

Association Between Cigarette Smoking and Colorectal Cancer in the Women's Health Initiative

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The evidence linking cigarette smoking to the risk of colorectal cancer is inconsistent. We investigated the associations between active and passive smoking and colorectal cancer among 146877 Women's Health Initiative participants. Women reported detailed smoking histories at enrollment. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the association between smoking and overall and site-specific risk of colorectal cancer. Invasive colorectal cancer was diagnosed in 1242 women over an average of 7.8 years (range = 0.003–11.2 years) of follow-up. In adjusted analyses, statistically significant positive associations were observed between most measures of cigarette smoking and risk of invasive colorectal cancer. Site-specific analyses indicated that current smokers had a statistically significantly increased risk of rectal cancer (HR = 1.95, 95% CI = 1.10 to 3.47) but not colon cancer (HR = 1.03, 95% CI = 0.77 to 1.38), compared with never smokers. Passive smoke exposure was not associated with colorectal cancer in adjusted analyses. Thus, active exposure to cigarette smoking appears to be a risk factor for rectal cancer.

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Among American women, nearly 11% of incident cancers and 10% of cancer deaths are due to colorectal cancer (1). The association between tobacco exposure and colorectal cancer is controversial. Early studies investigating cigarette smoking and colorectal cancer risk reported no association (2–8), possibly because the reported smoking duration was too short to demonstrate the hypothesized long induction period of smoking-associated colorectal cancer (9). Recent investigations, with more thorough measurement of smoking exposure and longer exposure periods, have reported a positive relationship between cigarette smoking and the risk of colorectal cancer (10–19), although some studies report that this relationship is limited to rectal cancer (20,21). Results from other studies are also inconsistent, with some reporting no association (22,23) and others reporting no association among women (24,25). The few studies examining the effect of passive smoke exposure on risk of colorectal cancer report conflicting results (24,26–28).

We investigated associations between cigarette smoking and colorectal cancer in the Women's Health Initiative (WHI).

The WHI includes an observational study and three clinical trials, which have been described previously (29–32). This report includes a pooled analysis of participants in the observational study and three clinical trials, excluding those with prior cancers other than nonmelanoma skin cancer (14193; 2546 in the clinical trials and 11647 in the observational study) or lack of follow-up (678; 220 in the clinical trials and 458 in the observational study). The final sample included 146877 women (81518 in the observational study and 65359 in the clinical trials) with follow-up through March 31, 2005 (mean 7.8 years, range = 0.003–11.2 years). All participants provided written informed consent; protocols and procedures were approved by Institutional Review Boards at participating institutions. Colorectal cancer cases were reported and adjudicated as previously described (33). This analysis included only patients with adjudicated colorectal cancer. We also examined subgroups of invasive colorectal cancer defined as colon, rectal (i.e., rectum and rectal-sigmoid colon), and right-sided (i.e., ascending colon and cecum) and left-sided (i.e., descending and sigmoid colon) cancer.

At baseline, participants were classified as “never,” “past,” or “current” smokers on the basis of whether they had ever smoked more than 100 cigarettes in their lifetime and if they smoked at the time of the survey. Women reporting any history of smoking provided data about their smoking and smoking cessation behavior with a choice of categoric responses; these categories were collapsed in the present analysis to avoid small cell counts (see Appendix). Women in the observational study also reported their exposure to passive (i.e., secondhand) smoke. Participants who ever lived or worked with a smoker were classified as “ever” exposed to passive smoke, and those who did not were classified as “never.” Analyses involving passive smoke exposure excluded women reporting any active smoking history.

Characteristics of the total population and cancer subgroups were compared with *t* tests for continuous variables and chi-square tests for categoric variables. Cox proportional hazards models were used to estimate the effects of the smoking variables on the risk of invasive colorectal cancer, colon, rectal, and right-sided and left-sided cancer. Separate regressions were performed for each cancer outcome, and one smoking variable was included per regression model. Variables associated with invasive colorectal cancer

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CONTEXT AND CAVEATS

Prior knowledge

The evidence for the association between cigarette smoking and the risk of colorectal cancer is inconsistent.

