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Article

Smoking Behavior and Prognosis After Colorectal Cancer Diagnosis: A Pooled Analysis of 11 Studies

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Abstract

Background: Smoking has been associated with colorectal cancer (CRC) incidence and mortality in previous studies, but current evidence on smoking in association with survival after CRC diagnosis is limited. **Methods:** We pooled data from 12 345 patients with stage I-IV CRC from 11 epidemiologic studies in the International Survival Analysis in Colorectal Cancer Consortium. Cox proportional hazards regression models were used to evaluate the associations of prediagnostic smoking behavior with overall, CRC-specific, and non-CRC-specific survival. **Results:** Among 12 345 patients with CRC, 4379 (35.5%) died (2515 from CRC) over a median follow-up time of 7.5 years. Smoking was strongly associated with worse survival in stage I-III patients, whereas no association was observed among stage IV patients. Among stage I-III patients, clear dose-response relationships with all survival outcomes were seen for current smokers. For example, current smokers with 40 or more pack-years had statistically significantly worse overall, CRC-specific, and non-CRC-specific survival compared with never smokers (hazard ratio [HR] =1.94, 95% confidence interval [CI] =1.68 to 2.25; HR = 1.41, 95% CI = 1.12 to 1.78; and HR = 2.67, 95% CI = 2.19 to 3.26, respectively). Similar associations with all survival outcomes were observed for former smokers who had quit for less than 10 years, but only a weak association with non-CRC-specific survival was seen among former smokers who had quit for more than 10 years. **Conclusions:** This large consortium of CRC patient studies provides compelling evidence that smoking is strongly associated with worse survival of stage I-III CRC patients in a clear dose-response manner. The detrimental effect of smoking was primarily related to noncolorectal cancer events, but current heavy smoking also showed an association with CRC-specific survival.

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Smoking is an established risk factor for colorectal adenomas (1,2) and colorectal cancer (CRC) (3-8) and recently has also been associated with increased CRC-specific mortality (3,9,10). In a meta-analysis that summarized evidence on the association between prediagnostic smoking and prognosis after CRC diagnosis, current smoking compared with never smoking was statistically significantly associated with 26% higher total mortality (11).

Four studies provided further evidence (12-15) that prediagnostic (12-15) and postdiagnostic (13) current smoking was associated with decreased overall and CRC-specific survival compared with never smoking. In a more recent large meta-analysis including primary data of incident CRC patients from 14 population-based prospective cohort studies, former and current smoking were associated with worse CRC prognosis compared with never smoking (16). However, in that study, smoking status was ascertained at the time of recruitment into the cohort, and smoking status and intensity at the time of CRC diagnosis was unknown.

Very few studies to date have investigated outcomes other than overall or CRC-specific survival, and exposure assessment was mostly restricted to smoking status and pack-years. Moreover, only a few studies have investigated associations between smoking cessation and CRC prognosis (13,14,16-18).

We aimed to investigate the impact of prediagnostic smoking behavior on a number of survival outcomes including overall, CRC-specific, and non-CRC-specific survival in a large international consortium of cohorts of CRC patients, with a particular focus on smoking history and intensity.

Methods

Study Population

This analysis included 11 studies from the International Survival Analysis in Colorectal Cancer Consortium (ISACC). We included data from 6 prospective US cohort studies [Cancer Prevention Study II Nutrition cohort (CPS-II) (19); Nurses' Health Study I (NHS I) (20-22); Physicians' Health Study (PHS) (23); Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (24,25); VITamins And Lifestyle (VITAL) study (26), and Women's Health Initiative (WHI) (27)], 1 prospective cohort study from Sweden (Northern Sweden Health and Disease Study [NSHDS]), 3 population-based case-control studies from Germany and the United States with follow-up of patients [Darmkrebs: Chancen der Verhuetung durch Screening (DACHS) (28,29); Diet, Activity and Lifestyle Survey (DALS) (30), and the Seattle Site of the Colon Cancer Family Registry (CCFR)], and data from the Early Detection Research Network (EDRN). These studies are also included in the Genetics and Epidemiology of Colorectal Cancer Consortium, which was primarily responsible for data harmonization (31,32). All CRC cases were confirmed by state federal or provincial cancer registry linkage, medical records, pathology reports, or death certificates and included follow-up for survival. Informed consent was obtained from all participants, and the studies were approved by the respective institutional review boards.

Data Collection and Follow-up

Information on demographic and lifestyle factors was collected by self-report using in-person interviews and/or structured questionnaires (33). As previously described, a multistep data harmonization procedure was carried out to combine data across the studies (33).

Smoking status was categorized as never, former, or current smoking and included the smoking status at time of diagnosis for patient cohorts based on case-control studies and the smoking status at baseline for population cohorts. Current smoking was defined as either regular or daily smoking, according to the respective study's definition. Never smoking was defined as never having smoked daily or regularly. Pack-years of smoking was calculated by multiplying the average number of packs of cigarettes smoked per day by smoking duration in years. Time since smoking cessation was calculated for former smokers, by subtracting age at smoking cessation from age at cancer diagnosis, and then categorized into 4 groups (>20, 10-20, 5-10, and <5 years).

