The Association between Cigarette Smoking and Risk of Colorectal Cancer in a Large Prospective Cohort from the United States

Lindsay M. Hannan, Eric J. Jacobs, and Michael J. Thun

Department of Epidemiology, American Cancer Society, Atlanta, Georgia

Abstract

Background: **Many studies have reported a 20% to 60% increase in risk of colorectal cancer associated with active smoking. However, neither the U.S. Surgeon General nor the IARC have classified the relationship as causal because of concern about residual confounding.**
Methods: **In a prospective study of 184,187 people followed from 1992 to 2005, we used Cox proportional hazard models to examine the relationship of cigarette smoking to incident colorectal cancer, controlling for screening and multiple known and putative risk factors. Information on smoking and time-varying covariates was updated in 1997, 1999, 2001, and 2003.**
Results: **The incidence of colorectal cancer was significantly higher in current [hazard ratios (HR), 1.27; 95% confidence intervals (CI), 1.06-1.52] and former smokers (HR, 1.23; 95% CI, 1.11-1.36) compared with lifelong nonsmokers in analyses that controlled for 13 covariates, including screening. The relative risk was greatest among current smokers with at least 50 years of smoking (HR, 1.38; 95% CI, 1.04-1.84). Among former smokers, risk of colorectal cancer decreased with greater time since cessation (*P* trend = 0.0003), and also decreased with earlier age at cessation (*P* trend = 0.0014). No association was seen among former smokers who had quit before age of 40 years or abstained for 31 years or more.**
Conclusions: **Long-term cigarette smoking is associated with colorectal cancer, even after controlling for screening and multiple other risk factors.** (Cancer Epidemiol Biomarkers Prev 2009;18(12):3362–7)

Introduction

Neither the U.S. Surgeon General (1) nor the IARC (2) have designated the evidence linking active smoking to colorectal cancer as sufficient for causality, despite elevated risk estimates observed in recent studies and strong and consistent evidence that smoking increases the risk of colorectal adenomatous polyps, the precursor to most colorectal cancers (2, 3). Both reviews (1, 2) have posited that observed associations may represent residual confounding by factors associated with smoking rather than an independent effect of smoking.

Current smoking is associated with physical inactivity (4, 5), greater consumption of alcohol (6-8), and lower consumption of fruits, vegetables, and fiber (6-9), all of which are factors known or suspected to increase the risk of colorectal cancer (10-13). In addition, smoking is associated with lower utilization of screening procedures that can identify and lead to the removal of precancerous lesions prior to malignant transformation (14, 15). Previous publications based on individual studies, and consequently, the large meta-analyses (16-18), have been limited by their inability to control simultaneously for all known or putative risk factors for colorectal cancer as well as screening.

One hypothesis about the relationship between cigarette smoking and colorectal cancer, first proposed by Giovannucci et al. (19, 20), is that smoking may affect an early stage in the development of colorectal cancer, and that several decades of follow-up may be needed to observe the resultant change in cancer incidence. If this hypothesis is correct, then large prospective studies of men and women who began smoking by the middle of the 20th century have become truly informative only during the last 10 to 15 years.

We examined the association between cigarette smoking and risk of incident colorectal cancer during 13 years of follow-up of a large prospective cohort in which individuals had initiated smoking an average of 44 years prior to enrollment. Our analyses are based on updated individual level information on smoking status, duration, intensity, time since cessation, and age at cessation, with adjustment for 13 covariates which could confound the relationship.

Materials and Methods

Participants were drawn from the Cancer Prevention Study II (CPS-II) Nutrition Cohort (hereafter called the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,187 men and women from the United States, that is described in detail elsewhere (21). Briefly, the Nutrition Cohort is a subgroup of the ~1.2 million participants in the CPS-II, a prospective mortality study established by the American Cancer Society in 1982. Participants in the larger study were

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Requests for reprints: Michael J. Thun, Epidemiology and Surveillance Research, American Cancer Society, 250 Williams Street Northwest, Atlanta, GA 30303-1002. Phone: 404-329-5747; Fax: 404-327-6450. E-mail: mthun@cancer.org

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recruited nationwide and completed only the single questionnaire at enrollment.

