Tobacco Smoking and Colorectal Cancer: A Population-based Case-control Study in Newfoundland and Labrador

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ABSTRACT

Objective: Newfoundland and Labrador (NL) has the highest incidence rate of both colorectal cancer (CRC) and smoking prevalence in Canada. The objective of this study was to examine if CRC is associated with smoking in this population.

Methods: Newly diagnosed cases identified between 1999 and 2003 were frequency-matched by 5-year age group and sex with controls selected from the residents of NL through random digit dialing. A total of 702 cases and 717 controls consented to participate in the study and completed a set of self-administered questionnaires. Measures of tobacco use included type of tobacco, age of initiation of smoking, years of smoking, years since started smoking, number of cigarettes smoked daily, pack years, and years since abstention from smoking. Odds ratios were estimated using multivariate logistic regression.

Results: In comparison with non-smokers, former and current smokers were at a significantly elevated risk of CRC with corresponding odds ratios of 1.36 and 1.96. The risk significantly increased with cigarette smoking years, the amount of cigarettes smoked daily, and cigarette pack years. The risk significantly decreased with years of abstention from smoking cigarettes. This association was stronger among drinkers and in men. In addition, this effect was observed to be slightly stronger for rectum than colon cancer.

Discussion: In summary, cigarette smoking increased the risk of CRC in the NL population. The risk of CRC associated with cigarette smoking varies by sex, drinking status, and site of CRC.

Key words: Colorectal cancer; smoking; odds ratio; case-control study

La traduction du résumé se trouve à la fin de l'article.

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Globally, colorectal cancer (CRC) is the third leading cause of death from cancer in males and the fourth leading cause of death from cancer in females.¹ In 2002, an estimated 1 million new cases of CRC were diagnosed, accounting for more than 9% of all new cases of cancer.² The incidence of CRC varies around the world: CRC is common in highly industrialized countries but is much more rare in Asia and Africa.^{1,2}

While research has shown that the incidence of CRC has been associated with dietary factors³⁻⁵ and physical inactivity,^{5,6} evidence on the relationship between CRC and tobacco use has been conflicting. A number of epidemiological studies have investigated the relationship between tobacco smoke and CRC in the last three decades, but few found a significant risk for CRC among smokers. Earlier studies found that greater risk of CRC was associated with smoking cigars and pipes, but not with smoking cigarettes.⁷⁻⁹ Among studies that reported an increased risk of CRC with cigarette smoking, the magnitude of risk was only 1.20-1.40.¹⁰⁻¹⁷ Inadequate adjustment for various potential confounders such as alcohol, physical activity, body size, dietary factors, and possibly unidentified confounders could account for the small increase in risk found with smoking in some studies. In fact, few potential confounders were adjusted for in most of the cohort studies. One third of the published studies considered only age or other relevant demographic factors.^{10,11,16,18-24} Some studies adjusted only for demographic factors and alcohol use,^{10,25,26} and less than half of the studies consid-

ered two or more of the potential confounders.^{11,15-17,21,23,27-33} Additionally, evidence of the association of CRC and smoking by sex, drinking status and subsites of CRC has been inconsistent.

Newfoundland and Labrador (NL), a province of Canada, has the highest incidence of CRC in the world.^{2,34} Historically, there has been a relatively high prevalence of tobacco use in the province, with an average rate of 34% during the period of 1985-2003.³⁵⁻³⁸ However, no studies were conducted to investigate the effect of tobacco smoking on the risk of developing CRC in NL. Using a population-based case-control study design, we assessed the relationship between various measures of smoking and the risk of CRC among NL residents aged 20-74 years, and conducted subgroup analyses by sex, drinking status and subsites of CRC.

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Table 1. Characteristics of CRC Cases and Controls and Prevalence Rates of Cigarette Smoking by Selected Variables of Demographics, Chronic Conditions, Medication and Lifestyles in the NL Population-based Case-control Study of CRC in 1999-2003

