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Risk of colorectal cancer associated with active smoking among female teachers

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Abstract

Purpose—The objective of this study was to examine the risk of colorectal cancer associated with active smoking among members of the California Teachers Study (CTS), a large cohort of female public school employees for whom highly detailed smoking information is available.

Methods—The analysis was conducted among the 122,264 CTS participants who lived in California at cohort entry in 1995/1996, had no prior history of colorectal cancer, and provided detailed smoking information. 1,205 cases of invasive colorectal cancer prospectively diagnosed

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in 1995–2009 were identified from the California Cancer Registry, including 650 in the proximal colon, 267 in the distal colon, and 288 in the rectum. Hazard ratios and 95 % confidence intervals were estimated using Cox proportional hazards models, stratified by age at cohort entry, and adjusted for race/ethnicity.

Results—Compared to never smokers, current smokers had an approximately 30 % increased risk of colorectal cancer. Overall, a slightly elevated risk was also noted for former smokers. Among former smokers, risks appeared to remain elevated for up to 20 years following cessation. Risks among former and current smokers increased with greater intensity and duration of smoking. Little evidence for heterogeneity in risk was noted for colon versus rectal cancer or for different subsites within the colon.

Conclusions—These results provide convincing evidence that heavy and/or long-term smoking is a risk factor for cancers of the colon and rectum. Such evidence should be considered when updating screening guidelines to include targeting people with long active smoking histories.

Keywords

Smoking; Colorectal cancer; Colon cancer; Rectal cancer; Risk; Women

Background

Colorectal cancer is the third most commonly diagnosed cancer and the third most deadly among both US women and men [1]. It is estimated that approximately 143,000 cases of colorectal cancer will be diagnosed and 52,000 people will die from this disease in 2012 [1]. While colorectal cancer is less common than either prostate cancer or breast cancer, colorectal cancer prognosis is substantially worse with a five-year survival rate of 64 %, primarily due to late stage at diagnosis [1]. Since the symptoms of colorectal cancer often do not present until late in the disease process, screening is critical to early detection and better survival. Current screening guidelines recommend that regular screening begins at age 50 years for those considered at ‘average’ risk, with earlier and more frequent screening recommended for those with a strong family history or known genetic risk factors [2]. Given that the majority of patients with colorectal cancer do not have a family history or genetic risk factor, defining targeted screening strategies that account for lifestyle-related factors could increase the number of early diagnoses and ultimately increase survival rates [2–4].

The role of smoking in the etiology of colorectal cancer has been the source of considerable debate. Reviews by the International Agency for Research on Cancer (IARC) and the U.S. Surgeon General, published in 2002 and 2004, respectively, concluded that the evidence was insufficient to identify smoking as a risk factor for colorectal cancer [5, 6]. Evidence has been accumulating over the last 10 years, and in its forthcoming report, IARC states the evidence is now “sufficient” to classify smoking as a human colorectal carcinogen [7]. Despite this new assessment, some unanswered questions regarding smoking and colorectal cancer risk remain including: the importance of timing versus overall duration and/or intensity of smoking; the degree to which smoking cessation results in reduction of risk; and whether risks vary by anatomic site (colon vs. rectal) and within subsites of the colon [8–11]. Furthermore, it has been suggested that smoking-related risks may be limited to or

stronger in men [9]. These are important questions to answer in order to improve the understanding of the etiologic mechanisms by which smoking affects risk and to inform primary and secondary prevention efforts.

The current analysis was conducted to evaluate the risk of colorectal cancer in a large prospective cohort of California women for whom extensive lifetime smoking histories have been collected. Due to the large size of the cohort and long length of cancer follow-up, which spans nearly 15 years, we had the opportunity to estimate risks by anatomic site and subsite and to evaluate a variety of details with respect to timing, duration, and dose of exposures.

Materials and methods

Study population

The study population for these analyses was drawn from the California Teachers Study (CTS) cohort, a large ongoing prospective study of female professional school employees in California. Participants in the CTS are 133,479 women who responded to a 1995 mailing to all 329,000 active and retired female enrollees in the State Teachers Retirement System (STRS). A full description of the CTS cohort is described elsewhere [12].

For the present analyses, CTS participants were excluded (in sequence) for the following reasons: lived outside California at baseline (n = 8,867); had an unknown history of prior cancer (n = 662); requested their data only be used for breast cancer analyses (n = 18); had a prior history of invasive or in situ colorectal cancer (n = 899); or had missing or unknown active smoking status (n = 769). The resulting study population was comprised of 122,264 women.

Use of human subjects' data in this study was approved by the Institutional Review Board (IRB) at all participating institutions and the California Health and Human Services Agency, Committee for the Protection of Human Subjects.

Outcome assessment

The CTS cohort is followed annually for cancer diagnosis, death, and change of address. Cancer outcomes are identified through annual linkages with the California Cancer Registry (CCR), a legally mandated statewide population-based cancer reporting system [13]. Mortality files, as well as reports from relatives, are used to ascertain date and cause of death. Address changes for continued follow-up are obtained by several methods including annual mailings, notifications of moves received from participants, and linkages to nationwide consumer reporting companies and the U.S. Postal Service National Change of Address database.

