Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Pooled Analysis of Smoking and Colorectal Cancer: Timing of Exposure and Interactions with Environmental Factors

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Abstract

Background: Considerable evidence suggests that cigarette smoking is associated with a higher risk of colorectal cancer (CRC). What is unclear, however, is the impact of quitting smoking on risk attenuation and whether other risk factors for CRC modify this association.

Methods: We conducted a pooled analysis of eight studies, including 6,796 CRC cases and 7,770 controls, to evaluate the association between cigarette smoking history and CRC risk and to investigate potential effect modification by other risk factors.

Results: Current smokers [OR, 1.26; 95% confidence interval (CI), 1.11–1.43] and former smokers (OR, 1.18; 95% CI, 1.09–1.27), relative to never smokers, showed higher risks of CRC. Former smokers remained at higher CRC risk, relative to never smokers, for up to about 25 years after quitting. The impact of time since quitting varied by cancer subsite: The excess risk due to smoking decreased immediately after quitting for proximal colon and rectal cancer but not until about 20 years post-quitting for distal colon cancer. Furthermore, we observed borderline statistically significant additive interactions between smoking status and body mass index [BMI; relative excess risk due to interaction (RERI)], 0.15; 95% CI, −0.01 to 0.31; $P = 0.06$] and significant additive interaction between smoking status and fruit consumption (RERI, 0.16; 95% CI, 0.01–0.30; $P = 0.04$).

Conclusion: CRC risk remained increased for about 25 years after quitting smoking, and the pattern of decline in risk varied by cancer subsite. BMI and fruit intake modified the risk associated with smoking.

Impact: These results contribute to a better understanding of the mechanisms through which smoking impacts CRC etiology. *Cancer Epidemiol Biomarkers Prev; 21(11); 1974–85. ©2012 AACR.*

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (1). Almost 60% of the cases occur in developed countries (1). The wide variation in CRC incidence across countries and the dramatic increase in CRC incidence with economic development after 1900 indicate that lifestyle and environment play prominent roles in the development of this disease (2–4). One lifestyle factor that may play a role in such geographic variation and temporal

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patterns of CRC incidence is cigarette smoking. Whereas cigarette consumption is now decreasing in developed countries, it is continuing to increase in many developing countries (e.g., China and India; ref. 5).

Although some earlier studies (6–8) did not detect a significant association between smoking and CRC, many studies provide support that cigarette smoking is a risk factor (9–17). Two recent meta-analyses suggested that current and former smokers have about an 18% higher risk of CRC than never smokers (9, 10). However, the impact of time since quitting smoking is still not well understood. In particular, there remain some questions as to how quickly the risk of CRC decreases after quitting smoking and whether the excess risk due to smoking could be completely eliminated. The answer to this question is important for public health, including screening decisions. Previous meta-analyses (9, 10) were based on summary statistics extracted from published articles, and therefore they could not uniformly categorize variables (such as time since quitting smoking) and control for other smoking-related variables and potential confounders which may lead to less precise estimates. More precise estimates of the association between smoking and CRC risk are important to aid understanding of the biologic mechanism underlying the association between smoking and CRC. Furthermore, it is not known whether factors associated with risk of CRC, such as body mass index (BMI), sex, fruit and vegetables consumption, or use of nonsteroidal anti-inflammatory drugs (NSAID; refs. 2, 18), modify the association between smoking and risk of CRC. An appropriately powered analysis of such interactions requires individual-level data and large sample sizes.

In this study, we used the data from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO; ref. 19) to examine the association between cigarette smoking and risk of CRC, including assessment of the impact of time since quitting smoking, and to investigate interactions between cigarette smoking and other lifestyle factors.

Materials and Methods

Study population

The GECCO study is supported by the U.S. National Cancer Institute and it is composed of well-characterized prospective cohorts and case–control studies of CRC (19). Details of studies have been described previously (19) and are provided in Supplementary Material S1. Five cohort studies [the Health Professionals Follow-up Study (HPFS; ref. 15); the Nurses' Health Study (NHS; ref. 14); the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; ref. 20); the VITamins and Lifestyle Study (VITAL; ref. 21); and the Women's Health Initiative (WHI; ref. 22)] and 3 population-based case–control studies [the Colon Cancer Family Registry (CCFR; ref. 23); the Diet, Activity and Lifestyle Survey (DALS; refs. 24, 25); and the Ontario Familial Colorectal Cancer Registry (OFCCR; ref. 26)] were included in this analysis. Subjects who were included in both the CCFR and the OFCCR were excluded from the CCFR. All participants gave informed consent, and studies were approved by the Institutional Review Board.

All CRCs were invasive colorectal adenocarcinomas, confirmed by medical records, pathologic reports, or death certificates. CRC cases had International Classification of Diseases, 9th edition (ICD 9) site codes of 153.0–153.4, 153.6–153.9, and 154.0–154.1. Cases arising from the cohort studies were included in this analysis with a matched set of controls. Details on matching criteria are described in the Supplementary Material. Inclusion was restricted to those with available DNA because GECCO is focused on genetic and environmental factors related to CRC. Subjects using pipes, cigars, or snuff were excluded.

