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ORIGINAL ARTICLE

Impact of prediagnostic smoking and smoking cessation on colorectal cancer prognosis: a meta-analysis of individual patient data from cohorts within the CHANCES consortium

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Background: Smoking has been associated with colorectal cancer (CRC) incidence and mortality in previous studies and might also be associated with prognosis after CRC diagnosis. However, current evidence on smoking in association with CRC prognosis is limited.

Patients and methods: For this individual patient data meta-analysis, sociodemographic and smoking behavior information of 12 414 incident CRC patients (median age at diagnosis: 64.3 years), recruited within 14 prospective cohort studies among previously cancer-free adults, was collected at baseline and harmonized across studies. Vital status and causes of death were collected for a mean follow-up time of 5.1 years following cancer diagnosis. Associations of smoking behavior with overall and CRC-specific survival were evaluated using Cox regression and standard meta-analysis methodology.

Results: A total of 5229 participants died, 3194 from CRC. Cox regression revealed significant associations between former [hazard ratio (HR) = 1.12; 95 % confidence interval (CI) = 1.04–1.20] and current smoking (HR = 1.29; 95% CI = 1.04–1.60) and poorer overall survival compared with never smoking. Compared with current smoking, smoking cessation was associated with

improved overall ($HR_{<10\,years} = 0.78$; 95% CI = 0.69–0.88; $HR_{\geq 10\,years} = 0.78$; 95% CI = 0.63–0.97) and CRC-specific survival ($HR_{\geq 10\,years} = 0.76$; 95% CI = 0.67–0.85).

Conclusion: In this large meta-analysis including primary data of incident CRC patients from 14 prospective cohort studies on the association between smoking and CRC prognosis, former and current smoking were associated with poorer CRC prognosis compared with never smoking. Smoking cessation was associated with improved survival when compared with current smokers. Future studies should further quantify the benefits of nonsmoking, both for cancer prevention and for improving survival among CRC patients, in particular also in terms of treatment response.

Key words: smoking, smoking cessation, colorectal neoplasms, survival, meta-analysis

Introduction

Tobacco smoking is a well-known risk factor for many diseases, including colorectal adenomas [1, 2] and colorectal cancer (CRC) [3–8]. In addition, it has been associated with increased overall [9, 10] as well as CRC-specific mortality [3, 11, 12] in previously cancer-free individuals. With improvements in cancer therapy and a growing number of cancer survivors, it becomes increasingly important to also evaluate smoking behavior in association with prognosis among already diagnosed CRC patients.

In a meta-analysis on the association between prediagnostic smoking and CRC prognosis after diagnosis, current smoking was significantly associated with a 26% poorer overall survival compared with never smoking [13]. Similarly, Zhu et al. [14] and Yang et al. [15] reported significantly increased overall mortality for current compared with never smokers in analyses among CRC survivors, and Walter et al. [16] observed a poorer survival in smokers with ≥20 pack years compared with never smokers, among CRC patients with nonmetastatic disease.

However, current evidence on smoking and its association with prognosis after CRC diagnosis is still very limited due to the few available published studies, which are mainly from the USA, and the heterogeneity in exposure and outcome assessment as well as in confounder adjustment across studies. Time since smoking cessation has rarely ever been investigated in association with CRC prognosis [14, 15, 17, 18]. We therefore aimed to provide a comprehensive assessment of the impact of smoking status and time since smoking cessation on overall and CRC-specific survival using an individual patient data meta-analysis within a large consortium of population-based cohorts.

Materials and methods

Study design and study population

Our investigation included 12 414 CRC patients, recruited within 14 population-based cohort studies from 10 different countries participating in the CHANCES consortium (Consortium on Health and Ageing: Network of Cohorts in Europe and the U.S.; www.chancesfp7.eu). CHANCES aims to identify determinants of health and quality of life in older adults. Details pertaining to the recruitment of participants, data collection, and data harmonization of cohorts included in CHANCES have been described elsewhere [19–21], and a summary of key characteristics of the incident CRC patients from these studies included in this analysis is provided in Table 1.

All studies in the CHANCES consortium have been conducted according to the Declaration of Helsinki. For each study, local ethical approval and informed consent from all study participants was obtained in accordance with local requirements.

CRC patients were selected from first incident cases (cancer free before CRC) ascertained by active follow-up or record linkage with national/regional cancer registries for all cohorts. CRC was defined according to the 10th edition of the International Classification of Diseases (ICD-10) codes C18-20. CRC stage was defined based on the Union for International Cancer Control classification as: stage I if tumor size (T) equal to 1 or 2, stage II if T equal to 3 or 4 but no lymph node involved ($N = 0$), stage III if lymph nodes were involved ($N \geq 1$) but with no evidence of distant metastases ($M \neq 1$) and stage IV if distant metastases were present ($M = 1$). Pooled mean time between cohorts' baseline to CRC diagnosis was 6.3 years and pooled mean follow-up time after CRC diagnosis was 5.1 years.

Covariate measurement

Current smoking status and time since smoking cessation information were acquired, either via self-administered questionnaires or via interview. This information was obtained at baseline in each study, i.e. before CRC diagnosis and before the start of follow-up. Current smoking status was categorized into never, former and current smoking and includes the smoking status at baseline. Current smoking was defined as either regular or daily smoking, dependent on the respective study's definition. Never smoking was defined as either never having smoked daily/regularly or as having smoked ≤100 cigarettes over one's lifetime. Time since smoking cessation was calculated in former smokers, taking age at cancer diagnosis minus age at smoking cessation (as reported before diagnosis, at recruitment into the respective cohorts). Time since smoking cessation was then categorized into two groups: smoking cessation <10 years ago and cessation ≥10 years ago. A more detailed categorization of smoking cessation was not possible in all cohorts due to the small number of cases. Except for the MORGAM FI and the Rotterdam Study (RS), all included studies reported time since smoking cessation for former smokers.

