review

Smoking and survival of colorectal cancer patients: systematic review and meta-analysis

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Smoking is a risk factor for colorectal cancer (CRC) incidence and mortality. However, little is known on smoking and its association with survival after CRC diagnosis. We conducted a systematic review and meta-analysis to summarize current evidence. A systematic literature search was carried out in MEDLINE and ISI Web of Science. We included studies that analyzed recurrence-free survival, disease-free survival, all-cause, and CRC-specific mortality according to smoking status. Data were extracted in duplicate. Standard methods of meta-analysis were applied. Sixteen studies from 11 countries were identified, comprising a total sample size of 62 278 CRC patients. Overall, in the 16 included studies, current smoking and, to a lesser extent, former smoking were rather consistently associated with a poorer prognosis compared with never smokers. Meta-analyses yielded random-effects hazard ratio estimates (95% confidence intervals) for all-cause mortality of 1.26 (1.15–1.37) and 1.11 (0.93–1.33) for current and former smokers, compared with never smokers, respectively. In particular, 30-day mortality was found to be increased by between 49% and 100% among current compared with never smokers. Our results support the existence of detrimental effects of smoking on survival also after CRC diagnosis. Perspectives for enhancing prognosis of CRC patients by smoking abstinence deserve increased attention in further research and clinical practice.

Key words: colorectal neoplasms, smoking, mortality, survival analysis, prognosis

introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related death worldwide. Globally, >1.2 million incident cases and 600 000 deaths occur each year [1]. Despite major improvements in early diagnosis and therapy, 5-year relative survival is still <65%, even in highly developed countries [2, 3].

Smoking is an established risk factor for occurrence of colorectal adenomas [4, 5] as well as CRC incidence and mortality [6], which suggests that it may affect prognosis of CRC patients as well. However, surprisingly few studies have addressed the association of smoking with survival after CRC diagnosis so far, and their results have been reported in a rather heterogeneous manner.

In this systematic review and meta-analysis, we provide a summary of the available literature on the association between past and current smoking behavior and survival of CRC patients, including all-cause mortality, CRC-specific mortality, disease-free survival, and recurrence-free survival. Particular attention is devoted to the role of smoking status, smoking intensity, and time since smoking cessation.

materials and methods

data sources and search strategy

A systematic literature search was carried out in MEDLINE and ISI Web of Science to identify observational studies that had evaluated survival in association with smoking in CRC patients until 1 August 2013, using neither filters nor language restrictions.

To include both articles with MeSH terms and without, the MEDLINE database was searched with the following search terms: (((((Colorectal neoplasm*) OR (Colorectal cancer) OR ('Colorectal neoplasms' [MeSH Terms])) OR ((Colorect* OR Rectal OR Rectum OR Colon) AND (Cancer OR Neoplasm*))) AND (Smok* OR Tobacco* OR Cigarette* OR 'Smoking' [MeSH Terms] OR 'Tobacco Use Disorder' [MeSH Terms]) AND (Surviv* OR Mortality* OR Prognosis OR (Period analysis) OR (Long term) OR 'Survival' [MeSH Terms] OR 'Mortality' [MeSH Terms] OR 'Mortality' [Subheading] OR 'Survival Analysis' [MeSH Terms] OR 'Prognosis' [MeSH Terms] OR 'Survivors'[Mesh:NoExp] OR 'Time' [MeSH Terms])). The search terms in ISI Web of Science were: TS = (((((Colorectal neoplasm*) OR (Colorectal cancer)) OR ((Colorect* OR Rectal OR Rectum OR Colon) AND (Cancer OR Neoplasm*))) AND (Smok* OR Tobacco* OR Cigarette*) AND (Surviv* OR Mortality* OR Prognosis OR (Period analysis) OR (Long term))).

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study selection

We included studies that analyzed the association of smoking with all-cause and CRC-specific mortality as well as disease-free and recurrence-free survival after CRC diagnosis. For inclusion in this review, the impact of smoking on the outcomes had to be quantified by effect measures such as hazard ratios or odds ratios or by descriptive analyses providing absolute or relative survival estimates according to smoking status. Smoking had to be reported by either smoking status, smoking intensity or time since smoking cessation. Articles reporting on various cancers that did not display specific results for CRC were excluded. From articles that reported on the same patient sample, we excluded the less informative article. Meeting abstracts were excluded if no subsequent article could be identified and the abstract itself did not give sufficiently detailed information. Articles not in English or German were excluded (Figure 1).

data extraction

Data extraction from eligible studies was carried out in duplicate by two investigators (VW and MH). Disagreements were solved by discussing and reviewing the respective issue. Cross-referencing of selected articles revealed no further eligible records; one additional study was traced by scanning articles related to the ones included.

