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Examining the Association Between Cigarette Smoking and Colorectal Cancer Using Historical Case-Control Data

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Abstract

BACKGROUND—The majority of recent, well-designed studies have shown that long-term cigarette smoking increases colorectal cancer risk, but older studies with shorter durations of exposure often found no association. This study aimed to examine colorectal cancer risk by smoking exposure using data collected in the late 1950s and early 1960s.

METHODS—This case-control study examined colorectal cancer risk by lifetime smoking history. There were 1,365 patients who visited Roswell Park Cancer Institute (RPCI) between 1957 and 1965 diagnosed with primary, incident colorectal cancers that were matched to 4,096 malignancy-free controls on gender and age. Odds ratios were calculated using separate logistic regression models for each smoking exposure, while controlling for other tobacco use, county of residence, race, age, gender, and body mass index (BMI).

RESULTS—The adjusted OR for individuals who reported their greatest level of smoking to be more than 1 pack/day was 0.87 (95% CI=0.67–1.15). Among those who smoked 42 or more years, the adjusted OR was 0.89 (95% CI=0.68–1.15) compared to those who never smoked. For individuals who smoked more than 45 pack-years, the OR was 0.92 (95% CI=0.72–1.19). The

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results did not differ significantly by gender, although men had considerably greater exposure compared to women. Results also did not differ by colorectal sub-site.

CONCLUSION—No association was found between long-term cigarette smoking and colorectal cancer risk. These results are in accord with studies that followed cohorts throughout the 1950s and 1960s. Methodological limitations, such as missing data on covariates and the higher incidence of smoking-related illness in a hospital setting, may have contributed to the null results found in this study. Prolonged population exposure to cigarettes and perhaps a changing product may explain why more recent studies have reported a positive association between smoking and colorectal cancer.

Keywords

colorectal cancer; cigarette smoking; case-control study

Introduction

The American Cancer Society estimates more than 148,000 Americans will be diagnosed with colorectal cancer and more than 49,000 Americans will die from this disease in 2008 [1]. Certain genetic syndromes (Familial Adenoma Polyposis, Hereditary Non-Polyposis Colorectal Cancer) and family history explain only a small percentage of total colorectal cancer cases [2]. Investigators believe that environmental/lifestyle factors are to blame for the majority. Evidence to support this theory comes from geographic variation in incidence rates and various migrant studies. Colorectal cancer incidence rates are more than 4-fold higher in Western nations than in developing nations, although incidence is increasing in the less developed countries [3]. Migrant studies show immigrant incidence rates quickly approach those of the host nation, usually within one or two generations [4,5]. Recent literature has identified a number of lifestyle risk factors that might be associated with colorectal cancer [1,6,6–22] including exposure to tobacco [23–27].

Cigarette smoke contains dozens of known and possible carcinogens [28]. They include polycyclic aromatic hydrocarbons (PAH), tobacco-specific nitrosamines (TSNA), and heterocyclic aromatic amines (HAA) [29]. Research has shown that over the past three decades, TSNA levels in cigarettes have risen 73% compared to PAH levels, which have declined 62% over the past 35 years [30]. Both TSNA and HAA have been linked to cancers in sites that are not in direct contact with cigarette smoke, including the digestive tract [31,32]. Studies have detected the presence of both TSNA and HAA in the digestive systems of animals and humans [33,34], and other research has shown that HAA exposure from cigarette smoke is similar to the exposure from diet [35].

A number of studies which examined smoking in relation to cancer in the 1950s and 1960s were among the first to offer solid epidemiologic proof of the link between cigarette smoking and lung cancer [36–42]. Those landmark studies and others also examined cigarette smoking in relation to colorectal cancer risk [43–46], and virtually all reported no association. Giovannucci et al. were among the first to report the association between cigarette smoking and colorectal cancer in 1994 and other large, well-designed studies soon followed [23–26,47,48]. It has since been suggested that the reason these studies failed to observe an association while more recent work has is the insufficient latency period in the earlier studies [49].

The current study uses data obtained from patient admissions at Roswell Park Cancer Institute between 1957 and 1965. Numerous studies have been published using this dataset [50–57]. Graham et al. used this dataset to examine diet in relation to colon and rectal cancer risk [49,58] and reported that smoking was not associated with risk of colon or rectal cancer,

although no statistics were reported and the exposure measures were not detailed. The Graham study's *a priori* hypothesis involved dietary factors, not smoking, in relation to colorectal cancer risk and used only male colorectal cancer cases seen between the years of 1959 and 1965. The current study was specifically designed to investigate the effect of smoking on colorectal cancer risk and included both male and female cases seen at the hospital between 1957 and 1965. In addition, more modern statistical methods, such as multivariate logistic regression, were used.