Before exclusions, the 8 studies comprised data from 7,310 cases and 8,113 controls. We excluded participants with missing information on smoking (223 cases and 76 controls) and appendix cancer cases (27 cases). Because the majority of study participants self-reported non-Hispanic white race/ethnicity (96.5% non-Hispanic white, 0.3% Hispanic, 1.1% African American, 1.1% Asian, 0.3% American Indian, 0.4% others, and 0.3% missing), we restricted our analysis to non-Hispanic white participants. After these exclusions, 6,796 cases of CRC and 7,770 controls remained in the analysis.

Statistical analysis

The descriptions of the smoking-related variables used in this study are provided in Supplementary Material S2. We used a 2-stage pooled approach to evaluate the association between smoking and risk of CRC: (i) using multiple logistic regression models to calculate study-specific OR and the corresponding 95% confidence intervals (CI) and (ii) using an inverse variance–weighted random-effects meta-analysis approach (27) to pool the study-specific ORs to generate summary ORs. For the analyses of smoking status and pack-years, the following covariates were adjusted: age at reference time, sex, BMI (<25, 25-<30, $\geq$30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), alcohol intake (0–1, 1–<28, >28 g/d, when available), and study site (if applicable); for the analyses of time since quitting smoking and age at cessation, multiple logistic regression models included the aforementioned covariates as well as categorized pack-years of smoking (never smoker, $\leq$20, 21–40, 41–60, >60 pack-years); for the analyses of smoking intensity and smoking duration, we additionally adjusted for smoking duration and smoking intensity, respectively. Additional adjustment for other variables, including family history of CRC, history of sigmoidoscopy/colonoscopy, use of NSAIDs, physical activity, and dietary variables (i.e., total energy, red meat, processed meat, dietary fiber, vegetables, and fruits), did not appreciably alter our estimates and were not included in final models. Trend tests were conducted for pack-years, time since quitting smoking, age at cessation, smoking intensity, and smoking duration by evaluating these

variables as continuous variables (for pack-years, smoking intensity, and smoking duration, never smokers were assigned to 0; for time since quitting smoking, current smokers were assigned to 0 and never smokers were excluded; for age at cessation, never and current smokers were excluded). We also conducted analyses by cancer subsite, colon (ICD 9: 153.0–153.4, 153.6, 153.7, or 153.9) versus rectum (ICD 9: 154.0 or 154.1), and for colon cancer, we further stratified by proximal (ICD 9: 153.0, 153.1, 153.4, or 153.6) versus distal colon (ICD 9: 153.2, 153.3, or 153.7) cancer. All cases in DALS are colon cancers, and hence, it was not included in analyses of rectal cancer. We stratified by study design (case–control vs. cohort study) to evaluate whether summary ORs were affected by study design and conducted leave-one study-out analyses (omitting each study in turn and redoing meta-analysis) to examine whether a single study dominated the summary ORs.

We used nonparametric regression analysis through fitting a restricted cubic spline (28, 29) to logistic regression models to examine CRC risk as a function of time since quitting and accounting for the possibly nonlinear relationship. We treated time since quitting as a continuous variable with current smokers assigned to 0 and used as the reference group (never smokers were excluded). For this analysis, all studies were merged into a single dataset with adjustment for study and the knots were established through automatically stepwise selection. Likelihood ratio tests were used to test nonlinearity by comparing spline models to a linear model (29).

To assess whether there were multiplicative interaction effects on the risk of CRC between smoking status (ever vs. never smoker) and risk factors including BMI (<25, ≥25 kg/m^2), sex (male, female), fruit and vegetable consumption [both dichotomized at sex- and study-specific medians (servings/d)], and use of NSAIDs (yes/no), we conducted analyses in logistic regression models (i) stratified by the potential effect modifiers and (ii) including multiplicative interaction terms of the potential modifiers and smoking status.

To evaluate additive interaction effects, we used linear OR models with interaction terms between the potential effect modifiers as listed above and smoking status (30). We used an inverse variance–weighted random-effects meta-analysis approach (27) to pool study-specific coefficient estimates of interaction terms. Wald tests were conducted to test whether summary estimates were equal to 0 and Wald-type CIs were computed. In linear OR models, the estimated coefficients of interaction terms are estimators of relative excess risk due to interaction (RERI; refs. 30, 31), a measure of additive interaction. In the calculation of RERI, we used never smoker, BMI < 25 kg/m^2, male, fruit and vegetable consumption greater than or equal to the sex- and study-specific median (servings/d), and any NSAID use as the reference groups. Studies that were restricted to one sex (HPFS, NHS, and WHI) were excluded in interaction analyses with sex.

In all pooled analyses, we calculated I^2 to estimate the percentage of total variation across studies due to heterogeneity beyond chance (32) and Q statistics to test heterogeneity across studies (33). All statistical tests were 2-sided. All analyses were conducted using R software version 2.14 and SAS version 9.2 (SAS Institute, Inc.).

Results

The basic characteristics of each study involved in this analysis are described in Table 1. The fraction of ever smokers across studies varied from 53% to 64% among cases and from 48% to 59% among controls. Our pooled analysis showed that the risk of CRC was 20% higher for ever smokers than for never smokers (OR, 1.20; 95% CI, 1.11–1.28; $I^2 = 0$, $P_{\text{heterogeneity}} = 0.82$; Table 2 and Fig. 1A). The results did not differ by cancer subsite [colon vs. rectal cancer ($P = 0.98$); proximal vs. distal colon cancer ($P = 0.99$); Tables 2 and 3 and Fig. 1B and C]. We observed elevated risk of CRC with increased pack-years of smoking overall and when stratified by colon and rectal cancers.

