

Cigarette Smoking and Colorectal Cancer Mortality in the Cancer Prevention Study II

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Background: Recent studies suggest that long-term cigarette smoking is associated with an increased risk of colorectal cancer. Whether the association is causal or due to confounding remains unclear. **Methods:** We examined cigarette smoking in relation to colorectal cancer mortality, evaluating smoking duration and recency and controlling for potential confounders in the Cancer Prevention Study II. This prospective nationwide mortality study of 1 184 657 adults (age ≥ 30 years) was begun by the American Cancer Society in 1982. After exclusions, our analytic cohort included 312 332 men and 469 019 women, among whom 4432 colon or rectal cancer deaths occurred between 1982 and 1996 among individuals who were cancer free in 1982. Rate ratios (RRs) and 95% confidence intervals (CIs) were estimated by fitting Cox proportional hazards models. All statistical tests were two-sided. **Results:** Multivariate-adjusted colorectal cancer mortality rates were highest among current smokers, were intermediate among former smokers, and were lowest in lifelong nonsmokers. The multivariate-adjusted RR (95% CI) for current compared with never smokers was 1.32 (1.16–1.49) among men and 1.41 (1.26–1.58) among women. Increased risk was evident after 20 or more years of smoking for men and women combined as compared with never smokers. Risk among current and former smokers increased with duration of smoking and average number of cigarettes smoked per day; risk in former smokers decreased significantly with years since quitting. If the multivariate-adjusted RR estimates in this study do, in fact, reflect causality, then approximately 12% of colorectal cancer deaths among both

men and women in the general U.S. population in 1997 were attributable to smoking. **Conclusions:** Long-term cigarette smoking is associated with increased risk of colorectal cancer mortality in both men and women. Clear reduction in risk is observed with early smoking cessation. [J Natl Cancer Inst 2000;92:1888–96]

Cigarette smoking is estimated to cause more than 400 000 deaths annually in the United States (1,2). Approximately 160 000 of these deaths involve eight cancers (lung, mouth, pharynx, larynx, esophagus, pancreas, kidney, and bladder) judged unequivocally to be caused by smoking (1,3,4). Colorectal cancer is not presently included among the smoking-related cancers by the Centers for Disease Control and Prevention (1) or by the International Agency for Research on Cancer (4), even though smoking is consistently associated with colorectal adenomatous polyps (5–12) and somewhat less consistently with colorectal cancer (13–45).

Epidemiologic data on cigarette smoking in relation to risk of colorectal cancer have been mixed. Weak associations, when present, could be due to uncontrolled confounding (46). More

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recent studies (23,25,26,29,32,34,42–45) have shown stronger associations than earlier studies, especially in relation to long-term continuing smoking. Giovannucci et al. (23,32,47) hypothesized that carcinogens in cigarette smoke may act to initiate tumors in the colon and rectum, so that an induction period of 35–40 years may be needed to increase incidence. If this were true, then earlier studies might have missed an association due to insufficient follow-up time for the necessary tumor growth period, particularly among women. Alternatively, residual confounding may still explain some or all of the observed association; not all recent studies have controlled for colorectal cancer risk factors that are associated with smoking in the United States (48), such as diet, physical inactivity, or low utilization of colorectal cancer screening.

About 25% of U.S. adults and 36% of high school students were current cigarette smokers in 1997; 23% of the adults were former smokers (49,50). If long-term smoking begun during youth is etiologically important in colorectal cancer, then this relationship could substantially increase estimates of smoking-attributable cancers, could affect future trends of colorectal cancer incidence and mortality, and could help to identify high-risk individuals to target colorectal cancer screening.

To address issues related to confounding and the hypothesized relevant smoking duration, we examined cigarette smoking and colorectal cancer mortality using 14 years (1982 through 1996) of prospective data from the Cancer Prevention Study II (CPS II). This cohort consists of large numbers of current and former cigarette smokers of both sexes, with detailed lifetime smoking history and data on a wide range of potentially confounding factors.

SUBJECTS AND METHODS

Study Population

CPS II is a large, prospective mortality cohort established by the American Cancer Society (ACS) in 1982, with 508 351 men and 676 306 women recruited by ACS volunteers in 50 states, the District of Columbia, and Puerto Rico. To be eligible for the study, individuals had to be age 30 years old or older and to reside

in a household in which at least one person was 45 years old or older. The median age at cohort entry was 57 years for men and 56 years for women.

Vital status of study participants was obtained by ACS volunteers in 1984, 1986, and 1988, and reported deaths were verified with death certificates. Since 1989, vital status has been ascertained via automated linkage of the CPS II study population with the National Death Index (NDI) for date and, since 1993, cause of death (51). The underlying cause of death, from death certificate or NDI, was classified according to the *International Classification of Diseases* (ICD), 9th Revision (52). As of December 31, 1996, a total of 129 642 men and 107 810 women have died, and 2892 (0.24%) men and women had follow-up truncated in 1988 because of insufficient information for NDI linkage. The outcome of interest was death due to colon or rectal cancer (ICD-9 codes 153.0–154.9) occurring between enrollment in 1982 through December 31, 1996. Colon and rectal cancer deaths were combined because of the potential for their mutual misclassification on death certificates (53).