According to established standards (MOOSE) [7], the quality of each included article was assessed. Quality criteria included: (i) clear definition and description of the study population, (ii) comprehensive and complete follow-up of CRC patients, (iii) suitable ascertainment of smoking and covariates (interviews/questionnaires or hospital records), and (iv) consideration (through stratification or adjustment) of at least the following covariates in the analysis: age, sex, and tumor stage.

From each study we extracted available information on study design, characteristics of the study population, and the most
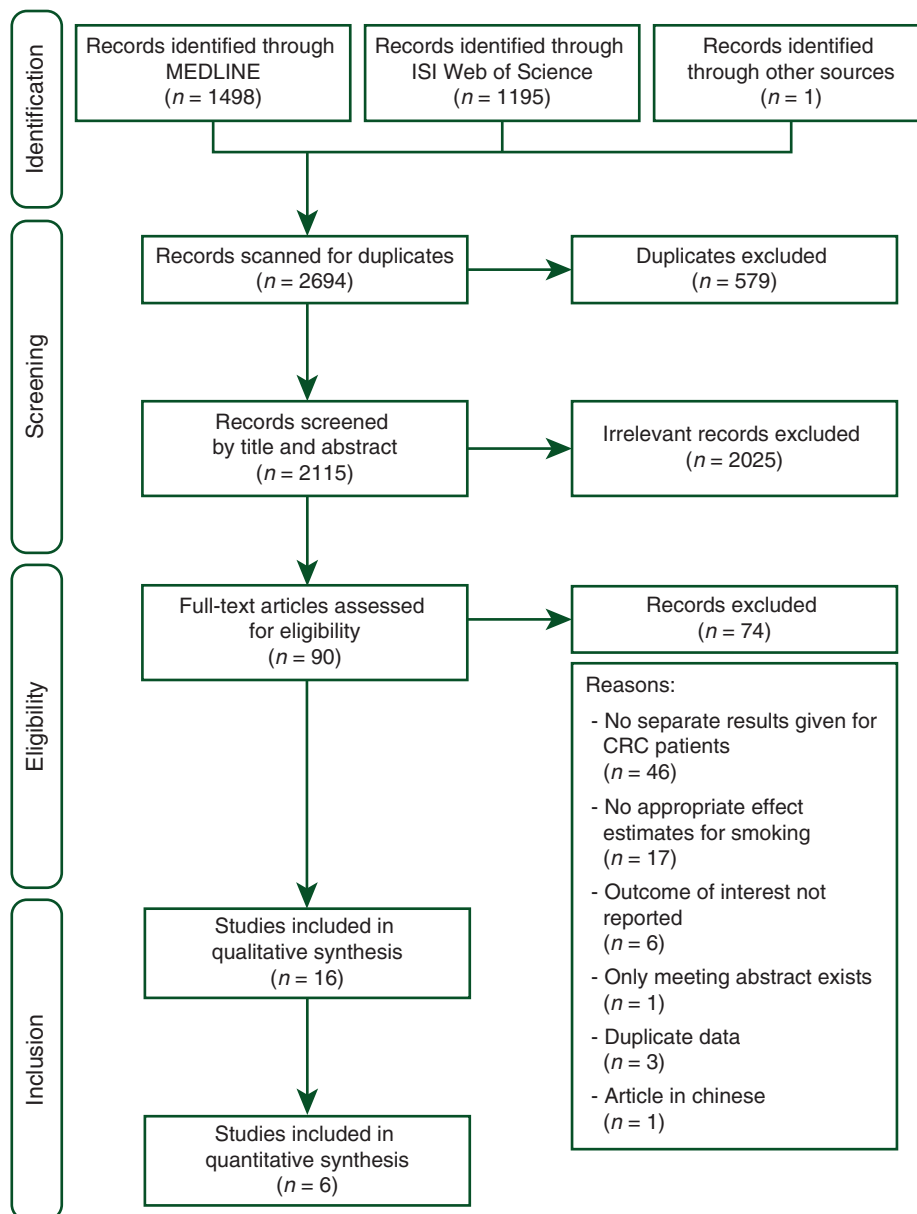
Figure 1. Flow diagram of systematic literature search.