Compared with never smokers, former smokers had statistically significant higher risks of CRC and colon cancer for up to about 25 years after quitting (Table 2;

Table 1. Description of the characteristics by study

				Smoking, *n* (%)						Age, mean (SD), y		Sex, % men	
				Never		Former		Current					
Study	Design	Case, *n*	Control, *n*	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
CCFR	Case–control	1,148	1,046	517 (45)	493 (47)	414 (36)	405 (39)	217 (18)	148 (14)	54 (11)	57 (11)	53	44
DALS	Case–control	1,450	1,475	592 (41)	701 (48)	650 (45)	577 (39)	208 (14)	197 (13)	64 (10)	64 (5)	56	56
HPFS	Cohort	339	627	133 (39)	288 (46)	190 (56)	305 (49)	16 (5)	34 (5)	67 (8)	66 (8)	100	100
NHS	Cohort	453	994	192 (42)	443 (45)	196 (43)	431 (43)	65 (14)	120 (12)	60 (7)	60 (6)	0	0
OFCCR	Case–control	1,064	1,202	442 (42)	497 (41)	530 (50)	589 (49)	92 (9)	116 (10)	61 (9)	62 (9)	40	55
PLCO	Cohort	541	551	235 (43)	272 (49)	249 (46)	240 (44)	57 (11)	39 (7)	64 (5)	64 (5)	57	57
VITAL	Cohort	340	344	124 (36)	159 (46)	186 (55)	165 (48)	30 (9)	20 (6)	67 (6)	67 (6)	55	55
WHI	Cohort	1,461	1,531	683 (46)	799 (52)	667 (46)	643 (42)	111 (8)	89 (6)	66 (7)	66 (6)	0	0
Total		6,796	7,770	2,918 (45)	3,652 (43)	3,082 (43)	3,355 (47)	796 (12)	763 (10)	62 (10)	63 (9)	39	40

Table 2. Association of smoking-related variables and risk of CRC, colon, and rectal cancer

	CRC				Colon cancer			Rectal cancer[a]		
Exposure	**Cases**	**Controls**	**OR (95% CI)[e]**	**I^2, %**	**Cases**	**OR (95% CI)[e]**	**I^2, %**	**Cases**	**OR (95% CI)[e]**	**I^2%**
Smoking status										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
Ever smoker	3,878	4,118	1.20 (1.11–1.28)	0	2,989	1.19 (1.10–1.29)	0	813	1.17 (1.03–1.33)	0
Former smoker	3,082	3,355	1.18 (1.09–1.27)	0	2,393	1.19 (1.09–1.29)	0	630	1.12 (0.98–1.28)	0
Current smoker	796	763	1.26 (1.11–1.43)	8	596	1.21 (1.06–1.37)	0	183	1.37 (1.11–1.68)	0
Pack-years of smoking										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
≤20	1,631	1,941	1.08 (0.99–1.18)	0	1,215	1.06 (0.96–1.16)	0	375	1.10 (0.94–1.28)	0
20–40	1,066	1,061	1.28 (1.15–1.42)	0	837	1.28 (1.15–1.44)	0	207	1.21 (1.00–1.46)	0
40–60	592	583	1.29 (1.12–1.48)	5	469	1.29 (1.12–1.49)	0	117	1.35 (1.06–1.73)	0
>60	400	336	1.37 (1.16–1.62)	1	321	1.32 (1.09–1.60)	10	73	1.40 (1.03–1.90)	0
P_{trend}[b]			2.510^{-8}			1.710^{-7}			0.01	
Time since quitting,[f] y										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
Current smoker	796	763	1.36 (1.12–1.64)	0	596	1.29 (1.05–1.58)	0	183	1.50 (1.05–2.13)	0
0–15	871	762	1.47 (1.21–1.78)	1	681	1.37 (1.07–1.76)	22	182	1.51 (1.05–2.17)	0
15–25	835	836	1.31 (1.07–1.60)	0	652	1.30 (1.05–1.61)	0	169	1.29 (0.90–1.85)	0
25–35	677	784	1.15 (0.85–1.55)	39	518	1.04 (0.68–1.57)	62	135	1.09 (0.73–1.64)	0
≥35	488	744	0.74 (0.47–1.18)	70	395	0.73 (0.45–1.17)	67	85	0.70 (0.40–1.22)	25
P_{trend}[c]			1.710^{-3}			0.01			3.110^{-5}	
Age at cessation,[f] y										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
<40	1,081	1,326	1.03 (0.79–1.34)	8	804	0.95 (0.68–1.33)	28	257	1.17 (0.71–1.92)	8
40–50	744	755	1.28 (0.96–1.70)	23	587	1.21 (0.86–1.69)	32	142	1.35 (0.86–2.11)	0
≥50	1,055	1,063	1.31 (1.01–1.70)	26	861	1.25 (0.92–1.70)	36	172	1.28 (0.86–1.93)	0
P_{trend}[d]			5.910^{-3}			7.810^{-3}			0.30	
Smoking intensity,[g] cigarettes/d										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
<20	1,529	1,732	1.28 (1.11–1.48)	0	1,158	1.23 (1.06–1.43)	0	332	1.44 (1.10–1.88)	0
20	1,212	1,211	1.30 (1.09–1.55)	31	946	1.29 (1.09–1.52)	16	247	1.40 (1.05–1.86)	15
>20	1,022	1,035	1.28 (1.10–1.49)	9	798	1.27 (1.09–1.48)	0	210	1.31 (0.93–1.83)	30
P_{trend}[b]			0.60			0.59			0.63	
Smoking duration,[h] y										
Never smoker	2,918	3,652	1.0		2,266	1.0		598	1.0	
<10	499	663	0.94 (0.78–1.13)	6	372	0.96 (0.77–1.20)	19	118	0.84 (0.61–1.15)	0
10–20	756	875	1.07 (0.93–1.24)	0	559	1.08 (0.92–1.27)	0	179	1.02 (0.79–1.33)	0
20–30	844	827	1.29 (1.11–1.50)	9	640	1.30 (1.11–1.52)	7	189	1.23 (0.96–1.59)	0
30–40	852	834	1.29 (1.12–1.48)	0	672	1.30 (1.13–1.51)	0	164	1.15 (0.87–1.51)	10
≥40	805	805	1.28 (1.10–1.49)	9	649	1.27 (1.09–1.48)	0	141	1.31 (0.93–1.83)	30
P_{trend}[b]			0.01			0.03			0.01	