Demographics	Case		Control		OR for Covariates		Cigarette smoking‡		
	N	%†	N	%†	OR†	95% CI	N	%	95% CI
Age group (years)									
20-54	186	26.50	185	25.80	1.00		230	61.99	57.05 - 66.94
55-64	242	34.47	264	36.82	0.91	0.70 - 1.19	344	67.98	63.91 - 72.05
65-74	274	39.03	268	37.38	1.02	0.78 - 1.32	374	69.00	65.91 - 72.05
Sex									
Female	276	39.32	293	40.86	1.00		303	53.25 ^Δ	49.15 - 57.36
Male	426	60.68	424	59.14	1.07	0.86 - 1.32	645	75.88	73.00 - 78.76
Region									
Urban	302	43.02	353	49.23	1.00		432	65.95	62.32 - 69.58
Rural	400	56.98	364	50.77	1.28	1.04 - 1.58 *	516	67.54	64.22 - 70.86
Education									
High school or less	446	63.53	349	48.68	1.00		563	70.82 ^Δ	67.65 - 73.98
College+	256	36.47	368	51.32	0.54	0.44 - 0.67 ***	385	61.70	57.88 - 65.52
Marital status									
Married	540	76.92	579	80.75	1.00		757	67.65	64.91 - 70.39
Single/div/sep/wid	162	23.08	138	19.25	0.80	0.62 - 1.03	191	63.67	58.22 - 69.12
Diabetes									
No	555	79.06	623	86.89	1.00		769	65.28 ^Δ	62.56 - 68.00
Yes	147	20.94	94	13.11	1.76	1.32 - 2.33 ***	179	74.28	68.74 - 79.80
Use of laxatives									
No	573	81.62	657	91.63	1.00		823	66.91	64.28 - 69.54
Yes	129	18.38	60	8.37	2.47	1.78 - 3.42 ***	125	66.14	59.38 - 72.89
Obesity									
No (BMI<30)	503	71.65	556	77.55	1.00		693	65.44	62.57 - 68.31
Yes (BMI≥30)	199	28.35	161	22.45	1.37	1.07 - 1.74 *	255	70.83	66.13 - 75.53
Alcohol once/week									
No	270	38.46	264	36.82	1.00		260	48.69 ^Δ	44.44 - 52.93
Yes	432	61.54	453	63.18	0.93	0.75 - 1.16	688	77.74	75.00 - 80.48
Cholesterol level									
Low	494	70.37	451	62.90	1.00		612	64.70 ^Δ	61.71 - 67.81
High	208	29.63	266	37.10	0.72	0.57 - 0.89 **	336	70.89	66.79 - 74.98
Aspirin									
No	522	74.62	492	68.62	1.00		649	64.00 ^Δ	61.05 - 66.96
Yes	180	25.38	225	31.38	0.75	0.60 - 0.95 *	299	73.83	69.54 - 78.11
Fruits daily									
1-2 servings	519	73.93	471	65.69	1.00		679	68.59 ^Δ	65.69 - 71.48
≥3 servings	183	26.07	246	34.31	0.68	0.54 - 0.85 ***	269	62.70	58.12 - 67.29
Calcium supplement									
No	608	86.61	568	79.22	1.00		811	68.96 ^Δ	66.31 - 71.61
Yes	94	13.39	149	20.78	0.60	0.44 - 0.78 ***	137	56.38	50.14 - 62.62

† Column % and Unadjusted OR and X² and Wald test: * p<0.05 ** p<0.01 *** p<0.001.

‡ Number, percentage of smokers and 95% CI of the percentage.

Δ shows a significant difference between subgroups.

METHODS

This study utilized data that had already been collected from an existing population-based case-control study of more than 4,000 participants from NL and Ontario. Details about this inter-provincial CRC team project can be found elsewhere.³⁹⁻⁴⁶ Briefly, cases were recruited using the Newfoundland and Labrador Colorectal Cancer Registry (NFCCR), while controls were random samples of the NL population aged 20-74.⁴¹ Eligible CRC cases were NL residents between 20 and 74 years old, newly diagnosed with CRC between January 1999 and December 2003, with histologically confirmed primary adenocarcinoma of the colon or rectum. Controls were frequency-matched according to sex and 5-year age group. Self-reported information including personal history, lifestyle and dietary characteristics were collected using a Personal History Questionnaire (PHQ) and Food Frequency Questionnaire (FFQ), respectively, with these questionnaires being developed for and utilized in the larger study. In addition, a blood sample was provided for possible genetic analysis. The questionnaires were mailed to all consenting eligible participants with self-addressed stamped envelopes. If a participant had not returned finished questionnaires within 3 weeks, a follow-up telephone call was made to ensure that the study package had been received. A telephone interview or assistance was offered when illiteracy or physical disability was a concern.

The PHQ consisted of 74 questions, addressing such issues as bowel screening history, medical conditions, use of medication, diet, physical activity, consumption of alcohol and tobacco, and socio-demographic measures such as education and income. As well, demographic information such as sex, age, date of birth, and marital status was collected. To define an urban versus rural place of residence, a community with a population of 10,000 or more was defined as urban,⁴⁷ one with less than 10,000 as rural. Of note, since the town of Gander's population is slightly under 10,000, it is similar to other urban areas in NL, and was also defined as urban in this study. For female participants, there were additional questions relating to reproductive factors and hormone replacement therapy.

