)	1.00
Colon cancer (C18)	195 (15)	646 (48)	1.28 (1.00–1.62)	45 (12)	190 (52)	1.96 (1.29–2.97)
Rectum cancer (C19, C20)	200 (18)	447 (41)	1.61 (1.25–2.08)	16 (13)	55 (43)	1.50 (0.77–2.91)
Stage I+II cancer	216 (17)	552 (43)	1.66 (1.30–2.12)	35 (13)	135 (48)	1.87 (1.19–2.96)
Stage III+IV cancer	175 (16)	538 (48)	1.22 (0.95–1.57)	25 (12)	110 (52)	1.63 (0.96–2.76)
Former smokers						
Controls	490 (32)	824 (54)	1.00	618 (41)	772 (51)	1.00
Colon cancer (C18)	495 (37)	646 (48)	1.41 (1.17–1.69)	130 (36)	190 (52)	0.97 (0.74–1.28)
Rectum cancer (C19, C20)	437 (40)	447 (41)	1.60 (1.32–1.95)	57 (46)	55 (43)	1.28 (0.84–1.94)
Stage I+II cancer	528 (41)	552 (43)	1.67 (1.39–2.01)	110 (39)	135 (48)	1.05 (0.78–1.42)
Stage III+IV cancer	491 (36)	538 (48)	1.31 (1.08–1.58)	76 (36)	110 (52)	1.01 (0.72–1.42)

[a]ORs are adjusted for matching factors age and sex, and additionally, for school education, participation in health screening examinations, history of colorectal cancer in a first-degree relative, former BMI, ever regular use of nonsteroidal anti-inflammatory drugs, ever use of hormone replacement therapy, diabetes, physical activity, and alcohol consumption.