Members of the CPS-II mortality cohort who resided in 21 states with population-based state cancer registries and were 50 to 74 years of age in 1992 were invited to participate in the Nutrition Cohort. Upon entry, participants completed a mailed questionnaire on demographic, medical, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, 2003, and 2005 to update exposure information and to ascertain newly diagnosed health problems, including cancer. The response rate among living participants for each of the follow-up questionnaires (after multiple mailings) was at least 89%. For the present study, the follow-up period ended on June 30, 2005. All aspects of the CPS-II Nutrition Cohort study were approved by the Emory University Institutional Review Board.

A total of 86,402 men and 97,785 women participated in the Nutrition Cohort. From this population, we excluded 10,129 (11.7%) men and 13,501 (13.8%) women who reported any prevalent cancer at baseline, with the exception of nonmelanoma skin cancer; 2,864 (3.3%) men and 2,795 (2.9%) women who were lost to follow-up; 1 man and 1 woman who reported being diagnosed 180 or more days prior to the verified diagnosis date; 16,526 (19.1%) men who reported ever having smoked pipes or cigars; and 2,972 (3.4%) men and 4,584 (4.7%) women who had missing or uninterpretable smoking data on their baseline questionnaire. Individuals were considered to be lost to follow-up if they did not return any of the questionnaires after baseline and were not identified as deceased prior to December 31, 1997.

We used Cox-proportional hazards models to examine the association between cigarette smoking and incident colorectal cancer after stratifying by single year of age and adjusting for potential risk factors with time since enrollment as the underlying time metric. Individuals contributed person-time to the analysis until they were diagnosed with colorectal cancer or were censored (i.e., died of causes other than colorectal cancer, reached the end of follow-up, failed to return a follow-up questionnaire, provided incomplete information on smoking habits on a follow-up questionnaire, reported unverified colorectal cancer, or were diagnosed with nonadenocarcinoma colorectal cancer or colorectal cancer *in situ*). If a participant did not return a questionnaire, or if they reported unverified colorectal cancer on a questionnaire, they were then censored 1 day after their return of the previous questionnaire. After all exclusions, 51,365 men and 73,386 women were included in the analysis.

A total of 1,962 verified incident cases of invasive colorectal cancer (1,006 men, 956 women) were identified between the time of enrollment in 1992/1993 and June 30, 2005. Self-reported cases were verified from medical records (n = 1,227) or through linkage to state cancer registries (n = 422). Additional cases (n = 313) were identified through linkage with the National Death Index, with all but 70 of the cases able to be linked to state cancer registries to obtain a date of diagnosis. These 70 colorectal cancer deaths were included as incident cases with the date of diagnosis assigned as the date of death. Incident cases of colorectal cancer were identified by ICD-9 codes 153-154.1 or by ICD-10 codes C18-C20.9. As discussed above, *in situ* cases were censored at the date of diagnosis, as were nonadenocarcinoma colorectal cancers, defined by ICD-9 histology codes as <8,140 and >8,574.

Cigarette smoking status ("never", "former", "current") was ascertained at enrollment in 1992/1993, and was updated in successive questionnaires. At baseline, participants were defined as a lifelong nonsmoker if they indicated having smoked fewer than 100 cigarettes in their lifetime. Participants were designated as current smokers if they reported smoking at the time of the questionnaire or as former smokers if they reported having successfully quit prior to the questionnaire. Smoking status was reassessed in questionnaires administered in 1997, 1999, 2001, and 2003. The 1999, 2001, and 2003 questionnaires requested only information on current smoking status ("Do you currently smoke cigarettes") and on the number of cigarettes currently smoked per day. Former smokers and continuing lifelong nonsmokers were therefore classified as such based on answers to previous questionnaires.

The information on smoking status was inconsistent for 1,813 men (3.5%) and 3,731 women (5.1%) who reported never having smoked on a follow-up questionnaire after previously reporting current or former smoking. These participants were considered to be former smokers rather than lifelong nonsmokers in time-dependent analyses. Individuals who, on the 1999 (n = 43), 2001 (n = 34), or 2003 (n = 58) questionnaire, indicated being a current smoker, but did not indicate current daily cigarette consumption and had reported being a lifelong nonsmoker in all previous questionnaires were considered to be lifelong nonsmokers under the assumption that they checked the wrong box.

The age at initiation at baseline for all current and former smokers was determined by combining information from the 1982 CPS-II questionnaire (returned by all participants in the Nutrition Cohort) and the 1992/1993 questionnaire. All other variables of smoking were treated as time-dependent variables.