Further sociodemographic and lifestyle information was collected via self-report at baseline. Other variables of interest included age at diagnosis, sex, body mass index (BMI, kg/m^2), alcohol intake, history of diabetes, and use of aspirin and other nonsteroidal anti-inflammatory drugs. Information on cancer site and cancer stage as determined by the American Joint Committee on Cancer or Surveillance, Epidemiology, and End Results (stage I-III or locoregional, stage IV or distant) was available for all included studies.

The details of assessing survival in the included studies have been described previously (19,22,26,28,30,34-38). Briefly, half of the studies used active follow-up to ascertain vital status (NHS, PHS, PLCO, and WHI); date and cause of death were confirmed via review of death certificates and/or medical records. For the other studies (VITAL, CPS-II, DACHS, DALS, CCFR, EDRN, NSHDS), vital status was determined through linkage to the National Death Index, national and/or state cancer registries, state death records, or population registries with cause of death verified by death certificates or medical records. In all studies, patients alive at the most recent follow-up or data linkage were censored on that date in the survival analysis.

Statistical Analysis

All statistical analyses were performed using the individual-level harmonized data pooled across studies. Patient characteristics were described overall and by smoking status, and the associations were evaluated with χ^2 tests. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for the association between prediagnostic smoking behavior and survival (overall, CRC-specific, and non-CRC-specific) after CRC diagnosis. Survival time was calculated as the time from diagnosis of CRC to death or end of follow-up. In analyses of CRC-specific survival, patients who died from causes other than CRC were censored at the time of death. Median follow-up time was calculated based on the Kaplan-Meier estimate of potential follow-up (39).

Fully adjusted models including age at diagnosis, sex, stage, study, location, and BMI were calculated. Other potential confounding variables that were considered but not included in the final models—because not all studies had this information available and because hazard ratios did not materially change—were alcohol intake, nonsteroidal anti-inflammatory drugs, and history of diabetes. Results from these models are included in Supplementary Table 1 (available online). Missing data for BMI (approximately 2%) were accounted for by mean and mode imputation, and a missing indicator variable was used for missing stage at diagnosis. Sensitivity analyses using multiple imputation to account for missing BMI were performed (Supplementary Tables 2 and 3, available online), with no important differences in the results observed compared with the main analyses. We

decided a priori to restrict the analyses on smoking history and intensity (cigarettes per day, years of smoking, years since cessation, and pack-years smoking) to nonmetastatic (stage I-III) patients, because metastatic patients may have already worse survival that may not be altered by previous smoking behavior. Sensitivity analyses stratifying by type of study were performed for smoking status in the entire sample and for stage I-III and stage IV patients.

All statistical tests were 2-sided, and *P* values of less than .05 were considered statistically significant. All analyses were performed using R version 4.0.2 (40).

Results

Patient Characteristics

From 16 studies in the ISACC, data were harmonized for 19 024 participants (9536 females, 9488 males). Five studies with extensive missing information on tumor stage (n = 6679) were excluded, leaving 11 studies and 12 345 participants for the current analysis: 9967 CRC patients with stage I-III disease and 1370 CRC patients with stage IV disease. All patients had complete information on smoking status and follow-up time. Details on the individual studies are provided in Supplementary Table 4 (available online). Among stage I-III patients, 3228 (32.4%) died during follow-up, of whom 1497 (46.4%) died from CRC. Among stage IV patients, 1151 (84.0%) died, with 1018 (88.4%) from CRC. Median follow-up time was 7.5 (interquartile range = 4.8-13.9) years.

Patient characteristics among 12 345 incident CRC cases from the 11 included studies are presented in Supplementary Table 5 (available online). Overall patient characteristics by smoking status are presented in Table 1. Patients were on average aged 66.7 years at diagnosis of CRC. There were 43.3% never, 44.1% former, and 12.6% current smokers at baseline. Of 1560 current smokers, 1430 (91.7%) had information on cigarettes per day with 23.5% smoking more than 20 cigarettes per day; 1522 (97.5%) had information on years smoked, with 75.0% having smoked for 30 or more years; and 1424 (91.3%) had information on pack-years, with 71.7% having smoked 20 or more pack-years. Of 5441 former smokers, 5049 (92.8%) had information on cigarettes per day, and 25.9% reported smoking more than 20 cigarettes per day; 5138 (94.4%) had information on years smoked, with 30.9% having smoked for 30 or more years; and 5318 (97.7%) had information available on time since smoking cessation, with 23.8% of patients having stopped smoking no later than 10 years before.

Prognosis According to Smoking Behavior

Among 12 345 patients with CRC, 4379 (35.5%) died, of which 2515 (57.4%) died from CRC. Median survival times were 17.3, 14.4, and 13 years for never, former, and current smokers, respectively. In multivariable analyses among stage I-III patients, when compared with never smokers, current (HR = 1.53, 95% CI = 1.37 to 1.71) and former (HR = 1.12, 95% CI = 1.04 to 1.21) smoking were associated with worse overall survival (Table 2). In analyses of CRC-specific survival, associations between current smoking and survival were more pronounced than for former smoking. Current, but not former, smoking was associated with worse CRC-specific survival (HR = 1.18, 95% CI = 1.00 to 1.40; HR = 1.03, 95% CI = 0.92 to 1.15, respectively). Current and former smoking were also associated with poorer non-CRC-specific survival in comparison with never smoking (HR = 2.05, 95% CI = 1.75 to 2.41; HR = 1.22, 95% CI = 1.09 to 1.37, respectively). Similar results were observed in sensitivity analyses stratifying by type of study (Supplementary Table 6, available online).