Table 1. Baseline characteristics of studies included in the review

First author	Year	Country	Recruitment	Follow-up		Subjects	Sex	Age		Stage	Smoking		Quality criteria				
				End	Median			Range	Median		D	T	PP	FU	SMK	AD	Score
Daniell [8]	1986	USA	1974–1983	1983	>2 years	322	M/F	NR	Smokers ~60–69	I–IV	X		X	X	X		3
Jadallah [9]	1999	NZ	1990–1992	5 years	44 months	241	M/F	NR	67.2[b]	I–III	X		X	X	X		3
Nickelsen [10]	2005	DK	2001–2002	30 days	–	2757	M/F	10–100[a]	72[a]	I–IV	X				X		1
Munro [11]	2006	GB	1997–1999	83 months[a]	56 months	284	M/F	NR	NR	NR		X	X	X			2
Park [12]	2006	KR	1996–2002	2004	45 months	1882	M	$\geq$20[a]	50.8[a,b]	NR	X				X		1
McCleary [13]	2010	USA	1999–2001	2007	64 months	1045	M/F	21–85	57–65	III		X	X	X	X		3
Richards [14]	2010	GB	1997–2006	2009	74 months	320	M/F	NR	65–74	I–III	X		X	X	X		3
Ali [15]	2011	IE	1994–2005	2005	NR	22 335	M/F	NR	69[b]	I–IV	X		X	X	X	X	4
Phipps [16]	2011	USA	1998–2007	2010	NR	2264	M/F	18–74[a]	50–59	I–IV	X	X	X	X	X		3
Aarts [17]	2012	NL	1991–2008	2010	NR	226	M/F	15–75[a]	70.4[b]	I–IV	X		X	X	X	X	4
Cavalli-Björkman [18]	2012	DK/SE/NO	2003–2006	2008	~10 months	781	M/F	22–95	71	IV	X		X		X		2
Sharma [19]	2012	USA	2005–2010	30 days	–	26 333	M/F	NR	60[a]	NR	X			X	X		2
Warren [20]	2013	USA	1982–1998	2010	12–27.7 years	359	M/F	NR	60.2[b]	NR	X			X	X	X	3
Diamantis [21]	2013	GR	1992–2007	>150 months	NR	291	M/F	NR	65	II–III		X	X	X	X		3
Boyle [22]	2013	AU	2005–2007	2012	5.6 years	879	M/F	40–79	65	I–IV		X	X	X	X	X	4
Phipps [23]	2013	USA	2004–2009	2011	3.5 years	1959	M/F	>18	58.1[b]	III		X	X		X	X	3

[a]Numbers reported for the overall, not the analytic sample.

[b]Mean instead of median.

D, smoking information collected before/at diagnosis; T, smoking information collected after diagnosis/at/after treatment; PP, clear definition/description of the study population; FU, comprehensive/complete follow-up; SMK, suitable ascertainment of smoking and other covariates; AD, adjustment/stratification for at least age, sex, and tumor stage; M, male; F, female; NR, not reported; USA, United States of America; NZ, New Zealand, DK, Denmark; GB, Great Britain; KR, South Korea; IE, Ireland; NL, The Netherlands; SE, Sweden; NO, Norway; GR, Greece; AU, Australia.

comprehensively adjusted effect measures. These were either adjusted hazard ratios (aHRs) or in the case of 30-day mortality adjusted odds ratios (aORs) with respective 95% confidence intervals (95% CIs) (Table 1).

statistical analysis

Studies with a quality score of at least 2 of 4 were included in the meta-analysis [13, 15–17, 20, 22]. We logarithmized extracted aHRs and estimated their standard errors indirectly according to methods described by Parmar et al. [24]. Then, both fixed- and random-effects models were calculated. The random-effects model allows for a variation of true effects across studies and was computed according to methods described by DerSimonian and Laird [25]. Random-effects estimates are reported as main results.

Heterogeneity of included studies was evaluated by the I^2 index [26, 27] and Cochran's Q test [28]. Publication bias was investigated by Funnel plots, the Begg and Mazumdar rank correlation test [29], the Egger test of the intercept [30], and the Trim and Fill method [31].

All analyses were carried out with the statistical software R, version 2.15.3 [32], and the R package meta, version 2.2-0 [33].

results

study characteristics

The systematic search identified 2694 articles (Figure 1). Of those, 579 were excluded as duplicates, 2025 by abstract scan, and 74 by full-text revision. Cross-referencing revealed no further relevant records; one article was found among articles related to the ones included. In the end, 16 articles describing 16 different studies were eligible for a qualitative synthesis [8–23] and 6 for an additional quantitative evaluation [13, 15–17, 20, 22].

Table 1 provides detailed information on the studies' baseline characteristics. Included articles were published between 1986 and 2013. The 16 studies comprise data from a total of 62 278 CRC patients with study population sizes ranging from 226 to 26 333 cases. Six studies were carried out in the USA [8, 13, 16, 19, 20, 23], two in Scandinavia [10, 18], two in the UK [11, 14], and one study each in South Korea [12], New Zealand [9], Ireland [15], the Netherlands [17], Greece [21], and Australia [22]. Nine studies reported all-cause mortality [9, 13–17, 20, 22], five CRC-specific mortality [11, 14, 16, 20, 22], one recurrence-free survival [13], two 30-day mortality after resection [10, 19], three disease-free survival [13, 21, 23], and seven absolute survival [8, 11, 13, 17, 18, 21, 22], either directly or displayed by Kaplan–Meier curves. One study included only men [12], two only stage III cancer cases [13, 23], one only metastatic CRC cases [18], two only stage I–III CRC cases [9, 14], one only stage II–III CRC cases [21], and three only colon cancer cases [8, 13, 17]. Covariates adjusted for varied between studies and can be viewed in Table 2 along with the respective effect measures.