Measurement of exposure

Participants were asked a series of questions on cigarette, cigar and pipe smoking to determine tobacco-relevant exposures (see Appendix 1). Subjects were classified into three cigarette-smoking categories: non-smokers, who had not smoked one cigarette a day for 3 months or longer; former smokers, who had stopped smoking cigarettes about one year before cancer diagnosis or investigation; and current smokers, who still smoked at least one cigarette a day during the year prior to diagnosis or investigation. Other derived variables of cigarette smoking included age at initiation of smoking

Table 2. OR of CRC and Corresponding 95% CI for Cigarette Smoke in the NL Population-based Case-control Study of CRC in 1999-2003

Tobacco Measure	Case		Control		Unadjusted		Adjusted†	
	N	%	N	%	OR	95% CI	OR	95% CI
Cigarette smoke		***						
Non-smoker	201	28.63	270	37.66	1.00		1.00	
Smoker	501	71.37	447	62.34	1.51	1.20 - 1.88 ***	1.49	1.16 - 1.92 ***
Cigarette status		***						
Former	352	50.14	351	48.95	1.35	1.06 - 1.70 *	1.36	1.04 - 1.77 *
Current	149	21.23	96	13.39	2.08	1.52 - 2.86 ***	1.96	1.40 - 2.76 ***
Cigarette age		**						
<16	172	24.50	153	21.34	1.51	1.14 - 2.01 **	1.47	1.07 - 2.03 *
≥16	329	46.87	294	41.00	1.50	1.18 - 1.92 ***	1.50	1.15 - 1.66 **
P-trend							**	
Cigarette years		***						
<20	119	16.95	150	20.92	1.07	0.79 - 1.44	1.15	0.83 - 1.59
20-29	136	19.37	113	15.76	1.62	1.20 - 2.20 **	1.62	1.16 - 2.28 **
≥30	246	35.04	184	25.66	1.80	1.38 - 2.34 ***	1.71	1.27 - 2.30 **
P-trend							**	
Years since initiation		**						
1-25	36	5.13	26	3.63	1.86	1.09 - 3.18 *	1.67	0.95 - 2.95
26-35	89	12.68	72	10.04	1.66	1.16 - 2.38 **	1.62	1.07 - 2.47 *
≥36	376	53.56	349	48.68	1.45	1.15 - 1.83 **	1.44	1.10 - 1.89 *
P-trend							ns	
Cigarettes daily		**						
<20	234	33.33	216	30.13	1.46	1.12 - 1.89 **	1.45	1.10 - 1.92 *
20-29	193	27.49	175	24.41	1.48	1.13 - 1.95 **	1.51	1.11 - 2.05 *
≥30	74	10.54	56	7.81	1.78	1.20 - 2.63 **	1.67	1.07 - 2.58 *
P-trend							*	
Pack years		***						
<20	198	28.21	201	28.03	1.32	1.01 - 1.73 *	1.36	1.03 - 1.82 *
20-39	172	24.50	146	20.36	1.58	1.19 - 2.11 **	1.60	1.11 - 2.19 **
≥40	131	18.66	100	13.95	1.76	1.28 - 2.42 ***	1.64	1.14 - 2.36 *
P-trend							**	
Years of abstinence		***						
0	149	21.23	96	13.39	2.08	1.52 - 2.86 ***	1.97	1.40 - 2.77 ***
<20	193	27.49	156	21.76	1.66	1.26 - 2.20 ***	1.61	1.19 - 2.19 *
20-29	96	13.68	94	13.11	1.37	0.98 - 1.92	1.37	0.95 - 1.99
≥30	63	8.97	101	14.09	0.84	0.58 - 1.21	0.90	0.60 - 1.33
P-trend							***	

Note: † OR estimates for cigarette smoke from binary logistic models adjusted for age, sex, education, marital status, rural/urban, diabetes, cholesterol, aspirin, alcohol use, BMI, fruits, laxatives and calcium. X² or Wald test or Cochran-Armitage test for trend: * p<0.05 ** p<0.01 *** p<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

(<16 years old and ≥16); number of cigarettes smoked per day (<20 cigarettes daily, 20-29 and ≥30); total number of years of cigarette smoking (<20 years, 20-29 and ≥30); years since started smoking (1-25 years, 26-35 and ≥36) and cigarette pack years (<20 pack years, 20-39 and ≥40). Pack years of smoking cigarettes were estimated using the average number of cigarettes smoked per day, divided by 20, and then multiplied by the number of years of cigarette smoking. Years of abstinence from smoking cigarettes were also estimated (0 years of abstinence from smoking, 1-19, 20-29 and ≥30). Approximately 5% of subjects had smoked cigars and approximately 10% had smoked pipes; however, there were no statistically significant relationships between CRC and cigar or pipe smoking, and thus, the results were not presented in this paper.