Women diagnosed with incident invasive carcinomas of the large bowel (International Classification of Disease Oncology codes C18.0, C18.2–C18.9 and C26.0 for cancer of the colon and C19.9 and C20.9 for cancer of the rectum) between the date they joined the cohort in 1995–1996 and 2009 comprised the case group. The anatomic subsites within the colon were further classified into proximal (C18.0, C18.2–C18.5) and distal (C18.6–C18.9,

C26.0). Information on stage of diagnosis was also extracted from the CCR data and characterized as localized, regional, distant, and unspecified.

Exposure assessment

Active Smoking Information—Highly detailed information on active smoking was collected on the baseline questionnaire in 1995–1996. Active smoking status was defined as having reported ever smoking 100 or more cigarettes and women were categorized as never, former, or current smokers. Among ever smokers (former or current smokers), details of smoking intensity and duration were also collected and categorized as follows: age of smoking initiation (≤15, 16–19, 20–24, ≥25, unknown); smoking intensity (average number of cigarettes per day, <10, 10–19, ≥20, unknown); total number of smoking years (<10, 10–19, 20–29, 30–39, ≥40, unknown); number of smoking pack-years (≤10, 11–20, 21–30, ≥31, unknown); and years since quitting smoking among former smokers (<5, 5–9, 10–19, ≥20, unknown). Because we did not have information about changes in smoking behavior during the follow-up of the study, for the variables that reflect time (e.g., number of smoking years, pack-years, and years since quitting), we created alternate variables to add time of follow-up to the time reported at baseline. These alternate variables were used in sensitivity analyses in which we estimated risks further accounting for time since study entry, assuming that smoking status had not changed during the follow-up period.

Covariate information

Data on potential confounders were gathered from information reported on two self-administered mailed surveys and included information on: age at baseline, race/ethnicity, menopausal status at cohort entry, family history of colon cancer, personal history of colorectal polyps, body mass index (BMI), physical activity, hormone therapy use, use of non-steroidal anti-inflammatory drugs, alcohol consumption, passive smoking exposures, and dietary factors (calcium, folate, iron, vitamin D, fat, fiber, caloric intake, consumption of red meat, organ meat, pork, processed meat, poultry, and fish/shellfish) collected from a modified Block questionnaire [14, 15].

Follow-up

Person-months at risk was calculated as the number of months between the time a woman joined the cohort (i.e., the date she completed her baseline questionnaire) and the earliest of four dates: the date of her invasive colorectal cancer diagnosis; the date of her first non-California residential address (lasting 4 months or longer); the date of her death; or December 31, 2009. Women who were diagnosed with in situ colorectal cancer during the follow-up period were censored at the time of their diagnoses.

Statistical analysis

Cox proportional hazards regression models were used to estimate hazard rate ratios (HRs) and 95 % confidence intervals (95 % CIs) for each smoking variable, using ages at the start and end of follow-up to define time on study. Initially, we calculated hazard ratios both with and without inclusion of passive smokers in the referent category of never smokers. Because these two alternative approaches yielded virtually identical point estimates, we chose to use

all never smokers (regardless of passive smoking exposure) as our referent category for all the smoking variables as it provided a larger group for comparison. Examination of Kaplan–Meier survival curves and log-minus-log survival plots indicated no apparent violation of the underlying assumption of proportional hazards upon which the Cox regression model is predicated [16]. All initial models were stratified by age at baseline (in single year increments) and adjusted for race/ethnicity (White (referent group), Black, Hispanic, Asian/Pacific Islander, and Other). Assessment of important covariates was conducted by individually adding each of the potential confounders to the models and evaluating whether the addition changed the regression coefficient for the smoking variable by 10 % or more. Furthermore, we used random forests techniques to identify potential confounders, taking into account both multiple testing and potential interactions [17]. As neither of these approaches identified any confounders beyond age and race/ethnicity, the final multivariable models only included adjustment for race/ethnicity and were stratified by age at baseline.

To evaluate whether smoking-related risks varied by anatomic site (colon vs. rectum) and subsites within the colon (proximal vs. distal), we tested for interactions in marginal competing risk models of the type described by Therneau [18]. Specifically, we built models stratified by site/subsite with and without inclusion of an interaction term for the smoking variable of interest and the site/sub-site and then compared the −2Log likelihood of the nested models to determine whether the interaction model fits significantly better. To evaluate whether smoking-related risks were different for pre/peri-menopausal versus post-menopausal women at baseline, we compared the log-likelihood ratios for models with and without interaction terms for menopausal status and the smoking exposure variables. Tests for significance of each effect individually were calculated only on a data set in which the effect was not coded as missing. Significance tests for individual effects were performed as follows. First, an “overall” (partial) likelihood ratio test was performed by comparing a model in which the term was treated as a categorical effect (Model A), to a model without the term (Model C). If the underlying effect was ordinal, a second “linear test for trend” was performed, comparing a model that treated the effect as numeric, coding never smokers as zero and using the median value in each level as a weight (Model B), to Model C. If that test proved statistically significant at the 0.05 level, then a second “residual” likelihood ratio test was performed comparing Model A to Model B, to detect the existence of an additional nonlinear component of trend. All models were run using the PHREG procedure in SAS Version 9.3. No formal *p* value adjustments for multiple testing were performed.