Associations of smoking with non-CRC-specific survival were similar among patients with stage I-III and stage IV cancers. However, in contrast to the findings among stage I-III patients, no associations were observed between smoking and overall or CRC-specific survival among stage IV cancers (Table 2). As a result, associations with CRC-specific survival among patients at all stages were similar but lower in magnitude compared with associations among stage I-III cancers. All further analyses were restricted to stage I-III CRC cancer patients.

Cigarettes per Day

Associations with poorer survival were much stronger for current smokers and for former smokers who smoked 20 or more cigarettes per day than for those who smoked less, with hazard ratios (for current smokers of 20 or more cigarettes per day compared with never smokers reaching levels of 1.81 (95% CI = 1.57 to 2.08), 1.29 (95% CI = 1.05 to 1.60), and 2.57 (95% CI = 2.11 to 3.13) for overall, CRC-specific, and non-CRC-specific survival, respectively (Table 3).

Years of Smoking

For former smokers, associations with poorer survival strongly varied by years of smoking (Table 3). Stronger associations with poorer survival were essentially restricted to patients who had smoked 40 or more years, with hazard ratios of 1.68 (95% CI = 1.46 to 1.93), 1.24 (95% CI = 0.99 to 1.56), and 2.08 (95% CI = 1.73 to 2.51) for overall, CRC-specific, and non-CRC-specific survival, respectively. By contrast, there was only little variation of hazard ratios by years of smoking among current smokers.

Years Since Cessation

Former smokers who had quit for less than 10 years had similarly worse survival as current smokers, whereas associations with poor survival were much weaker or absent in former smokers who had quit for more than 10 years (Table 3).

Pack-Years of Smoking

Among former smokers, associations with poorer survival were furthermore restricted to those who had smoked at least 20 pack-years, with strong associations being restricted to overall and non-CRC-specific survival for former smokers who had smoked 40 or more pack-years (Table 3). With the exception of smokers who had smoked less than 20 pack-years, current smokers had worse survival than former smokers for each category of pack-years. Compared with never smokers, the strongest increase in mortality was seen for current smokers with 40 or more pack-years exposure (HR = 1.94, 95% CI = 1.68 to 2.25; HR = 1.41, 95% CI = 1.12 to 1.78; HR = 2.67, 95% CI = 2.19 to 3.26, for overall, CRC-specific, and non-CRC-specific survival, respectively).

Discussion

In this large international CRC consortium, based on data from more than 12 000 men and women with CRC, we observed statistically significant associations between former and current