Each study obtained dates and causes of death from official registers or death certificates. Follow-up times started at the time of a patient's CRC diagnosis and continued until the end point was reached or until a study's observation time ended. Outcome measures of interest were overall and CRC-specific mortality, with end points being death from any cause and death from CRC, respectively.

Further sociodemographic and lifestyle information was collected within the CHANCES studies via self-administered questionnaire at baseline. Covariates of interest for our survival analysis included age, sex, cancer stage, body mass index (BMI), alcohol consumption, education, physical activity and history of diabetes. Cancer stage information was not available for the present analyses for the following cohorts: EPIC-Elderly NL, MORGAM (-FI, -NI, -SE), RS, TROMSØ and VIP. Physical activity was not available for the present analyses in MORGAM FI and MORGAM SE and history of diabetes was not available in MORGAM FI. All other covariate information was available in all of the included studies.

Table 1. Sociodemographic and lifestyle characteristics at baseline of the incident colorectal cancer cases included for cohorts in the CHANCES consortium

	COSM	EPIC				ESTHER	MORGAM			NIH-AARP	RS	SMC	TROMSØ	VIP
		DK	ES	GR	NL		FI	NI	SE					
Variable	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Total	901	330	93	88	153	160	342	76	54	8214	257	612	340	794
Median follow-up after diagnosis (years)	2	2	3	2	3	4	5	3	3	5	3	3	3	3
Age at diagnosis (years)[a]	66 (59–72)	63 (61–64)	62 (61–64)	68 (65–71)	65 (62–67)	65 (61–69)	55 (47–61)	56 (53–58)	66 (55–69)	65 (61–68)	68 (63–74)	66 (58–72)	66 (58–72)	59 (50–60)
Sex														
Male	901 (100)	179 (54)	56 (60)	50 (57)	10 (7)	100 (63)	179 (52)	76 (100)	22 (41)	5523 (67)	115 (45)	–	185 (54)	407 (51)
Female	–	151 (46)	37 (40)	38 (43)	143 (93)	60 (38)	163 (48)	–	32 (59)	2691 (33)	142 (55)	612 (100)	155 (46)	387 (49)
Cancer stage														
I	68 (15)	0 (0)	0 (0)	0 (0)	n.a.	0 (0)	n.a.	n.a.	n.a.	868 (31)	n.a.	47 (15)	n.a.	n.a.
II	159 (34)	83 (73)	34 (74)	20 (100)	n.a.	77 (50)	n.a.	n.a.	n.a.	765 (27)	n.a.	89 (28)	n.a.	n.a.
III	125 (27)	12 (11)	7 (15)	0 (0)	n.a.	51 (33)	n.a.	n.a.	n.a.	719 (25)	n.a.	104 (33)	n.a.	n.a.
IV	109 (24)	18 (16)	5 (11)	0 (0)	n.a.	27 (17)	n.a.	n.a.	n.a.	472 (17)	n.a.	76 (24)	n.a.	n.a.
Tumor location														
Colon	558 (62)	191 (58)	58 (62)	57 (65)	115 (75)	95 (60)	199 (58)	38 (51)	33 (61)	6013 (73)	128 (50)	434 (71)	241 (71)	512 (64)
Rectum	343 (38)	139 (42)	35 (38)	31 (35)	38 (25)	63 (40)	143 (42)	37 (49)	21 (39)	2201 (27)	129 (50)	178 (29)	99 (29)	282 (36)
BMI (kg/m^2)[a,b]	26 (24–28)	26 (24–29)	29 (27–32)	29 (26–32)	26 (23–29)	28 (26–31)	27 (25–31)	27 (25–28)	27 (25–30)	27 (24–30)	26 (24–28)	25 (23–27)	26 (24–29)	26 (24–28)
Alcohol (g/day)[a,b]	9 (3–19)	13 (5–35)	9 (0–31)	1 (0–12)	2 (0–7)	5 (0–13)	2 (0–9)	14 (0–38)	1 (0–4)	2 (0–15)	3 (0–15)	3 (0–7)	2 (0–5)	2 (0–6)
Education[b]														
Primary	661 (74)	126 (38)	80 (87)	73 (84)	50 (33)	120 (75)	210 (62)	0 (0)	25 (46)	73 (1)	62 (24)	481 (79)	203 (60)	305 (40)
Secondary	113 (13)	142 (43)	10 (11)	8 (9)	86 (57)	31 (20)	110 (33)	68 (89)	19 (35)	2338 (29)	171 (67)	28 (5)	84 (25)	341 (44)
College or university	122 (14)	60 (18)	2 (2)	6 (7)	16 (11)	8 (5)	18 (5)	8 (11)	10 (19)	5547 (70)	22 (9)	103 (17)	52 (15)	124 (16)
Vigorous physical activity[b]														
No	552 (63)	53 (26)	90 (98)	67 (77)	68 (46)	109 (68)	n.a.	68 (89)	n.a.	4606 (57)	24 (16)	418 (71)	230 (69)	555 (78)
Yes	318 (37)	152 (74)	2 (2)	20 (23)	81 (54)	51 (32)	n.a.	8 (11)	n.a.	3529 (43)	122 (84)	170 (29)	102 (31)	158 (22)
History of diabetes[b]														
No	818 (91)	300 (96)	82 (88)	76 (86)	144 (94)	128 (80)	n.a.	75 (99)	51 (94)	7239 (88)	245 (96)	583 (95)	325 (96)	768 (97)
Yes	83 (9)	11 (4)	11 (12)	12 (14)	9 (6)	32 (20)	n.a.	1 (1)	3 (6)	975 (12)	11 (4)	29 (5)	13 (4)	26 (3)
Smoking status[b]														
Never	298 (33)	83 (25)	52 (56)	49 (56)	83 (54)	66 (42)	151 (44)	18 (24)	26 (48)	2545 (31)	97 (38)	343 (56)	107 (31)	352 (44)
Former	372 (41)	116 (35)	19 (20)	29 (33)	50 (33)	70 (44)	125 (37)	35 (47)	17 (31)	4642 (57)	111 (43)	136 (22)	143 (42)	245 (31)
Current	231 (26)	131 (40)	22 (24)	10 (11)	20 (13)	22 (14)	66 (19)	22 (29)	11 (20)	1027 (13)	49 (19)	133 (22)	90 (26)	197 (25)
Time since smoking cessation (years)[c]														
Median	26	23	22	20	26	21	n.a.	13	20	n.a.	n.a.	24	18	25
<10 years	21 (6)	12 (11)	2 (11)	2 (7)	3 (6)	16 (23)	n.a.	13 (37)	1 (6)	1244 (27)	n.a.	11 (8)	44 (31)	15 (7)
≥10 years	346 (94)	94 (89)	17 (89)	26 (93)	46 (94)	54 (77)	n.a.	22 (63)	16 (94)	3398 (73)	n.a.	125 (92)	99 (69)	212 (93)