The mean quality score over all 16 studies was 2.75 with three studies showing the highest quality score of 4. Five studies adjusted their effect measures for at least age, sex, and some measure of tumor stage [15, 17, 20, 22, 23]. Two studies lacked three of four key quality criteria (study population description, complete follow-up, and proper adjustment) [10, 12] and were

therefore not considered for inclusion in the meta-analysis due to low methodological quality.

current smoking

The effect estimates reported for the comparison of current smoking with never smoking are summarized in Table 2. All-cause mortality was increased among smokers by 5–51% compared with never smokers in six of seven studies reporting on this end point. In two of the studies, associations were statistically significant [15, 16]. Subgroup analyses showed a mortality increase for female current smokers in one [22] of two studies providing sex-specific analyses [20, 22]. In the random-effects model of the meta-analysis, smokers showed a 26% higher mortality from any cause than never smokers (aHR: 1.26; 95% CI 1.15–1.37) (Figure 2A). There was a moderate degree of heterogeneity ($I^2 = 35.2\%$) and no indication of publication bias (data not shown). In addition to comparing current and never smokers, one other study compared current with former or never smokers [9]. This study found more than twofold increased all-cause mortality for current smokers.

The association between current smoking versus never smoking and death from CRC was reported in three studies [16, 20, 22]. One of those [16] showed that current smokers were 30% more likely to die of CRC than never smokers (95% CI 1.09–1.74). In particular, an increased risk for current smokers could be seen in women, in patients of at least 50 years of age, in patients with tumors of the proximal colon, and in patients with high-level microsatellite instability (MSI-H) (supplementary Table S1, available at Annals of Oncology online). One study by Munro et al. [11] compared the CRC-specific mortality risk of current smokers with the risk of former and never smokers combined, and found that current smokers were more than twice as likely to die of CRC than former and never smokers (Table 2).

Thirty-day mortality was reported on in two studies (Table 2). Both Nickelsen et al. [10] and Sharma et al. [19] found the risk to die within 30 days after tumor resection to be significantly elevated in current smokers (aHR: 2.00; 95% CI 1.04–3.85 and aHR: 1.49; 95% CI 1.09–2.05). Among the studies reporting absolute survival rates [8, 11, 13, 17, 18, 22], current smokers showed lower all-cause and CRC-specific survival rates than never smokers (supplementary Table S2, available at Annals of Oncology online). No study reported on relative survival.

The association between current smoking and recurrence-free survival was assessed in only one study from the USA [13], and no association was found (data not shown). Disease-free survival of current smokers was assessed in two studies [13, 23]. One of those, the study by Phipps et al. [23] revealed a significantly increased risk for current compared with never smokers to suffer recurrence or die of any cause (aHR: 1.47; 95% CI 1.04–2.09).

former smoking

The study by Phipps et al. [16] was the only one reporting a significantly increased risk for all-cause mortality in former compared with never smokers (aHR: 1.26; 95% CI 1.07–1.49) (Table 2). Park et al. [12] reported a protective effect of former smoking on all-cause mortality when compared with never smoking (aHR: 0.67; 95% CI 0.51–0.88). The meta-analysis of