Other variables considered in the analyses were: age; sex; region (urban/rural); birth country; race; education; marital status; alcohol use; family CRC history (yes/no); other personal cancer history (yes/no); physician-diagnosed diabetes (yes/no); physician-diagnosed hypercholesterolemia (yes/no); regular use of aspirin such as Anacin®, Bufferin®, Bayer®, Excedrin®, Ecotrin® (yes/no); intake of fruits, vegetables and red meats; body mass index (BMI); physical activity; lifetime use of bulk-forming laxatives and other laxatives such as Ex-Lax® (yes/no); and lifetime use of calcium pills or tablets and calcium-based antacids such as Tums®, Rolaids® and extra-strength Rolaids® (yes/no). Intake of fruits/vegetables/red meats (≤2 or ≥3 servings daily) was investigated using responses to the questions: "About one year before [your recent cancer diagno-

sis]/[this survey], on average, how often did you eat a piece or serving of fruit/vegetables/red meat?" Servings of fruit were defined as: 1 medium-sized fresh fruit; ½ cup of chopped, cooked or canned fruit; ¼ cup of dried fruit; 6 ounces of fruit juice (50-100% pure juice). Servings of vegetables were defined as: 1 cup raw, leafy vegetables; ½ cup of other vegetables, cooked or chopped raw; 6 ounces of vegetable juice. Red meat servings were defined as 2-3 ounces (a piece of meat about the size of a deck of cards). Respondents were classified into physically active and non-physically active groups. Physically active was defined as participating regularly in physical activities for a total of at least 30 minutes a week in one's 20s, 30s and 40s, and 50s. Respondents were classified into non-obese (BMI<30) and obese (BMI≥30). BMI was estimated based on the height and weight questions, "About how tall are you, without your shoes on?" and "How much did you weigh about one year before your recent cancer diagnosis (cases) or this survey (controls)?" Subjects were classified as drinkers if they ever consumed any alcoholic beverages once a week for 6 months or longer. Otherwise they were classified as non-drinkers. The covariates that were selected for multivariate logistic regression analyses are presented in Table 1.

Statistical analyses

A descriptive analysis was conducted to present the characteristics of the sample. The independent effect of cigarette smoking on the relative risk of CRC was estimated using adjusted odds ratios (OR) calculated in multivariate binary and multinomial logistic regres-

Table 3. Adjusted OR of CRC and Corresponding 95% CI for Cigarette Smoke in Men and Women in the NL Population-based Case-control Study of CRC in 1999-2003

Tobacco Measure	Men				Women			
	Case	Control	OR	95% CI†	Case	Control	OR	95% CI†
Cigarette smoke	***							
Non-smoker	81	124	1.00		120	146	1.00	
Smoker	345	300	1.73	1.22 - 2.46 **	156	147	1.21	0.83 - 1.75
Cigarette status	***				**			
Former	254	238	1.64	1.13 - 2.36 *	98	113	1.07	0.72 - 1.60
Current	91	62	2.06	1.30 - 3.27 ***	58	34	1.85	1.09 - 3.13 *
Cigarette age	**				**			
<16	137	126	1.61	1.07 - 2.42 *	35	27	1.50	0.80 - 2.80
≥16	208	174	1.81	1.24 - 2.65 **	121	120	1.15	0.78 - 1.69
P-trend			**			ns		
Cigarette years	**				***			
<20	91	91	1.61	1.04 - 2.47 *	28	59	0.62	0.36 - 1.07
20-29	88	77	1.73	1.10 - 2.72 *	48	36	1.66	0.97 - 2.85
≥30	166	132	1.84	1.23 - 2.76 **	80	52	1.70	1.07 - 2.70 **
P-trend			*			*		
Years since initiation	**							
1-25	15	14	1.54	0.67 - 3.54	21	12	1.75	0.79 - 3.89
26-35	53	42	1.67	0.94 - 2.98	36	30	1.57	0.84 - 2.92
≥36	277	244	1.76	1.21 - 2.56 **	99	105	1.13	0.75 - 1.70
P-trend			*			ns		
Cigarettes daily	**							
<20	127	115	1.72	1.15 - 2.59 **	107	101	1.16	0.77 - 1.74
20-29	149	133	1.71	1.15 - 2.56 *	44	42	1.27	0.74 - 2.17
≥30	69	52	1.79	1.09 - 2.95 *	5	4	1.91	0.42 - 8.66
P-trend			*			ns		
Pack years	**							
<20	121	115	1.70	1.13 - 2.55 *	77	86	1.03	0.66 - 1.59
20-39	111	98	1.64	1.07 - 2.52 *	61	48	1.55	0.94 - 2.54
≥40	113	87	1.89	1.21 - 2.93 *	18	13	1.15	0.50 - 2.64
P-trend			*			ns		
Years of abstinence	***				***			
0	91	62	2.07	1.31 - 3.29 ***	58	34	1.79	1.05 - 3.05 *
<20	124	106	1.71	1.13 - 2.61 *	69	50	1.60	0.98 - 2.60
20-29	77	64	1.88	1.18 - 3.01 **	19	30	0.71	0.36 - 1.42
≥30	53	68	1.27	0.77 - 2.10	10	33	0.41	0.18 - 0.93 *
P-trend			***			ns		