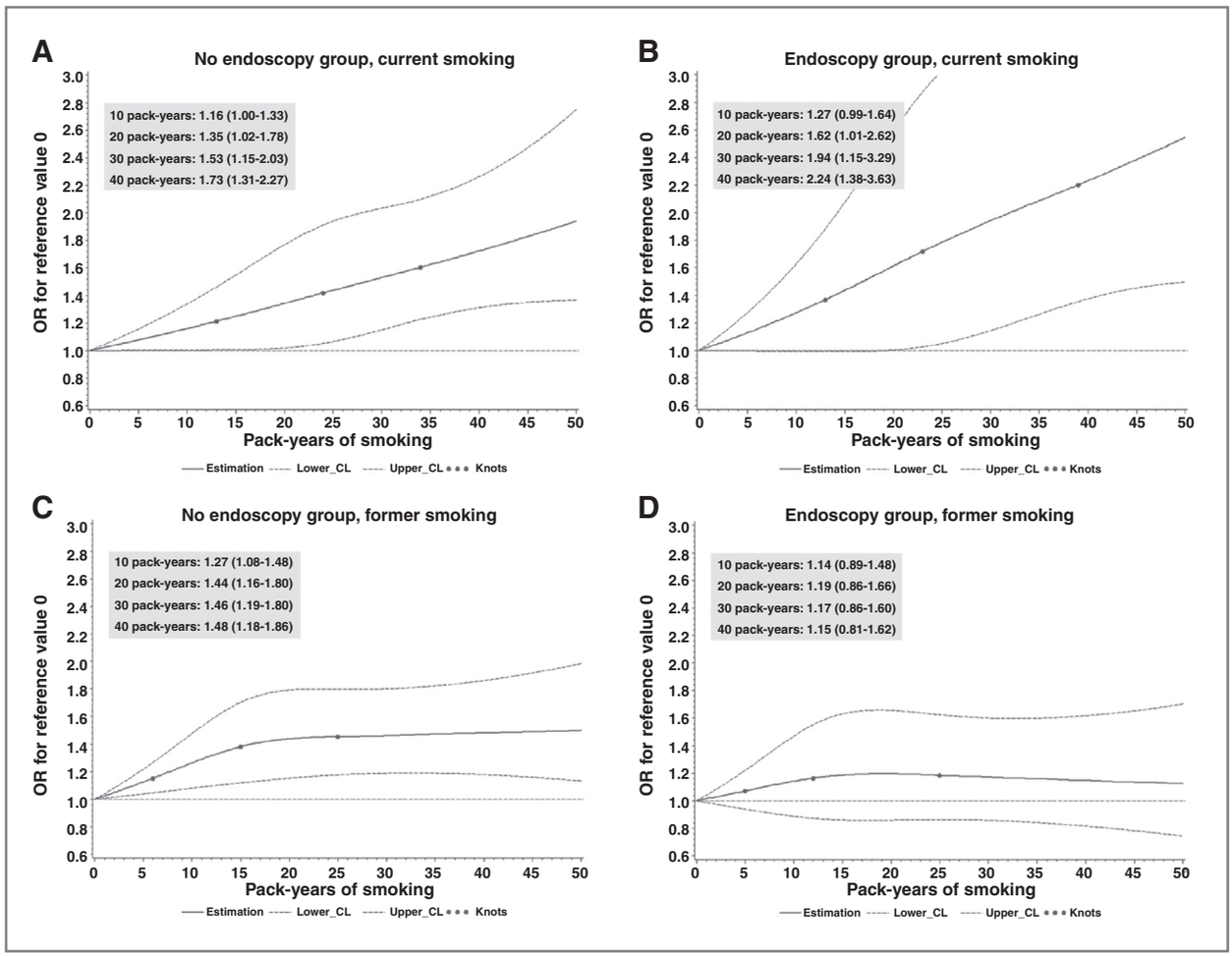

Figure 2. Dose–response analyses of the association of pack-years of smoking and colorectal cancer risk when compared with nonsmokers for A, current smoking and no previous endoscopy; B, current smoking and endoscopy in the preceding 10 years; C, former smoking and no previous endoscopy; and D, former smoking and endoscopy in the preceding 10 years. Solid line, OR of colorectal cancer; dashed lines, 95% CIs. The 25th, 50th, and 75th percentile of pack-years of smoking among the controls were used to define the knots (bullet points).

additional results are provided on the association of colorectal cancer risk with pack-years of smoking, duration of smoking, and average number of cigarettes smoked per day.

Discussion

In this study, a previous endoscopy of the large bowel modified the observed effect of smoking on colorectal cancer risk. Ever-regular smoking was associated with increased risk in the group with no previous lower gastrointestinal endoscopy, but no association was seen among those with a lower gastrointestinal endoscopy in the preceding 10 years. However, if smoking was continued or stopped less than 20 years in the past, risk of colorectal cancer was still increased despite previous endoscopy.

Lower gastrointestinal endoscopy has been used by an increasing proportion of older adults over the past two decades in Western societies (8–11), particularly after expert committees started to recommend screening by lower gastrointestinal endoscopy for the prevention and early detection of colorectal cancer (12–15). Utilization of endoscopy in Germany (and in this study) refers to colonoscopy in the vast majority of examinations. In Germany, a first screening colonoscopy is offered from the age of 55 years since the year 2002. In addition, diagnostic colonoscopies are conducted because of detection of fecal occult blood in stool or follow-up of symptoms, and surveillance colonoscopies after findings of adenomatous polyps. Compared with several other European countries, Germany's prevalence is among the highest (25), but the prevalence in the United States was found to be even higher (26). If adenomas are detected, different surveillance intervals are recommended for the next colonoscopy, which are similar to the U.S. recommendations, depending on whether a low-risk (5 years) or a high-risk adenoma situation (3 years or less) was present (23). In general, carriers of adenomas are at increased risk of

colorectal cancer compared with noncarriers, even after removal of adenomas.

In meta-analyses of observational studies, ever smoking was associated with increased risk of colorectal cancer incidence (e.g., pooled relative risk 1.18, 1.11–1.25; ref. 2). Although a very large number of studies have investigated the association of smoking and colorectal cancer, only few considered information on lower gastrointestinal endoscopy in their analyses (27–32). Potential modifying effects by previous utilization of lower gastrointestinal endoscopy (as illustrated in Fig. 1) were not assessed in these studies and, to our knowledge, not in any other study on smoking and colorectal cancer risk. As suggested by our study, the carcinogenic risk associated with smoking may be underestimated if previous utilization of large gastrointestinal endoscopy is not considered.