We constructed a time-varying model to examine the association between smoking status (never, current, former) and incident colorectal cancer. Additional time-varying models comparing current smokers to lifelong nonsmokers examined increasing levels of cigarette smoking duration (<40, 40-49, >50 y), years since cessation (<40, 40-49, >50 y), and years since smoking initiation (<40, 40-49, >50 y). Analyses of former smokers examined how age at quitting (<40, 40-49, 50-59, and >60), and years since cessation (>30, 30-21, 20-11, 10-1 y) modified risk compared with lifelong nonsmokers. Each measure of exposure was assessed using sex-specific models as well as models with both sexes combined. Trend tests were obtained for increasing levels of smoking by assigning an ordinal value to each successive level and reporting the resulting P value. Nonsmokers were not included in the test for trend.

Multivariate models were adjusted for known and putative risk factors for colorectal cancer. These potential confounders were body mass index (<18.5, 18.5-24.9, 25-29.9, >30 kg/m^2, missing), educational attainment (some high school, high school/vocational school graduate, some college, college graduate, graduate school, missing), family history of colorectal cancer (yes, no), physical activity (quartiles, in metabolic equivalents (METs), missing), race (white, other), multivitamin use (current

user, not current user, missing), aspirin use (no use, 1-14, 15-29, 30-59, >60 pills per month, missing), alcohol use (nondrinker, <1, 1, >1 to 2, >2 to 3, >3 drinks/d, missing), vegetable consumption (quartiles, missing), red and processed meat consumption (quartiles, missing), and history of colorectal endoscopy (ever, never, missing). Models that combined men and women also controlled for sex, and models including women were controlled for estrogen-only hormone replacement therapy use (never, current, former, missing), estrogen and progesterone combined hormone replacement therapy (never, current, former, missing) and "other" hormone replacement therapy (yes, no, missing). All covariate values were based on information obtained at enrollment with the exception of multivitamin use, aspirin use, alcohol use, hormone replacement therapy use, and history of endoscopy which were updated during follow-up. History of endoscopy use was not ascertained until the 1997 questionnaire; therefore participants were considered to have missing endoscopy information for the period 1992 to 1997. Alcohol use during the last 4 y of follow-up was based on the 1999 questionnaire.

Results

Smoking, demographic, and other characteristics of the analytic cohort are shown in Table 1. In 1992 at baseline, a total of 33,029 (64.3%) men and 32,102 (43.7%) women in the analytic cohort reported ever having smoked at least 100 cigarettes in their lifetime. Of these, 84.0% of men and 81.3% of women reported having stopped smoking prior to enrollment, reflecting the older age of the participants at baseline. Those who continued to smoke in 1992 comprised only 9.0% of the analytic cohort and 17.4% of ever smokers. The mean and median number of years between smoking initiation and enrollment was 44 in those who reported a history of smoking.

Current smokers had lower educational attainment than both former smokers and never smokers with respect to completing either high school or college. The educational level of former smokers, however, differed by sex. Female former smokers were more educated than either never or current smokers, whereas the educational level of male former smokers was intermediate between that of current and never smokers. The cohort was predominantly white, irrespective of smoking status (Table 1).

Male and female current smokers reported less physical activity, greater consumption of alcohol and of red and processed meat, lower intake of fruits and vegetables and fiber, less multivitamin use, and a lower prevalence of colorectal endoscopy when compared with never smokers. The patterns among former smokers were more complex and differed by sex. Among men, former smokers were intermediate between current and never smokers with respect to physical inactivity, consumption of alcohol, red and processed meat, vegetables and fiber. However, male former smokers had the highest body mass index and equaled or exceeded never smokers with respect to their use of aspirin, multivitamins, and history of endoscopy.

Female former smokers had the lowest consumption of red and processed meat and the highest reported vegetable consumption and use of multivitamins and endoscopy. Compared with never smokers, they consumed more alcohol but were similar with respect to use of aspirin and hormone replacement therapy.

The incidence of colorectal cancer was ~30% higher in current than never smokers [hazard ratios (HR), 1.27; 95% confidence intervals (95% CI), 1.06-1.52] in analyses that combined men and women, and adjusted for all measured risk factors (Table 2). The association was weaker, although still statistically significant, among former smokers (HR, 1.23; 95% CI, 1.11-1.36). The association with former smoking seemed similar for cancers of the colon (HR, 1.19; 95% CI, 1.06-1.34) and rectum (HR, 1.26; 95% CI, 1.02-1.55), whereas the association with current smoking seemed stronger for colon cancer (HR, 1.28; 95% CI, 1.04-1.57) than for rectal cancer (HR, 0.97; 95% CI, 0.63-1.47), although numbers were limited (results shown in text only).