Study design

Pooled analysis of the association between cigarette smoking and colorectal cancer among participants in the observational study and the three clinical trials of the Women's Health Initiative.

Contribution

Statistically significant positive associations between most measures of cigarette smoking and colorectal cancer were observed. Current smokers have a statistically significantly increased risk of rectal cancer but not colon cancer, compared with never smokers. Passive smoke exposure was not associated with colorectal cancer in adjusted analyses.

Implications

Active cigarette smoking appears to be a risk factor for rectal cancer.

Limitations

Smoking exposure was self-reported and does not account for any change in smoking behavior during follow-up. Because multiple comparisons were performed, the findings of this study might be due to chance. The rate of current smoking in women in this study was lower than US women with similar ages.

in bivariate analyses were included as covariates in the regression models if their *P* value was .10 or less. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for the smoking variables in each model. Tests for linear trend were performed by sequentially coding each level of the categoric smoking variables beginning with zero and then testing for a linear trend across the groups. Models were additionally adjusted for the possible effect of study design and hormone trial treatment arm by stratification (categorized as observational study, nonhormone trial-clinical trial, estrogen trial active arm, estrogen trial placebo arm, estrogen and progestin active arm, and estrogen and progestin placebo arm). The proportional hazards assumption was checked by modeling colorectal cancer by a time by

smoking interaction term in a proportional hazards model along with a smoking main effects term. This procedure was done for each of the smoking variables; none indicated that the proportional hazards assumption was violated. All tests were two-sided. All analyses were performed in SAS version 9.0 (SAS Institute, Inc, Cary, NC).

The 1242 cases of incident invasive colorectal cancer were distributed as follows: 1075 were colon, 176 were rectal, 461 were right-sided, and 296 were left-sided cancers. Table 1 describes the characteristics of the sample by colorectal cancer status. Women not diagnosed with colorectal cancer were younger ($P < .001$), less likely to have a family history of colorectal cancer ($P = .02$), and had lower body mass index ($P < .001$) than those diagnosed with colorectal cancer. There were statistically significant differences between patients with colorectal cancer and participants without colorectal cancer with respect to current smoking status ($P = .05$), age at smoking initiation ($P = .03$), cigarettes smoked per day ($P = .006$), and duration of smoking ($P < .001$).

Table 2 reports multivariable associations between smoking characteristics and total colorectal cancer, colon cancer, and rectal cancer. For total colorectal cancer, statistically significant positive trends were observed for cigarettes per day, duration of smoking, and age at cessation. Similar patterns were observed for colon, rectal, and right-sided cancers, although no statistically significant associations were observed for left-sided cancers (data not shown). Compared with never smokers, current smokers experienced a statistically significantly increased risk of rectal cancer (HR = 1.95, 95% CI = 1.10 to 3.47) but not colon cancer (HR = 1.03, 95% CI = 0.77 to 1.38). No statistically significant associations were observed between passive smoking and colorectal cancer.

The elevated risk of rectal cancer appears to drive the associations between smoking behavior and overall colorectal cancer risk. This observation has been reported in previous studies (20,21). Comparisons among site-specific cancer subgroups showed positive associations for right-sided but not left-sided colon cancers. Carcinogens found in cigarettes

may reach the colorectal mucosa through direct ingestion (34) or through the circulatory system (35). Colorectal adenomas are known to be precursor lesions for colorectal cancer, and an increased risk of adenomas has been observed among past and current smokers (10,11,36–40). Cigarette smoking may increase the risk of developing hyperplastic polyps (41–46), which may also be related to the development of colorectal cancer (47–50).