Table 1. Patient characteristics according to smoking status

Characteristic	Total	Smoking status			P[a]
		Never smokers	Former smokers	Current smokers	
Total, No. (%)	12345	5344 (43.3)	5441 (44.1)	1560 (12.6)	
Mean age (SD) at diagnosis, y	66.7 (10.9)	66.9 (11.5)	67.9 (9.8)	61.4 (11.1)	<.001
Age at diagnosis, No. (%), y					
<30	23 (0.2)	12 (0.2)	2 (0.04)	9 (0.6)	<.001
30-<60	3079 (24.9)	1315 (24.6)	1118 (20.5)	646 (41.4)	
60-<70	4260 (34.5)	1721 (32.2)	1971 (36.2)	568 (36.4)	
70-<80	3976 (32.2)	1778 (33.3)	1897 (34.9)	301 (19.3)	
≥80	1007 (8.2)	518 (9.7)	453 (8.3)	36 (2.3)	
Sex, No. (%)					
Men	5740 (46.5)	1939 (36.3)	3004 (55.2)	797 (51.1)	<.001
Women	6605 (53.5)	3405 (63.7)	2437 (44.8)	763 (48.9)	
Tumor location, No. (%)					
Proximal	5150 (42.9)	2323 (44.6)	2250 (42.4)	577 (38.8)	<.001
Distal	3607 (30.1)	1529 (29.4)	1649 (31.1)	429 (28.9)	
Rectum	3234 (27.0)	1352 (26.0)	1402 (26.4)	480 (32.3)	
Missing	354	140	140	74	
Tumor stage, No. (%)					
I-III or locoregional	9967 (87.9)	4330 (87.7)	4434 (88.9)	1203 (85.1)	<.001
IV or distal	1370 (12.1)	605 (12.3)	555 (11.1)	210 (14.9)	
Missing	1008	409	452	147	
Body mass index, No. (%)					
<18.5 kg/m^2	99 (0.8)	46 (0.9)	25 (0.5)	28 (1.8)	<.001
18.5-24.9 kg/m^2	4070 (33.6)	1826 (34.9)	1608 (30.1)	636 (41.5)	
25.0-29.9 kg/m^2	5040 (41.7)	2106 (40.3)	2342 (43.9)	592 (38.6)	
≥30 kg/m^2	2887 (23.9)	1247 (23.9)	1364 (25.5)	276 (18.0)	
Missing	249	119	102	28	
Alcohol, No. (%)					
Non-drinker	3711 (41.3)	1999 (50.9)	1369 (33.7)	343 (34.4)	<.001
1-28 g/d	4161 (46.3)	1681 (42.8)	2038 (50.2)	442 (44.4)	
>28 g/d	1112 (12.4)	245 (6.2)	656 (16.1)	211 (21.2)	
Missing	3361	1419	1378	564	
Diabetes, No. (%)					
Yes	1212 (11.4)	508 (11.1)	601 (12.7)	103 (7.8)	<.001
No	9435 (88.6)	4083 (88.9)	4135 (87.3)	1217 (92.2)	
Missing	1698	753	705	240	
Use of NSAIDs					
Yes	1351 (11.6)	549 (10.9)	645 (12.6)	157 (10.8)	.02
No	10263 (88.4)	4496 (89.1)	4475 (87.4)	1292 (89.2)	
Missing	731	299	321	111	
Cigarettes per day, No. (%)[b]					
<10	2251 (34.7)	—	1835 (36.3)	416 (29.1)	<.001
10-20	2585 (39.9)	—	1907 (37.8)	678 (47.4)	
>20	1643 (25.4)	—	1307 (25.9)	336 (23.5)	
Missing	522	—	392	130	
Years smoked, No. (%)[b]					
<20	2434 (36.5)	—	2266 (44.1)	168 (11.0)	<.001
20-<30	1498 (22.5)	—	1285 (25.0)	213 (14.0)	
30-<40	1431 (21.5)	—	1011 (19.7)	420 (27.6)	
≥40	1297 (19.5)	—	576 (11.2)	721 (47.4)	
Missing	341	—	303	38	
Pack-years, No. (%)[b]					
<10	1881 (29.3)	—	1696 (33.9)	185 (13.0)	<.001
10-<20	1271 (19.8)	—	1053 (21.1)	218 (15.3)	
20-<40	1806 (28.1)	—	1310 (26.2)	496 (34.8)	
≥40	1466 (22.8)	—	941 (18.8)	525 (36.9)	
Missing	577	—	441	136	
Years since cessation, No. (%)[c]					
>20	2610 (49.1)	—	2610 (49.1)	—	—

(continued)

Table 1. (continued)

Characteristic	Total	Smoking status			P[a]
		Never smokers	Former smokers	Current smokers	
>10-20	1444 (27.2)	—	1444 (27.2)	—	
>5-≤10	660 (12.4)	—	660 (12.4)	—	
≤5	604 (11.4)	—	604 (11.4)	—	
Missing	123	—	123	—	

[a]P values were calculated using 2-sided χ^2 tests. NSAIDs = nonsteroidal anti-inflammatory drugs.
[b]Total and percentages based on former smokers and current smokers only (n = 7001).
[c]Based on former smokers only (n = 5441). Missing values are excluded from all percentage calculations.

smoking and poorer overall survival. Compared with never smoking, current smoking was also associated with worse CRC-specific survival. Clear dose-response relationships were generally seen when we further investigated the associations of smoking behavior by cigarettes per day, years of smoking, and pack-years of smoking with all survival outcomes. Former smokers who quit less than 10 years ago had poorer overall and non-CRC-specific survival compared with never smokers, and former smokers who quit more than 10 years ago showed no statistically significant difference compared with never smokers. These findings reflect the benefit of quitting smoking earlier in life, also in regard to survival outcomes after a CRC diagnosis.

Smoking is a well-established risk factor for colorectal adenomas and CRC (1,2,10,41) and has been associated with overall and CRC-specific mortality (3,9,10,42,43). In 2 previous meta-analyses on the association between prediagnostic smoking and CRC prognosis, current smoking has been statistically significantly associated with poorer overall survival compared with never smoking (HR = 1.29, 95% CI = 1.04 to 1.60) (11,16). The results of our current investigation, of which subsamples of 3 studies (13,15,18) were included in 1 of the meta-analyses, are in accordance with previous results on overall survival (HR = 1.35, 95% CI = 1.23 to 1.49) (11).

Studies on the association of former smoking with overall survival have reported mixed results (18,44-46). A meta-analysis of 4 studies found a non-statistically significant association between former smoking and overall survival (11), whereas another larger pooled meta-analysis found statistically significant 10%-12% worse overall survival for former smokers when compared with never smoking (16). In this current analysis, former smokers among stage I-III CRC patients had a 12% higher overall mortality compared with never smokers. Furthermore, when looking at the association between former smokers stratified by number of cigarettes per day and overall survival, a statistically significant association was only observed between former smokers who had smoked at least 20 cigarettes per day, and a weaker non-statistically significant association was seen for former smokers who had smoked less than 20 cigarettes per day.