Percentages calculated after exclusion of missing values; some percentage totals exceed 100% due to rounding.

[a]Continuous variable described by median and interquartile range.

[b]Information collected at time of recruitment into the study (baseline), preceding cancer diagnosis.

[c]Former smokers only.

COSM, Cohort of Swedish Men; Diag, diagnosis; DK, Denmark; EPIC, European Prospective Investigation into Cancer and Nutrition; ES, Spain; ESTHER, Early Recognition and Optimized Treatment of Chronic Diseases in the Older Population; GR, Greece; MORGAM, Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) Risk, Genetics, Archiving and Monograph; MORGAM FI, Finrisk Study (Finland); MORGAM NI, PRIME Belfast Study (Northern Ireland); MORGAM SE, Northern Sweden MONICA examinations (Norrbotten county only); n.a., not available; NIH-AARP, National Institute of Health—American Association of Retired Persons; NL, The Netherlands; RS, Rotterdam Study; SMC, Swedish Mammography Cohort; TROMSØ, The Tromsø Study; VIP, Västerbotten Intervention Programme.

Statistical analysis

The number of CRC patients with complete data and the distribution of covariates and smoking variables within each of the CHANCES studies were evaluated in descriptive analyses. Cox proportional hazards regression was conducted to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between smoking behavior and survival after CRC diagnosis. In addition to crude estimates, we report estimates from models with three different, a priori defined levels of adjustment: (i) adjustment for age (continuous) and sex; (ii) additional adjustment for BMI (continuous; in kg/m^2), daily alcohol intake (continuous; in g/day), education (primary, secondary, university), vigorous physical activity (yes, no), tumor site (colon, rectum) and history of diabetes (yes, no); (iii) additional adjustment for cancer stage (I, II, III, IV, missing). Only studies with available cancer stage were therefore included in analyses using model C adjustment. Survival analyses were first conducted separately for each of the included studies, using predefined SAS version 9.3 (SAS Institute, Cary, NC) analysis scripts supplied to all included studies. Cohort-specific results were then pooled using random effects meta-analysis. Random-effects models allow for a variation of true effects across all included studies and were computed using Microsoft Excel 2010 (Redmond, WA) according to methods described by DerSimonian and Laird [22]. Heterogeneity among the included studies was evaluated by the I^2 index [23, 24].

The main analyses were conducted on the whole patient sample. Because metastatic CRC patients may benefit less from quitting smoking, we carried out additional analyses restricted to nonmetastatic disease (stages I–III) patients only. Because the time interval between smoking exposure assessment and CRC diagnosis varied within and between cohorts (mean = 6 years), we stratified the analyses according to recent and distant time since smoking exposure assessment, defined as below and above the mean time since smoking exposure assessment, respectively. Additional analyses were conducted stratified by cancer site to investigate potentially differing associations between colon and rectal cancer patients.

Results

Descriptive analyses

Covariate distributions among the 12 414 incident CRC cases from the 14 included CHANCES studies are presented in Tables 1 and 2. In total, 63% were men and the median age at CRC diagnosis was 64.3 years. Our analytic sample included 34% never, 49% former and 16% current smokers. Of 6110 former smokers, in 5839 information on time since smoking cessation was available, with a median of 23.6 years of cessation at diagnosis and a proportion of 24% of patients who stopped smoking <10 years ago and 76% who stopped ≥10 years ago. Cancer stage was available in a total of 3935 study participants with 25% stage I, 31% stage II, 26% stage III and 18% stage IV CRC. Median BMI in the sample was 26.7 kg/m^2 and median alcohol consumption was 3.1 g/day. The total number of deaths in our total study sample was 5229, with 3194 cases of CRC-specific death.

Prognosis according to smoking behavior

Pooled results of survival analyses among all included patients are presented in Table 3, and stratified by study in Figure 1. When compared with never smoking, significant associations between former (HR = 1.12; 95% CI = 1.04–1.20) and current smoking (HR = 1.29; 95% CI = 1.04–1.60) and poorer overall survival were found. With the exception of crude estimates in former smokers, the significant associations were robust to all covariate adjustments. Relevant between study heterogeneity could not be seen in analyses on former smoking, but was quite high in analyses on current smoking ($I^2 = 64\%$, $P < 0.05$) (Figure 1). In sensitivity analyses where NIH-AARP was removed from the pooled estimate, heterogeneity was reduced to $I^2 = 5\%$ and the association between current smoking and overall survival to borderline significance (HR = 1.16; 95% CI = 0.99–1.35). Looking at time since smoking cessation, in comparison with current smokers, having stopped smoking <10 years or ≥10 years ago was significantly associated with improved overall survival, even after comprehensive adjustment ($HR_{<10\,years} = 0.78$; 95% CI = 0.69–0.88; $HR_{\geq 10\,years} = 0.78$; 95% CI = 0.63–0.97). In terms of direction and magnitude, found associations between smoking behavior and overall survival show a very homogeneous picture across all adjustment settings.