Our study had several limitations. Given the multiple comparisons performed, our findings could be due to chance. The finding of no association between passive smoking and colorectal cancer is in agreement with a recent study (26). Exposure to passive smoking is difficult to measure; therefore, our results may have been affected by measurement error that obscured a true effect. Our use of self-reported smoking exposures using categories of exposure is a potential limitation. Small cell counts in the highest categories of the smoking variables necessitated collapsing of categories, and the broad groupings used limit our ability to detect dose-response effects. Furthermore, our results do not account for changes in smoking behavior occurring after the baseline visit. External validity may be limited because the rate of current smoking was lower in the study sample (6.9%) than in similar-age US women (8.1%, aged ≥ 65 years) (51), although the prevalence of past smoking in the study sample (41.7%) was identical to the rate reported for US men and women aged 65–74 years (52).

The study population of more than 140 000 women, many of whom reported lengthy smoking histories, is a substantial strength. Other strengths include the prospective nature, diverse population, and central adjudication of colorectal cancer outcomes.

In summary, we report an increased risk of colorectal cancer, specifically of rectal cancer, with cigarette smoking, in agreement with previous studies (10–19). Our data add to the extensive evidence indicating that preventing smoking initiation and decreasing the duration of smoking might reduce colorectal cancer risk.

Table 1. Baseline characteristics of study population, overall and by colorectal cancer outcome*

	Total	No CRC	Invasive CRC	P value*
Demographics				
Mean age at entry in WHI, y (SD)	63.08 (7.20)	63.06 (7.20)	65.86 (6.80)	<.001
Age category at entry in WHI, No. (%)				
50–59 y	49606 (33.8)	49341 (33.9)	239 (19.2)	<.001
60–69 y	66017 (44.9)	65371 (44.9)	587 (47.3)	
70–79 y	31254 (21.3)	30783 (21.2)	416 (33.5)	
Race/Ethnicity, No. (%)				
White	120886 (82.3)	119740 (82.3)	1030 (82.9)	.08
Black	13423 (9.1)	13276 (9.1)	129 (10.4)	
Hispanic	5980 (4.1)	5944 (4.1)	34 (2.7)	
American Indian	641 (0.4)	635 (0.4)	5 (0.4)	
Asian/Pacific Islander	3917 (2.7)	3889 (2.7)	25 (2.0)	
Unknown	2030 (1.4)	2011 (1.4)	19 (1.5)	
Medical history				
First-degree relatives with CRC, No. (%)				
None	112587 (85.5)	111579 (85.6)	912 (82.7)	.02
1	16898 (12.8)	16709 (12.8)	167 (15.1)	
≥2	2141 (1.6)	2112 (1.6)	24 (2.2)	
History of diabetes, No. (%)				
No	138276 (94.2)	137027 (94.2)	1122 (90.4)	<.001
Yes	8510 (5.8)	8379 (5.8)	119 (9.6)	
Health behaviors				
Colonoscopy or sigmoidoscopy, No. (%)				
None	68470 (49.3)	67774 (49.3)	622 (54.0)	<.001
<5 years ago	44091 (31.8)	43760 (31.8)	297 (25.8)	
≥5 years ago	26271 (18.9)	26010 (18.9)	234 (20.3)	
Mean body mass index, kg/m ² (SD)	27.98 (5.93)	27.97 (5.93)	28.73 (6.00)	<.001
Body mass index category, No. (%)				
<25 kg/m ²	50961 (35.0)	50551 (35.0)	368 (29.9)	<.001
25 to <30 kg/m ²	50695 (34.8)	50208 (34.8)	436 (35.4)	
≥30 kg/m ²	43946 (30.2)	43473 (30.1)	427 (34.7)	
Physical activity, No. (%)				
None	22176 (15.9)	21946 (15.9)	207 (17.8)	.001
0 to <3.75 kcal/wk per kg	25404 (18.2)	25166 (18.2)	213 (18.3)	
3.75 to <8.75 kcal/wk per kg	24672 (17.7)	24429 (17.7)	217 (18.7)	
8.75 to <17.5 kcal/wk per kg	32296 (23.1)	31980 (23.1)	293 (25.2)	
≥17.5 kcal/wk per kg	35119 (25.1)	34849 (25.2)	232 (20.0)	
Duration of regular NSAID use, No. (%)				
<1 y	106786 (72.7)	105766 (72.7)	917 (73.8)	.12
1–4 y	20332 (13.8)	20132 (13.8)	182 (14.7)	
≥5 y	19759 (13.5)	19597 (13.5)	143 (11.5)	
Smoking characteristics				
Smoking status, No. (%)				.05
Never smoker	74361 (51.3)	73708 (51.3)	586 (47.9)	
Past smoker	60533 (41.7)	59926 (41.7)	549 (44.9)	
Current smoker	10073 (6.9)	9972 (6.9)	89 (7.3)	
Age at smoking initiation, No. (%)				.03
Never smoked	74361 (51.1)	73708 (51.2)	586 (47.8)	
<20 y	40013 (27.5)	39634 (27.5)	345 (28.2)	
≥20 y	31028 (21.3)	30696 (21.3)	294 (24.0)	
Cigarettes per day smoked				.006
Never smoked	74361 (52.2)	73708 (52.2)	586 (48.7)	
<25	56300 (39.5)	55746 (39.5)	491 (40.8)	
≥25	11790 (8.3)	11657 (8.3)	126 (10.5)	
Duration of smoking, y				<.0001
Never smoked	74361 (52.0)	73708 (52.0)	586 (48.6)	
<20	31690 (22.2)	31441 (22.2)	221 (18.3)	
20–29	15023 (10.5)	14851 (10.5)	154 (12.8)	
30–39	12721 (8.9)	12586 (8.9)	125 (10.4)	
≥40	9244 (6.5)	9112 (6.4)	119 (9.9)	
Passive smoking status†				.75
Never exposed	3768 (9.3)	3738 (9.3)	28 (9.9)	
Ever exposed	36713 (90.7)	36422 (90.7)	256 (90.1)	