[a]For rectum cancer—all studies were included except DALS.
[b]Included never smokers and assigned them to 0.
[c]Excluded never smokers and assigned current smokers to 0.
[d]Among former smokers.
[e]Adjusted for age, sex, BMI (<25, 25–<30), ≥30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), alcohol intake (0–1, 1–<28, >28 g/d, when available), and study site (if applicable).
[f]Additionally adjusted for pack-years of smoking (never smoker, ≤20, 21–40, 41–60, >60 pack-years).
[g]Additionally adjusted for smoking duration (never smoker, <10, 10–19, 20–29, 30–39, ≥40 years).
[h]Additionally adjusted for smoking intensity (never smoker, <20, 20, >20 cigarettes/d).

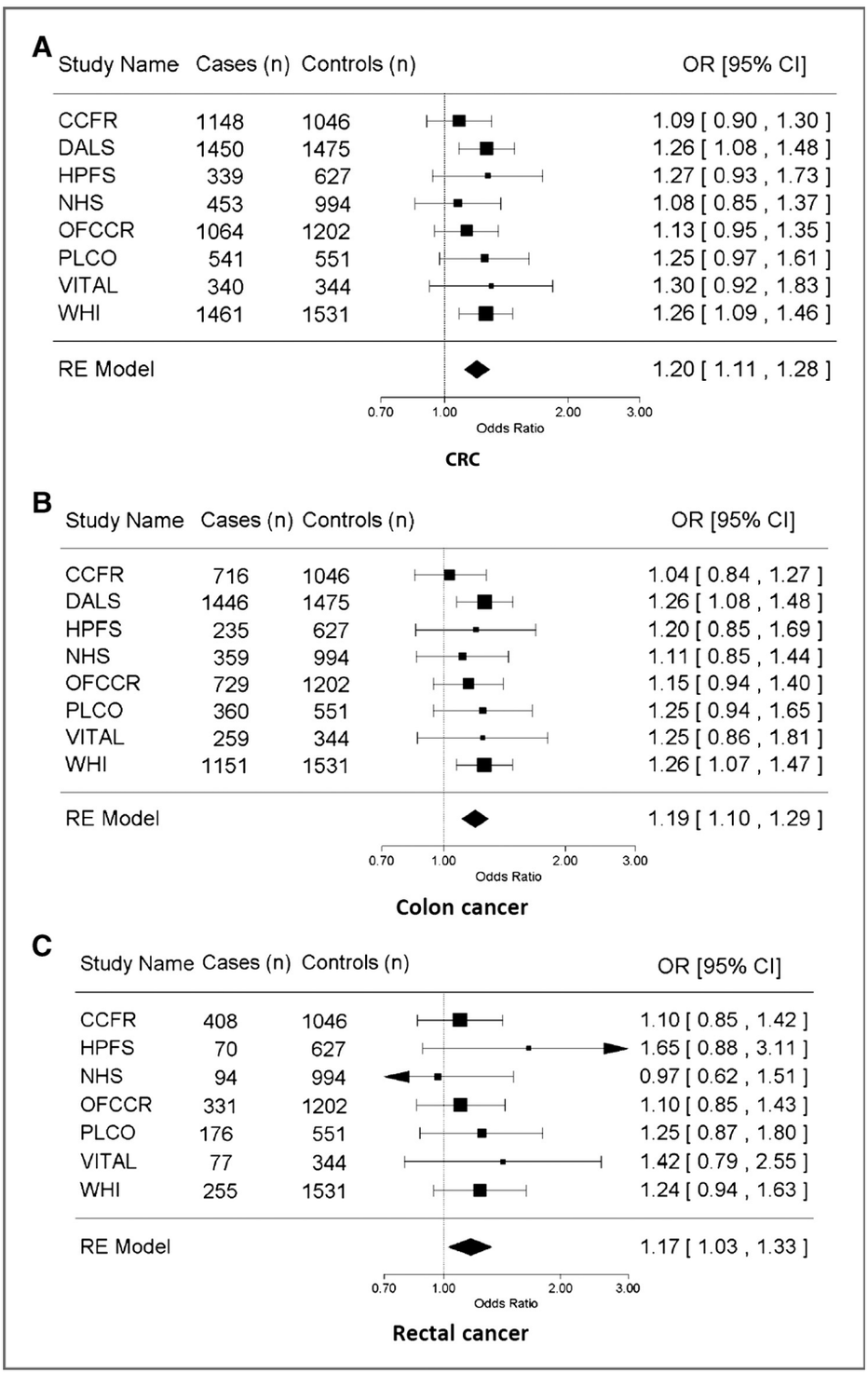

Figure 1. Forest plot for smoking status (ever vs. never) and risk of (A) CRC, (B) colon cancer, and (C) rectal cancer; adjusted for age, sex, BMI (<25, 25–<30, ≥30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), alcohol intake (0–1, 1–<28, >28 g/d, when available), and study site (if applicable). RE model: random-effects model.