Results

1,205 women with invasive colorectal cancer were prospectively diagnosed between 1995/1996 (when they joined the cohort) and 2009 among the 122,264 CTS participants eligible for this study. The tumor characteristics of the cases in our study are summarized in Table 1. Forty-two percent were diagnosed at the localized stage; 37 % were diagnosed at the regional stage; and 17 % were diagnosed at the distant stage. The majority of cases were cancers of the colon (n = 917; 76 %), 71 % of which were diagnosed in the proximal colon. These tumor characteristics are similar to those observed in the general US population of non-Hispanic white women [19].

The demographic characteristics and smoking behaviors of the 122,264 study participants are summarized in Table 2. The study population predominantly includes white (87 %), middle-aged women, ranging in age from 22 to 104 years with approximately half between the ages of 40 and 59 years at cohort entry in 1995/1996. As expected, cases tended to be older than non-cases, and marginally more likely to be non-Hispanic white. Nearly two-thirds of the study population were life-long never smokers, 29 % were former smokers, and only 5 % were current smokers upon joining the cohort. Compared to women who did not develop colorectal cancer, cases were more likely to be former or current smokers and to smoke more cigarettes/day, for more years, resulting in more pack-years of smoking.

The risks of colorectal cancer associated with active smoking, stratified by age and adjusted for race/ethnicity, are presented in Table 3. Compared to never smokers, current smokers had a significantly elevated risk of colorectal cancer (HR = 1.28, 95 % CI = 1.00–1.63), while former smokers exhibited a more modest, non-significant risk elevation (HR = 1.10, 95 % CI = 0.97–1.24). Risks increased with increasing smoking intensity (*p* value for linear trend = 0.02), years of smoking (*p* value for linear trend = 0.02), and pack-years (*p* value for linear trend = 0.01). Among former smokers, all point estimates of risk were elevated except among those women who had quit 20 or more years prior to the study. While risk estimates based on the reported years of cessation prior to baseline were only modestly elevated and not statistically significant for most categories of cessation duration, the results were more dramatic in our sensitivity analyses in which we added years of follow-up to the time since quitting reported at baseline. In these analyses, we observed increased risk estimates for all durations of cessation, with the exception of those who had at least 20 years of smoking cessation (HR = 0.86, 95 % CI = 0.75–1.00 for 20+ years; HR = 2.10, 95 % CI = 1.67–2.66 for 10–19 years; HR = 12.3, 95 % CI = 8.12–18.6 for 5–9 years; HR = 25.5, 95 % CI = 10.4–62.9 for <5 years). While hazard ratios tended to increase for categories representing earlier ages at smoking initiation, all confidence intervals included one and the test for linear trend was not significant (*p* value = 0.33).

Overall smoking-related risk estimates were similar for colon and rectal cancer (Table 3) and, with the exception of pack-years, the formal tests for heterogeneity of effect between the two sites yielded *p* values >0.05. The risk of colon cancer appeared to increase with increasing pack-years [HR for 31+ pack-years = 1.51, 95 % CI = 1.21–1.88, *p* (linear trend <0.01)], while rectal cancer was not associated with increasing pack-years [HR for 31+ pack-years = 0.89, 95 % CI 0.54–1.47, *p* (linear trend = 0.58)], *p* (heterogeneity) = 0.04. Notably, the number of rectal cancers, especially in the highest exposure smoking group, was quite small (*n* = 17).

Table 4 presents the hazard ratios for smoking associated with tumors of the proximal and distal colon separately. While point estimates of risk generally tended to be higher for cancers of the distal colon, formal tests for heterogeneity of effect across subsites of the colon did not detect any evidence for heterogeneity (*p* values ranged from 0.50 to 0.95). The number of cases with distal colon cancer, however, tended to be quite small, especially among the highest exposure group of smokers (Table 4).

Risk analyses, stratified by menopausal status at baseline, provided no evidence of heterogeneity in risk with point estimates similar for pre/peri-menopausal and post-menopausal women and all likelihood ratio tests yielding *p* values greater than 0.05 (data not shown).

Because we did not identify any factors beyond age and race as significant confounders, we did not extensively evaluate potential effect modifiers. However, in response to a recent report from the GEECO pooled analysis that both fruit consumption and BMI were modest effect modifiers of the relationship between smoking and colorectal cancer risk [20], we specifically examined these relationships in our study population by adding multiplicative interaction terms between these factors and smoking and used the likelihood ratio test to evaluate the significance of effect modification. While we found no evidence for an interaction with fruit consumption (likelihood ratio *p* value = 0.64), we did see a marginally significant interaction between BMI and pack-years of smoking ($p = 0.05$). However, contrary to the findings from the GEECO pooled analysis which reported stronger smoking-related risks among overweight and obese women, we saw no evidence of this in our data. The hazard ratios for ≥31 pack-years were 1.63 (95 % CI = 1.23–2.18) for women with BMI ≤25 kg/m^2 women; 1.53 (95 % CI = 1.07–2.09) for women with BMI 25–29 kg/m2; and 1.70 (95 % CI = 1.06–2.74) for women with BMI≥30.