Methods

The data used in these analyses were collected from individuals who were admitted to Roswell Park Memorial Institute between 1957 and 1965. A detailed questionnaire was administered to each individual by a blinded interviewer before the patient was given a diagnosis, in an attempt to limit bias. The questionnaire included the subject's previous medical problems, diet/cooking habits, reproductive history, alcohol usage, parental and sibling health history, occupational history, and smoking history. Actual participation rates were not collected, but participation rates based on informal estimates are believed to be approximately 85%. The majority of individuals who did not complete the questionnaire were those who were too ill, state prisoners, and those under 18 years of age.

This study uses a hospital-based case-control design, in which 1,365 colorectal cancer cases were frequency matched on gender and age (5-year intervals) to 4,096 controls on a 3:1 control:case ratio. Cases were defined as those with primary, histologically confirmed, incident colorectal cancer (ICD-O Codes 153, 154, and 159)[59] and were 40 years of age or older. Colorectal malignancies that resulted from other primary tumors were excluded from the analyses. Eligible controls were free of cancer (except non-melanomous skin cancer), benign neoplasms of the intestine, and other disorders of the colon (chronic enteritis, ulcerative colitis). The resulting control group consisted of individuals between the ages of 40 and 86 with the following types of non-neoplastic diseases: diseases of the genitourinary organs (21%), no diagnosis (12%), diseases of the skin (9%), diseases of the respiratory system (8%), diseases of the buccal system (6%), bone and joint diseases (6%), diseases of the thyroid (4%), diseases of the stomach (4%), diseases of the circulatory system (4%), thyroid disorders (3%), venereal disease (3%), accident trauma (2%), infectious diseases (2%), cardiovascular disorders (2%), and all other diseases (14%). Both cases and controls were excluded from the analyses if they were missing information on smoking habits. Overall, 89.6% of all participants fully answered the tobacco history and there was no significant difference in the proportion of those missing smoking history between cases and controls.

The questionnaire used in this study contained 23 questions about the subject's cigarette smoking history in the period before his/her illness. The nature of the questions ranged from general (How many years have you smoked?) to very specific (How many puffs do you take in a 4-minute period?). The main exposure variables were created from those questions and included smoking status, amount smoked, years smoked, age at smoking initiation, and pack-years. The final exposure variable is a novel exposure assessment called lifetime tar grams. Current and former smokers reported the four most recent brands of cigarettes smoked and the duration smoked for each brand. The machine-determined tar levels were obtained for specific cigarettes brands from analyses by Foster D. Snell, Inc. and published in Reader's Digest during the period from 1959–1965. [60] Brand-specific tar levels were multiplied by smoking duration for each brand and amount smoked to obtain the number of lifetime tar grams. Current machine-determined tar levels do not accurately estimate human exposure currently due to cigarette design features (e.g. filters, filter ventilation, etc.), but were more likely to do so during the period in which participants were enrolled[29,61,62].

Continuous variables were broken into tertiles based on the controls' exposure with never smokers serving as the reference group.

Potential confounders were identified from the literature and extracted from specific items on the questionnaire. The questionnaire instructed participants to answer questions about lifestyle habits in the period before their illness. The potential confounders included age, gender, race, body mass index (BMI), other tobacco use, county of residence, fruit consumption, vegetable consumption, beef consumption, total meat consumption, and alcohol intake. Due to the high percentage of missing data (~40%) for dietary and alcohol measures, these variables could not be included as potential confounders. Sensitivity analyses were performed to note the effect of diet and alcohol on crude odds ratios.