Among current smokers, increasing levels of smoking duration seemed to be associated with increased risk of colorectal cancer (P trend = 0.052), with the association between current smoking and colorectal cancer strongest among those who had smoked for 50 or more years. In sex-specific models of current smokers, the highest risk among men was seen in individuals who had smoked for 50 or more years (HR, 1.43; 95% CI, 0.99-2.07), and in women who had smoked for 40 to 49 years (HR, 1.56; 95% CI, 1.09-2.23). The older age of the cohort limited the range of smoking duration and the number of current smokers.

Among former smokers, the association with colorectal cancer was limited to those who had quit at age 40 years or older and those with 30 or fewer years since cessation. Former smokers who had quit <10 years previously (HR, 1.48; 95% CI, 1.27-1.73) seemed to have the greatest risk, which was similar to the estimate observed among current smokers who had smoked for at least 50 years. Risk of colorectal cancer decreased with time since cessation (P trend = 0.0003), and earlier age at cessation (P trend = 0.0014). Similar trends were seen in sex-specific analyses.

In analyses by stage, the HRs associated with former smoking were similar for localized (HR, 1.18; 95% CI, 1.01-0.1.37), regional (1.26; 1.08-1.47), and distant disease (1.26; 0.96-1.67). The risk associated with current smoking seemed higher for distant cancer (2.18; 1.45-3.26) than for local (0.88; 0.64-1.22) or regional cancer (1.21; 0.91-1.62) although the CIs were wide for distant disease.

To examine the effect of individual covariates, we fit models that matched on age but included only smoking status and one additional covariate. Adjustment for education, exercise, and consumption of red and processed meat changed the HR estimate by >5% among men; only fiber consumption changed the point estimate for former or current smoking by >5% in women.

Discussion

Our principal finding from this large cohort study is that long-term cigarette smoking was associated with an increased risk of colorectal cancer, even after adjusting for multiple covariates known to affect risk. A central aim of our study was to assess whether the association between cigarette smoking and risk of colorectal cancer would persist in analyses adjusted for multiple risk factors and screening. We were able to control for 13 known or putative risk factors for colorectal cancer, including

screening, thereby greatly reducing the likelihood of confounding. The association was only slightly stronger in current than in former smokers and seemed strongest in those who had smoked for at least 50 years. No association was observed in former smokers who quit before age 40 or who had abstained from smoking for more than 30 years.

Our findings partly support the hypothesis by Giovannucci that three to four decades of follow-up may be needed for an effect of smoking on early stages of intestinal carcinogenesis to have a detectable effect on colorectal cancer incidence. In our study, 90% of ever smokers had accrued at least 35 years since smoking initiation when first enrolled, reflecting their older age at baseline. We could not examine whether shorter times since initiation were also associated with risk. However, we suspect that long-term continued smoking might affect late as well as early stages of tumor development. The absence of an association in participants who had stopped 30 or more years previously suggests that continued smoking might have a promoting effect on colorectal cancer, as well as an early-stage effect on tumor initiation.

Our results supplement a large recent meta-analysis (18), in which, among ever smokers, an increase in risk

Table 1. Characteristics of study participants by cigarette smoking status at baseline (CPS-II Nutrition Cohort, men and women)