Supplementary Fig. S1). We observed similar trends for colon and rectal cancer, although risk of those quitting smoking 15–25 years was not statistically significant for rectal cancer; however, this is probability due to limited power as risk estimates were similar for colon and rectal cancer. When further stratified by subsite within the colon, risk reduced after a short time since quitting for proximal colon cancer, whereas for distal colon cancer, the risk estimates remained statistically significant up to 25 years after quitting smoking (Table 3). To further investigate the association between time since quitting smoking and risk, we ran the nonparametric regression

Table 3. Association of smoking-related variables and risk of proximal and distal colon cancer

	Proximal colon cancer			Distal colon cancer		
Exposure	**Cases**	**OR (95% CI)[d]**	**I^2, %**	**Cases**	**OR (95% CI)[d]**	**I^2, %**
Smoking status						
Never smoker	1,266	1.0		933	1.0	
Ever smoker	1,633	1.18 (1.08–1.30)	0	1,258	1.18 (1.07–1.31)	0
Former smoker	1,313	1.17 (1.06–1.29)	0	1,008	1.20 (1.08–1.34)	0
Current smoker	320	1.26 (1.08–1.47)	0	250	1.10 (0.93–1.31)	0
Pack-years of smoking						
Never smoker	1,266	1.0		933	1.0	
≤20	671	1.07 (0.95–1.20)	0	511	1.05 (0.92–1.20)	0
20–40	456	1.28 (1.12–1.47)	0	354	1.25 (1.08–1.46)	0
40–60	255	1.28 (1.07–1.53)	2	202	1.33 (1.10–1.61)	0
>60	165	1.15 (0.87–1.52)	28	139	1.40 (1.11–1.77)	0
P_{trend}[a]		4.510^{-4}			2.110^{-5}	
Time since quitting,[e] y						
Never smoker	1,266	1.0		933	1.0	
Current smoker	320	1.23 (0.95–1.60)	2	250	1.24 (0.94–1.62)	0
0–15	341	1.16 (0.80–1.68)	40	318	1.51 (1.15–1.96)	0
15–25	337	1.10 (0.84–1.44)	0	294	1.47 (1.11–1.96)	0
25–35	293	0.91 (0.59–1.39)	43	210	1.16 (0.79–1.70)	22
≥35	255	0.69 (0.40–1.18)	60	130	0.74 (0.43–1.25)	46
P_{trend}[b]		0.04			0.01	
Age at cessation,[e] y						
Never smoker	1,266	1.0		933	1.0	
<40	432	0.87 (0.58–1.29)	44	355	1.15 (0.81–1.63)	0
40–50	314	1.05 (0.74–1.49)	36	257	1.53 (1.10–2.12)	0
≥50	493	1.24 (0.98–1.60)	20	342	1.51 (1.13–2.01)	0
P_{trend}[c]		0.04			0.05	
Smoking intensity,[f] cigarettes/d						
Never smoker	1,266	1.0		933	1.0	
<20	639	1.21 (1.01–1.45)	0	478	1.22 (0.99–1.50)	0
20	530	1.36 (1.14–1.62)	0	388	1.19 (0.97–1.45)	0
>20	411	1.22 (1.00–1.50)	13	360	1.25 (1.02–1.54)	0
P_{trend}[a]		0.85			0.36	
Smoking duration,[g] y						
Never smoker	1,266	1.0		933	1.0	
<10	211	1.00 (0.79–1.26)	0	153	0.94 (0.72–1.22)	0
10–20	297	1.01 (0.83–1.23)	0	242	1.13 (0.91–1.40)	0
20–30	335	1.23 (1.02–1.48)	0	289	1.40 (1.10–1.78)	23
30–40	361	1.23 (1.03–1.47)	0	289	1.36 (1.11–1.65)	0
≥40	372	1.22 (1.00–1.50)	13	253	1.25 (1.02–1.54)	0
P_{trend}[a]		0.23			0.02	

[a]Included never smokers and assigned them to 0.

[b]Excluded never smokers and assigned current smokers to 0.

[c]Among former smokers.

[d]Adjusted for age, sex, BMI (<25, 25–<30, ≥30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), alcohol intake (0–1, 1–<28, >28 g/d, when available), and study site (if applicable).

[e]Additionally adjusted for pack-years of smoking (never smoker, ≤20, 21–40, 41–60, >60 pack-years).

[f]Additionally adjusted for smoking duration (never smoker, <10, 10–19, 20–29, 30–39, ≥40 years).

[g]Additionally adjusted for smoking intensity (never smoker, <20, = 20, >20 cigarettes/d).