Analytic Cohort

Excluded from this analysis are individuals who reported a previous cancer (other than nonmelanoma skin) at cohort enrollment and those with missing cigarette smoking status or covariate data (Table 1). Cohort members excluded because of missing information were significantly older and less likely to have graduated from high school. Information on cigar or pipe smoking was collected from men only; those who reported any use were excluded from all analyses on cigarette smoking and were examined separately for cigar/pipe smoking. The final analytic cohort consists of 312 332 men and 469 019 women.

Cigarette Smoking Information

When enrolled in 1982, study participants completed and returned by mail a questionnaire that included questions on current and past tobacco use, diet, alcohol consumption, exercise, occupation, medical history, and family cancer history. Cigarette smoking status was ascertained by the question, “Do you now or have you ever smoked cigarettes, at least one a day for one year’s time?” Ever smokers were then asked questions on the average number of cigarettes smoked per day, the age they started smoking, and the total number of years that they smoked. Former smokers also were asked the age at which they quit smoking. Computed exposure variables included lifetime number of pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked) and years since smoking cessation. Exposure to smoking was defined by smoking status at baseline (never, current, or former), number of years of smoking, average number of cigarettes smoked per day, pack-years, age at which smoking started, and, among former smokers, age at which they quit smoking and number of years since they quit.

Table 1. Number of study participants, contributed person-years, and number of colorectal cancer deaths by exclusion criteria (Cancer Prevention Study II, men and women, 1982 through 1996)

	Men			Women		
	No. of participants	Person-years	No. of colorectal cancer deaths	No. of participants	Person-years	No. of colorectal cancer deaths
Total	508 351	6 420 307	4513	676 306	8 996 692	4252
Exclusions						
Prevalent cancer*	25 242	256 184	881	57 107	682 574	921
Cigar/pipe smoker	96 198	1 234 525	751			
Missing information on the following variables						
Cigarette smoking	34 548	407 253	364	65 606	855 024	464
Food intake	22 420	277 950	203	51 080	668 790	351
Body mass index	6784	84 578	47	10 802	141 064	79
Education	4271	51 168	48	6854	88 022	45
Exercise	3105	37 584	30	9641	124 952	75
Race	1367	18 125	8	1988	26 800	12
Alcohol consumption	1099	13 351	15	2095	27 654	18
Aspirin use	811	9537	6	1749	22 610	8
Multivitamin use	174	2155	4	365	4829	3
Analytic cohort	312 332	4 027 895	2156	469 019	6 354 373	2276

*Except nonmelanoma skin cancer.

Table 2. Selected characteristics of study participants by cigarette smoking status at baseline (Cancer Prevention Study II, men and women, 1982 through 1996)

Characteristic	Men			Women		
	Never smoker	Current smoker	Former smoker	Never smoker	Current smoker	Former smoker
Total	107 960	85 787	118 585	274 041	99 078	95 900
Median age at cohort entry	56	54	57	56	53	54
Median body mass index, kg/m ²	26	25	26	24	23	24
Race—nonwhite, %	6	7	4	6	7	4
Education beyond high school, %	70	59	65	55	56	67
Family history of colorectal cancer, %	5	4	5	6	6	5
Physical inactivity—little or no exercise, %	22	28	24	26	29	29
Two or more daily drinks of alcohol, %	13	33	25	6	20	16
Low or no consumption of vegetables, %	17	23	16	20	24	14
No consumption of high-fiber grain foods, %	19	32	22	19	27	17
High consumption of fatty meats, %	19	27	20	24	25	20
Regular aspirin use (% ≥15/mo, ≥1 y)	7	7	9	8	7	9
Multivitamin user, %	31	28	30	37	37	43
Estrogen replacement therapy—current use, %				9	9	11
Median age started smoking, y		17	18		19	18
Median No. of years of smoking, y		36	23		31	18
Median No. of cigarettes smoked per day		20	20		20	13
Median No. of pack-years		42	26		29	11
Median age at death (any cause), y	75	68	73	78	69	73

Covariate Information

Potential confounders were chosen on the basis of their observed associations with colorectal cancer mortality and with cigarette smoking (Table 2) and on previously reported risk factors associated with colon cancer mortality in CPS II (54–56). Covariates included in data analyses were race (white, black, or other); body mass index (BMI) (kg/m²) computed from self-reported height and weight at baseline (<18.5, 18.5–24.9, 25.0–29.9, 30.0–39.9, or ≥40 kg/m²); educational level (some high school, high school graduate, some college or trade school, college graduate, or postgraduate work); family history of colorectal cancer (yes or no); exercise (none, slight, moderate, or heavy); current multivitamin use (yes or no); a variable combining aspirin use frequency (never occasional, one to 14 per month, or ≥15 per month) and duration (never, 1–9 years, 10–19 years, or ≥20 years); current alcohol consumption (nondrinker, occasional/less than one daily drink, one drink daily, two to three drinks daily, or four or more drinks daily); and intake of vegetables, high-fiber grain foods, and fatty meats (in quintiles) from a dietary questionnaire of 32 food items and 10 beverages. Statistical models among women also included use of estrogen replacement therapy (never, former, current, ever use but status in 1982 unknown, or missing). While BMI may be both a potential confounder and intermediate variable between cigarette smoking and colorectal cancer mortality, we present results adjusting for BMI because it is an independent risk factor in our study population (56), and similar results were obtained with and without its inclusion. We excluded from the analysis persons with noninterpretable responses on these covariates (Table 1) and classified persons who systematically used blanks (instead of zero) to represent nonuse for certain medications, multivitamins, or alcoholic beverages as nonusers of these products.