Student's t-tests were used to calculate the difference between continuous variables for case/control status, while χ^2 statistics were calculated to test the difference between categorical variables. Unconditional multivariate logistic regression was used to calculate odds ratios (OR) and the corresponding 95% confidence intervals (95% CI). Separate regression models were constructed for each exposure measure. Case/control status was used as the dependent outcome, and age, gender, race, BMI, other tobacco use, and county of residence were covariates. Other tobacco was defined as a dichotomous variable: those answering 'yes' to using cigars, pipes, or chewing tobacco were considered other tobacco users. Sensitivity analyses were also performed in this study. Crude odds were calculated for those not missing dietary data; dietary variables were then added to the models, and their effects on crude odds ratios were noted. Odds ratios were also calculated for colorectal sub-sites, which included the proximal colon (ICD-O 153.2, 153.3, 153.7), distal colon (ICD-O 153.0, 153.4, 153.6), and rectum (ICD-O 154) [59]. Analyses were also stratified by gender and age at initiation of smoking to explore for the presence of interaction.

Results

Table 1 describes the demographics and lifestyle factors of colorectal cancer cases and control subjects. The cases and controls were similar in both age (P=0.92) and gender (P=1.00), because controls were matched to cases on those two factors prior to the analyses. There were no statistical differences between cases and controls in BMI, alcohol consumption, and dietary measures.

Table 2 reports the overall odds ratios from the various smoking exposure measures used in this study. Descriptive statistics show that only 40% of men reported being a lifelong never smoker, while 42% reported being a current smoker. The average male smoker in this analysis reported taking in an average of 7,000 grams (> 15 pounds) of tar during his lifetime. Almost 75% of women stated they were lifelong never smokers, with only 21% reporting that they currently smoked. The study found a low prevalence of former smokers for both males (18%) and females (5%). Being either a former smoker (OR_{adj}=1.22; 95%CI=0.94–1.56) or current smoker (OR_{adj}=0.79; 95%CI=0.66–0.96) was not associated with an increase in overall colorectal cancer odds. Those who reported smoking more than 1 pack of cigarettes per day at the highest level of smoking were not at increased odds for colorectal cancer (OR_{adj}=0.87; 95%CI=0.67–1.15). In addition, those who reported smoking for more than 41 years (OR_{adj}=0.89; 95%CI=0.68–1.15) and more than 45 pack-years (OR_{adj}=0.92; 95%CI=0.72–1.19) demonstrated no increase in colorectal cancer odds. Individuals exposed to more than 8,900 grams of tar over their lifetime had colorectal cancer odds similar to those of never smokers (OR_{adj}=1.04; 95%CI=0.69–1.56). Adjusting for race, age, gender, body mass index, county of residence, and other tobacco use had little effect on crude OR. In data not shown, odds stratified by age at smoking initiation did not indicate the presence of interaction.

Table 3 displays the odds ratios for smoking exposure by colorectal sub-site. In general, the odds were greater for rectal cancer than for both proximal and distal colon cancer. No increase in proximal or distal colon cancer odds ratios were noted for current smokers, those who smoked for more than 41 years, those with more than 45 pack-years, or any other smoking exposure. No significant association was noted for rectal cancer odds for current smokers (OR_{adj}=0.95; 95%CI=0.75–1.22), those with 42 or more years of smoking (OR_{adj}=1.13; 95%CI=0.87–1.47), those with 46 or more pack-years (OR_{adj}=1.26; 95%CI=0.92–1.72), or any other exposure.

Table 4 shows overall colorectal cancer odds ratios by various smoking exposures, stratified by gender. Generally speaking, the colorectal cancer odds ratios for those in the highest exposure categories were greater for males than for females. Regardless, the interaction term between gender and smoking exposure was not significant when placed into a logistic model.

In data not shown, the odds ratios were greatest for rectal cancer in the heaviest smoking males. Men with more than 41 years of smoking had a nonsignificant increase in odds of 38% (P=0.08), and men with more than 45 pack-years of smoking had a nonsignificant increase in odds of 45% (P=0.06). This finding is agreement with other research, which has also found smokers to be at greater risk for rectal cancer than for colon cancer [25,47,63–65].

Discussion

This retrospective study of men and women seen at Roswell Park Cancer Institute between 1957 and 1965 demonstrates a lack of an association between colorectal cancer odds and long-term cigarette smoking. The odds were consistent across different exposure measures, and stratification by gender and colorectal sub-site did not alter the results. The addition of covariates to logistic regression models did not significantly change risk estimates. These results are consistent with epidemiologic studies that examined colorectal cancer odds ratios in relation to smoking by following participants in the 1950s and 1960s.