A number of studies have also previously investigated smoking status in association with CRC-specific survival (13,15,16,18,44,47-49) of which subsamples of 3 of these studies are included in the present analysis (13,15,18). Results from these studies were heterogeneous, but generally, associations were strongest between current or ever smoking and poorer CRC-specific survival. In the most recent large pooled meta-analysis (16), current smoking was non-statistically significantly associated with worse CRC-specific survival, and former smoking was not associated with CRC-specific survival. Consistent with these results, we found current smoking to be associated with CRC-specific survival (HR = 1.18, 95% CI = 1.00 to 1.40) among stage I-III CRC patients and no association for former smoking. In further analyses, according to the number of cigarettes per day, we only observed a statistically significant association between current smokers who smoked 20 or more cigarettes per day and CRC-specific survival. Former smoking irrespective of the number of cigarettes per day was not associated with CRC-specific survival. Stronger associations observed for current and former smoking with non-CRC-specific survival suggest that smoking status has a weak interaction with CRC as a determinant of survival but influences overall survival through factors not related to the CRC disease.

Only a few studies to date have investigated smoking cessation in association with CRC prognosis, and the results have been mixed (13,14,16-18). Most previous studies compared individuals who had stopped smoking with never smokers; 2 of these previous studies found statistically significant associations between time since cessation and poorer overall survival compared with never smokers (13,18), whereas 2 studies did not observe any associations (14,17). Ordonez-Mena et al. (16) found that both short and long durations of smoking cessation (<10 years and ≥10 years) were associated with improved overall survival compared with current smoking. In this analysis, we found worse overall survival among patients who quit less than 10 years ago compared with never smokers. However, compared with never smokers, statistically significantly worse survival was not observed among patients who quit smoking more than 10 years ago, indicating a mortality benefit of smoking cessation. Regarding non-CRC-specific survival, we found strong associations among those who quit 10 or less years ago and patients who quit more than 10-20 years ago, in comparison with never smoking.

Results from previous studies on the association between years since smoking cessation and CRC-specific survival (13,16,18) have been inconsistent. One study found poorer CRC-specific survival among smokers who quit 25 or more years ago, compared with never smoking, but no associations among smokers who quit less than 25 years ago (18), and another found no associations with CRC-specific survival irrespective of the time since quitting smoking (13). In contrast, a more recent large pooled meta-analysis using data from the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States reported smoking cessation to be associated with improved survival when compared with current smokers (16).

The overall health benefit of smoking cessation is well documented (50). CRC survivors who do not die from cancer could still die because of causes other than CRC of which smoking may still be a risk factor. Whether smoking cessation after CRC

Table 2. Overall, CRC-specific and non-CRC-specific survival according to smoking status among 12 345 CRC patients[a]

	Stage I-III patients			Stage IV patients			Stage I-IV patients		
Survival outcome	Never smokers	Former smokers	Current smokers	Never smokers	Former smokers	Current smokers	Never smokers	Former sSmokers	Current smokers
Overall survival									
No. at risk (events)	4739 (1224)	4886 (1545)	1350 (459)	605 (510)	555 (470)	210 (171)	5344 (1734)	5441 (2015)	1560 (630)
HR (95% CI)	1.00 (Referent)	1.12 (1.04 to 1.21)	1.53 (1.37 to 1.71)	1.00 (Referent)	0.96 (0.84 to 1.09)	0.98 (0.82 to 1.18)	1.00 (Referent)	1.07 (1.00 to 1.14)	1.35 (1.23 to 1.49)
CRC-specific[b,c]									
No. at risk (events)	4644 (621)	4789 (681)	1294 (195)	586 (458)	541 (416)	200 (144)	5230 (1079)	5330 (1097)	1494 (339)
HR (95% CI)	1.00 (Referent)	1.03 (0.92 to 1.15)	1.18 (1.00 to 1.40)	1.00 (Referent)	0.93 (0.81 to 1.06)	0.95 (0.78 to 1.15)	1.00 (Referent)	0.98 (0.90 to 1.07)	1.07 (0.95 to 1.21)
Non-CRC-specific[b,c,d]									
No. at risk (events)	4644 (532)	4789 (781)	1294 (226)	565 (25)	524 (38)	198 (17)	5230 (557)	5330 (819)	1494 (243)
HR (95% CI)	1.00 (Referent)	1.22 (1.09 to 1.37)	2.05 (1.75 to 2.41)	1.00 (Referent)	1.33 (0.79 to 2.23)	2.08 (1.10 to 3.95)	1.00 (Referent)	1.23 (1.10 to 1.37)	2.05 (1.76 to 2.39)

[a]Models adjusted for age, sex, study, stage (except stage IV analysis), cancer site, body mass index. CI = confidence interval; CRC = colorectal cancer; HR = adjusted hazard ratio.
[b]The Northern Sweden Health and Disease Study not included in CRC-specific and non-CRC-specific analyses because of no data (n = 291).
[c]Patients with missing information on CRC-specific and non-CRC-specific survival (n = 94).
[d]For stage IV specific analysis, Physicians' Health Study and Early Detection Research Network studies additionally excluded because of no occurring non-CRC-specific events (n = 40).

diagnosis lowers CRC-specific mortality warrants further investigation in future large studies. Unfortunately, we were not able to examine associations with postdiagnostic smoking behavior within the ISACC consortium, and currently, limited evidence is available that examines smoking behavior after a CRC diagnosis and associations with survival (13,18). In 1 study, both overall and CRC-specific survival were higher for smokers who quit smoking after diagnosis than for those who continued smoking (13), but in another study, smokers who quit smoking after diagnosis had only lower CRC-specific mortality but not overall mortality compared with those who continued smoking (18).