Discussion

Our results add convincing evidence to the growing body of literature that active smoking increases the risk of colorectal cancer, especially among smokers with the most intense and/or longest duration of exposure. Importantly, our findings indicate that this effect is not confined to men but is apparent in women as well. Our results also add to the sparse and mixed literature regarding the degree to which smoking-related risks may vary by anatomic site or subsite within the colon.

The colorectal cancer risk estimates for smoking status from our study (HR = 1.28 for current smokers; HR = 1.10 for former smokers) are consistent with findings from a number of recently published pooled and meta-analyses on this topic in which summary measures of risk have ranged from 1.12 to 1.26 for current smokers and 1.18 to 1.20 for former smokers [8–11, 20]. The marginally lower risk estimate for former smokers in the current study is likely a reflection of the fact that nearly half of the former smokers in our study population quit smoking more than 20 years before joining the cohort, by which time their risk appears to no longer be elevated.

While our analyses showed a linear trend of increasing risk with increasing measures of dose and duration (i.e., cigarettes/day, years of smoking, and pack-years), risk estimates only achieved statistical significance at the 0.05 level among the heaviest smokers (≥20 cigs/day) and after a duration of 40 years or 31 pack-years of smoking, regardless of whether duration of smoking was estimated at baseline or incorporated time on study [as part of our sensitivity analyses (*data not shown*)]. These results are consistent with the notion originally suggested by Giovannucci that a 35-year induction period may be required before an effect can be seen [21]. This long latency period has been offered as an explanation for the lack of

an effect reported in early studies on this topic in the US, especially among women, who did not start smoking en masse until the latter half of the 1900s and thus lacked sufficient latency for an effect to emerge in studies conducted prior to 1990 [21].

The degree to which smoking-related colorectal cancer risks are similar among men and women has been a matter of debate. Initially, the preponderance of data seemed to suggest that the effect of smoking was either limited to, or at least stronger, among men than among women [21]. Explanations offered for this apparent difference have included both limitations in exposure potential (given the apparent long latency) as well as real sex-related biologic differences potentially arising from differential interactions between smoking and protective endogenous estrogens, body mass index, and/or abdominal adiposity [11]. Two recent meta-analyses of prospective cohort studies on this topic reported that risks for current smoking continued to be higher among men than among women [9, 11], although only one found these differences to be statistically significant at the 0.05 level [11]. In contrast, a meta-analyses that included both cohort and case–control studies published during the same time period reported no evidence for differences in risk by sex [8]. More recent findings, however, from The European Prospective Investigation Into Cancer (EPIC) [22] and the Cancer Prevention Study II(CPS-II) [23], both of which reported no differences in risk by sex, were not included in these meta-analyses. Regardless of whether risks are higher in men than in women, there is now convincing evidence that risks are apparent in women. Along with the elevated risks found in our study and those reported among the female participants in the EPIC and CPS-II cohorts, elevated risks also have been reported among members of the Norwegian Women and Cancer Study [24] and the Women's Health Initiative [25], both large well-conducted prospective cohort studies among women. The Norwegian study, however, only observed an effect for rectal but not colon cancer, a finding that also was reported among members of the Canadian Breast Screening Study over 10 years ago [26].

The issue of whether the risk of colorectal cancer associated with smoking varies by anatomic site and subsite within the colon is of growing interest. Because only 20–30 % of colorectal cancers occur in the rectum, sample sizes typically have been insufficient to examine risks separately for rectal cancer. Combining cancers of the colon and rectum, however, assumes a constancy of risk across the sites that may not be appropriate and could mask important effects. Evidence that tumors of the colon and rectum, as well as subsites within the colon, may have distinct etiologies is growing [27–29]. Segments of the large bowel differ with respect to their embryonic origins and their physiologic functions [28]. The ability of the colorectal mucosa to metabolize carcinogens appears to vary by site and antigen expression differs by tumor site within the colon [30]. A number of risk factors including physical activity, alcohol intake, and certain dietary factors appear to have differential effects within subsites of the colon and rectum [28, 29, 31].

The evidence to date for differential effects of active smoking on risk of rectal versus colon cancer is somewhat mixed. While some studies have observed no differences in risk between anatomic sites [22, 32–36], the preponderance of studies seems to suggest risk may be slightly higher for rectal than for colon cancer [8, 10, 11, 25, 26, 37–43]. In contrast, our results provide little evidence for differential effects of smoking on the risk for tumors of the

colon and rectum. In fact, if any differences exist, the risks in our study appear to be marginally stronger for colon than for rectal cancer. For pack-years of smoking, our findings suggested an increasing risk associated with increasing pack-years for colon cancer but not for rectal cancers (p for heterogeneity = 0.04). For all other smoking exposure variables, p values evaluating heterogeneity in risk across sites were ≥0.35. These analyses, however, were likely limited by the small number of rectal cancer cases, especially within the highest exposure categories (n = 17 for ≥31 pack-years). Our finding of a marginally stronger risk for colon compared to rectal cancer, however, is consistent with an emerging literature suggesting that smoking-related risks are stronger for some molecularly defined colorectal tumor subtypes, including microsatellite instability (MSI)-high and CpG island methylator (CIMP)-positive tumors, both of which are more common in women and more commonly occur in the colon, rather than the rectum [44–46]. Unfortunately, we did not have available information on molecular subtypes.