Note: † OR for cigarette smoke from binary logistic regression models adjusted for age, education, marital status, rural/urban, diabetes, cholesterol, aspirin, alcohol use, BMI, fruits, hormone replacement (in women), laxatives and calcium. χ^2 or Wald test or Cochran-Armitage test for trend: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. Cochran-Armitage test for trend: ns=not significant at 5%.

sion models.^{48,49} Each measure of smoking evaluated was modeled independently from the others given that these measures were highly correlated. Those who have never smoked served as the reference group in all analyses. Based on univariate logit analysis of the pooled data set, any variable whose univariate test had a p -value < 0.20 was considered as a candidate for the multivariate logistic regression analyses.⁴⁸ All selected variables by univariate analysis were included in the models regardless of their “statistical significance”. The rationale for this approach is to provide as much control of confounding as possible within the given data set.⁴⁸ This is based on the fact that it is possible for individual variables not to exhibit strong confounding, but when taken collectively, considerable confounding may be present in the data.⁴⁸ Independent variables with particularly high inter-correlations (> 0.30) were identified and less precise measures were excluded,⁴⁹ and the variable pool was reduced in order to avoid synonymous variables and collinearity.⁵⁰ Data were complete for approximately 90% of study subjects. For missing data, values were imputed. The mean of the non-missing values for continuous variables was used as the estimate of missing continuous data and the mode value is used as the estimate of missing categorical data.⁵¹ Testing for linear trends was carried out by representing the categories of exposure with ordinal variables, considered as continuous, and examining the significance of the coefficient with a z -test.^{52,53} The analyses were also conducted by sex, drinking status and site of CRC in order to investigate the modified effects of these factors on the association

between smoking and CRC.^{52,53} Population attributable risk (PAR) and the 95% confidence interval (CI) of PAR were calculated by determining the 95% CI for $\log(P[OR-1])$ on the basis of the standard errors for P and OR and transforming back to the 95% CI for the PAR.⁵⁴ All statistical analyses were completed using SAS 9.1.⁵⁵ Significance tests assumed two-tailed p -values or 95% CIs.

RESULTS

Characteristics of the cases and controls

A total of 702 CRC cases and 717 controls were included in the study. The mean age was 60.3 years old (SD: 9.5) for cases and 60.4 years old (SD: 9.4) for controls. Caucasians accounted for over 94% of the sample and more than 93% of participants were Canadian-born. Over 97% did not have a familial history of CRC. Approximately 13% of the sample had other cancer diagnosis but there was no significant difference between cases and controls. The primary results suggested a significantly increased risk of CRC among those who lived in a rural area and had lower education. CRC cases tended to be those who had diabetes and were obese. Having high cholesterol level, taking calcium pills and tablets, eating more fruits and using aspirin decreased the risk of CRC. Prevalence of cigarette smoking significantly differed by most selected covariates (Table 1).