Food-intake variables were derived by summing the number of days per week that each participant reported consuming vegetables (carrots, tomatoes, potatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/Brussels sprouts), high-fiber grain foods (bran/corn muffins, brown rice/whole wheat/barley, and oatmeal/shredded wheat/bran cereals), and fatty meats (beef, pork, ham, liver, smoked meats, fried bacon, fried hamburger, and frankfurters/sausage). Responses to specific food items that were systematically left blank were inferred to indicate nonconsumption if valid responses were provided for other food items. Participants who reported consumption of fewer than five foods were excluded from all analyses (Table 1).

Statistical Methods

Colorectal cancer mortality rates were directly standardized to the age distribution of the total cohort of men and women. Maximum likelihood estimates of age-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) were obtained

from fitting Cox proportional hazards models (57) with never smokers as the reference category. The observation period for each study participant terminated on the first of the following dates: death or December 31, 1996.

Multivariate-adjusted models included all covariates shown in Table 2. We computed the proportion of colorectal cancer deaths attributable to smoking both in smokers and in the total population based on multivariate-adjusted risk estimates and prevalence estimates of current and former smoking in the U.S. adult population in 1997 (49,58). *P* values for trend were estimated by modeling smoking characteristics as continuous variables, separately by smoking status, excluding never smokers (59). Because smoking duration is a function of age at smoking initiation and cessation and is closely associated with amount smoked, we estimated the independent importance of each smoking characteristic when modeled jointly with smoking duration, separately by smoking status (60). All analyses were performed with the use of the SAS statistical software package (61). All statistical tests were two-sided.

RESULTS

Participant Characteristics by Smoking Status

Twenty-eight percent of men and 21% of women reported current smoking at baseline, and 38% of men and 20% of women reported former smoking at baseline (Table 2). Current smokers of both sexes had lower BMI and reported more daily drinks of alcohol, lower intake of vegetables and high-fiber grain foods, and higher intake of fatty meats than never or former smokers. Compared with never and former smokers, male current smokers reported lower educational levels and less physical activity. Former-smoking women were more likely to report higher educational levels, current use of multivitamins and estrogen replacement therapy, regular aspirin use, and lower intake of fatty meats than never- or current-smoking women.

Cigarette Smoking Characteristics and Colorectal Cancer Mortality

In both sexes, current and former smokers in 1982 had significantly higher death rates for colorectal cancer compared with never smokers, with current smokers being at the highest risk (Table 3). The elevated risk remained statistically significant

Table 3. Colorectal cancer mortality rates and age-adjusted and multivariate*-adjusted rate ratios (RRs) and 95% confidence intervals (CIs), by cigarette smoking status (Cancer Prevention Study II, men and women, 1982 through 1996)

Cigarette smoking status	No. of colorectal cancer deaths	Person-years	Age-adjusted mortality rate per 100 000	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)
Men					
Total	2156	4 027 895	59		
Never smoker	683	1 431 504	51	1.00 (referent)	1.00 (referent)
Current smoker	558	1 074 694	67	1.44 (1.28–1.61)	1.32 (1.16–1.49)
Former smoker	915	1 521 697	60	1.21 (1.10–1.34)	1.15 (1.04–1.27)
Women					
Total	2276	6 354 373	39		
Never smoker	1355	3 718 502	36	1.00 (referent)	1.00 (referent)
Current smoker	476	1 325 142	51	1.42 (1.28–1.58)	1.41 (1.26–1.58)
Former smoker	445	1 310 729	41	1.15 (1.03–1.28)	1.22 (1.09–1.37)

*Multivariate models include age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models for women also include use of estrogen replacement therapy.

after adjustment for potential confounding variables; the multivariate-adjusted RR (95% CI) for current smoking status was 1.32 (1.16–1.49) among men and 1.41 (1.26–1.58) among women; RR (95% CI) for former smoking was 1.15 (1.04–1.27) among men and 1.22 (1.09–1.37) among women.

When analyzed separately, the association between current cigarette smoking was similar for colon and rectal cancer mortality; multivariate-adjusted RRs (95% CI) for colon cancer mortality were 1.34 (1.17–1.53) among men and 1.43 (1.26–1.61) among women, and estimates for rectal cancer mortality were

1.21 (0.88–1.66) among men and 1.31 (0.96–1.80) among women.