The literature examining smoking-related risks by sub-sites within the colon is even more sparse [22, 39, 43, 47]. Two studies reported higher point estimates of smoking-related risks for tumors of the proximal colon than for tumors of the distal colon [47, 48]. A recent case–control study conducted in Hawaii suggested effects might vary by site and subsite differently in men and women with smoking-related effects stronger in the distal colon and rectum among women but not among men [49]. Results from our study, which overall tended to generate point estimates of risk slightly higher (albeit not statistically significant at the 0.05 level) for tumors of the distal compared to those of the proximal colon, are consistent with those reported in the Hawaiian study. Given the dearth of data on this issue, it is an important area for future inquiry. Clarification of risks, and how they might vary by site and subsite, could help elucidate etiologic mechanisms underlying risk. Furthermore, how risks vary by site and subsite within the colon could help inform the on-going debate over optimal screening guidelines which currently recommend for average risk individuals the less invasive and less expensive sigmoidoscopy that only allows examination of the rectum and distal colon over colonos-copy which examines the entire large bowel.

Our findings suggest that earlier age at smoking initiation incurs a larger risk than smoking that is started later in life (HR = 1.22 for smoking initiation ≤15 years of age; HR = 0.90 for smoking initiation ≥25 years of age). Due to the relatively few cases who started smoking prior to age 16 (n = 39) or at 25 years or later (n = 53), our study was underpowered to fully evaluate this issue. Our findings, however, are consistent with the handful of studies that have examined risks associated with age at smoking initiation[22, 25, 47, 50–54], most of which have reported increased risks with earlier ages at initiation [25, 47, 50, 52–55]. Interestingly, the most recent and one of the largest studies conducted to date reported no association between age at smoking initiation and colorectal cancer risk among members of the EPIC cohort [22]. In a recent meta-analysis, Liang reported that for each 10-year delay in smoking initiation, there was a 4.4 % reduction in risk ratios for colorectal cancer [10].

Finally, the issue of whether colorectal cancer risks diminish with increasing duration of smoking cessation is an important one, both in terms of helping to understand the mechanisms by which smoking increases risks, as well as to inform public health messaging. In his review of the literature over a decade ago, Giovannucci concluded that after smoking

cessation, some colorectal cancer risk appears to persist indefinitely [21]. More recent data, however, including our own, suggest that while increased colorectal cancer risks do persist for many years after quitting, they do eventually approach those of non-smokers. Five recent studies have reported that risks declined to those of never smokers after prolonged periods of cessation, perhaps as long as 20–30 years [22, 23, 25, 35, 56]. While the lack of information on changes in smoking behavior during the 14 years of follow-up precludes our ability to precisely define the period of smoking cessation among the former smokers in our study, our primary results and even more so, the results from our sensitivity analyses, support the notion that only after at least 20 years of cessation does the risk of colorectal cancer return to that of life-time non-smokers. A recently published pooled analysis from the GEECO study reported that the excess risk associated with smoking disappeared immediately after quitting for proximal colon and rectal cancer, but persisted for nearly 20 years for distal colon cancer [20]. Our analyses provided no evidence of differences in risk reduction following cessation by site or subsite, but as stated earlier, our study was not ideally suited to evaluate this question given the lack of information about changes in smoking behavior during the follow-up of our cohort.

Our study has a number of limitations worth noting. While our analysis showed no evidence that risk estimates were different for post- compared to pre/peri-menopausal women, given that both menopausal status and smoking behaviors are highly age-dependent, our ability to evaluate this issue may have been compromised by the high degree of collinearity between these variables.

While an abundance of information on colorectal cancer risk factors has been collected on the CTS cohort, unfortunately information on colorectal cancer screening practices is not available. Statewide population data indicate that women who smoke may be less likely to undergo regular colorectal cancer screening [57]. If smokers in the CTS are also less likely to undergo colorectal cancer screening than their non-smoking counterparts, this could bias our results. The CTS, however, is comprised of women with generally good health care access and utilization with high rates of mammography and cervical cancer screening [12]. To evaluate this issue, we examined whether the distribution of stage at diagnosis and self-reported history of colorectal polyps varied by smoking status in our study population. No significant differences in stage at diagnosis were observed and both current and former smokers were slightly *more* likely to report a history of polyps than were never smokers. Since worse adherence to colorectal cancer screening guidelines among smokers would most likely result in later stages at diagnosis and decrease the likelihood of discovery of colorectal polyps, these analyses provide reassuring, although indirect, evidence that our results are not likely due to bias introduced by our inability to control for colorectal screening practices.

Another constraint of our study was the inability to account for differences in genetic susceptibility to tobacco exposures. While the issue of genetic polymorphisms has not yet been widely addressed in the literature on tobacco exposures and colorectal cancer, some data suggest that risk may vary by polymorphisms in genes that affect the metabolism of smoking-related carcinogens [46, 55, 58– 63]. Unfortunately, it was beyond the scope of the current study to incorporate information on potentially relevant genetic polymorphism. While lack of such data precludes our ability to examine whether individuals with certain

polymorphisms may be more or less susceptible to the carcinogenic effects of tobacco smoke, it does not impact the validity of the results as presented.