The potential for confounding was a concern in this study because colorectal cancer has been shown to be associated with a number of lifestyle factors including meat consumption, fruit/vegetable consumption, body mass index, and alcohol intake. The addition of the variables race, age, gender, body mass index, county of residence, and other tobacco use to logistic models generally increased odds but not significantly. Data were collected on diet and alcohol intake, but unfortunately many participants were missing those data, and those variables were not placed into logistic models. Based on age, gender, and smoking history, the data appeared to be randomly missing and did not follow any pattern. Sensitivity analyses were performed in which crude estimates were calculated for those who were not missing these data. Next, dietary and alcohol variables were placed into the models, and their effect on risk estimates was noted. The addition of these variables to the statistical models did not have a significant effect (changed odds ≥ 10%) on the vast majority of models. Therefore, it is unlikely that the failure to include these variables in the logistic models had a significant effect on odds ratios. It is also possible that methodological limitations inherent to hospital-based case-control studies, such as high smoking rates among controls, may have contributed to the lack of increased odds for heavy, long-term smokers and colorectal cancer.

The choice of whether or not to use those with respiratory system diseases in the control group was debated amongst the coauthors. Many of the co-authors (A.H., K.B.M., M.E.R) have extensive experience in case-control study conduct and were actively involved in

control group selection. After discussion, the consensus of the co-authors was that restricting the controls to those without respiratory diseases may violate case-control principles, in which both cases and controls must come from the same target population [66–68]. The restriction could create an artificial decrease in the likelihood of smoking among controls compared to cases and possibly bias risk estimates. However, a sensitivity analysis was conducted using an alternate control group (matched 1:1) that excluded those with respiratory system diseases. The ORs for the alternate control group were similar to the ORs for the original control group and the results are displayed on Table 5.

The discrepancy in results between studies in the past that failed to link smoking to colorectal cancer and more recent studies which have linked the two may be due to long exposure times to cigarettes and the failure of earlier studies to take the long latency period into account. In addition, cigarettes have undergone multiple changes over the past 5 decades, and levels of certain carcinogens have changed. Smoking cigarettes exposes the smoker to polycyclic aromatic hydrocarbons (PAH), heterocyclic aromatic amines (HAA), and tobacco specific nitrosamines (TSNA) [29,69]. These carcinogens have been linked to cancers of the bladder and pancreas, organs not in direct contact with smoke [70]. HAA, present in both cigarettes and well-done red meat, is possibly linked to colorectal cancer [71]. These carcinogens reach the bowel by means of direct circulation [72] or direct ingestion [73]. In the 1950s and before, most cigarettes were unventilated; today virtually all cigarettes are ventilated. One study found that ventilated cigarettes are more mutagenic and cytotoxic than unventilated cigarettes [74]. The main type of tobacco in typical cigarettes smoked during the 1950s and before was flue-cured tobacco. Currently, the main types are air-cured tobacco and reconstituted tobacco, which contain greater amounts of HAA and TSNA [29,75–77]. Epidemiologic studies have shown that the risk of bladder cancer for persons using air-cured tobacco products is more than double that of users of flue-cured tobacco [75]. It is possible that, in addition to longer exposure times, changes in cigarette content and technology have increased the amounts of various carcinogens resulting in an increased risk for colorectal cancer over the past five decades.

One of the major weaknesses of this study was the lack of control for factors with known associations to colorectal cancer. Dietary and alcohol intake data were collected but not used in this analysis due to the large amount of missing information. Also, no information was available on family history of colorectal cancer and physical activity, which are important risk factors implicated in the development of colorectal cancer. Other studies have demonstrated that the addition of potential confounding variables such as dietary variables, alcohol intake, and amount of physical activity did not have a considerable effect on risk estimates [24,25]. Because many of the odds estimates were around null or below, it is unlikely that the addition of any of these factors would have resulted in finding a true excess risk among the heaviest smokers. Additionally, the odds ratio for current smokers was significantly less than zero, which may have been due to the symptoms of colorectal cancer causing current smokers to quit and subsequently be classified as former smokers.

Selection bias was another limitation of this study and is a concern in almost every case-control study. This study was especially prone to selection bias because the controls were selected from hospital patients who presented with non-malignant conditions. The controls in this study had a high rate of smoking, which may have been higher than the smoking prevalence of the overall population of Western New York at that time. Other studies have observed a higher rate of smoking in hospital-based controls compared to the general population [78,79]. An elevated smoking prevalence in the control population would have driven odds down and away from an association. Recall bias can also play a role in case-control studies; cases tend to recall past events or behaviors differently than controls. The

amount of recall bias in this study was limited by administering the questionnaire before a diagnosis was given.