Table 2. Mortality of CRC patients for the different comparisons

Comparison	First author	Year	All-cause mortality		CRC-specific mortality		30-day mortality		Disease-free survival	
			aHR	95% CI	aHR	95% CI	aOR	95% CI	aHR	95% CI
Current versus never smokers	Nickelsen[a] [10]	2005					**2.00**	**1.04–3.85**		
	Park [b] [12]	2006	0.94	0.77–1.16						
	McCleary[c] [13]	2010	1.38	0.87–2.18					1.10	0.73–1.64
	Ali[d] [15]	2011	**1.20**	**1.13–1.28**						
	Phipps[e] [16]	2011	**1.51**	**1.24–1.83**	**1.30**	**1.09–1.74**				
	Aarts[f] [17]	2012	1.30	0.70–2.30						
	Sharma[g] [19]	2012					**1.49**	**1.09–2.05**		
	Warren[h] [20]	2013	1.05	0.62–1.78	0.70	0.36–1.36				
	Boyle[i] [22]	2013	1.31	0.86–2.01	1.31	0.82–2.09				
	Phipps[j] [23]	2013							**1.47**	**1.04–2.09**
Former versus never smokers	Nickelsen[a] [10]	2005					1.80	0.87–3.73		
	Park[b] [12]	2006	**0.67**	**0.51–0.88**						
	McCleary[c] [13]	2010	1.17	0.87–1.57					1.18	0.92–1.50
	Phipps[e] [16]	2011	**1.26**	**1.07–1.49**	1.14	0.93–1.38				
	Aarts [f] [17]	2012	1.00	0.60–1.80						
	Sharma[g] [19]	2012					1.03	0.79–1.34		
	Boyle [i] [22]	2013	0.87	0.64–1.18	0.94	0.67–1.30				
	Phipps[j] [23]	2013							1.20	0.99–1.46
Current versus former/never smokers	Jadallah[k] [9]	1999	**2.26**	**1.31–3.90**						
	Munro[l] [11]	2006			**2.24**	**1.25–4.01**				
Ever versus never smokers	Richards[m] [14]	2010	**1.52**	**1.06–2.18**	1.46	0.92–2.32				
	Phipps[e] [16]	2011	**1.33**	**1.14–1.55**	**1.21**	**1.01–1.45**				
	Phipps[j] [23]	2013							**1.23**	**1.02–1.49**
<20 versus 0 Py	Park[b] [12]	2006	0.96	0.76–1.22						
≥20 versus 0 Py			1.13	0.84–1.50						
0–10 versus 0 Py	McCleary[c] [13]	2010	1.01	0.67–1.54					0.99	0.70–1.41
10–20 versus 0 Py			1.19	0.86–1.65					1.17	0.89–1.55
≥20 versus 0 Py			1.23	0.88–1.71					1.21	0.92–1.61
<20 versus 0 Py	Phipps[e] [16]	2011	**1.23**	**1.03–1.47**	1.19	0.97–1.46				
20–40 versus 0 Py			**1.33**	**1.08–1.63**	1.13	0.87–1.46				
>40 versus 0 Py			**1.56**	**1.26–1.93**	**1.34**	**1.01–1.76**				
≤10 versus 0 Py	Diamantis[n] [21]	2013							**1.76**	**1.11–2.79**

Bold numbers indicate significant values at the 0.05 level.

[a]Age, sex, American Society of Anaesthesiologists' physical status classification (ASA status).

[b]Age, alcohol, body mass index (BMI), fasting serum glucose level, cholesterol, physical activity, food preference, blood pressure, and comorbidity.

[c]Age, sex, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, BMI, and clinical bowel obstruction at diagnosis.

[d]Age, sex, stage, grade, and inflammatory bowel disease.

[e]Age, sex, time diagnosis to interview, preventive CRC screening history, and education.

[f]Age, sex, stage, year diagnosis, education, comorbidity, alcohol, and physical activity.

[g]Age, sex, functional status, obesity, history of diabetes, comorbidity, ethanol, steroid, ASA status, and wound class.

[h]Age, sex, stage, race, diagnosis date, BMI, and pack years history.

[i]Age, sex, stage, socioeconomic status, diabetes, physical activity, and BMI.
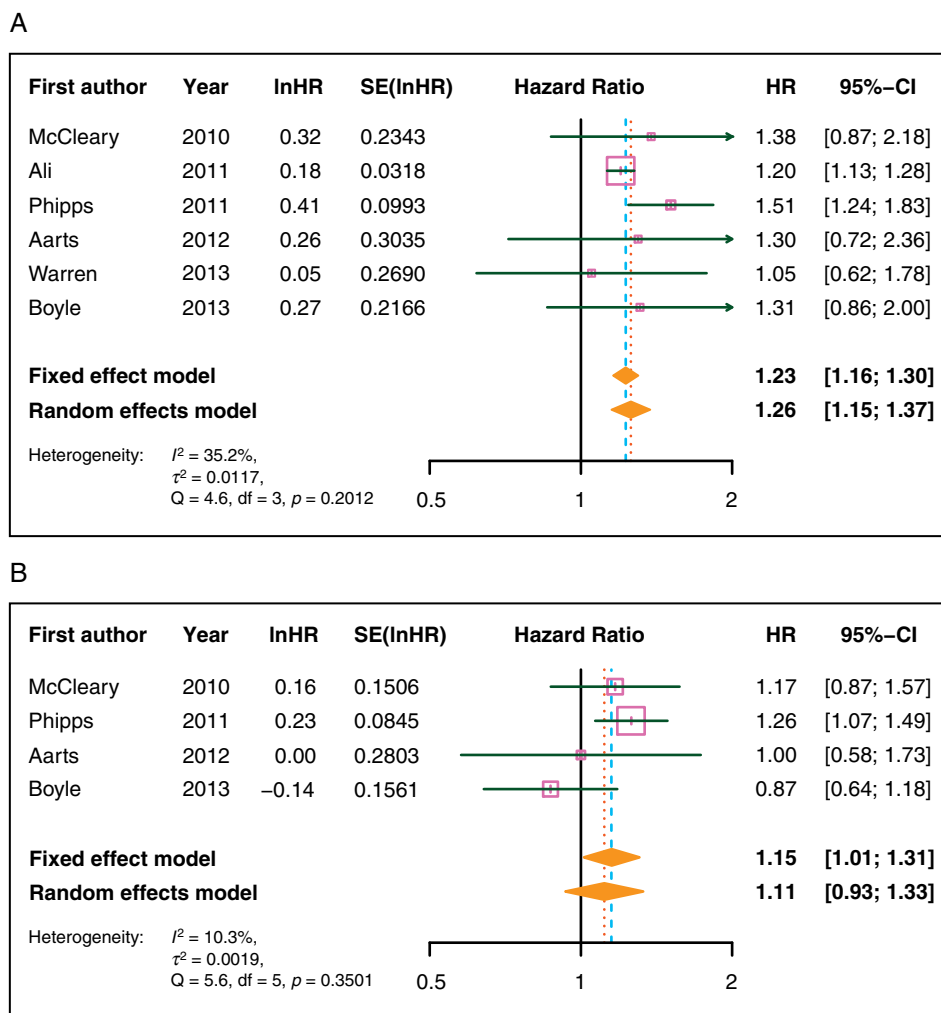
[j]Age, sex, T stage, tumor site, number of involved lymph nodes, DNA mismatch repair status, performance score, physical activity, BMI, and alcohol consumption.