In analyses of CRC-specific survival, in comparison with never smokers, significant associations between current smoking and poorer survival were seen for both crude and age and sex adjusted estimates. However, in model B and C only nonsignificant associations were observed. In analyses of time since smoking cessation, compared with current smokers, significant associations between ≥10 years since smoking cessation and improved CRC-specific survival were found (HR = 0.76; 95% CI = 0.67–0.85), and the association was robust throughout the different covariate adjustments. No associations were found between <10 years since smoking cessation and CRC-specific survival.

An additional adjustment for stage, where available, did not change HR estimates for smoking status or cessation and overall or CRC-specific survival. Likewise, no change in model results was observed when comparing association estimates with and without adjustment for stage in only those studies that reported on stage (data not shown).

Pooled results from stage-specific analyses among stages I–III patients, conducted only on studies with available stage information, are presented in Table 4. Compared with never smokers, significant associations were observed between former smoking and poorer overall survival (HR = 1.17; 95% CI = 1.07–1.28) for all levels of adjustment. Associations between current smoking and survival were more pronounced than for former smoking, but did not remain significant after model A or C adjustment. When looking at time since smoking cessation, significant associations were seen between ≥10 years of cessation and improved overall survival and in model C also between <10 years of cessation and improved overall survival. In the crude Cox model, significant associations were observed between current smoking and poorer CRC-specific survival, although these associations were not significant after multivariate adjustment. No associations were seen between former smoking and CRC-specific survival. For time since smoking cessation, similar to models on overall survival, we found significant associations between ≥10 years of cessation and improved CRC-specific survival in comparison with current smokers, but no association with <10 years of cessation.

Table 5 presents pooled results of survival analyses of associations between smoking variables and survival, conducted in subgroups of patients according to time from smoking behavior assessment until CRC diagnosis. Overall, results were comparable between recent and distant assessment of smoking behavior groups, although of slightly lower magnitude among those with a more distant exposure assessment. In both groups former

Table 2. Pooled characteristics of all included CRC patients in total and according to vital status

Variable	Total		Alive		Dead			
					Death from any cause		Death from CRC	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Total	12414	(100)	7185	(58)	5229	(42)	3194	(26)
Age (years)[a]	64.3	(59.3–67.7)	62.9	(58.6–66.8)	65.5	(60.5–68.8)	64.7	(59.4–68.2)
Sex								
Male	7803	(63)	4443	(62)	3360	(64)	1971	(62)
Female	4611	(37)	2742	(38)	1869	(36)	1223	(38)
Cancer stage[b]								
I	983	(25)	803	(34)	180	(12)	49	(5)
II	1227	(31)	881	(37)	346	(22)	156	(16)
III	1018	(26)	606	(25)	412	(27)	275	(28)
IV	707	(18)	105	(4)	602	(39)	514	(52)
Tumor location								
Colon	8672	(70)	5007	(70)	3656	(70)	2202	(69)
Rectum	3739	(30)	2177	(30)	1571	(30)	991	(31)
BMI (kg/m^2)[a]	26.7	(24.2–29.6)	26.6	(24.2–29.4)	26.8	(24.2–29.8)	26.6	(24.0–29.5)
Alcohol (g/day)[a]	3.1	(0.5–14.5)	3.1	(0.6–14.3)	3.0	(0.3–14.6)	3.4	(0.5–15.1)
Education								
Primary	2469	(20)	1177	(17)	1292	(25)	850	(27)
Secondary	3549	(29)	2058	(29)	1491	(29)	899	(29)
University	6098	(50)	3790	(54)	2308	(45)	1365	(44)
Vigorous physical activity								
No	6840	(59)	3926	(58)	2914	(61)	1751	(61)
Yes	4713	(41)	2874	(42)	1839	(39)	1132	(39)
History of diabetes								
No	11153	(90)	6614	(92)	4539	(87)	2865	(90)
Yes	1239	(10)	563	(8)	676	(13)	319	(10)
Smoking status								
Never	4270	(34)	2595	(36)	1675	(32)	1121	(35)
Former	6110	(49)	3579	(50)	2531	(48)	1453	(45)
Current	2031	(16)	1010	(14)	1021	(20)	619	(19)
Time since smoking cessation (years)[c]								
Median (IQR)	23.6	(15.3–32.3)	25.4	(16.5–34.4)	22.5	(13.5-–30.7)	22.6	(13.9–30.9)
<10 years	1384	(24)	774	(22)	610	(26)	331	(25)
≥10 years	4455	(76)	2678	(78)	1777	(74)	1017	(75)

[a]Continuous variable described by median and IQR. Summary median and IQR were calculated from cohort-specific medians and IQRs and pooled by weighting on the sample size within each given subgroup (i.e. overall, among those alive, among those dying from any-cause, and among those dying from CRC). Some percentage totals exceed 100% due to rounding.

[b]Information on cancer stage was available, and thus these analyses were restricted to data from the following cohorts: COSM, EPIC DK, EPIC ES, EPIC GR, ESTHER, NIH-AARP and SMC.

[c]Former smokers only; data on smoking cessation were not available for MORGAM FI and RS.

CRC, colorectal cancer; IQR, interquartile range.

($HR_{Recent} = 1.15$; 95% CI = 1.05–1.26; $HR_{Distant} = 1.13$; 95% CI = 1.01–1.25) and current smoking ($HR_{Recent} = 1.41$; 95% CI = 1.12–1.77; $HR_{Distant} = 1.30$; 95% CI = 1.08–1.57) were significantly associated with poorer overall survival when compared with never smoking. Compared with current smokers, patients with <10 years since smoking cessation had improved overall survival irrespective of exposure ascertainment timing. In contrast, smoking cessation ≥10 years ago was associated with improved overall survival only in the recent exposure assessment group. Looking at CRC-specific survival, current smokers showed associations with poorer survival in both groups, although estimates were more pronounced in the recent assessment group ($HR_{Recent} = 1.37$; 95% CI = 1.18–1.59; $HR_{Distant} = 1.22$; 95% CI = 1.03–1.43). In terms of smoking cessation time, <10 years of cessation was significantly associated with improved survival only in distantly assessed patients and ≥10 years was significantly associated with improved survival in recently assessed patients.