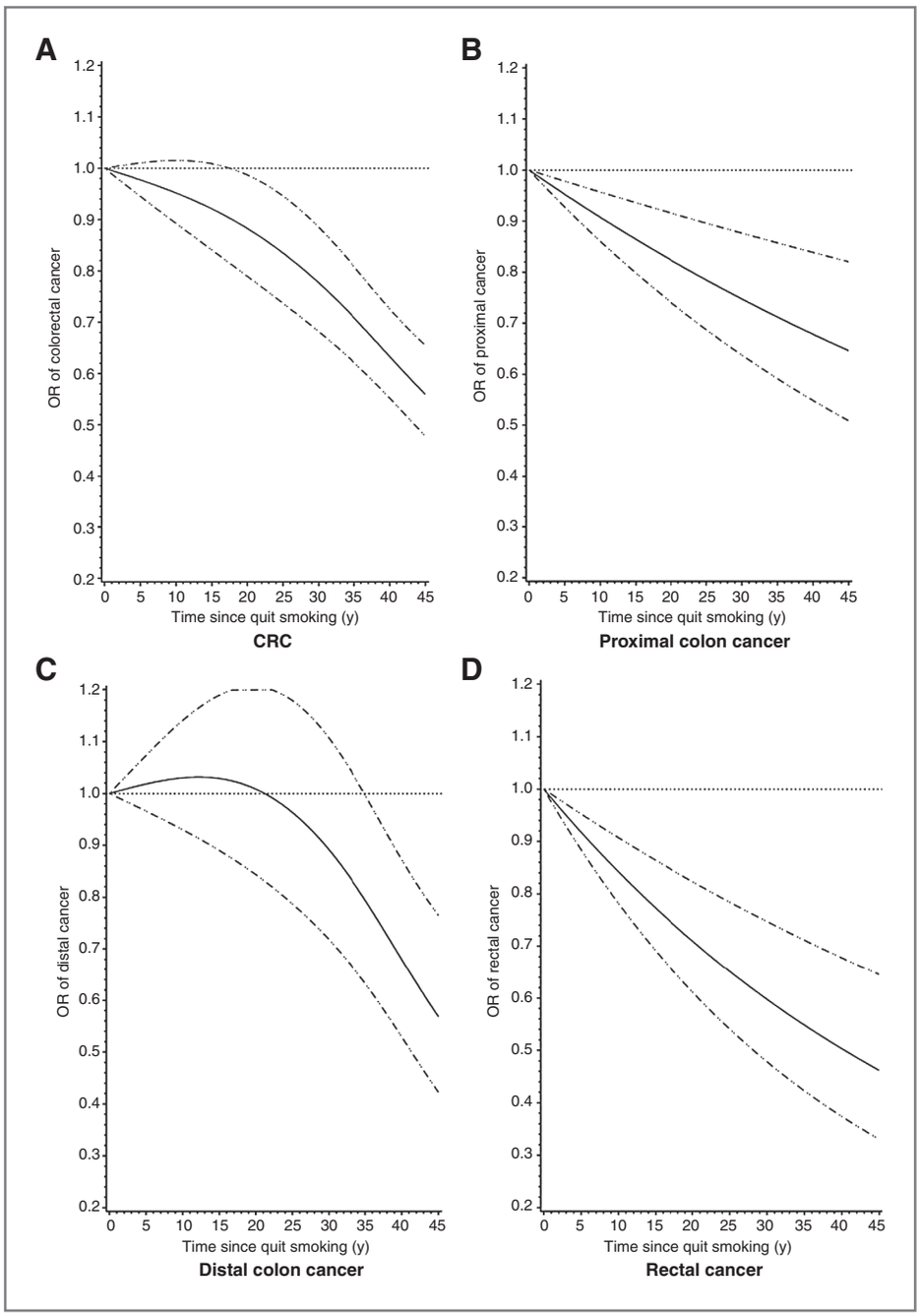

Figure 2. Nonparametric regression curve for the association between time since quit smoking and risk of (A) CRC, (B) proximal colon cancer, (C) distal colon cancer, and (D) rectal cancer; never smokers were excluded; current smoker was assigned to 0 and used as reference group; stratified by study and additionally adjusted for age, sex, BMI (<25, 25–<30, ≥30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), and pack-years (≤20, 21–40, 41–60, >60 pack-years). Solid line is regression curve and dotted line is 95% CI.

model among smokers only (using current smokers as the reference group). We found that risk declined immediately after quitting smoking for CRC (Fig. 2A). Subsite stratification showed a similar pattern for proximal colon and rectal cancer (Fig. 2B and D), whereas risk did not decline until about 20 years for distal colon cancer ($P_{\text{nonlinearity}} = 0.002$; Fig. 2C). We found between-study heterogeneity in the highest categories of time since quitting smoking for colorectal and colon cancer ($I^2 \geq 60\%$, $P_{\text{heterogeneity}} \leq 0.02$). When excluding one study at a time from this meta-analysis, exclusion of VITAL reduced heterogeneity the most (for CRC: $I^2 = 41\%$, $P_{\text{heterogeneity}} = 0.12$, and for colon cancer $I^2 = 30\%$, $P_{\text{heterogeneity}} = 0.19$ for colon cancer), whereas summary risk estimates did not change substantially (OR, 0.90; 95% CI, = 0.64–1.26 for CRC; OR = 0.91; 95% CI, 0.66–1.27 for colon cancer).