CRC and types of tobacco use

The study found a significant independent association between smoking cigarettes and CRC (Table 2). There was a 49%, 36% and

Table 4. Adjusted OR of CRC and Corresponding 95% CI for Cigarette Smoke among Drinkers and Non-drinkers in the NL Population-based Case-control Study of CRC in 1999-2003

Tobacco Measure	Drinkers				Non-drinkers			
	Case	Control	OR†	95% CI	Case	Control	OR†	95% CI
Cigarette smoke	***							
Non-smoker	70	127	1.00		131	143	1.00	
Smoker	362	326	1.82	1.28 - 2.58 **	139	121	1.18	0.81 - 1.70
Cigarette status	***				*			
Former	259	257	1.67	1.16 - 2.58 *	93	94	1.05	0.57 - 1.69
Current	103	69	2.33	1.49 - 3.65 **	46	27	1.57	0.89 - 2.75
Cigarette age	***							
<16	136	124	1.68	1.11 - 2.54	36	29	1.36	0.75 - 2.45
≥16	226	202	1.89	1.31 - 2.74 **	103	92	1.12	0.76 - 1.67
P-trend			**				ns	
Cigarette years	***				*			
<20	89	106	1.47	0.96 - 2.25	30	44	0.77	0.44 - 1.34
20-29	98	83	2.07	1.33 - 3.21 **	38	30	1.23	0.69 - 2.19
≥30	175	137	1.96	1.32 - 2.93 **	71	47	1.51	0.94 - 2.41
P-trend			**				ns	
Years since initiation	***							
1-25	24	19	1.99	0.97 - 4.04	12	7	1.38	0.50 - 3.80
26-35	68	58	1.87	1.12 - 3.14 *	21	14	1.48	0.66 - 3.33
≥36	270	249	1.78	1.22 - 2.59 **	106	100	1.09	0.73 - 1.64
P-trend			ns				ns	
Cigarettes daily	***							
<20	159	134	2.03	1.37 - 3.00 *	75	82	0.89	0.58 - 1.36
20-29	141	146	1.58	1.06 - 2.36 *	52	29	1.99	1.14 - 3.48 *
≥30	62	46	1.91	1.13 - 3.23 *	12	10	1.47	0.56 - 3.85
P-trend			ns				ns	
Pack years	***							
<20	143	139	1.79	1.21 - 2.66 *	55	62	0.89	0.56 - 1.41
20-39	120	106	1.90	1.25 - 2.89 *	52	40	1.39	0.83 - 2.32
≥40	99	81	1.73	1.10 - 2.74 *	32	19	1.78	0.90 - 3.50
P-trend			ns				ns	
Years of abstinence	***				**			
0	103	69	2.34	1.50 - 3.67 **	46	27	1.55	0.88 - 2.72
<20	141	119	1.87	1.25 - 2.81 *	52	37	1.43	0.85 - 2.41
20-29	72	70	1.71	1.07 - 2.73 *	24	24	1.09	0.56 - 2.11
≥30	46	68	1.19	0.71 - 2.00	17	33	0.55	0.28 - 1.09
P-trend			***				ns	

Note: † OR for cigarette smoke from binary logistic regression models adjusted for age, sex, education, marital status, rural/urban, diabetes, cholesterol, aspirin, alcohol use, BMI, fruits, laxatives and calcium. X² or Wald test or Cochran-Armitage test for trend: * p<0.05 ** p<0.01 *** p<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

96% higher risk of CRC among all, former and current smokers, respectively, compared to non-smokers. The adjusted ORs also showed that the risk of CRC increased significantly with smoking cigarette years, the number of cigarettes smoked daily, and cigarette pack years. The risk of CRC decreased significantly with years of abstinence from smoking.

CRC and cigarette smoking by sex

Cigarette smoking increased the risk of CRC among men and women, but demonstrated a stronger effect for males than females (Table 3). Among males: there was a 73%, 64% and 106% higher risk of CRC among all, former and current cigarette smokers, respectively, compared to non-smokers; the risk of CRC was significantly increased with smoking cigarette years, years after smoking began, the number of cigarettes smoked daily, and cigarette pack years; and the risk significantly decreased with years of abstinence from smoking.

CRC and cigarette smoking by drinking status

Among drinkers, there was a 67% and 133% higher risk of CRC among former and current smokers, respectively, compared to non-smokers. The risk of CRC significantly increased with smoking years and decreased with years of abstinence from smoking (Table 4). However, among non-drinkers, the study only found a weak relationship between smoking and the risk of CRC.

Colon and rectum cancer and cigarette smoking

The adjusted ORs showed a significant effect of smoking cigarettes on both colon and rectum cancer (Table 5); however, the adjusted ORs of subsites for CRC for smokers versus non-smokers demonstrate a stronger effect of smoking cigarettes on rectum cancer than colon cancer.