Strengths of this study include the ascertainment of a detailed smoking history from participants, including information that allowed the creation of a measure of lifetime tar grams for many participants. The patient population, which drawn almost exclusively from the Western New York region, increases the representativeness of the study population.

In conclusion, consistent with other studies of smoking and colorectal cancer performed in this time period, no association was observed, although more recent studies have observed an association. Reasons for this discrepancy could be a shorter period of exposure in the older studies or changing toxicity of the tobacco products themselves over time. Future studies examining the effect of different types of tobacco on colorectal cancer risk could shed light on this issue.

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Table 1

Description of Cases and Controls for Demographics and Lifestyle Factors

Characteristic	Colorectal Cases	Control Subjects	P-Value
Total, N	1,365	4,096	
Age, avg	64.6	64.6	0.93
Male, %	52.7%	52.7%	1.00
Body Mass Index (kg/m^2)	26.3 N = 1,066	26.6 N = 3,480	0.08
Other Tobacco Use (%)	13.3% N = 1,241	11.8% N = 3,687	0.07
Average Weekly Vegetable Servings	10.7 N = 815	10.9 N = 2,588	0.20
Average Weekly Fruit Servings	3.5 N = 836	3.4 N = 2,688	0.29
Average Weekly Beef Servings	3.4 N = 849	3.3 N = 2,751	0.14
Average Weekly Total Meat Servings	8.2 N = 831	8.1 N = 2,674	0.19
Lifetime Alcoholic Drinks	4,408 N = 1,014	4,930 N = 2,606	0.13

Table 2

Adjusted odds ratios for overall colorectal cancer with corresponding 95% confidence intervals associated with various smoking exposures

	Colorectal Cases		Control Subjects		Adjusted Odds Ratio*	
Variable	**N**	**(%)**	**N**	**(%)**	**OR**	**95% Confidence Interval**
Smoking Status						
Never	745	(59.9%)	2,055	(55.5%)	1.00	Referent
Former Smoker	156	(12.6%)	412	(11.1%)	1.22	0.94 – 1.56
Current Smoker	342	(27.5%)	1,234	(33.3%)	0.79	0.66 – 0.96
Amount Smoked						
Never Smoker	745	(59.9%)	2,055	(55.5%)	1.00	Referent
< 1 Pack/Day	127	(10.3%)	396	(10.8%)	0.95	0.74 – 1.23
1 Pack/Day	252	(20.2%)	853	(23.0%)	0.85	0.69 – 1.05
> 1 Pack/Day	119	(9.6%)	397	(10.7%)	0.87	0.67 – 1.15
Years Smoked						
Never Smoker	745	(59.7%)	2,040	(54.9%)	1.00	Referent
1–27 Years	165	(13.2%)	544	(14.6%)	0.89	0.71 – 1.11
28–41 Years	169	(13.6%)	563	(15.1%)	0.84	0.66 – 1.06
> 41 Years	168	(13.5%)	570	(15.3%)	0.89	0.68 – 1.15
Pack-Years						
Never Smoker	745	(60.6%)	2,040	(55.7%)	1.00	Referent
1–24 Pack-Years	162	(13.2%)	527	(14.4%)	0.92	0.73 – 1.15
25–45 Pack-Years	157	(12.8%)	557	(15.2%)	0.82	0.65 – 1.05
> 45 Pack-Years	165	(13.4%)	536	(14.6%)	0.92	0.72 – 1.19
Lifetime Tar Grams♪						
Never Smoker	355	(69.9%)	1,136	(67.8%)	1.00	Referent
1–3,133 Grams	57	(11.2%)	174	(10.4%)	1.13	0.78 – 1.64
3,133–8,989	45	(8.9%)	186	(11.1%)	0.85	0.57 – 1.28
> 8,989	51	(10.0%)	180	(10.7%)	1.04	0.69 – 1.56

*Adjusted for race, age, gender, body mass index, county of residence, and other tobacco use.