	Men			Women		
	Never smoker (n = 18,336)	Former smoker (n = 27,759)	Current smoker (n = 5,270)	Never smoker (n = 41,284)	Former smoker (n = 26,091)	Current smoker (n = 6,011)
Age at baseline, median (IQR)	63 (59-68)	64 (60-68)	62 (58-66)	62 (58-67)	62 (57-67)	61 (56-65)
Smoking history at baseline, median (IQR)						
Years of smoking	—	23 (15-34)	43 (38-48)	—	20 (10-30)	40 (31-44)
Cigarettes/d	—	-	20 (10-30)	—	—	15 (10-20)
Years since cessation	—	20 (10-28)	—	—	20 (10-29)	—
Years since Initiation	—	47 (42-50)	45 (40-49)	—	43 (38-48)	41 (37-46)
Education (%)						
Did not finish high school	5.7	9.8	11.8	5.2	3.9	7.1
High school graduate/ vocational	22.7	27.6	31.6	41.0	32.4	39.6
Some college	16.1	21.6	23.9	23.7	28.0	26.8
College graduate	54.6	40.4	31.8	29.5	35.0	25.8
White (%)	97.6	97.8	97.2	97.4	97.8	97.3
Positive family history of colorectal cancer (%)	5.2	5.0	4.7	6.0	5.9	5.5
Physical inactivity (MET <3.5) (%)	9.7	12.2	23.7	8.5	8.6	15.3
Body mass index (%)						
Underweight/normal, <25 kg/m^2	40.9	32.3	41.3	50.4	52.3	60.6
Overweight, 25-29.9 kg/m^2	46.0	50.5	45.3	31.8	31.0	28.0
Obese, >30 kg/m^2	11.6	15.9	12.2	16.3	15.3	10.3
Alcohol consumption (%)						
Nondrinker	44.6	29.7	29.6	55.3	33.4	36.8
<1 drink/d	37.6	38.2	33.5	33.8	44.4	36.5
1 drink/d	8.9	13.6	10.1	4.8	11.2	10.3
2 drinks/d	2.5	7.0	10.2	1.2	5.2	8.5
≥3 drinks/d	2.3	7.4	11.8	0.5	2.5	3.8
Vegetable consumption (%)						
Quartile 1 (lowest)	19.1	21.1	29.1	19.2	16.3	25.6
Quartile 2	21.2	20.7	21.3	19.8	19.3	20.7
Quartile 3	24.3	23.6	20.4	24.9	25.3	21.7
Quartile 4 (highest)	27.3	25.1	17.8	27.4	31.4	22.0
Fiber/whole grain consumption (%)						
Quartile 1 (lowest)	18.2	23.6	36.5	17.2	19.4	31.0
Quartile 2	20.0	21.7	22.8	21.8	23.6	24.2
Quartile 3	22.9	21.1	15.9	24.5	24.4	18.9
Quartile 4 (highest)	30.8	24.1	13.4	27.8	25.0	15.8
Red/processed meat consumption (%)						
Quartile 1 (lowest)	22.4	19.0	7.6	35.4	40.1	26.5
Quartile 2	21.8	20.1	14.8	25.7	25.5	25.0
Quartile 3	25.4	25.5	25.2	20.6	18.7	24.2
Quartile 4 (highest)	22.3	25.9	41.1	9.7	8.1	14.3
Aspirin use (%)						
No use	51.9	46.5	49.6	60.1	58.5	59.2
1-14 pills/mo	13.1	12.0	13.7	13.6	12.9	13.4
15-29 pills/mo	9.3	9.2	8.0	7.3	7.6	6.9
30-59 pills/mo	19.0	24.0	19.2	11.0	12.8	11.0
≥60 pills/mo	4.3	5.4	6.2	5.2	5.7	6.5
Hormone replacement therapy use (%)						
Never	—	—	—	44.3	38.6	48.0
Current	—	—	—	32.3	36.9	27.2
Former	—	—	—	22.3	23.4	23.7
Current multivitamin use (%)	31.6	31.9	27.9	40.4	43.0	36.9
Ever had endoscopy as of 1997 (%)	51.8	49.6	32.3	45.3	49.1	34.0

Abbreviation: IQR, interquartile range.

Table 2. Age- and multivariate-adjusted HRs and 95% CIs by cigarette smoking characteristics among current and former smokers compared with never smokers (CPS-II Nutrition Cohort, 1992-2005)