DISCUSSION

This population-based case-control study suggests that cigarette smoking significantly increased the risk of CRC. At a population level, the estimated population attributable risk of CRC (PAR) associated with smoking was 13.18% (95% CI 6.80-19.58) in this population. The observed association was persistent regardless of how tobacco use was defined and cannot be explained by known confounding factors. Given the inconsistency in the existing literature around this issue, this study provides new and important evidence supporting the positive association between cigarette smoking and CRC. The effects of smoking on CRC seem to be stronger in males and alcohol drinkers. Smoking also demonstrated a slightly stronger effect on rectum than colon cancer.

Compared to previous similar studies,¹⁰⁻¹⁷ our study suggests a stronger association between smoking and CRC. The present study demonstrated a clear dose-response relationship, showing that the risk of CRC increased with cigarette smoking years, the amount of cigarettes smoked per day, and smoking cigarette pack years. This is consistent with other studies that reported statistically signifi-

Table 5. Adjusted OR of Colon and Rectum Cancer and Corresponding 95% CI for Cigarette Smoke in the NL Population-based Case-control Study of CRC in 1999-2003

Tobacco Measure	Control	Colon Cancer			Rectum Cancer		
		Case	OR†	95% CI	Case	OR†	95% CI
Cigarette smoke	***						
Non-smoker	270	140	1.00		61	1.00	
Smoker	447	330	1.49	1.12 - 1.97 *	171	1.56	1.09 - 2.25 *
Cigarette status	***						
Former	351	243	1.41	1.01 - 2.05 *	109	1.31	0.89 - 1.93
Current	96	87	1.70	1.15 - 2.98 *	62	2.41	1.52 - 3.83 ***
Cigarette age	**						
<16	153	116	1.54	1.07 - 2.20 *	56	1.36	0.86 - 2.15
≥16	294	214	1.47	1.09 - 1.98 *	115	1.66	1.13 - 2.43 **
P-trend			*			*	
Cigarette years	***						
<20	150	73	1.08	0.76 - 1.83	46	1.36	0.85 - 2.16
20-29	113	94	1.72	1.17 - 2.87 **	42	1.53	0.94 - 2.48
≥30	184	163	1.70	1.09 - 2.45 *	83	1.78	1.16 - 2.72 *
P-trend			**			*	
Years since initiation	***						
1-25	26	24	1.65	0.88 - 3.09	12	1.67	0.77 - 3.64
26-35	72	52	1.52	0.95 - 2.44	37	1.83	1.05 - 3.19 *
≥36	349	254	1.44	1.06 - 1.94 *	122	1.48	0.99 - 2.20
P-trend			ns			ns	
Cigarettes daily	**						
<20	216	161	1.44	1.05 - 1.98 *	73	1.46	0.97 - 2.20
20-29	175	122	1.48	1.05 - 2.10 *	71	1.67	1.08 - 2.58 *
≥30	56	47	1.66	1.01 - 2.71 *	27	1.75	0.96 - 3.18
P-trend			*			*	
Pack years	**						
<20	201	124	1.27	0.92 - 1.76	74	1.58	1.04 - 2.39 *
20-39	146	117	1.70	1.20 - 2.40 *	55	1.56	0.99 - 2.44
≥40	100	89	1.72	1.15 - 2.58 *	42	1.54	0.92 - 2.57
P-trend			**			ns	
Years of abstinence	***						
0	96	87	1.76	1.20 - 2.58 **	62	2.43	1.53 - 3.86 ***
<20	156	142	1.81	1.29 - 2.54 **	51	1.29	0.82 - 2.03
20-29	94	56	1.22	0.80 - 1.85	40	1.79	1.08 - 2.95 *
≥30	101	45	0.95	0.61 - 1.49	18	0.86	0.46 - 1.59
P-trend			**			***	

Note: † OR for cigarette smoke from logistic regression models was adjusted for age, sex, education, marital status, rural/urban, diabetes, cholesterol, aspirin, alcohol use, BMI, fruits, laxatives and calcium. X² or Wald test or Cochran-Armitage test for trend: * p<0.05 ** p<0.01 *** p<0.001. Cochran-Armitage test for trend: ns=not significant at 5%.

cant dose-response trends with the amount smoked daily for CRC and its subsites.^{10-17,56-58}

Studies on CRC have varied in their assessment of duration of smoking. Some evidence exists to suggest that the risk for CRC increased with earlier age at initiation.^{11,16} However, our study did not show this feature. While other studies found a statistically significant increase of CRC incidence after 30 years of smoking,⁵⁹ our study showed a significantly increased risk after 20 years or more of smoking. Other studies found that cigarette smoking was unrelated to CRC until 35 years after smoking began, and that the relationship became progressively more strongly related with time.²⁹ However, our study showed that the risk of CRC increased after 25 years since smoking began, and the risk did not increase with time. These studies and our study suggest that smoking may act as an initiator of CRC and a longer induction period may be needed before the association of the cancer with smoking can be observed.