♪Lifetime Tar Grams = Brand Specific Tar Level * (Cigs/Day * 365) * Years

Table 3

Adjusted odds ratios stratified by colorectal sub-site with corresponding 95% confidence intervals associated with various smoking exposures

	Proximal Colon Cancer		Distal Colon Cancer		Rectal Cancer	
	Adjusted Odds Ratio*		Adjusted Odds Ratio*		Adjusted Odds Ratio*	
Variable	**OR**	**95% Confidence Interval**	**OR**	**95% Confidence Interval**	**OR**	**95% Confidence Interval**
Smoking Status		N = 3,541		N =3,618		N = 3,957
Never	1.00	Referent	1.00	Referent	1.00	Referent
Former Smoker	1.20	0.83 – 1.68	1.34	0.91 – 1.91	1.17	0.85 – 1.61
Current Smoker	0.69	0.46 – 1.02	0.55	0.32 – 0.88	0.95	0.75 – 1.22
Amount Smoked		N = 3,544		N = 3,621		N = 3,960
Never Smoker	1.00	Referent	1.00	Referent	1.00	Referent
< 1 Pack/Day	0.90	0.52 – 1.56	0.77	0.48 – 1.25	1.01	0.73 – 1.39
1 Pack/Day	0.73	0.45 – 1.17	0.78	0.53 – 1.14	0.95	0.75 – 1.22
> 1 Pack/Day	0.81	0.44 – 1.48	0.46	0.25 – 0.84	1.19	0.88 – 1.60
Years Smoked		N = 3,587		N = 3,661		N = 4,003
Never Smoker	1.00	Referent	1.00	Referent	1.00	Referent
1–27 Years	0.94	0.59 – 1.49	0.73	0.48 – 1.12	0.92	0.69 – 1.22
28–41 Years	0.82	0.49 – 1.35	0.59	0.37 – 0.95	0.97	0.73 – 1.28
> 41 Years	0.52	0.28 – 0.97	0.71	0.44 – 1.16	1.13	0.87 – 1.47
Pack-Years		N = 3,544		N = 3,621		N = 3,960
Never Smoker	1.00	Referent	1.00	Referent	1.00	Referent
1–24 Pack-Years	0.82	0.50 – 1.36	0.84	0.56 – 1.26	0.94	0.69 – 1.26
25–45 Pack-Years	0.81	0.48 – 1.36	0.67	0.43 – 1.05	0.94	0.69 – 1.29
> 45 Pack-Years	0.72	0.40 – 1.30	0.56	0.33 – 0.97	1.26	0.92 – 1.72
Lifetime Tar Grams♪		N = 1,629		N = 1,664		N = 1,755
Never Smoker	1.00	Referent	1.00	Referent	1.00	Referent
1–3,133 Grams	1.43	0.69 – 2.95	0.77	0.37 – 1.61	1.26	0.76 – 2.07
3,133–8,989	0.63	0.24 – 1.68	1.05	0.55 – 2.02	0.89	0.51 – 1.55
> 8,989	1.10	0.48 – 2.53	0.59	0.25 – 1.41	1.15	0.67 – 1.97

*Adjusted for race, age, gender, body mass index, county of residence, and other tobacco use.

♪Lifetime Tar Grams = Brand Specific Tar Level * (Cigs/Day * 365) * Years

Table 4

Adjusted odds ratios stratified by gender with corresponding 95% confidence intervals associated with various smoking exposures