Overall, our study makes an important contribution to the increasingly convincing body of evidence that active smoking is a risk factor for colorectal cancer. Our results are particularly compelling given some of the unique strengths of our study, including the focus on women and the prospective design, which avoids the potential for recall bias common to studies of well-recognized carcinogens such as smoking. Furthermore, we were able to account for a wide spectrum of potential confounders including highly detailed dietary information, alcohol consumption, BMI, physical activity, medication, and hormone use, as well passive smoking exposures. Because none of these variables changed the coefficients for any of our smoking-related variables in our regression analyses, our final models did not include adjustment for these factors. Although not presented in this manuscript, we also ran regression models that included all potential confounders (as listed in above methods section) as covariates simultaneously. The smoking-related hazard ratios generated from these models remained essentially the same, albeit with marginally wider confidence intervals (*data not shown*). Given that the primary reason for IARC's prior reluctance to conclude that smoking was a colorectal carcinogen was “principally because of concern about confounding by other risk factors” [6], our results provide some reassurance that the results from earlier studies that did not have the ability to adequately adjust for potential con-founders were likely not biased due to residual confounding.

The results presented from the current analysis, in the context of the growing body of evidence that smoking increases the risk of colorectal cancer, should be considered when evaluating colorectal cancer screening guidelines. Because colorectal cancer is often a silent disease with the presentation of no early symptoms, screening is critical to early detection and better survival. There has been an emerging interest in tailoring screening recommendations to include information on lifestyle factors that might place individuals at an increased risk of colorectal cancer. Long-term heavy smoking should be one such factor to consider in this regard.

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Table 1

Tumor characteristics among 1,205 invasive cases of colorectal cancer diagnosed in 122,264 CTS participants, 1995–2009

Tumor characteristics	*n*	%
Stage		
Localized	504	42
Regional	443	37
Distant	208	17
Unspecified	50	4
Colon	917	76
Proximal		
Cecum	271	22
Ascending colon	187	16
Hepatic flexure	56	5
Transverse colon	106	9
Splenic flexure	30	2
Total proximal	650	71
Distal		
Descending colon	35	3
Sigmoid	194	16
Large intestine, NOS	38	3
Total distal	267	29
Rectal	288	24
Recto sigmoid junction	90	7
Rectum	198	16

Table 2

Demographic and smoking exposure characteristics among 122,264 CTS participants, by case status

	Case (*n* = 1,205)		Non-case (*n* = 121,059)		Total (*n* = 122,264)		*p* value (χ^2)
	n[a]	%	*n*[a]	%	*n*[a]	%	
Age at baseline (years)							
<40	28	2	21,108	17	21,136	17	
40–49	130	11	32,003	26	32,133	26	
59–59	226	19	29,705	25	29,931	24	
60–69	325	27	20,040	17	20,365	17	
70–79	338	28	12,926	11	13,264	11	
80–89	150	12	4,786	4	4,936	4	
≥90	8	1	491	<1	499	<1	<0.0001
Race/Ethnicity							
White	1,071	89	104,749	87	105,820	87	
Black	44	4	3,194	3	3,238	3	
Hispanic	26	2	5,160	4	5,186	4	
Asian/Pacific Islander	28	2	4,336	4	4,364	4	
Other	36	3	3,620	3	3,656	3	0.0001
Active smoking status							
Never	719	60	80,243	66	80,962	66	
Former	414	34	34,683	29	35,097	29	
Current	72	6	6,133	5	6,205	5	<0.0001
Smoking intensity (average number of cigarettes per day)							
Never smokers	719	60	80,243	66	80,962	66	
<10	205	17	18,678	15	18,883	15	
10–19	152	13	12,284	10	12,436	10	
≥20	110	9	8,848	7	8,958	7	<0.0001
Total number of smoking years							
Never smokers	719	60	80,243	66	80,962	66	

	Case		Non-case		Total		*p* value (χ^2)
	(*n* = 1,205)		(*n* = 121,059)		(*n* = 122,264)		
	n[a]	%	*n*[a]	%	*n*[a]	%	
<10	73	6	10,330	9	10,403	9	
10–19	93	8	10,100	8	10,193	8	
20–29	92	8	7,501	6	7,593	6	
30–39	83	7	5,622	5	5,705	5	
≥40	102	8	4,420	4	4,522	4	<0.0001
Number of smoking pack-years							
Never smokers	719	60	80,243	66	80,962	66	
≤10	202	17	19,844	16	20,046	16	
11–20	58	5	7,050	6	7,108	6	
21–30	57	5	4,186	3	4,243	3	
≥31	114	9	6,150	5	6,264	5	<0.0001
Years since quitting smoking							
Never smokers	719	60	80,243	66	80,962	66	
≥20	200	17	15,561	13	15,761	13	
10–19	103	9	9,653	8	9,756	8	
5–9	40	3	3,890	3	3,930	3	
<5	36	3	3,164	3	3,200	3	
Current smokers	72	6	6,133	5	6,205	5	<0.0001
Age of smoking initiation							
Never smokers	719	60	80,243	66	80,962	66	
≤15	39	3	4,328	4	4,367	4	
16–19	221	18	20,083	17	20,304	17	
20–24	130	11	9,849	8	9,979	8	
≥25	53	4	3,713	3	3,766	3	<0.0001

[a]Numbers do not sum to total due to missing/unknown values

Table 3

Risk of colorectal, colon and rectal cancer associated with active smoking among 122,264 CTS participants, estimated by Cox proportional hazards models, adjusted for race/ethnicity and stratified by age