Table 3. Summary HRs and 95% CIs derived from meta-analyses with CHANCES cohort-specific estimates for the association of smoking status and time since smoking cessation with overall and CRC-specific survival in all CRC patients

	At risk	Events	HR (95% CI)			
			Crude	Model A[a]	Model B[b]	Model C[c]
Overall survival						
Smoking status						
Never	4278	1679	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	6112	2531	1.07 (0.97–1.18)	1.10 (1.03–1.18)	1.12 (1.04–1.20)	1.12 (1.04–1.20)
Current	2032	1022	1.23 (1.04–1.46)	1.25 (1.05–1.49)	1.28 (1.04–1.57)	1.29 (1.04–1.60)
Time since smoking cessation[d]						
Current smokers	1916	947	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 years	1333	589	0.85 (0.68–1.07)	0.81 (0.67–0.99)	0.78 (0.69–0.88)	0.78 (0.69–0.88)
≥10 years	4506	1770	0.80 (0.69–0.93)	0.77 (0.65–0.92)	0.76 (0.60–0.96)	0.78 (0.63–0.97)
CRC-specific survival						
Smoking status						
Never	4278	1124	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	6112	1453	1.00 (0.92–1.08)	0.98 (0.91–1.07)	1.00 (0.91–1.09)	1.00 (0.91–1.09)
Current	2032	620	1.20 (1.06–1.35)	1.15 (0.98–1.35)	1.14 (0.94–1.38)	1.15 (0.95–1.41)
Time since smoking cessation[d]						
Current smokers	1916	570	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 years	1333	305	0.97 (0.63–1.48)	0.94 (0.62–1.44)	0.82 (0.55–1.24)	0.84 (0.60–1.20)
≥10 years	4506	1049	0.77 (0.69–0.86)	0.76 (0.68–0.84)	0.75 (0.66–0.86)	0.76 (0.67–0.85)

[a]Model A was adjusted for sex and age.

[b]Model B was adjusted for sex, age, BMI, education, alcohol intake, tumor site (colon/rectum), diabetes and vigorous physical activity; adjustment for vigorous physical activity was not possible in MORGAM FI and SE; adjustment for diabetes was not possible in MORGAM FI.

[c]Model C was adjusted for all covariates adjusted for in Model B, and where possible, additionally for stage.

[d]Since time since smoking cessation information was not available for the MORGAM FI and Rotterdam Study (RS), the number of current smokers in the reference category also excludes patients from these two studies; in analyses on smoking status these two studies were not excluded.

HR, hazard ratio; CI, confidence interval.

Supplementary Table S1, available at *Annals of Oncology* online, presents associations between the smoking variables and survival, conducted in subgroups of patients according to cancer site. Current smoking was associated with poorer overall survival in both colon and rectal cancer patients, while for former smoking associations seem more pronounced in rectal cancer patients. Looking at CRC-specific survival, associations were likewise more pronounced in rectal cancer patients. Associations between increasing time since smoking cessation and improved survival were significant and consistent irrespective of the regarded cancer site subgroup.

Discussion

This individual patient data meta-analysis based on data from 12 414 CRC patients collected within the CHANCES consortium showed significant associations between former and current smoking and poorer overall survival. Compared with current smoking, smoking cessation was associated with improved overall survival independent of time of cessation and with improved CRC-specific survival in former smokers with ≥10 years since cessation. Results were comparable in nonmetastatic CRC patients. Associations between current smoking and poorer overall and CRC-specific survival were most pronounced when smoking exposure had been ascertained <6 years before CRC diagnosis.

Smoking is a well-known risk factor for many adverse health outcomes including CRC and its precursors [1, 3, 12]. Previous studies have shown that smoking might also be associated with an adverse prognosis in CRC after diagnosis [13]. However, the number of studies examining this issue is limited, especially on exposure measures exceeding simple assessments of smoking status only. A previous meta-analysis summarized current evidence on smoking behavior and its association with CRC prognosis, finding that studies mostly assessed overall survival rather than CRC-specific survival [13].

Studies on former smoking in association with overall survival have reported mixed results [18, 25–27] and when pooled, revealed a nonsignificant association [13]. In more recent analyses, Yang et al. found a significant association between former smoking and poorer overall survival, while Zhu et al. [14] found no association and Walter et al. [16] likewise, even when examining only former smokers with ≥20 pack years compared with never smokers. In this current analysis, with a much larger sample size than previous studies on former smoking, we found a significant association between former smoking and a 10%–12% higher overall mortality when compared with never smoking. A possible