Statistically significant increased risk was observed among current smokers after 20 or more years of smoking in men and women combined (Table 4); multivariate-adjusted RRs (95% CI) were 1.33 (1.10–1.61) for smoking 20–29 years, 1.38 (1.22–1.57) for smoking 30–39 years, and 1.39 (1.25–1.55) for smoking 40 or more years. Risk estimates, in general, increased with number of cigarettes smoked per day, pack-years, and younger age at initiation and were statistically significant at nearly all

Table 4. Age- and multivariate*-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) by cigarette smoking characteristics among current smokers compared with never smokers (Cancer Prevention Study II, men and women, 1982 through 1996)

	Men			Women			Men and women
	Deaths	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)	Deaths	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)	Multivariate* RR (95% CI)
Never smokers	683	1.00 (referent)	1.00 (referent)	1355	1.00 (referent)	1.00 (referent)	1.00 (referent)
Current smokers							
Years of smoking†							
<20	12	1.34 (0.74–2.41)	1.24 (0.68–2.24)	28	1.09 (0.75–1.61)	1.07 (0.73–1.58)	1.11 (0.81–1.54)
20–29	46	1.45 (1.05–2.00)	1.33 (0.96–1.84)	81	1.35 (1.07–1.71)	1.33 (1.05–1.69)	1.33 (1.10–1.61)
30–39	177	1.46 (1.21–1.75)	1.34 (1.11–1.62)	163	1.42 (1.20–1.68)	1.41 (1.19–1.68)	1.38 (1.22–1.57)
≥40	323	1.43 (1.25–1.64)	1.31 (1.13–1.51)	204	1.51 (1.30–1.75)	1.51 (1.29–1.76)	1.39 (1.25–1.55)
<i>P</i> trend‡		.6441	.7576		.2425	.1665	.2407
Cigarettes smoked per day†							
<20	145	1.38 (1.15–1.65)	1.29 (1.07–1.55)	189	1.33 (1.14–1.55)	1.32 (1.13–1.55)	1.31 (1.17–1.48)
20 (1 pack)	162	1.36 (1.15–1.62)	1.25 (1.05–1.50)	176	1.55 (1.32–1.81)	1.52 (1.29–1.79)	1.39 (1.23–1.57)
21–39	123	1.44 (1.18–1.75)	1.33 (1.08–1.62)	60	1.25 (0.97–1.63)	1.26 (0.97–1.65)	1.32 (1.13–1.55)
≥40 (≥2 packs)	128	1.65 (1.36–2.00)	1.46 (1.19–1.79)	51	1.69 (1.27–2.24)	1.65 (1.24–2.21)	1.54 (1.31–1.81)
<i>P</i> trend		.1192	.2439		.0837	.0399	.0314
Pack-years of smoking							
<20	78	1.43 (1.13–1.80)	1.32 (1.04–1.68)	124	1.30 (1.08–1.56)	1.28 (1.06–1.55)	1.30 (1.12–1.51)
20–39	130	1.31 (1.08–1.59)	1.22 (1.00–1.49)	82	1.41 (1.12–1.76)	1.41 (1.12–1.77)	1.30 (1.12–1.51)
40–59	172	1.46 (1.24–1.73)	1.35 (1.13–1.61)	80	1.29 (1.03–1.62)	1.29 (1.02–1.62)	1.35 (1.17–1.55)
≥60	178	1.52 (1.28–1.79)	1.36 (1.13–1.62)	190	1.60 (1.37–1.86)	1.59 (1.35–1.87)	1.48 (1.31–1.66)
<i>P</i> trend		.1919	.3740		.0721	.0321	.0490
Age started smoking, y†							
≤15	146	1.52 (1.27–1.82)	1.36 (1.12–1.64)	54	1.79 (1.36–2.36)	1.74 (1.31–2.29)	1.47 (1.26–1.71)
16–19	258	1.48 (1.28–1.72)	1.36 (1.16–1.58)	193	1.43 (1.23–1.67)	1.43 (1.21–1.67)	1.40 (1.25–1.56)
≥20	143	1.29 (1.08–1.55)	1.21 (1.01–1.47)	225	1.36 (1.18–1.57)	1.36 (1.18–1.57)	1.31 (1.16–1.46)
<i>P</i> trend		.4143	.5519		.0176	.0132	.0206

*Multivariate models include age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models among women only also include use of estrogen replacement therapy.

†Analyses of number of years of smoking, average number of cigarettes smoked per day, and age at which smoking started do not control for one another.

‡Test for trend excludes nonsmokers.

exposure levels. Significant trends toward increasing risk were observed with number of cigarettes smoked per day, pack-years, and younger age at initiation.

Former smokers of both sexes were at increased risk after smoking for 20 years, with significant dose-response observed with increasing smoking duration, number of cigarettes smoked per day, pack-years, older age at quitting, and fewer years since smoking cessation (Table 5). Multivariate-adjusted RRs (95% CI) for men and women combined were 1.17 (1.04–1.31) for smoking 20–29 years, 1.25 (1.11–1.41) for smoking 30–39 years, and 1.37 (1.19–1.57) for smoking 40 or more years. Compared with never smokers, there was no increased risk among men who quit at least 20 years before study enrollment and women who quit smoking more than 10 years before study enrollment.

Adjusting for multiple covariates increased risk estimates for former-smoking women and had little net effect on estimates for current-smoking women (Tables 3–5). Although no single co-

variate changed risk estimates substantially, their cumulative effect consistently reduced risk estimates for former- and current-smoking men.