Smoking variable	Colorectal cancer		Colon cancer		Rectal cancer		*p* (heterogeneity)
	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	
Active smoking status							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	
Former	414	1.10 (0.97, 1.24)	316	1.10 (0.95, 1.26)	98	1.10 (0.86, 1.42)	
Current	72	1.28 (1.00, 1.63)	53	1.25 (0.94, 1.66)	19	1.36 (0.85, 2.20)	0.95
Smoking intensity (average number of cigarettes per day)							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	
<10	205	1.04 (0.89, 1.21)	151	0.99 (0.83, 1.19)	54	1.17 (0.86, 1.59)	
10–19	152	1.15 (0.97, 1.38)	113	1.13 (0.92, 1.39)	39	1.23 (0.87, 1.75)	
≥20	110	1.23 (1.00, 1.50)	90	1.33 (1.07, 1.67)	20	0.90 (0.57, 1.44)	0.45
Tests for effect							
Overall		$p = 0.14$ (3 *df*)		$p = 0.07$ (3 *df*)		$p = 0.49$ (3 *df*)	
Linear trend		$p = 0.02$ (1 *df*)		$p = 0.01$ (1 *df*)		$p = 0.99$ (1 *df*)	
Residual		$p = 0.90$ (2 *df*)		$p = 0.93$ (2 *df*)		n/a	
Total number of smoking years							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	
<10	73	0.97 (0.76, 1.24)	48	0.87 (0.65, 1.17)	25	1.27 (0.83, 1.94)	
10–19	93	1.00 (0.81, 1.25)	66	0.95 (0.73, 1.23)	27	1.17 (0.78, 1.76)	
20–29	92	1.11 (0.89, 1.38)	76	1.20 (0.94, 1.53)	16	0.81 (0.49, 1.36)	
30–39	83	1.12 (0.89, 1.41)	62	1.09 (0.84, 1.42)	21	1.22 (0.77, 1.93)	
≥40	102	1.27 (1.03, 1.57)	81	1.27 (1.00, 1.61)	21	1.27 (0.80, 2.02)	0.35
Tests for effect							
Overall		$p = 0.33$ (5 *df*)		$p = 0.20$ (5 *df*)		$p = 0.58$ (5 *df*)	
Linear trend		$p = 0.02$ (1 *df*)		$p = 0.04$ (1 *df*)		$p = 0.40$ (1 *df*)	
Residual		$p = 0.95$ (4 *df*)		$p = 0.58$ (4 *df*)		n/a	
Number of smoking pack–years							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	

Smoking variable	Colorectal cancer		Colon cancer		Rectal cancer		*p* (heterogeneity)
	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	
≤10	202	1.09 (0.94, 1.28)	144	1.03 (0.86, 1.24)	58	1.29 (0.95, 1.73)	
11–20	58	0.74 (0.57, 0.97)	37	0.62 (0.45, 0.87)	21	1.13 (0.72, 1.78)	
21–30	57	1.19 (0.91, 1.56)	46	1.26 (0.93, 1.70)	11	0.96 (0.52, 1.78)	
≥31	114	1.37 (1.12, 1.67)	97	1.51 (1.21, 1.88)	17	0.89 (0.54, 1.47)	0.04
Tests for effect							
Overall		$p<0.01$ (4 *df*)		$p<0.01$ (4 *df*)		$p = 0.51$ (4 *df*)	
Linear trend		$p = 0.01$ (1 *df*)		$p<0.01$ (1 *df*)		$p = 0.58$ (1 df)	
Residual		$p = 0.01$ (3 *df*)		$p<0.01$ (3 *df*)		n/a	
Years since quit smoking							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	
≥20	200	0.98 (0.83, 1.14)	148	0.93 (0.78, 1.12)	52	1.12 (0.82, 1.54)	
10–19	103	1.15 (0.94, 1.42)	78	1.16 (0.92, 1.48)	25	1.12 (0.73, 1.70)	
5–9	40	1.19 (0.86, 1.64)	34	1.35 (0.95, 1.91)	6	0.71 (0.32, 1.61)	
<5	36	1.44 (1.03, 2.01)	27	1.44 (0.98, 2.12)	9	1.43 (0.73, 2.79)	
Current smokers	72	1.28 (1.00, 1.63)	53	1.25 (0.94, 1.66)	19	1.36 (0.85, 2.20)	0.59
Tests for effect							
Overall		$p = 0.16$ (4 *df*)		$p = 0.10$ (4 *df*)		$p = 0.65$ (4 *df*)	
Linear trend		$p = 0.87$ (1 *df*)		$p = 0.55$ (1 *df*)		$p = 0.46$ (1 *df*)	
Residual		n/a		n/a		n/a	
Age of smoking initiation							
Never smokers	719	1.00 (referent)	548	1.00 (referent)	171	1.00 (referent)	
≤15	39	1.22 (0.88, 1.69)	31	1.32 (0.92, 1.90)	8	0.96 (0.47, 1.95)	
16–19	221	1.13 (0.97, 1.32)	164	1.12 (0.94, 1.33)	57	1.17 (0.87, 1.59)	
20–24	130	1.10 (0.91, 1.32)	94	1.03 (0.83, 1.28)	36	1.32 (0.92, 1.90)	
≥25	53	0.90 (0.68, 1.20)	44	0.94 (0.69, 1.28)	9	0.75 (0.38, 1.48)	0.49
Tests for effect							
Overall		$p = 0.34$ (4 *df*)		$p = 0.51$ (4 *df*)		$p = 0.42$ (4 *df*)	
Linear trend		$p = 0.33$ (1 *df*)		$p = 0.52$ (1 *df*)		$p = 0.41$ (1 *df*)	
Residual		n/a		n/a		n/a	