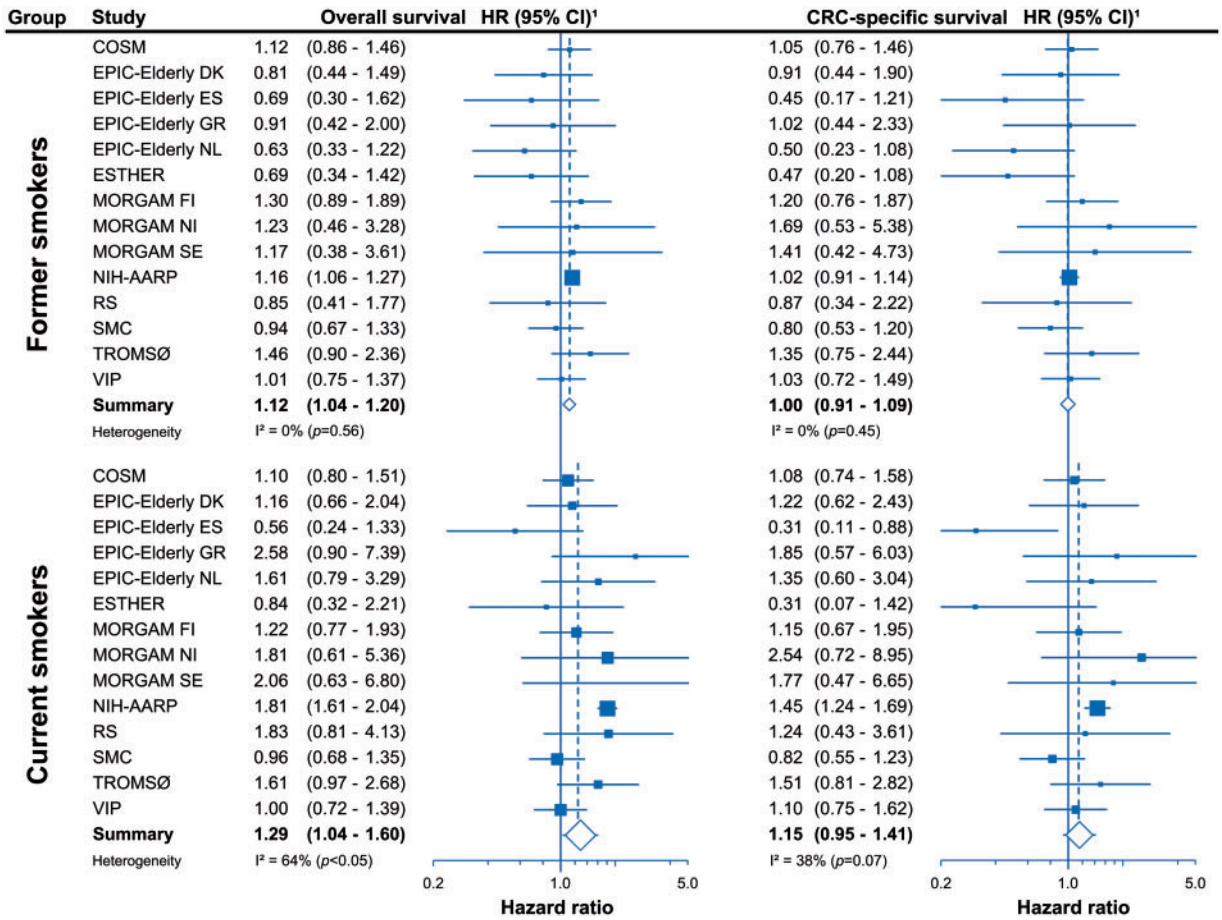

Figure 1. Forest plots for the association between former and current smoking (reference: never smoking) and overall and CRC-specific survival. Abbreviations: HR, hazard ratio; CI, confidence interval; CRC, colorectal cancer. Abbreviated study names: COSM, Cohort of Swedish Men; DK, Denmark; EPIC, European Prospective Investigation into Cancer and Nutrition; ES, Spain; ESTHER, Early Recognition and Optimized Treatment of Chronic Diseases in the Older Population; GR, Greece; MORGAM, Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) Risk, Genetics, Archiving and Monograph; MORGAM FI, Finrisk Study (Finland); MORGAM NI, PRIME Belfast Study (Northern Ireland); MORGAM SE, Northern Sweden MONICA examinations (Norrbotten county only); NIH-AARP, National Institute of Health—American Association of Retired Persons; NL, The Netherlands; RS, Rotterdam Study; SMC, Swedish Mammography Cohort; TROMSØ, The Tromsø Study; VIP, Västerbotten Intervention Programme. [1]HRs and 95% CIs were adjusted for sex, age, BMI, education, alcohol intake, tumor site, diabetes and vigorous physical activity; estimates from COSM, EPIC-DK/-ES/-GR, ESTHER, NIH-AARP and SMC were additionally adjusted for tumor stage; adjustment for vigorous physical activity was not possible for MORGAM FI and SE; adjustment for diabetes was not possible in MORGAM FI.

explanation might be indeed the large sample size in the current investigation, providing the statistical power needed to reveal such rather modest associations. In addition, former smokers certainly represent a very diverse group, with differences in time since cessation, smoking duration and intensity, and in their reasons for smoking cessation, as this could be a health or lifestyle choice. Overall though, effect magnitudes seem comparable with previous meta-analysis results showing a nonsignificant but 11% increased mortality among former compared with never smokers [13].

Prediagnostic current smoking has been investigated in association with CRC prognosis in previous studies [14–18, 25–32] and has been shown to be significantly associated with poorer overall survival when compared with never smokers in a previous meta-analysis [13]. Likewise, Yang et al. [15] and Zhu et al. [14] reported significant associations between current smoking and poorer overall survival. Walter et al. [16] found a significant association between current smoking in combination with ≥20 pack years and poorer overall survival, when compared with never smokers. The results of our current investigation are in accordance with this, and the magnitude of the observed HRs seems comparable between the previous [13] and the current meta-analysis [with a mortality increase of 26% and 29% (Model C), respectively].

Previous investigations on smoking and CRC-specific survival have been sparse. Only seven studies investigated smoking status in association with this outcome [15, 16, 18, 26, 30–32]. Five studies compared current with never [15, 16, 18, 26, 32], three studies former with never [15, 18, 26], one study current with former/never [30] and two studies ever with never smokers [18, 31]. Results have been mixed but associations were strongest between current or ever smoking and poorer CRC-specific survival

Table 4. Summary HRs and 95% CIs derived from meta-analyses with CHANCES cohort-specific estimates for the association of smoking status and time since smoking cessation with overall and CRC-specific survival in stages I–III CRC patients[a]

	At risk	Events	HR (95% CI)		
			Crude	Model A[b]	Model C[c]
Overall survival					
Smoking status					
Never	2857	863	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	4812	1716	1.19 (1.09–1.31)	1.16 (1.06–1.26)	1.17 (1.07–1.28)
Current	1280	569	1.36 (1.05–1.76)	1.26 (0.89–1.77)	1.32 (0.92–1.89)
Time since smoking cessation					
Current	1280	290	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 years	1192	484	1.06 (0.61–1.84)	0.90 (0.59–1.37)	0.75 (0.65–0.86)
≥10 years	3608	1226	0.69 (0.59–0.80)	0.71 (0.56–0.90)	0.76 (0.54–1.07)
CRC-specific survival					
Smoking status					
Never	2857	532	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	4812	893	1.04 (0.94–1.16)	1.03 (0.92–1.15)	1.00 (0.79–1.27)
Current	1280	290	1.26 (1.03–1.55)	1.02 (0.69–1.52)	1.11 (0.72–1.70)
Time since smoking cessation					
Current	1280	290	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 years	1192	232	1.50 (0.67–3.34)	1.35 (0.64–2.83)	1.15 (0.53–2.50)
≥10 years	3608	659	0.76 (0.64–0.91)	0.76 (0.62–0.94)	0.72 (0.61–0.84)