There are a number of strengths of the present study. First, pooling studies from a large consortium with harmonized exposure and outcome data resulted in a large sample to investigate associations of smoking behavior and survival after a diagnosis of CRC. Second, we were able to adjust for several relevant confounding variables. Other strengths of the present study include the comprehensive follow-up procedures carried out by each individual study, which ensured thorough vital status assessment, completeness of follow-up, and a long duration of follow-up in each study. However, as this study includes harmonized data from 11 epidemiological studies, we cannot rule out differences in the completeness of follow-up between studies. We also acknowledge some further limitations of our study. Among the studies included in the consortium, there were differences in the timing of smoking assessment and the ascertainment of smoking status; however, stratified analyses by type of study showed similar patterns of association between smoking status and the survival outcomes. Some studies had much more detailed information, whereas others were more limited. Additionally, we did not have harmonized information on postdiagnostic smoking status; therefore, it was not possible to assess potential changes in smoking behavior, which could have affected the overall results. Further limitations include the limited availability of harmonized treatment information and information on CRC recurrence. Finally, we cannot rule out the possibility of residual confounding due to unmeasured or inaccurately measured variables; although sensitivity analyses presented in the supplement showed no relevant changes in the measures of association for models including several confounding variables, the possibility remains that other factors such as comorbidities, diet, or physical activity might influence the outcomes.

In conclusion, in this large study examining the association between prediagnostic smoking and CRC survival, former and current smoking were associated with worse overall survival, which was dependent on the number of pack-years smoked. Current, but not former, smokers had poorer CRC-specific survival. Patients who quit smoking at least 10 years before diagnosis presented similar survival outcomes compared with never smokers, indicating a clear benefit of smoking cessation, but poorer overall and non-CRC-specific survival were observed for former smokers who quit less than 20 years ago. Future research is needed to investigate how smoking cessation after CRC diagnosis may influence CRC survival.

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Table 3. Overall, CRC-specific and non-CRC-specific survival according to smoking behavior among 10 975 stage I-III CRC patients[a]

	Overall survival		CRC-specific survival[b,c]		Non-CRC-specific survival[b,c]	
Smoking behavior	No. at risk (events)	HR (95%CI)	No. at risk (events)	HR (95% CI)	No. at risk (events)	HR (95% CI)
Cigarettes per day[d]						
Never smokers	4624 (1202)	1.00 (Referent)	4513 (618)	1.00 (Referent)	4513 (530)	1.00 (Referent)
Former smokers						
<20	2363 (652)	1.05 (0.95 to 1.16)	2034 (329)	1.02 (0.89 to 1.17)	2358 (318)	1.07 (0.93 to 1.24)
≥20	2174 (764)	1.26 (1.14 to 1.38)	2157 (321)	1.06 (0.92 to 1.23)	2157 (426)	1.45 (1.27 to 1.66)
Current smokers						
<20	615 (179)	1.35 (1.15 to 1.58)	595 (85)	1.12 (0.89 to 1.41)	595 (84)	1.59 (1.26 to 2.01)
≥20	624 (250)	1.81 (1.57 to 2.08)	610 (106)	1.29 (1.05 to 1.60)	610 (132)	2.57 (2.11 to 3.13)
Years of smoking[d,e]						
Never smokers	4624 (1202)	1.00 (Referent)	4513 (618)	1.00 (Referent)	4513 (530)	1.00 (Referent)
Former smokers						
<20	2024 (524)	0.99 (0.89 to 1.10)	1983 (266)	1.00 (0.66 to 1.77)	1983 (233)	0.97 (0.83 to 1.13)
20-40	2068 (673)	1.14 (1.03 to 1.25)	2017 (293)	1.03 (0.90 to 1.19)	2017 (352)	1.26 (1.10 to 1.45)
≥40	523 (250)	1.68 (1.46 to 1.93)	521 (91)	1.24 (0.99 to 1.56)	521 (157)	2.08 (1.73 to 2.51)
Current smokers						
<20	148 (33)	1.53 (1.08 to 2.17)	144 (17)	1.08 (0.66 to 1.77)	144 (14)	2.26 (1.32 to 3.88)
20-40	539 (158)	1.43 (1.20 to 1.69)	500 (79)	1.19 (0.94 to 1.52)	500 (58)	1.73 (1.31 to 2.30)
≥40	628 (256)	1.60 (1.39 to 1.83)	611 (95)	1.21 (0.97 to 1.51)	611 (151)	2.16 (1.80 to 2.59)
Years since smoking cessation[f]						
Never smokers	4739 (1224)	1.00 (Referent)	4611 (621)	1.00 (Referent)	4611 (532)	1.00 (Referent)
Former smokers						
≤10	1128 (408)	1.46 (1.30 to 1.64)	1091 (169)	1.16 (0.98 to 1.38)	1091 (218)	1.86 (1.59 to 2.19)
10-20	1312 (403)	1.11 (0.99 to 1.25)	1267 (185)	1.02 (0.87 to 1.21)	1267 (194)	1.24 (1.05 to 1.47)
≥20	2332 (694)	0.98 (0.89 to 1.07)	2289 (306)	0.94 (0.82 to 1.08)	2289 (355)	0.99 (0.87 to 1.14)
Pack-years of smoking[d,g]						
Never smokers	4624 (1202)	1.00 (Referent)	4513 (618)	1.00 (Referent)	4513 (530)	1.00 (Referent)
Former smokers						
<20	2450 (650)	1.02 (0.92 to 1.12)	2443 (332)	1.01 (0.88 to 1.15)	2443 (311)	1.03 (0.90 to 1.19)
20-40	1184 (395)	1.18 (1.05 to 1.32)	1175 (9)	1.03 (0.86 to 1.22)	1175 (216)	1.31 (1.11 to 1.54)
≥40	856 (355)	1.49 (1.32 to 1.69)	850 (140)	1.17 (0.97 to 1.41)	850 (209)	1.83 (1.54 to 2.16)
Current smokers						
<20	342 (80)	1.14 (0.91 to 1.44)	328 (36)	1.01 (0.88 to 1.15)	328 (39)	1.62 (1.17 to 2.25)
20-40	434 (133)	1.47 (1.22 to 1.76)	421 (70)	1.26 (0.98 to 1.62)	421 (52)	1.54 (1.15 to 2.05)
≥40	457 (214)	1.94 (1.68 to 2.25)	451 (84)	1.41 (1.12 to 1.78)	451 (124)	2.67 (2.19 to 3.26)