	Males						Females					
	Colorectal Cases		Control Subjects		Adjusted Odds Ratio*		Colorectal Cases		Control Subjects		Adjusted Odds Ratio*	
Variable	**N**	**(%)**	**N**	**(%)**	**OR**	**95% Confidence Interval**	**N**	**(%)**	**N**	**(%)**	**OR**	**95% Confidence Interval**
Smoking Status												
Never	274	(42.9%)	748	(39.2%)	1.00	Referent	471	(78.0%)	1,307	(72.9%)	1.00	Referent
Former Smoker	127	(19.9%)	324	(17.0%)	1.42	1.01 – 1.98	29	(4.8%)	88	(4.9%)	0.99	0.61 – 1.59
Current Smoker	238	(37.2%)	835	(43.8%)	0.92	0.68 – 1.23	104	(17.2%)	399	(22.2%)	0.74	0.56 – 0.97
Years Smoked												
Never Smoker	274	(42.7%)	734	(38.2%)	1.00	Referent	471	(77.9%)	1,306	(72.7%)	1.00	Referent
1–27 Years	87	(13.6%)	233	(12.1%)	1.23	0.85 – 1.77	78	(12.9%)	311	(17.3%)	0.70	0.52 – 0.95
28–41 Years	120	(18.7%)	417	(21.7%)	0.88	0.63 – 1.23	49	(8.1%)	146	(8.1%)	0.98	0.68 – 1.41
> 41 Years	161	(25.1%)	537	(28.0%)	1.01	0.74 – 1.38	7	(1.2%)	33	(1.8%)	0.67	0.27 – 1.67
Pack-Years												
Never Smoker	274	(43.7%)	734	(39.1%)	1.00	Referent	471	(78.2%)	1,306	(73.2%)	1.00	Referent
1–24 Pack-Years	84	(13.4%)	249	(13.3%)	1.12	0.78 – 1.62	78	(13.0%)	278	(15.6%)	0.82	0.60 – 1.10
25–45 Pack-Years	123	(19.6%)	409	(21.8%)	1.00	0.72 – 1.39	34	(5.6%)	148	(8.3%)	0.62	0.40 – 0.95
> 45 Pack-Years	146	(23.3%)	483	(25.8%)	1.02	0.74 – 1.40	19	(3.2%)	53	(3.0%)	1.19	0.67 – 2.11
Lifetime Tar Grams♪												
Never Smoker	65	(37.6%)	216	(37.4%)	1.00	Referent	290	(86.6%)	920	(83.7%)	1.00	Referent
1–3,133 Grams	35	(20.2%)	92	(15.9%)	1.41	0.83 – 2.38	22	(6.6%)	82	(7.5%)	0.98	0.56 – 1.72
3,133–8,989	32	(18.5%)	117	(20.3%)	1.05	0.62 – 1.76	13	(3.9%)	69	(6.3%)	0.62	0.30 – 1.27
> 8,989	41	(23.7%)	152	(26.3%)	1.05	0.64 – 1.71	10	(3.0%)	28	(2.5%)	1.33	0.57 – 3.08

*Adjusted for race, age, gender, body mass index, county of residence, and other tobacco use.

♪Lifetime Tar Grams = Brand Specific Tar Level * (Cigs/Day * 365) * Years

Table 5

Adjusted odds ratios for overall colorectal cancer with corresponding 95% confidence intervals associated with various smoking exposures

	Original Control Group		Alternate Control Group	
	Adjusted Odds Ratio*		Adjusted Odds Ratio*	
Variable	**OR**	**95% Confidence Interval**	**OR**	**95% Confidence Interval**
Smoking Status		N = 4,944		N = 2,484
Never	1.00	Referent	1.00	Referent
Former Smoker	1.22	0.94 – 1.56	1.35	1.01 – 1.81
Current Smoker	0.79	0.66 – 0.96	0.85	0.69 – 1.05
Amount Smoked		N = 4,944		N = 2,484
Never Smoker	1.00	Referent	1.00	Referent
< 1 Pack/Day	0.95	0.74 – 1.23	0.97	0.73 – 1.29
1 Pack/Day	0.85	0.69 – 1.05	0.89	0.70 – 1.12
> 1 Pack/Day	0.87	0.67 – 1.15	0.99	0.73 – 1.34
Years Smoked		N = 4,964		N = 2,478
Never Smoker	1.00	Referent	1.00	Referent
1–27 Years	0.89	0.71 – 1.11	1.18	0.90 –1.53
28–41 Years	0.84	0.66 – 1.06	1.09	0.82 – 1.44
> 41 Years	0.89	0.68 – 1.15	1.16	0.86 – 1.56
Pack-Years		N = 4,889		N = 2,478
Never Smoker	1.00	Referent	1.00	Referent
1–24 Pack-Years	0.92	0.73 – 1.15	1.21	0.93 – 1.56
25–45 Pack-Years	0.82	0.65 – 1.05	0.98	0.74 –1.29
> 45 Pack-Years	0.92	0.72 – 1.19	1.26	0.94 – 1.68
Lifetime Tar Grams♪		N = 2,184		N = 1,039
Never Smoker	1.00	Referent	1.00	Referent
1–3,133 Grams	1.13	0.78 – 1.64	1.01	0.67 – 1.50
3,133–8,989	0.85	0.57 – 1.28	1.17	0.78 – 1.75
> 8,989	1.04	0.69 – 1.56	1.39	0.93 – 2.09

*Adjusted for race, age, gender, body mass index, county of residence, and other tobacco use.

♪Lifetime Tar Grams = Brand Specific Tar Level * (Cigs/Day * 365) * Years