[k]Stage and blood transfusion.

[l]Stage, number of positive lymph nodes, deprivation, and comorbidity.

[m]Age, stage, elective/emergency operation, systemic inflammatory response (modified Glasgow Prognostic Score), and patient physiology (physiological and operative severity score for the enumeration of mortality and morbidity).

[n]Stage, raised tumor markers, and pre-treatment performance status.

A

First author	Year	lnHR	SE(lnHR)	Hazard Ratio	HR	95%–CI
McCleary	2010	0.32	0.2343		1.38	[0.87; 2.18]
Ali	2011	0.18	0.0318		1.20	[1.13; 1.28]
Phipps	2011	0.41	0.0993		1.51	[1.24; 1.83]
Aarts	2012	0.26	0.3035		1.30	[0.72; 2.36]
Warren	2013	0.05	0.2690		1.05	[0.62; 1.78]
Boyle	2013	0.27	0.2166		1.31	[0.86; 2.00]
Fixed effect model					**1.23**	**[1.16; 1.30]**
Random effects model					**1.26**	**[1.15; 1.37]**

Heterogeneity: $I^2 = 35.2\%$,
$\tau^2 = 0.0117$,
$Q = 4.6$, df = 3, $p = 0.2012$

B

First author	Year	lnHR	SE(lnHR)	Hazard Ratio	HR	95%–CI
McCleary	2010	0.16	0.1506		1.17	[0.87; 1.57]
Phipps	2011	0.23	0.0845		1.26	[1.07; 1.49]
Aarts	2012	0.00	0.2803		1.00	[0.58; 1.73]
Boyle	2013	–0.14	0.1561		0.87	[0.64; 1.18]
Fixed effect model					**1.15**	**[1.01; 1.31]**
Random effects model					**1.11**	**[0.93; 1.33]**

Heterogeneity: $I^2 = 10.3\%$,
$\tau^2 = 0.0019$,
$Q = 5.6$, df = 5, $p = 0.3501$

Figure 2. Meta-analysis results for all-cause mortality in (A) current and (B) former smokers, compared with never smokers.

four studies combined [13, 16, 17, 22], excluding Park et al. due to low study quality, yielded a pooled effect estimate for all-cause mortality of 1.11 (95% CI 0.93–1.33), for former compared with never smokers (Figure 2B).

In a subgroup analysis by Boyle et al. [22], an adverse effect of former compared with never smoking was observed in stage IV cancer patients (supplementary Table S1, available at Annals of Oncology online). Former smokers showed higher crude survival rates than current smokers within all studies that reported crude all-cause or CRC-specific mortality [8, 11, 13, 17, 18, 22] (supplementary Table S2, available at Annals of Oncology online). No study could show a significant effect of former smoking on CRC-specific mortality [16, 22], 30-day mortality [19], disease-free survival [13, 23] (Table 2), or recurrence-free survival [13] (data not shown) within its total study population.

ever smoking

Three studies combined groups of current and former smokers in a category of ever smokers. Richards et al. found a significant effect of ever smoking on all-cause mortality (aHR: 1.52; 95% CI 1.06–2.18). The association was only slightly lower, but failed to

reach statistical significance for CRC-specific mortality (aHR: 1.46; 95% CI 0.92–2.32) [14]. Phipps et al. [16] observed significantly increased risks for both outcomes for ever compared with never smokers (Table 2). Looking at disease-free survival, a more recent study by Phipps et al. [23] showed significantly increased risks for ever compared with never smokers (aHR: 1.23; 95% CI 1.02–1.49). This study also looked at subgroups of patients and found increased risks to suffer recurrence or die in ever smokers who were male, 50 years or younger, had a T3 tumor, 1–3 affected lymph nodes, a distal colon tumor, a mutated KRAS status, a wild-type BRAF status, and a proficient mismatch repair status (supplementary Table S3, available at Annals of Oncology online).