[a]Analyses were restricted to data from the following cohorts with available tumor stage information: COSM, EPIC DK, EPIC ES, EPIC GR, ESTHER, NIH-AARP and SMC.
[b]Model A was adjusted for sex and age.
[c]Model C was adjusted for sex, age, BMI, education, alcohol intake, tumor site, diabetes, vigorous physical activity and tumor stage.

[15, 18, 30]. In our analysis of 12 414 CRC patients, we observed statistically nonsignificant associations between current smoking and poorer CRC-specific survival, but former smoking was not associated with CRC-specific survival.

In our study, we found higher mortality associated with current smoking to be more pronounced in rectal cancer patients. In colon cancer patients associations were only present when looking at overall survival. In previous studies CRC site subgroups have rarely been investigated [14, 16, 18, 25, 26]. Previously found associations between smoking and decreased survival have been mainly restricted to colon cancer, but were comparable between overall and CRC-specific survival [14, 16, 18, 25, 26]. In rectal cancer, previous results have been nonsignificant and inconclusive [14, 16, 18, 26]. These mixed results emphasize on the need for larger investigations in these subgroups, to clarify how smoking might worsen prognosis depending on cancer site.

Smoking cessation in association with CRC prognosis has rarely been investigated in previous studies [14, 15, 17, 18]. In our analysis, compared with current smokers, we observed associations of both short and long durations of cessation with improved overall survival. All previous studies on this topic compared persons who had stopped smoking with never smokers and only two previous studies found significant associations between time since cessation and poorer overall survival compared with never smokers [15, 18]. McCleary et al. [17] and Zhu et al. [14] did not observe such associations. Based on current and previous results this topic certainly warrants further research.

Concerning CRC-specific mortality, only two previous studies investigated the association between years since smoking cessation and CRC-specific survival, lacking a clear trend [15, 18]. In our analysis, we saw highly significant associations between longer time since smoking cessation and reduced mortality by ∼25%, in comparison with current smokers. Considering that at the same time no significant association between current compared with never smoking and CRC-specific survival was found, this seems a bit controversial, suggesting a larger mortality reduction by smoking cessation for ≥10 years than by never smoking. However, found associations, although not significant, go into the same effect direction and the lack of significance for the mortality risk estimates of current compared with never smokers is supposedly just an issue of insufficient sample size, lacking the power to reach significance.

In analyses stratified by time of smoking exposure assessment, significant associations between smoking and CRC prognosis remained evident. However, associations were more pronounced in patients with a more recent exposure assessment than in patients with an assessment ≥6 years ago. Presumably, the information ascertained <6 years before diagnosis can be considered more likely to resemble the real exposure present before, at or after CRC diagnosis, than the information ascertained ≥6 years ago, which might have led to a reduction in misclassification. In addition, some long-term current smokers might have already died before a potential CRC diagnosis, leading to an underestimation of effects that is potentially larger with increasing time since information ascertainment.

Table 5. Summary HRs and 95% CIs derived from meta-analyses with CHANCES cohort-specific estimates for the association of smoking status and time since smoking cessation with overall and CRC-specific survival in all CRC patients according to time between smoking exposure assessment and CRC diagnosis

	Recent assessment of smoking exposure[a]			Distant assessment of smoking exposure[a]		
	At risk	Events	HR (95% CI)[b]	At risk	Events	HR (95% CI)[b]
Overall survival						
Smoking status						
Never	2068	895	1.00 (Reference)	2202	780	1.00 (Reference)
Former	3342	1529	1.15 (1.05–1.26)	2768	1002	1.13 (1.01–1.25)
Current	900	547	1.41 (1.12–1.77)	1131	474	1.30 (1.08–1.57)
Time since smoking cessation[c]						
Current	881	533	1.00 (Reference)	1035	414	1.00 (Reference)
<10 years	812	404	0.79 (0.65–0.97)	521	185	0.80 (0.65–0.99)
≥10 years	2461	1080	0.69 (0.54–0.90)	2045	690	0.88 (0.67–1.15)
CRC-specific survival						
Smoking status						
Never	2068	571	1.00 (Reference)	2202	550	1.00 (Reference)
Former	3342	838	1.01 (0.90–1.14)	2768	615	1.04 (0.91–1.18)
Current	900	320	1.37 (1.18–1.59)	1131	299	1.22 (1.03–1.43)
Time since smoking cessation[c]						
Current	881	311	1.00 (Reference)	1035	259	1.00 (Reference)
<10 years	812	202	0.70 (0.41–1.21)	521	103	0.76 (0.57–1.00)
≥10 years	2461	617	0.74 (0.64–0.86)	2045	432	0.89 (0.69–1.15)

[a]Smoking exposure assessment was considered recent or distant if ascertained <6 years or ≥6 years before CRC diagnosis, respectively.
[b]HRs and 95% CIs were adjusted for sex, age, BMI, education, alcohol intake, tumor site, diabetes and vigorous physical activity; adjustment for vigorous physical activity was not possible in MORGAM FI and SE; adjustment for diabetes was not possible in MORGAM FI.
[c]Since time since smoking cessation information was not available for MORGAM FI and Rotterdam Study (RS), the number of current smokers in the reference category also excludes patients from these two studies; in analyses on smoking status these two studies were not excluded.