[a] Numbers do not sum to total due to missing/unknown values

[b] HR = hazard ratio; CI = confidence interval

Table 4

Risk of proximal and distal colon cancer associated with active smoking among 122,264 CTS participants, estimated by Cox proportional hazards models, adjusted for race/ethnicity and stratified by age

Smoking variable	Proximal colon cancer		Distal colon cancer		*p* (heterogeneity)
	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	
Active smoking status					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	
Former	224	1.06 (0.90, 1.25)	92	1.19 (0.92, 1.55)	
Current	35	1.14 (0.80, 1.61)	18	1.56 (0.95, 2.54)	0.67
Smoking intensity (average number of cigarettes per day)					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	
<10	106	0.96 (0.77, 1.19)	45	1.09 (0.78, 1.53)	
10–19	81	1.10 (0.87, 1.40)	32	1.20 (0.82, 1.76)	
≥20	62	1.26 (0.96, 1.65)	28	1.54 (1.03, 2.32)	0.94
Tests for effect					
Overall		$p = 0.31$ (3 *df*)		$p = 0.21$ (3 *df*)	
Linear trend		$p = 0.08$ (1 *df*)		$p = 0.04$ (1 *df*)	
Residual		n/a		$p = 0.94$ (2 *df*)	
Total number of smoking years					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	
<10	35	0.91 (0.65, 1.30)	13	0.77 (0.44, 1.36)	
10–19	43	0.86 (0.63, 1.18)	23	1.18 (0.76, 1.83)	
20–29	53	1.15 (0.86, 1.53)	23	1.33 (0.86, 2.07)	
30–39	45	1.05 (0.77, 1.44)	17	1.20 (0.72, 1.99)	
≥40	57	1.16 (0.88, 1.54)	24	1.62 (1.04, 2.53)	0.86
Tests for effect					
Overall		$p = 0.62$ (5 *df*)		$p = 0.23$ (5 *df*)	
Linear trend		$p = 0.27$ (1 *df*)		$p = 0.03$ (1 *df*)	
Residual		n/a		$p = 0.75$ (4 *df*)	
Number of smoking pack-years					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	

Smoking variable	Proximal colon cancer		Distal colon cancer		*p* (heterogeneity)
	# cases[a]	HR (95 % CI)[b]	# cases[a]	HR (95 % CI)[b]	
≤10	96	0.96 (0.76, 1.20)	48	1.23 (0.89, 1.70)	
11–20	29	0.66 (0.45, 0.97)	8	0.50 (0.25, 1.02)	
21–30	32	1.18 (0.82, 1.70)	14	1.47 (0.85, 2.54)	
≥31	71	1.46 (1.13, 1.89)	26	1.63 (1.07, 2.48)	0.81
Tests for effect					
Overall		*p* =0.01 (4 *df*)		*p* = 0.01 (4 *df*)	
Linear trend		*P* = 0.01 (1 *df*)		*p* = 0.07 (1 *df*)	
Residual		*p* = 0.03 (3 *df*)		n/a	
Years since quit smoking					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	
≥20	104	0.89 (0.71, 1.10)	44	1.07 (0.76, 1.50)	
10–19	55	1.14 (0.86, 1.52)	23	1.21 (0.78, 1.88)	
5–9	25	1.36 (0.91, 2.05)	9	1.30 (0.66, 2.54)	
<5	20	1.48 (0.94, 2.32)	7	1.35 (0.63, 2.88)	
Current smokers	35	1.14 (0.80, 1.61)	18	1.56 (0.95, 2.54)	0.95
Tests for effect					
Overall		*p* = 0.12 (4 *df*)		*p* = 0.84 (4 *df*)	
Linear trend		*p* = 0.33 (1 *df*)		*p* = 0.66 (1 *df*)	
Residual		n/a		n/a	
Age of smoking initiation					
Never smokers	391	1.00 (referent)	157	1.00 (referent)	
≤15	16	0.96 (0.58, 1.59)	15	2.18 (1.28, 3.72)	
16–19	116	1.09 (0.88, 1.34)	48	1.19 (0.86, 1.66)	
20–24	70	1.04 (0.80, 1.34)	24	1.00 (0.65, 1.54)	
≥25	31	0.89 (0.61, 1.28)	13	1.10 (0.62, 1.94)	0.50
Tests for effect					
Overall		*p* = 0.88 (4 *df*)		*p* = 0.13 (4 *df*)	
Linear trend		*p* = 0.88 (1 *df*)		*p* = 0.33 (1 *df*)	
Residual		n/a		n/a	

[a] Numbers do not sum to total due to missing/unknown values

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[b] HR = hazard ratio; CI = confidence interval