smoking intensity

Five studies reported effect measures for the relationship between survival and smoking intensity [12, 13, 16, 21, 23]. Four of them assessed intensity by lifetime pack years (Py) [12, 13, 16, 21] and one looked at cigarettes per day and years of smoking separately [23]. One study reported CRC-specific mortality [16], one recurrence-free survival [13], three disease-

survival [13, 21, 23], and three investigated the association between smoking intensity and all-cause mortality [12, 13, 16].

Several of the stratum-specific effect estimates reported in Table 2 were not statistically significant. However, nevertheless, a positive dose–response relationship between the amount of smoking and all-cause, CRC-specific mortality, and disease-free survival could be seen. In a subgroup of MSI-H patients, a fivefold increased risk for CRC-specific mortality was reported by Phipps et al. [16] for a dosage of >40 Py compared with 0 Py (aHR: 5.19; 95% CI 1.64–16.45) (supplementary Table S1, available at Annals of Oncology online).

time since smoking cessation

For patients, who quit smoking <10 years ago, a substantially increased risk for all-cause mortality was found in the study by Phipps et al. [16] (aHR: 1.48; 95% CI 1.16–1.89). A higher risk for both CRC-specific and all-cause mortality was still present in patients who had quit smoking at least 25 years ago compared with never smokers (aHR: 1.33; 95% CI 1.03–1.74 and aHR: 1.34; 95% CI 1.08–1.66). Similarly, the risk of recurrence or death, reported by disease-free survival, was significantly increased in patients with smoking abstinence of at least 10 years compared with never smokers (aHR: 1.24; 95% CI 1.00–1.55) in a recent study by Phipps et al. [23]. McCleary et al. [13] did not find significant associations between time since smoking cessation and recurrence-free survival or all-cause mortality (numbers not reported).

discussion

Smoking is an established risk factor for CRC incidence and mortality. Yet, there are few studies investigating survival after CRC diagnosis in association with smoking. To our knowledge, this is the first systematic review and meta-analysis on that topic. Sixteen articles matched our inclusion criteria, of which six were included in meta-analyses. Current smoking was associated with an increase in all-cause mortality compared with never smokers by 26%. CRC-specific mortality was increased for current and ever smokers in the majority of the included studies, and 30-day mortality was without exception significantly higher in current smokers. Studies assessing mortality or disease-free survival according to smoking intensity indicated consistent dose–response relationships. Results further indicate a detrimental effect of smoking on disease-free survival.

In past studies, smoking was associated with an increased risk of all-cause [34, 35] and CRC-specific mortality [6]. Our meta-analysis showed that an increase in all-cause mortality is also evident in CRC patients after diagnosis. An increase of 26% and 11% was estimated for current and former smokers compared with never smokers, respectively, even though the latter was not statistically significant. Although direct evidence is sparse, these patterns suggest that a substantial burden of mortality of CRC patients could be avoided by smoking cessation. However, the timeframe is unknown in which changes in smoking behavior would improve long-term survival. Former smokers are very heterogeneous in terms of time since cessation, consumed doses, and duration of smoking phases. Two [16, 22] of the four studies assessing former versus never smoking and all-cause mortality

[13, 16, 17, 22] defined former smoking as having quit smoking for at least 1 year, minimizing the proportion of recent changers. Phipps et al. [16] found that smokers, who had quit <10 years ago, still had an increased total mortality. Looking at smoking intensity, we saw a consistent dose–response relationship between pack years and risk of all-cause mortality. Taken together, these patterns suggest a strong role of both current smoking and the lifetime amount of smoking, and underline that smoking prevention and cessation which are beneficial for many health outcomes are also crucial for enhancing CRC patient survival.

As smoking also influences comorbidities [36], part of the excess risk of smoking CRC patients may result from excess mortality from other causes. In our review, associations of smoking with CRC-specific mortality were slightly lower than those with all-cause mortality. Nevertheless, there seems to be some excess CRC-specific mortality that is attributable to smoking. As for all-cause mortality, this excess mortality seems to be lower in former smokers. In addition, a dose–response relationship of smoking intensity with CRC-specific mortality was demonstrated. Similar to all-cause mortality, the relationship between smoking and CRC-specific death seems to be related to the cumulative lifetime exposure to smoking rather than recent changes [16]. Subgroup analyses indicate that effects on CRC-specific mortality might be driven by certain patient characteristics, such as: age, sex, tumor site, tumor stage, and MSI status [16, 22]. An association between smoking and MSI-H has been reported in previous studies [37–39]. In addition, a meta-analysis on CRC survival showed longer survival in MSI-H tumor patients compared with microsatellite stable (MSS) patients [40]. However, in Phipps et al. [16], MSI-H status combined with current smoking was associated with highly increased CRC mortality, suggesting that the survival advantage of MSI-H patients might not be shared by smokers.