If former smokers quit smoking before age of the 40 years, we did not observe an elevated risk of CRC relative to never smokers, whereas CRC risk was increased in

those with older ages at cessation (Table 2). These results were similar for colon and rectal cancer. Risk of CRC did not vary by smoking intensity. Risk of CRC was significantly increased in ever smokers who smoked for at least 20 years but was not increased for those who smoked less than 20 years. A similar result was observed for colon and rectal cancer, although results for rectal cancer were not statistically significant and, overall, showed a less clear trend.

We observed a borderline statistically significant additive interaction between smoking and BMI ($P = 0.06$) and a statistically significant additive interaction between smoking and fruit consumption ($P = 0.04$; Table 4). Compared with normal-weight never smokers, the pooled RERI is 0.15 (95% CI, −0.01 to 0.31; $I^2 = 0$, $P_{\text{heterogeneity}} = 0.93$), that is, 15% of the excess risk of CRC for ever smokers with BMI $\geq$ 25 kg/m^2 was attributable to the interaction between smoking and BMI. Compared with never smokers with high fruit consumption, the pooled RERI is 0.16 (95% CI, 0.01–0.30; $I^2 = 0$, $P_{\text{heterogeneity}} = 0.79$), that is, 16% of the excess risk of CRC among ever smokers with low fruit consumption was attributable to the interaction between smoking and lower fruit consumption. When we stratified the analysis by other environmental risk factors of interest, the association between CRC and smoking status (ever vs. never) was stronger among overweight and obese participants and those with low fruit consumption. No other statistically significant interactions (additive or multiplicative) were observed. Because the associations with smoking status were similar across cancer sites, we did not conduct interaction analyses by cancer site.

Discussion

In our large pooled analysis, we confirmed results from previous studies showing that smoking is associated with increased risk of CRC. Excess risks remained up to about 25 years after quitting smoking, but risk starts to decline immediately after quitting smoking for proximal colon and rectal cancer and about 20 years later for distal colon cancer. Furthermore, we observed marginal statistically significant additive interactions of smoking with both BMI and fruit consumption.

There remains debate in the literature about the impact of time since quitting smoking on risk of CRC. Some studies have suggested that excess risk of CRC persists indefinitely among former smokers (14–16, 34), whereas other studies have suggested that the higher risk of CRC for former smokers is attenuated and eventually becomes comparable with that of never smokers (11, 12); however, results are not consistent when the risk starts to decline and when the excess risk is fully eliminated. When we evaluated these questions consistently across studies, we found that compared with current smokers, former

Table 4. Meta-analysis for the interaction effects between smoking status (ever vs. never) and variables possible or established risk factors of CRCs

Risk factor of CRC	Case	Control	OR (95% CI)[b, d]	I^2, %[2]	*P* for multiplicative interaction[b, c]	RERI (95% CI)[b, d]	I^2, %	*P* value for additive interaction[b, d]
BMI<25	2,375	3,137	1.14 (1.10–1.27)	0	0.210	0.15 (-0.01–0.31)	0	0.06
BMI≥25	4,293	4,472	1.24 (1.13–1.35)	0				
Male[a]	2,341	2,454	1.23 (1.09–1.38)	0	0.496	−0.05 (-0.25–0.16)	0	0.66
Female	2,202	2,164	1.18 (1.08–1.29)	0				
Fruit consumption (<median)	3,114	3,404	1.27 (1.14–1.41)	0	0.112	0.16 (0.01–0.30)	0	0.04
Fruit consumption (≥median)	3,272	3,951	1.13 (1.03–1.25)	0				
Vegetables consumption (<median)	2,825	3,156	1.18 (1.06–1.32)	0	0.492	−0.02 (-0.19–0.15)	0	0.81
Vegetables consumption (≥median)	3,618	4,235	1.21 (1.10–1.34)	8				
Any NSAID usage (yes)	2,201	3,195	1.23 (1.09–1.39)	0	0.900	0.14 (-0.04–0.32)	0	0.14
Any NSAID usage (no)	4,539	4,492	1.21 (1.11–1.32)	0				

[a]In interaction analysis with sex, studies only including one sex were excluded (HPFS, NHS, and WHI).

[b]Adjusted for age, sex, BMI (<25, 25–<30, ≥30 kg/m^2), education (high school graduate or less, some college or technical school, and college graduate or higher), alcohol intake (0–1, 1–<28, >28 g/d, when available), and study site (if applicable).

[c]Multiplicative interaction effects were evaluated by use of logistic regression models with interactive terms.

[d]Additive interaction effects were examined by use of linear OR models with interactive terms; in the calculation of RERI, the reference groups are nerve smoker, BMI (<25 kg/m^2), male, fruit consumption [≥sex, study specific median (servings/d)], vegetables consumption [≥sex, study-specific median (servings/d)], any NSAID use (yes), and alcohol intake (≤1 g/d).

smokers experienced a lower risk of CRC soon after quitting, although they still had a higher risk than never smokers up to about 25 years since quitting. Furthermore, we observed differences in this pattern by cancer subsite: risk started to decline among former smokers right after quitting smoking for proximal colon and rectal cancer and about 20 years later for distal colon cancer. Growing evidence suggests that there are the substantial subsite differences in CRC by genetic etiology, gene expression, molecular pathogenesis, and protein profiles (2, 35, 36). These disparities may contribute to the observed different associations with time since quitting by cancer subsite. In particular, recent studies have indicated that smoking is more strongly associated with a particular molecular phenotype of colorectal tumors, those that are microsatellite instability (MSI)-high and possess mutations in the *BRAF* gene (37, 38), as well as with the relevant precursor lesions (39). As these tumors are seen more frequently in the proximal than in the distal colon (35), smoking cessation may benefit proximal more than distal tumors. As we observed, however, our failure to find different risks associated with smoking in the distal and proximal colon suggests that additional factors may be involved. Further research is required to explore the mechanism underlying the difference in our findings by cancer subsite. Our large pooled analysis suggests that the risk in former smokers remains increased for a long time compared with never smokers.