Among continuing smokers, the multivariate-adjusted RR associated with smoking duration was consistently highest among smokers of 40 or more cigarettes per day (Table 6; Fig. 1). After adjustment for smoking duration and covariates, the only smoking characteristic that remained significantly associated with risk was years since smoking cessation among male former smokers (data not shown).

Cigar/Pipe Smoking and Colorectal Cancer Mortality

Current smokers who had smoked exclusively cigars or pipes for 20 years or more were also at increased risk of colorectal cancer mortality compared with never smokers of cigarettes, cigars, or pipes: multivariate-adjusted RR (95% CI) = 1.34 (1.11–1.62).

Table 5. Age- and multivariate*-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) by cigarette smoking characteristics among former smokers compared with never smokers (Cancer Prevention Study II, men and women, 1982 through 1996)

	Men			Women			Men and women
	Deaths	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)	Deaths	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)	Multivariate* RR (95% CI)
Never smokers	683	1.00 (referent)	1.00 (referent)	1355	1.00 (referent)	1.00 (referent)	1.00 (referent)
Former smokers							
Years of smoking†							
<20	229	1.02 (0.88–1.19)	1.02 (0.88–1.19)	171	1.03 (0.88–1.21)	1.10 (0.94–1.30)	1.06 (0.95–1.18)
20–29	255	1.22 (1.06–1.41)	1.16 (1.00–1.34)	101	1.07 (0.87–1.31)	1.14 (0.93–1.40)	1.17 (1.04–1.31)
30–39	247	1.30 (1.12–1.50)	1.20 (1.04–1.40)	98	1.24 (1.01–1.52)	1.31 (1.07–1.62)	1.25 (1.11–1.41)
≥40	184	1.39 (1.18–1.65)	1.28 (1.08–1.51)	75	1.52 (1.20–1.93)	1.58 (1.24–2.00)	1.37 (1.19–1.57)
P trend‡		.0001	.0006		.0187	.0407	.0001
Cigarettes smoked per day†							
<20	219	1.12 (0.96–1.31)	1.11 (0.95–1.29)	256	1.11 (0.97–1.27)	1.20 (1.04–1.38)	1.15 (1.04–1.28)
20 (1 pack)	298	1.13 (0.98–1.29)	1.08 (0.94–1.24)	107	1.12 (0.92–1.36)	1.18 (0.96–1.44)	1.11 (1.00–1.25)
21–39	142	1.21 (1.01–1.45)	1.16 (0.96–1.39)	40	1.41 (1.03–1.93)	1.50 (1.09–2.06)	1.24 (1.06–1.45)
≥40 (≥2 packs)	256	1.44 (1.25–1.66)	1.30 (1.12–1.50)	42	1.25 (0.92–1.70)	1.28 (0.94–1.74)	1.33 (1.16–1.51)
P trend		.0022	.0452		.3854	.5353	.0324
Pack-years of smoking							
<20	267	1.04 (0.91–1.20)	1.04 (0.90–1.20)	187	1.14 (0.98–1.33)	1.22 (1.05–1.43)	1.11 (1.00–1.23)
20–39	285	1.19 (1.04–1.37)	1.14 (0.99–1.31)	134	1.04 (0.87–1.24)	1.11 (0.93–1.33)	1.14 (1.02–1.27)
40–59	165	1.27 (1.07–1.50)	1.18 (0.99–1.41)	46	1.27 (0.94–1.70)	1.33 (0.99–1.79)	1.23 (1.06–1.42)
≥60	198	1.53 (1.31–1.79)	1.36 (1.16–1.60)	78	1.34 (1.07–1.69)	1.38 (1.10–1.75)	1.38 (1.21–1.58)
P trend		.0001	.0004		.3449	.5401	.0005
Age started smoking, y†							
≤15	206	1.41 (1.21–1.65)	1.28 (1.09–1.50)	36	1.25 (0.89–1.74)	1.29 (0.92–1.80)	1.30 (1.13–1.50)
16–19	418	1.18 (1.05–1.34)	1.12 (0.99–1.27)	196	1.18 (1.01–1.37)	1.26 (1.08–1.47)	1.17 (1.06–1.29)
≥20	290	1.15 (1.00–1.32)	1.13 (0.98–1.30)	210	1.10 (0.95–1.27)	1.17 (1.01–1.36)	1.15 (1.04–1.27)
P trend		.8421	.6274		.4153	.3276	.7108
Age quit smoking, y							
≤30	91	0.90 (0.72–1.13)	0.91 (0.73–1.13)	70	0.91 (0.71–1.16)	0.98 (0.77–1.25)	0.94 (0.80–1.11)
31–40	205	1.11 (0.95–1.30)	1.08 (0.92–1.26)	93	1.07 (0.87–1.33)	1.15 (0.93–1.43)	1.11 (0.98–1.26)
41–50	280	1.27 (1.10–1.46)	1.19 (1.03–1.37)	93	0.96 (0.78–1.18)	1.03 (0.83–1.27)	1.16 (1.03–1.30)
51–60	235	1.39 (1.20–1.62)	1.29 (1.11–1.51)	122	1.46 (1.21–1.76)	1.54 (1.28–1.87)	1.38 (1.23–1.55)
≥61	104	1.31 (1.06–1.62)	1.21 (0.98–1.50)	67	1.45 (1.13–1.86)	1.50 (1.16–1.93)	1.32 (1.12–1.55)
P trend		.0001	.0009		.0127	.0383	.0001
No. of years since smoking cessation							
≤10	317	1.39 (1.22–1.59)	1.28 (1.11–1.47)	174	1.34 (1.14–1.57)	1.39 (1.18–1.63)	1.32 (1.19–1.47)
11–19	293	1.32 (1.15–1.51)	1.24 (1.08–1.43)	115	1.03 (0.85–1.24)	1.10 (0.90–1.33)	1.20 (1.08–1.35)
≥20	304	1.00 (0.87–1.15)	0.99 (0.86–1.13)	155	1.07 (0.90–1.26)	1.16 (0.98–1.37)	1.04 (0.94–1.16)
P trend		.0001	.0009		.0127	.0383	.0001