* For comparison of patients with invasive colorectal cancer and those without colorectal cancer. CRC = colorectal cancer; WHI = Women's Health Initiative; SD = standard deviation; NSAID = nonsteroidal anti-inflammatory drug.

† Excluding women reporting any history of active smoking.

Table 2. Multivariable associations between smoking characteristics and colorectal cancer, overall and by subsite*

	Invasive CRC		Invasive colon cancer		Invasive rectal cancer	
	HR (95% CI)	P value†	HR (95% CI)	P value†	HR (95% CI)	P value†
Smoking status		.09		.28		.05
Never smoker	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Past smoker	1.13 (0.99 to 1.29)		1.12 (0.97 to 1.29)		1.15 (0.80 to 1.67)	
Current smoker	1.12 (0.86 to 1.46)		1.03 (0.77 to 1.38)		1.95 (1.10 to 3.47)	
Age at smoking initiation, y		.12		.27		.13
Never smoked	1.00 (referent)		1.00 (referent)		1.00 (referent)	
<20	1.14 (0.97 to 1.33)		1.13 (0.96 to 1.33)		1.14 (0.75 to 1.75)	
≥20	1.12 (0.95 to 1.31)		1.08 (0.91 to 1.29)		1.39 (0.91 to 2.10)	
Cigarettes per day		.006		.01		.31
Never smoked	1.00 (referent)		1.00 (referent)		1.00 (referent)	
<25	1.08 (0.94 to 1.24)		1.05 (0.90 to 1.21)		1.29 (0.90 to 1.86)	
≥25	1.41 (1.14 to 1.76)		1.47 (1.16 to 1.85)		1.14 (0.59 to 2.18)	
Duration of smoking, y		.006		.03		.05
Never smoked	1.00 (referent)		1.00 (referent)		1.00 (referent)	
<20	0.94 (0.79 to 1.13)		0.95 (0.79 to 1.15)		0.87 (0.52 to 1.43)	
20–29	1.36 (1.12 to 1.66)		1.27 (1.02 to 1.58)		1.95 (1.20 to 3.17)	
30–39	1.19 (0.96 to 1.49)		1.18 (0.93 to 1.50)		1.24 (0.68 to 2.27)	
≥40	1.23 (0.97 to 1.55)		1.19 (0.93 to 1.54)		1.53 (0.83 to 2.83)	
Age at smoking cessation, y		.008		.06		.01
Never smoked	1.00 (referent)		1.00 (referent)		1.00 (referent)	
<30	0.94 (0.72 to 1.23)		0.95 (0.72 to 1.27)		0.79 (0.36 to 1.73)	
30–39	0.86 (0.67 to 1.11)		0.87 (0.67 to 1.14)		0.84 (0.42 to 1.70)	
40–49	1.26 (1.02 to 1.56)		1.24 (0.98 to 1.56)		1.39 (0.78 to 2.46)	
≥50	1.28 (1.07 to 1.55)		1.24 (1.02 to 1.52)		1.53 (0.93 to 2.52)	
Current smoker	1.13 (0.87 to 1.47)		1.04 (0.78 to 1.39)		1.93 (1.08 to 3.44)	
Time since cessation, y		.70		.69		.90
Never smoked	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Current smoker	1.14 (0.88 to 1.49)		1.05 (0.78 to 1.40)		1.98 (1.11 to 3.52)	
<10	1.25 (0.86 to 1.82)		1.15 (0.76 to 1.75)		1.81 (0.77 to 4.26)	
10–19	1.34 (1.10 to 1.64)		1.32 (1.06 to 1.64)		1.45 (0.84 to 2.50)	
20–29	1.18 (0.95 to 1.47)		1.16 (0.92 to 1.46)		1.27 (0.71 to 2.28)	
30–39	0.92 (0.72 to 1.17)		0.90 (0.70 to 1.17)		1.10 (0.59 to 2.06)	
≥40	0.93 (0.71 to 1.22)		0.97 (0.73 to 1.29)		0.53 (0.19 to 1.46)	
Passive smoking status‡		.73		.99		.40
Never exposed	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Ever exposed	0.93 (0.61 to 1.42)		1.00 (0.63 to 1.59)		0.63 (0.21 to 1.84)	