In our review, we also looked at 30-day mortality after resection. Physicians should promote smoking cessation before surgery, because changes in smoking behavior can lower smoking induced complications [41]. Our results suggest that changes in smoking behavior can, in fact, lower the 30-day mortality risk after tumor resection. Both studies investigating the issue found significantly increased risks for current compared with never smokers and less increased risks for former compared with never smokers [10, 19]. Nevertheless, it is currently unknown, to what extent also short-term changes can influence a patient's post-surgical mortality risk. However, since short-term changes do reduce the risk for post-surgical complications of cancer patients [41, 42], a beneficial effect of smoking cessation even after cancer diagnosis and before surgery seems both plausible and likely. Smoking cessation should be promoted, also shortly before a surgery, and its impact on short- and long-term outcomes should be evaluated in further research.

Possible mechanisms linking smoking and CRC outcomes are manifold and incompletely understood. Apart from other adverse effects, interference of smoking with specific CRC therapy, such as chemo- or radiotherapy, appears plausible. Vincenzi et al. [43] found that cigarette smoking during cetuximab-based treatment may be responsible for a decreased response rate and shorter time to tumor progression in CRC patients. Furthermore, nicotine has shown anti-apoptotic effects on cancer cells *in vitro* and *in vivo* [44, 45], lowering the therapeutic response to both chemo- and

radiotherapy. In colon cancer cells, studies have shown a nicotine-induced increased proliferation and suppressed apoptosis *in vitro* [46]. Such effects could strongly influence a patient's prognosis and could therefore be influenced by smoking cessation.

Our review points to areas of research that require enhanced attention to enable a more complete understanding of the role in CRC prognosis and the potential to enhance prognosis of CRC patients by smoking prevention and cessation. In particular, studies on CRC outcomes should include more comprehensive assessments of the smoking history, both during lifetime and during the course of the disease. For example, in addition to pack years, other smoking intensity measures should be considered. An analysis by pack years assumes smoking duration and number of packs per day as equally influential, which must not be true [47]. Finally, increased efforts should be made to support smoking cessation and abstinence among CRC patients, and the impact of such efforts which might be embedded in comprehensive tertiary prevention programs should be carefully evaluated by randomized trials.

This review and meta-analysis has specific strengths and limitations. Strengths include the comprehensive search in multiple databases, as well as strict adherence to standards of study selection, data extraction, and reporting [7]. Despite the comprehensive search strategy, we cannot exclude the possibility of having missed relevant studies, in particular studies reported in languages other than English or German. There may have been negative studies that were never published as full length articles, even though there was no indication of publication bias in our meta-analyses. Heterogeneity in reporting made comprehensive summarization of results difficult. Although 16 studies were identified overall, the numbers of studies for each of the four end points was rather limited. In particular, meaningful meta-analyses could only be carried out on the increase in all-cause mortality for current and former smokers compared with never smokers. Comparability was further hampered by various definitions and categorizations of smoking exposure, heterogeneity in inclusion and exclusion criteria, and covariates adjusted for. In particular, the lack of or incomplete adjustment for co-morbidities may have resulted in incomplete control for confounding in some studies. Likewise, other lifestyle factors and their potential change with smoking habits over time were only considered to a varying and limited extent in the studies reported to date. Furthermore, the included studies did not investigate the mechanisms by which smoking did affect survival, such as a possible impact on CRC metastasis, which should be addressed in future research. Smoking exposure was ascertained by self-report in all studies and may have been subject to reporting bias. Furthermore, the timing of smoking ascertainment differed, and none of the studies had included ascertainment of smoking over time after diagnosis and treatment.

Despite these limitations, our results support the existence of detrimental effects of smoking on survival, also after CRC diagnosis. They point to the potential of enhancing perspectives of cancer survival by enhanced efforts of smoking prevention and promotion of smoking cessation and abstinence, both in general and among CRC patients in particular. Further observational and intervention studies should aim for a more comprehensive elucidation of the effects of such efforts.

disclosure

The authors have declared no conflicts of interest.

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KEY MESSAGE

This systematic review supports the existence of detrimental effects of smoking on survival, also after CRC diagnosis. The results point to the potential of enhancing perspectives of cancer survival by enhanced efforts of smoking prevention and promotion of smoking cessation, also among CRC patients. Pertinent efforts should be intensified and accompanied by thorough scientific evaluation.