*Multivariate models include age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models among women only also include use of estrogen replacement therapy.

†Analyses of number of years of smoking, average number of cigarettes smoked per day, and age at which smoking started do not control for one another.

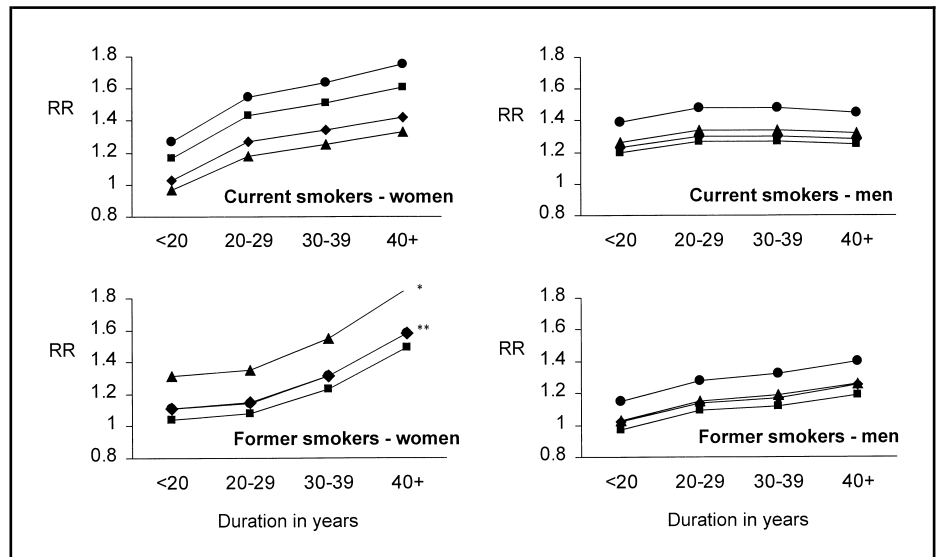
‡Test for trend excludes nonsmokers.

Table 6. Multivariate*-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) for cigarettes smoking (duration and dose) and colorectal cancer mortality (Cancer Prevention Study II, current and former smokers)

No. of years smoked cigarettes	Average No. of cigarettes smoked per day			
	<20	20	21–39	≥40
Current-smoking men				
<20	1.23 (0.67–2.24)	1.20 (0.65–2.21)	1.26 (0.68–2.36)	1.39 (0.75–2.60)
20–29	1.30 (0.92–1.85)	1.27 (0.89–1.81)	1.34 (0.93–1.93)	1.48 (1.03–2.14)
30–39	1.30 (1.03–1.65)	1.27 (1.01–1.60)	1.34 (1.05–1.71)	1.48 (1.16–1.89)
≥40	1.28 (1.05–1.56)	1.25 (1.03–1.51)	1.32 (1.06–1.64)	1.45 (1.17–1.81)
Current-smoking women				
<20	1.03 (0.70–1.53)	1.17 (0.78–1.76)	0.97 (0.61–1.54)	1.27 (0.79–2.04)
20–29	1.27 (0.98–1.64)	1.43 (1.10–1.87)	1.18 (0.84–1.66)	1.55 (1.08–2.22)
30–39	1.34 (1.08–1.65)	1.51 (1.22–1.86)	1.25 (0.93–1.67)	1.64 (1.20–2.24)
≥40	1.42 (1.18–1.73)	1.61 (1.33–1.96)	1.33 (1.00–1.78)	1.75 (1.28–2.37)
Former-smoking men				
<20	1.02 (0.85–1.22)	0.97 (0.81–1.16)	1.03 (0.82–1.28)	1.15 (0.94–1.40)
20–29	1.14 (0.94–1.37)	1.09 (0.91–1.29)	1.15 (0.93–1.42)	1.28 (1.07–1.54)
30–39	1.17 (0.97–1.43)	1.12 (0.94–1.34)	1.19 (0.96–1.47)	1.32 (1.11–1.59)
≥40	1.25 (1.01–1.54)	1.19 (0.98–1.45)	1.26 (1.00–1.58)	1.40 (1.15–1.71)
Former-smoking women				
<20	1.11 (0.93–1.32)	1.04 (0.81–1.34)	1.31 (0.91–1.87)	1.11 (0.78–1.57)
20–29	1.15 (0.92–1.44)	1.08 (0.83–1.40)	1.35 (0.94–1.93)	1.14 (0.80–1.63)
30–39	1.31 (1.04–1.66)	1.23 (0.95–1.60)	1.55 (1.08–2.21)	1.31 (0.92–1.86)
≥40	1.58 (1.22–2.06)	1.49 (1.12–1.97)	1.86 (1.28–2.70)	1.58 (1.10–2.27)