The biologic mechanisms behind observed adverse associations between smoking and prognosis should also be considered. First of all, smokers are at an increased risk for surgical complications [33]. Furthermore, in previous studies nicotine was shown to inhibit chemo- and radiotherapy response in vitro and in vivo [34, 35]. Vincenzi et al. [36] found associations between cigarette smoking and a decreased response to cetuximab-based chemotherapy and a shorter time to progression in CRC patients. Nicotine may also activate certain pathways that stimulate proliferation and suppress apoptosis in colon cancer cells [37]. In addition, nicotine could enhance cell migration and therefore support cancer progression [38]. In previous studies, smoking has also been found to be differentially associated with CRC prognosis dependent on certain molecular subtypes of tumors, although the reported results were mixed [14, 18, 39]. Overall, biologic mechanisms underlying the association of smoking with CRC prognosis are not yet fully understood. Smoking prevention and cessation have been shown to be beneficial for many health outcomes and similar recommendations are warranted for cancer survivors as well, even if the full potential for CRC prognosis improvement requires more precise quantification and explanation.

This study includes one of the largest samples ever assembled to study smoking in association with CRC prognosis. We were able to combine studies from multiple countries, each of which was analyzed according to a common protocol including comprehensive adjustment for potential confounding factors. We included not only overall, but also CRC-specific survival as outcomes and were also able to investigate the association between smoking cessation and prognosis, which has rarely ever been investigated in previous studies. With our very large study sample we covered a wide geographical area which improves generalizability of results.

Limitations also need to be discussed. First, information on smoking exposure was collected not at CRC diagnosis but up to several years before (mean: 6.3 years), which might have led to misclassification, in particular for smokers who might have quit or resumed smoking between data collection and CRC diagnosis. This may have led to an underestimation of detrimental effects of current smoking and of beneficial effects of smoking cessation, a conclusion that is supported by our findings of stronger effects among patients with shorter time interval between smoking ascertainment and CRC diagnosis.

Unfortunately, it was not possible to evaluate smoking intensity, duration, different tobacco products or postdiagnostic smoking behavior in our analysis. For our evaluation, we used smoking behavior at baseline, assuming no change in behavior until diagnosis and after, which is prone to misclassification bias. In addition, we cannot exclude the presence of residual confounding through unmeasured factors, such as e.g. second-hand smoke. Moreover, we lacked information on changes in lifestyle over time, which is unfortunate, as time varying models might

have offered a more accurate insight into the quantification of changes in mortality risk associated with changes in lifestyle over time. We did not conduct competing risk analyses due to the very low number of non-CRC deaths in some of the cohorts. Although we tried to adjust our analyses for stage, this was unfortunately not possible in all of our included studies and in all of the patients due to the large number of missing values in cohorts for whom cancer stage was collected. Nevertheless, analyses with and without adjustment for stage showed no meaningful differences (data not shown).

In our analyses of the association between current smoking and overall survival (compared with never smokers), heterogeneity was quite high. In particular the NIH-AARP cohort includes a supposedly quite selected study population of potentially more health-conscious people (70% of persons with college or university education) which might result in an underrepresentation of current smokers in our analytic sample and a lower self-report bias and might explain some of the found heterogeneity between studies. Furthermore, heterogeneity might result from differential age distributions between studies and, in a conservative approach, we decided to report only random effects estimates. Although data were harmonized between studies according to a common scheme, the studies' designs and methods used for collection of exposure variables and covariates were not completely uniform. Also, we may assume that heavy and/or long-term smoking might be underrepresented in our analysis, creating a possible survivor bias, with those smokers remaining in our cohorts being on average a slightly hardier group. Therefore, our estimates might underestimate the real association between current smoking and poorer prognosis. We cannot exclude that social desirability might also have played a role in our exposure measurement which usually leads to an underreporting of smoking.

Conclusion

In conclusion, in this large meta-analysis examining the association between smoking and CRC prognosis, former and current smoking were associated with poorer overall survival. We showed smoking cessation to be associated with improved overall and CRC-specific survival in comparison with current smoking. Future studies should further quantify the benefits of not smoking, both for cancer prevention and for improving survival among CRC patients, in particular also in terms of interactions between smoking and treatment response.

Ethics approval and consent to participate

The included studies have been approved by local ethics committees: COSM: Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden); EPIC-Elderly: Ethics Committee of the International Agency for Research on Cancer and at each participating centre; EPIC-Elderly DK: The National Committee on Health Research Ethics; EPIC-Elderly ES: Comité de Ética de Investigación Clínica (CEIC); EPIC-Elderly GR: ethics committees of the University of Athens Medical School and the Hellenic Health Foundation; EPIC-Elderly NL: Institutional Review Board of the University Medical Center Utrecht and the Medical Ethical Committee of TNO Nutrition and Food Research; ESTHER: Medical Faculty of the University of Heidelberg and the Medical Association of Saarland; MORGAM FI: 1980s: no ethics approval required for observational studies (but current laws allow the use of these data for public health research), 1990s: Ethics committee of the National Public Health Institute (KTL), 2002: Ethics Committee of Epidemiology and Public Health in Hospital District of Helsinki and Uusimaa; MORGAM NI: Queen's University of Belfast Ethical Committee (Belfast, Northern Ireland); MORGAM SE: Research Ethics Committee of Umeå University (Umeå, Sweden); NIH-AARP: Special Studies Institutional Review Board of the NCI; RS: Erasmus University Medical Centre (Rotterdam, the Netherlands); SMC: Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden); TROMSØ: Regional Committee for Medical and Health Research Ethics and the Data Inspectorate of Norway; VIP: Regional Ethical Review Board of Umeå University (Umeå, Sweden).

Consent for publication

Informed consent has been obtained from all participants included in the analyzed studies, and the studies are being conducted in accordance with the declaration of Helsinki.

Availability of data and materials

The CHANCES participating cohorts' data are available only to the collaborating scientists from the respective CHANCES participating centers. The data may be available upon request for some of the participating centers but not for all due to relevant data protection laws.

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Disclosure

The authors have declared no conflicts of interest.

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