	All			Men			Women		
	Cases	Age-adjusted HR	Multivariate HR* (95% CI)	Cases	Age-adjusted HR	Multivariate HR* (95% CI)	Cases	Age-adjusted HR	Multivariate HR* (95% CI)
Never smokers	813	1.00	1.00 (reference)	303	1.00	1.00 (reference)	510	1.00	1.00 (reference)
Former smokers	993	1.34	1.23 (1.11-1.36)	619	1.35	1.26 (1.09-1.45)	374	1.15	1.19 (1.04-1.37)
Current smokers	156	1.57	1.27 (1.06-1.52)	84	1.54	1.24 (0.96-1.59)	72	1.47	1.30 (1.01-1.68)
Former smokers									
Age at cessation									
Before age 40	261	1.07	1.05 (0.91-1.22)	166	1.15	1.15 (0.95-1.39)	95	0.85	0.92 (0.74-1.16)
40-49 y of age	242	1.41	1.31 (1.13-1.52)	151	1.33	1.27 (1.04-1.55)	91	1.32	1.40 (1.12-1.76)
50-59 y of age	260	1.60	1.44 (1.24-1.66)	164	1.59	1.45 (1.19-1.77)	96	1.41	1.43 (1.14-1.78)
Age 60 or older	160	1.49	1.29 (1.08-1.54)	95	1.48	1.29 (1.01-1.63)	65	1.35	1.30 (1.00-1.70)
			P trend = 0.0014			P trend = 0.08			P trend = 0.003
Years since cessation									
≥31 y ago	239	1.03	1.03 (0.89-1.19)	147	1.06	1.07 (0.88-1.31)	92	0.90	0.99 (0.79-1.25)
21-30 y ago	238	1.37	1.28 (1.10-1.49)	160	1.43	1.36 (1.12-1.66)	78	1.09	1.15 (0.90-1.46)
11-20 y ago	232	1.48	1.33 (1.14-1.55)	139	1.42	1.30 (1.05-1.59)	93	1.37	1.39 (1.11-1.75)
1-10 y ago	214	1.72	1.48 (1.27-1.73)	130	1.70	1.48 (1.19-1.83)	84	1.53	1.47 (1.16-1.86)
			P trend = 0.0003			P trend = 0.033			P trend = 0.002
Current smokers									
Duration of smoking									
<40 y	29	1.19	1.02 (0.69-1.49)	12	1.25	0.98 (0.54-1.80)	17	1.14	1.04 (0.63-1.71)
40-49 y	71	1.68	1.32 (1.02-1.72)	36	1.46	1.12 (0.77-1.64)	35	1.75	1.56 (1.09-2.23)
50+ y	56	1.82	1.38 (1.04-1.84)	36	1.85	1.43 (0.99-2.07)	20	1.52	1.32 (0.83-2.09)
			P trend = 0.052			P trend = 0.24			P trend = 0.16

*Multivariate models are adjusted for age, body mass index, education, family history of colorectal cancer, physical activity, race, aspirin use, alcohol use, vegetable consumption, fiber/whole grain consumption, red and processed meat consumption, and history of endoscopy.

was observed with an increase of 40 years in smoking duration in analyses that controlled for fewer covariates. The overall relative risk estimates in the meta-analysis of colorectal cancer incidence for both current smokers (RR, 1.17; 95% CI, 0.97-1.40) and former smokers (RR, 1.25; 95% CI, 1.04-1.51) were similar to those observed in our study.

Our study replicates the findings of an analysis of smoking and risk of colorectal cancer mortality among participants in the main CPS-II cohort (22). During the first 14 years of follow-up, both current smoking (HRs, 1.32 and 1.41 in men and women, respectively) and former smoking (HRs, 1.15 and 1.22 in men and women, respectively) were significantly associated with colorectal cancer mortality. Increased death rates were observed only after 20 to 30 years of active smoking in both current and former smokers; decreased risk of mortality was observed with increasing years since cessation and with younger ages at cessation.

In addition to the availability of information on multiple risk factors, the strengths of our study include its size, older age distribution of the cohort, and the availability of updated information on the smoking habits and behaviors of the participants. The older age of the cohort provided sufficient time since smoking initiation to detect an increase in risk of colorectal cancer resulting from an effect of smoking on an early stage of carcinogenesis. Because we possessed updated information on smoking habits, we were able to ascertain changes in smoking status, with smoking cessation during the course of the study accounting for the majority of change. In our study, 56% of individuals who were current smokers at baseline and who returned at least two questionnaires during their participation in the study quit smoking at least once. Only a handful of past cohort studies that have examined smoking and risk of colorectal cancer have collected and used time-varying smoking exposure data (23-27).

The main limitation of our study is the inherent difficulty of distinguishing an independent effect of smoking from residual confounding by other factors when the strength of the association, if causal, likely ranges between 1.3 and 1.5. This is especially true in the analyses of current smoking, in which residual confounding from covariates that were measured imprecisely or not at all could cause the association to be overestimated. A second limitation of the study is that we had no tumor samples with which to stratify cases by tumor microsatellite instability. Tumors with high microsatellite instability may be more strongly associated with current smoking than those with low microsatellite instability (28, 29). Nevertheless, our findings strengthen the evidence that long-term smoking increases the risk of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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