*Multivariate models include age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models among women only also include use of estrogen replacement therapy. (See Fig. 1 for overall patterns of smoking duration and dose in different strata.)

Fig. 1. Multivariate-adjusted rate ratios (RRs) of colorectal cancer mortality associated with cigarette smoking duration stratified by number of cigarettes smoked per day in current and former smoking Cancer Prevention Study II men and women (1982 through 1996). RRs were adjusted for age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models among women also include use of estrogen replacement therapy. *RR = 1.86; ** = categories of <20 and ≥40 cigarettes per day overlap. ◆ = <20 cigarettes per day; ■ = 20 cigarettes per day; ▲ = 20–39 cigarettes per day; and ● = ≥40 cigarettes per day.



Attributable Fraction in the Population and Among Cigarette Smokers

If the multivariate-adjusted RRs in CPS II were valid estimates of a causal relationship, then the proportion (95% CI) of colorectal cancer deaths in the U.S. population attributable to current cigarette smoking would be 8.1% (4.2%–11.9%) among men and 8.3% (5.4%–11.4%) among women; the proportion attributable to former smoking would be 3.9% (1.1%–6.8%) among men and 4.0% (1.7%–6.6%) among women. Taken together, the proportion of colorectal cancer deaths in the population attributable to any cigarette smoking would be approximately 12.0% among men and 12.3% among women. Among current cigarette smokers, the proportion of colorectal cancer

deaths attributable to smoking was estimated to be 24.2% (13.8%–32.9%) among men and 29.1% (20.6%–36.7%) among women.

DISCUSSION

Our main finding is that men and women who smoked cigarettes for 20 or more years at study enrollment experienced higher colorectal cancer death rates, even when we adjusted for multiple potential confounders. Consistent with a causal relationship with smoking, risk was higher in current than in former smokers and increased with smoking duration, number of cigarettes smoked per day, and pack-years. Risk estimates were higher for current than for former smokers in nearly every strata.

tum of smoking duration, amount, and age at initiation. Among former smokers, risk decreased with the number of years since smoking cessation. Former smokers who quit smoking at least 20 years before study enrollment were not at demonstrably increased risk compared with never smokers. Our results are consistent with both an early- and late-stage effect of cigarette smoking in colorectal carcinogenesis and highlight the importance of earlier smoking cessation as well as the avoidance of smoking initiation.

Central to the question of whether cigarette smoking plays a causal role in colorectal cancer is the extent to which nutritional or other unmeasured factors such as colorectal cancer screening may confound the relationship, particularly since risk estimates range between 1.1 and 2.0 in most studies (20,23,25,26,29,32,34,42–44). The small but statistically significant increase in risk associated with smoking is remarkably consistent across studies, regardless of the number or type of covariates adjusted for (or not) in analysis. Three studies (20,43,44) adjusted for physical activity; one adjusted also for the use of aspirin or other nonsteroidal anti-inflammatory drugs (44), two factors that have been consistently associated with lower colorectal cancer risk in many observational studies (62). Four studies (23,26,43,44) adjusted for some measure of diet, while a fifth (42) reported no appreciable confounding by dietary variables. The only study of incidence or mortality that adjusted for screening sigmoidoscopy (as well as other variables) in women (42) reported relative risk estimates similar to our results for smoking duration and years since quitting.

In CPS II, adjusting for measured potential confounders for colorectal cancer affected the association with smoking differently by sex and smoking status. Such adjustment increased risk estimates among female former smokers, had little net effect on risk estimates among female current smokers, and decreased risk estimates in men. The slight decrease in adjusted estimates in men was comparable to that reported by the Health Professionals' Follow-up Study (23), which controlled for saturated fat, folate, and dietary fiber and was one of the few studies that reported age- and multivariate-adjusted risk estimates. Although the possibility of residual confounding cannot be completely excluded, the internal consistency of our findings and the fact that adjusting for measured potential confounders actually strengthened the association between smoking and colorectal cancer mortality in CPS II female former smokers, a particularly health-conscious subgroup, suggest that the observed associations are unlikely to be explained solely by confounding.

While numerous studies (13–45) have examined the relationship between ever or current cigarette smoking and colorectal cancer incidence or mortality, only more recent studies (primarily since 1994) have examined gradients of smoking duration, amount, or timing. Most studies have shown increases in risk with pack-years (23,25,26,44), smoking duration (29,42,44), younger age at initiation (25,42,44), smoking in the distant past (23,32,43,45), or long-term continuous smoking (34). The only recent prospective study (27) that found no association with long-term smoking was conducted among male Swedish construction workers followed for 20 years. One third of this cohort was younger than age 30 years at cohort entry, and over half were younger than age 40 years, substantially younger than other cohorts in which associations were observed.