* Adjusted for the following variables: age, ethnicity, study arm, family history of colorectal cancer, total physical activity metabolic equivalents, duration of nonsteroidal anti-inflammatory drug use, alcohol, hormone therapy use (never, past, current), colonoscopy, history of diabetes, total dietary calcium, total dietary fiber, percent energy from fat, hemoglobin, waist circumference, and red meat intake; stratified by study (observational study, clinical trial–nonhormone trial, hormone trial treatment assignment). CRC = colorectal cancer; HR = hazard ratio; CI = confidence interval.

† For test of trend. All statistical tests were two-sided.

‡ Excluding women reporting any history of active smoking.

Appendix: Original and Recategorized Smoking Variables

Appendix Table 1. Age at smoking initiation: original and recategorized smoking variables

Age at smoking initiation, y		No.	Percent
Original value	Recategorized value		
Missing	Missing	1475	1.00
Missing	Never smoked	74361	50.63
<15	<20	4780	3.25
15–19	<20	35233	23.99
20–24	≥20	21963	14.95
25–29	≥20	4853	3.30
30–34	≥20	2036	1.39
35–39	≥20	1112	0.76
40–45	≥20	599	0.41
45–49	≥20	287	0.20
50–54	≥20	178	0.12

Appendix Table 2. Number of cigarettes smoked per day: original and recategorized smoking variables

No. of cigarettes smoked per day		No.	Percent
Original value	Recategorized value		
Missing	Missing	4426	3.01
Missing	Never smoked	74361	50.63
<1	≤24	3169	2.16
1–4	≤24	12536	8.54
5–14	≤24	21744	14.80
15–24	≤24	18851	12.83
25–34	≥25	6146	4.18
35–44	≥25	3833	2.61
≥45	≥25	1811	1.23

Appendix Table 3. Duration of smoking: original and recategorized smoking variables

Duration of smoking, y		No.	Percent
Original value	Recategorized value		
Missing	Missing	3838	2.61
Missing	Never smoked	74361	50.63
5–9	≤19	7048	4.80
10–19	≤19	24642	16.78
20–29	20–29	15023	10.23
30–39	30–39	12721	8.66
40–49	≥40	7309	4.98
≥50	≥40	1935	1.32

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