Our study is in line with previous studies reporting that among former smokers risk of colorectal cancer is increased for up to 30 years after smoking cessation (32, 33). In the present study, smoking cessation within the past <20 years was still associated with higher colorectal cancer risk even though a colorectal endoscopy had been conducted in the preceding 10 years. Reasons may include that precursors or molecular subtypes of colorectal cancer were not detected or were not yet detectable during endoscopy. Supporting this theory of an involvement of both biologic and technical factors, smoking was found to be more strongly associated with specific subtypes of colorectal cancer, such as high-level microsatellite instability (MSI-high) colorectal cancer, CpG island methylator phenotype (CIMP-high), and mutations in the *BRAF* gene (34), all of which are primarily prevalent in right-sided colorectal cancers (35). Colonoscopy with polypectomy was shown to be less effective in reducing the risk of right-sided colorectal cancer than with respect to left-sided colorectal cancer (7, 36, 37), and specific subtypes or precursors may have been overseen. Recent findings also point to an association of smoking with the occurrence of flat adenomas, which are more difficult to detect (38). Taken together, although an overall significantly lower risk was observed following endoscopy with potential polypectomy in the preceding 10 years, this study also suggests that lower gastrointestinal endoscopy may not or not fully compensate for colorectal cancer risk associated with smoking if continued until higher adult age. Compared with never smokers without a preceding lower gastrointestinal endoscopy, moderate risk reduction of colorectal cancer was observed even among current smokers with a preceding lower gastrointestinal endoscopy. However, risk reduction was much stronger among never smokers with a preceding lower gastrointestinal endoscopy.

Strengths of our study include its large size, which enabled assessment of smoking-associated colorectal cancer risk by utilization of lower gastrointestinal endoscopy and tests for interaction with smoking. Diagnosis of colorectal cancer was confirmed for all patients by medical records, including pathology reports. Detailed information on smoking over lifetime and on many relevant risk or protective factors of colorectal cancer was available to adjust for in multivariate analyses. About utilization of preceding colorectal endoscopies, information was based on endoscopy reports that were available for most self-reported endoscopies. In addition, the overall validity of self-reported colorectal endoscopies has been demonstrated in a subsample of the study population (20).

Potential weaknesses of this observational study include selection bias among controls (response rate: 51%) and possibly incomplete or inadequate adjustment for confounding despite the extensive characterization of the participants available from personal interviews. Also, the study was primarily designed to assess the potential of endoscopic screening that, on the other hand, facilitated a clear division of groups with and without preceding lower gastrointestinal endoscopy. Lifetime history of smoking and other factors affecting colorectal cancer risk in our multivariate analyses were retrospectively assessed. In particular, it is difficult to retrospectively assess the number of cigarettes smoked at various ages over lifetime. Thus, the number of pack-years and the age at cessation of smoking will only be an approximation in this study. Despite its overall large size, the study only allowed for limited subgroup analyses, and the study was not sufficiently powered to detect moderate effect modifications and weaker associations of smoking and colorectal cancer risk after stratifying by endoscopy status.

Despite these limitations, this study found effect modification of the association of smoking and colorectal cancer risk by lower gastrointestinal endoscopy. Consideration of history of endoscopy is essential for estimating carcinogenic effects of smoking with respect to colorectal cancer in populations and during times with widespread utilization of lower gastrointestinal endoscopy. The persisting increased risk among current, but not among former smokers after lower gastrointestinal endoscopy furthermore suggests that the strong protective effect of lower gastrointestinal endoscopy may be substantially compromised by continued smoking. Accordingly, activities aiming at smoking cessation and smoking prevention may increase the efficacy of lower gastrointestinal endoscopy. Lower gastrointestinal endoscopy, be it in the context of diagnosis or screening, should go along with efforts to support smoking cessation in people who still smoke.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The sponsors did not have any role in this study.

Authors' Contributions

Conception and design: M. Hoffmeister, J. Chang-Claude, H. Brenner
Development of methodology: M. Hoffmeister
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Hoffmeister, J. Chang-Claude, H. Brenner
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Hoffmeister, L. Jansen, C. Stock, H. Brenner

Writing, review, and/or revision of the manuscript: M. Hoffmeister, L. Jansen, C. Stock, J. Chang-Claude, H. Brenner
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Hoffmeister
Study supervision: M. Hoffmeister, H. Brenner

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