CPS II is the largest prospective study of cigarette smoking and colorectal cancer mortality reported among men and

women, adding substantially to the available prospective data on women in whom the association has been less consistently observed than in men. The Nurses' Health Study is the only prospective study of incidence reporting an association in women, with an RR (95% CI) of 1.47 (1.07–2.01) after 35–39 years since start of smoking at least 10 cigarettes per day and adjusting for age and BMI (32). The size of CPS II allowed for detailed examination of gradients in smoking characteristics separately in current and former smokers. We were able to examine the effect of cigarette smoking among men who reported no cigar or pipe smoking, which has been associated with colorectal cancer risk (14,44), and to examine the effect of long-term cigar or pipe smoking among men who reported no cigarette smoking. The prospectively collected information on smoking and relevant covariates minimized the potential for differential misclassification of exposure information.

Our study is limited in that smoking status was determined only once at study baseline. If some current smokers quit smoking during the 14-year follow-up, as is likely, then our risk estimates could underestimate the true risk among continuing smokers. The prevalence of current cigarette smoking in CPS II, a self-selected population, may be lower than that in the general population. If current smoking interacts with other unhealthy habits, such as heavy alcohol consumption or inadequate nutrient intake, then the generalizability of our results to these subgroups may be somewhat reduced. As a mortality study, our risk estimates reflect the association between cigarette smoking on colorectal cancer survival as well as incidence. We had no information on screening for colorectal cancer or stage of disease at diagnosis. Cigarette smoking is associated with later stage of colorectal cancer at diagnosis (63), leading to poorer prognosis and survival. However, other cohort studies (23,32) have reported findings similar to ours for colorectal cancer incidence. While we found no published report on colorectal cancer screening prevalence by cigarette smoking, data from the 1990–1994 National Health Interview Surveys (64) show that, compared with never smokers, current-smoking women are less likely and former-smoking women are significantly more likely to be screened for breast and cervical cancers. Thus, our study alone cannot exclude the possibility that continuing smokers experienced higher death rates from colorectal cancer than nonsmokers because of less screening and later stage of disease at diagnosis. However, the statistically significant increased risk of colorectal cancer mortality among former-smoking women in our study argues against appreciable confounding by colorectal cancer screening, since these women are perhaps the most likely to be screened. It is noteworthy that the one study that adjusted for screening sigmoidoscopy (42) yielded results similar to ours. The consistently observed relationship between cigarette smoking and risk of adenomatous polyps (5–12) also suggests that confounding by screening is unlikely to explain the increased risk observed in studies of colorectal cancer incidence and mortality.

Cigarette smoke contains more than 55 carcinogens, including polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines, and *N*-nitrosamines (65). There is already some direct evidence that tobacco carcinogens damage DNA in the human colonic epithelium. In one small study (66), DNA adducts to metabolites of benzo[*a*]pyrene, a potent PAH, were detected in colonic mucosa more frequently and at higher concentrations in smokers than in nonsmokers. This result is of

particular interest because DNA adduct levels in the epithelium of the colon have been found at higher levels in colorectal cancer case subjects than in control subjects (67). Future studies using tobacco-specific carcinogen-DNA adducts as biomarkers of exposure in the colon may provide more direct evidence of the etiologic role of cigarette smoking in colorectal cancer carcinogenesis. The strength of association between cigarette smoking and colorectal cancer risk may increase when examined within subgroups of individuals defined by indices of genetic susceptibility, such as DNA repair activity or carcinogen metabolism or detoxification gene polymorphisms. Examining this relationship by colorectal subsite also may yield associations of greater strength, since several studies (16,22,25,26,42) have shown an association between smoking and risk of rectal cancer, although there was no strong difference by subsite in our data. The increased risk of colorectal cancer mortality associated with current pipe or cigar smoking of 20 or more years in CPS II men further supports a causal role for tobacco carcinogens in colorectal cancer.

If the relative risk estimates associated with cigarette smoking in our study were causal, then the proportion of colorectal cancer deaths in the general population attributable to smoking in 1997 would be approximately 12% in men and 12% in women, which approximates estimates obtained from other studies of colorectal cancer incidence and mortality (23,25,42). If long-term cigarette smoking indeed causes a portion of colorectal cancers, one of the most common cancers in Western populations, then we estimate that the total number of deaths in the general U.S. population attributable to smoking would increase by more than 6800 per year based on smoking prevalence in the United States in 1997.

Cigarette smoking has been proposed as an exposure that may be partially responsible for the divergent colorectal cancer incidence and mortality trends in men and women between the 1950s and early-1980s (68). Since the smoking epidemic in U.S. women began later in time than in men (69), the impact of long-term cigarette smoking among women and youth could be reflected in future colorectal cancer incidence and mortality trends.

In summary, the precise and internally consistent risk estimates derived from this large prospective study support reconsidering the classification of colorectal cancer as, in part, a smoking-related cancer.

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NOTES

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