It has been suggested that pack-years of smoking, a combination of smoking intensity and duration, may misrepresent the individual effects of these 2 characteristics because they may not equally contribute to disease risk (40, 41). Thus, we evaluated the effects of smoking intensity and duration separately while controlling one variable for the other. Our results suggested that both duration and intensity increased CRC risk and that patterns with both variables appeared nonlinear. This nonlinear plateau effect is consistent with some previous studies (12, 42) and has been observed for other cancers [e.g., lung, liver, kidney, pancreas, and bladder cancer (refs. 43, 44)]. This finding may point to potential molecular mechanisms such as saturation of smoking-derived carcinogen activation pathways (45, 46).

We were able to investigate interactions of smoking with various environmental risk factors. We observed statistical evidence for additive interaction between fruit intake and smoking status on risk of CRC. An interaction with plant foods has been reported for other cancers as well [e.g., lung cancer (ref. 47) and pancreatic cancer (ref. 48)]. The potential biologic mechanism for this interaction may be that anticarcinogenic components in fruits modify the effects of smoking through reducing DNA damage and mutation from smoking carcinogens (49). We also found a borderline statistically significant additive interaction between BMI and smoking status. The biologic mechanism for the interaction between BMI and smoking status is unclear, but possible explanations include the pro-oxidant and inflammatory effects of increased insulin, glucose, insulin-like growth factors (IGF), and related compounds that accompany overweight and obesity which, in turn, may enhance the rate of accumulation of DNA damage due to smoking (50) and that immunosuppressive effects of specific free fatty acids (FFA) from adipocytes may increase the susceptibility to cancer triggered by smoking (51). However, given the marginal significance of our findings, it will be important that these results are replicated in other large studies, such as available in the Cohort Consortium (52). We note that when exploring interactions on the multiplicative scale, we observed no interaction. Rothman and colleagues (53, 54) have remarked that assessment of interaction should mainly be based on an additive scale and it has been illustrated that under causal pie models, biologic interaction results in departure from additivity of disease rates (55).

This pooled analysis has several strengths, including the large sample size and the availability of individual-level data from each study on detailed smoking exposures, major confounders, and potential effect modifiers. The availability of individual data permitted us to consistently and flexibly evaluate exposure–disease relationship, potential confounding, and interaction effects. We observed little evidence for heterogeneity and risk estimates overall did not vary substantially between studies. Our results were not dominated by a single study and did not vary by study design (case–control vs. cohort studies).

There are also some limitations to this analysis. Because we restricted the analysis to non-Hispanic white participants with available DNA as the parent study from which these data were drawn (GECCO) is focused on genetic and environmental factors, it is likely that our study populations do not represent the full range of socioeconomic status or racial and ethnic groups. However, effect estimates of smoking status and the relationship with pack-years are consistent with those from previous meta-analyses (9, 10). In addition, similar association between CRC and smoking was observed in Asians (56, 57). Case–control studies could be affected by recall bias. However, studies showed that recalled information on tobacco use is valid and reliable (58, 59), and furthermore, results from case–control and cohort studies were similar. The reference time at which smoking exposure was assessed for HPFS and NHS was at time of blood draw rather than time of enrollment. Accordingly, prevalent cases may bias smoking effect estimates in the 2 studies. Nevertheless, dropping prevalent cases ($n = 91$) in these 2 studies did not influence our results. Because of the difference in study design, current smoking was defined differently in cohort versus case–control studies. However, this has not led to obvious heterogeneity in results. We adjusted for BMI as a potential confounder in our study but BMI could be either a confounder or a mediator of the association between smoking and CRCs, given the impact of smoking on BMI. However, the results without adjustment for BMI are similar to those with BMI adjustment and our conclusions do not change. When evaluating additive interaction, we

used asymptotic variance estimates from linear OR models in meta-analysis approach and calculated Wald-type CIs for pooled estimates of additive interaction effects. Some researchers indicated that Wald-type CI based on asymptotic variance may have poor coverage at typical sample size and likelihood-based CI may be preferred (60, 61). However, studies showed that in large sample sizes or at disease prevalence below 10%, Wald-type CI works well and is similar to likelihood-based CI (30, 62).

In summary, our findings confirmed previous results of positive association between smoking and CRCs. We evaluated the effect of time since quitting smoking in detail and found that the increased risk persisted for about 25 years after quitting smoking; however, risk started to decline immediately after quitting smoking for proximal colon and rectal cancer and about 25 year later for distal colon cancer. The observed effect modification of smoking and CRCs by BMI and fruit consumption, if replicated in future independent studies, could contribute to better understanding of the mechanisms and potentially improving strategies for CRC prevention.

Disclosure of Potential Conflicts of Interest

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the CFRs, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the CFR. A.T. Chan declares a minor conflict of interest in his role as a consultant/advisory board member of Bayer HealthCare, Pfizer Inc., and Millenium Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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