[a]All models adjusted for age, sex, study, stage, cancer site, and body mass index. CI = confidence interval; CRC = colorectal cancer; HR = adjusted hazard ratio.
[b]The Northern Sweden Health and Disease Study not included in CRC-specific and non-CRC-specific analyses because of no data (n = 248).
[c]Patients with missing information on CRC-specific and non-CRC-specific survival excluded (n = 44; for years since smoking cessation n = 81).
[d]The Early Detection Research Network study participants excluded because of no available information (n = 218).
[e]Patients with missing information on years of smoking (n = 195).
[f]Patients with missing information on smoking cessation (n = 114).
[g]Patients with missing information on pack-years (n = 303).

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Data Availability

Data is available upon reasonable request to the authors and depending on the individual study.

References

1. Botteri E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB. Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology*. 2008; 134(2):388–395.
2. Hoffmeister M, Schmitz S, Karmrodt E, et al. Male sex and smoking have a larger impact on the prevalence of colorectal neoplasia than family history of colorectal cancer. *Clin Gastroenterol Hepatol*. 2010;8(10):870–876.
3. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008;300(23): 2765–2778.
4. Gong J, Hutter C, Baron JA, et al. A pooled analysis of smoking and colorectal cancer: timing of exposure and interactions with environmental factors. *Cancer Epidemiol Biomarkers Prev*. 2012;21(11):1974–1985.
5. Hurley S, Goldberg D, Nelson DO, et al. Risk of colorectal cancer associated with active smoking among female teachers. *Cancer Causes Control*. 2013; 24(7):1291–1304.
6. Parajuli R, Bjerkaas E, Tverdal A, et al. The increased risk of colon cancer due to cigarette smoking may be greater in women than men. *Cancer Epidemiol Biomarkers Prev*. 2013;22(5):862–871.
7. Rasool S, Kadla SA, Rasool V, Ganai BA. A comparative overview of general risk factors associated with the incidence of colorectal cancer. *Tumour Biol*. 2013;34(5):2469–2476.
8. Leufkens AM, Van Duijnhoven FJ, Siersema PD, et al. Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. *Clin Gastroenterol Hepatol*. 2011;9(2):137–144.
9. Hou L, Jiang J, Liu B, et al. Association between smoking and deaths due to colorectal malignant carcinoma: a national population-based case-control study in China. *Br J Cancer*. 2014;110(5):1351–1358.
10. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer*. 2009;124(10):2406–2415.
11. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. *Ann Oncol*. 2014; 25(8):1517–1525.
12. Pelser C, Arem H, Pfeiffer RM, et al. Prediagnostic lifestyle factors and survival after colon and rectal cancer diagnosis in the National Institutes of Health (NIH)-AARP Diet and Health Study. *Cancer*. 2014;120(10):1540–1547.
13. Yang B, Jacobs EJ, Gapstur SM, Stevens V, Campbell PT. Active smoking and mortality among colorectal cancer survivors: the Cancer Prevention Study II nutrition cohort. *J Clin Oncol*. 2015;33(8):885–893.
14. Zhu Y, Yang SR, Wang PP, et al. Influence of pre-diagnostic cigarette smoking on colorectal cancer survival: overall and by tumour molecular phenotype. *Br J Cancer*. 2014;110(5):1359–1366.
15. Walter V, Jansen L, Hoffmeister M, Ulrich A, Chang-Claude J, Brenner H. Smoking and survival of colorectal cancer patients: population-based study from Germany. *Int J Cancer*. 2015;137(6):1433–1445.
16. Ordonez-Mena JM, Walter V, Schottker B, et al. Impact of prediagnostic smoking and smoking cessation on colorectal cancer prognosis: a meta-analysis of individual patient data from cohorts within the CHANCES consortium. *Ann Oncol*. 2018;29(2):472–483.
17. McCleary NJ, Niedzwiecki D, Hollis D, et al. Impact of smoking on patients with stage III colon cancer: results from Cancer and Leukemia Group B 89803. *Cancer*. 2010;116(4):957–966.
18. Phipps AI, Baron J, Newcomb PA. Prediagnostic smoking history, alcohol consumption, and colorectal cancer survival: the Seattle Colon Cancer Family Registry. *Cancer*. 2011;117(21):4948–4957.
19. Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. *Cancer*. 2002;94(9):2490–2501.
20. Belanger CF, Hennekens CH, Rosner B, Speizer FE. The Nurses' Health Study. *Am J Nurs*. 1978;78(6):1039–1040.
21. Belanger C, Speizer FE, Hennekens CH, Rosner B, Willett W, Bain C. The Nurses' Health Study: current findings. *Am J Nurs*. 1980;80(7):1333.
22. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health*. 1997;6(1):49–62.

23. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321(3):129–135.
24. Prorok PC, Andriole GL, Bresalier RS, et al.; for the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Control Clin Trials*. 2000;21(suppl 6):273s–309s.
25. Gohagan JK, Prorok PC, Hayes RB, Kramer BS; for the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials*. 2000; 21(suppl 6):251s–272s.
26. White E, Patterson RE, Kristal AR, et al. VITamins and Lifestyle cohort study: Study design and characteristics of supplement users. *Am J Epidemiol*. 2004; 159(1):83–93.
27. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Controlled Clinical Trials*. 1998; 19(1):61–109.
28. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med*. 2011;154(1):22–30.
29. Lilla C, Verla-Tebit E, Risch A, et al. Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev*. 2006;15(1):99–107.
30. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer–beyond physical activity. *Cancer Res*. 1997;57(1):75–80.
31. Peters U, Hutter CM, Hsu L, et al. Meta-analysis of new genome-wide association studies of colorectal cancer risk. *Hum Genet*. 2012;131(2):217–234.
32. Peters U, Jiao S, Schumacher FR, et al. Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. *Gastroenterology*. 2013;144(4):799–807.e724.
33. Hutter CM, Chang-Claude J, Slattery ML, et al. Characterization of gene-environment interactions for colorectal cancer susceptibility loci. *Cancer Res*. 2012;72(8):2036–2044.
34. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*. 1991;338(8765): 464–468.
35. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA*. 2009;302(6):649–658.
36. Curb JD, McTiernan A, Heckbert SR, et al.; for the WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Annals of Epidemiology*. 2003;13(suppl 9): S122–128.
37. Miller AB, Yurgalevitch S, Weissfeld JL; for the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Death review process in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21(suppl 6):400s–406s.
38. Hoffmeister M, Jansen L, Rudolph A, et al. Statin use and survival after colorectal cancer: the importance of comprehensive confounder adjustment. *J Natl Cancer Inst*. 2015;107(6):djv045.
39. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343–346.
40. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018.
41. Hoffmeister M, Jansen L, Stock C, Chang-Claude J, Brenner H. Smoking, lower gastrointestinal endoscopy, and risk for colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2014;23(3):525–533.
42. Baer HJ, Glynn RJ, Hu FB, et al. Risk factors for mortality in the Nurses' Health Study: s competing risks analysis. *Am J Epidemiol*. 2011;173(3): 319–329.
43. Lantz PM, Golberstein E, House JS, Morenoff J. Socioeconomic and behavioral risk factors for mortality in a national 19-year prospective study of U.S. adults. *Soc Sci Med*. 2010;70(10):1558–1566.
44. Boyle T, Fritschi L, Platell C, Heyworth J. Lifestyle factors associated with survival after colorectal cancer diagnosis. *Br J Cancer*. 2013;109(3): 814–822.
45. Park SM, Lim MK, Shin SA, Yun YH. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. *J Clin Oncol*. 2006;24(31): 5017–5024.
46. Aarts MJ, Kamphuis CB, Louwman MJ, Coebergh JW, Mackenbach JP, van Lenthe FJ. Educational inequalities in cancer survival: a role for comorbidities and health behaviours? *J Epidemiol Community Health*. 2013;67(4): 365–373.
47. Munro AJ, Bentley AH, Ackland C, Boyle PJ. Smoking compromises cause-specific survival in patients with operable colorectal cancer. *Clin Oncol (R Coll Radiol)*. 2006;18(6):436–440.
48. Richards CH, Leitch EF, Horgan PG, Anderson JH, McKee RF, McMillan DC. The relationship between patient physiology, the systemic inflammatory response and survival in patients undergoing curative resection of colorectal cancer. *Br J Cancer*. 2010;103(9):1356–1361.
49. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. *Int J Cancer*. 2013;132(2):401–410.
50. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013; 368(4):341–350.