The benefit of smoking cessation was also evaluated in our study. The results showed that the risk of CRC significantly decreased with years of abstinence from smoking and there was no significant difference in the risk between smokers who stopped smoking for 20 years or more and non-smokers. Other studies also reported a reduced risk of CRC after years of smoking cessation, but the risk remained substantially elevated even after 20 years of smoking cessation.¹⁵

Several cohort studies reported that the association between smoking and CRC is stronger in men than in women.^{12,15,24} However, one study reported a significantly increased risk associated

with smoking only in women and not in men.⁶⁰ Another study showed the association between smoking and CRC was equally strong in both sexes.¹⁶ While two case-control studies showed smoking was a risk factor only in men,^{9,61} three case-control studies of those showing smoking implicated as a risk factor of CRC showed no clear gender differences.^{57,62,63} Our study found an elevated risk related to smoking among men compared to women. This may be explained by there having been fewer cigarettes smoked by women or more years of abstinence from smoking. There may be hormone-related differences in susceptibility to smoking.

Our study found that smoking cigarettes demonstrated a stronger risk of CRC among drinkers than non-drinkers. This combined effect may be because tobacco smoke is a major source of a wide variety of carcinogens including heterocyclic hydrocarbons and nitroamines, and alcohol might serve as a solvent for polycyclic aromatic hydrocarbons and similar organic compounds from cigarettes, transporting these chemicals to sites they otherwise would not reach.^{64,65}

Smoking cigarettes in our study demonstrated a slightly stronger effect on the risk of rectum cancer compared to colon cancer. This result is consistent with previous studies.^{12-14,27,66,67} The biological mechanism behind this subsite specificity is unknown, but differences in the embryonic tissues of the colon and rectum and in patterns of growth factors and receptors may be relevant.^{10,68,69} Also, nicotine may have a differential effect on the colon and rectum,

Appendix 1. Questions on tobacco smoking in the NL population-based case-control study of CRC

- Q1. Have you ever smoked at least one cigarette a day for 3 months or longer?
• yes • no → Please go to #64 • don't know → Please go to #64
- Q1a. When did you first start smoking at least one cigarette a day?
• age at first use or ____ year of first use • don't know
- Q1b. During periods when you smoked regularly, how many cigarettes did you typically smoke in a day?
____ cigarettes per day • don't know
- Q1c. About one year before your recent cancer diagnosis, were you still smoking at least one cigarette a day?
• yes • no • don't know
- Q1d. Do you still smoke at least one cigarette a day?
• yes • no → Please go to #63f • don't know → Please go to #63f
- Q1e. When did you stop smoking at least one cigarette a day (meaning stop smoking permanently)?
____ age at first use or ____ year of first use • don't know
- Q1f. How many years, in total, did you smoke at least one cigarette a day for 3 months or longer? (If you have stopped and restarted at least once, count only the time when you were smoking.)
____ total number of years • don't know
- Q2. Have you ever smoked at least one cigar a month for at least 3 months?
• yes • no → Please go to #65 • don't know → Please go to #65
- Q2a. When did you first start smoking at least one cigar a month?
____ age at first use or ____ year of first use • don't know
- Q2b. During periods when you smoked regularly, how many cigars did you typically smoke in a month?
____ cigars per month • don't know
- Q2c. About one year before your recent cancer diagnosis, were you still smoking at least one cigar a month?
• yes • no • don't know
- Q2d. Do you still smoke at least one cigar a month?
• yes • no → Please go to #64f • don't know → Please go to #64f
- Q2e. When did you stop smoking at least one cigar a month (meaning stop smoking permanently)?
____ age at first use or ____ year of first use • don't know
- Q2f. How many years, in total, did you smoke at least one cigar a month for 3 months or longer? (If you have stopped and restarted at least once, count only the time when you were smoking.)
____ total number of years • don't know
- Q3. Have you ever smoked at least one pipe a month for at least 3 months?
• yes • no → Please go to #66 • don't know → Please go to #66
- Q3a. When did you first start smoking at least one pipe a month?
____ age at first use or ____ year of first use • don't know
- Q3b. During periods when you smoked regularly, how many pipes did you typically smoke in a month?
____ pipes per month • don't know
- Q3c. About one year before your recent cancer diagnosis, were you still smoking at least one pipe a month?
• yes • no • don't know
- Q3d. Do you still smoke at least one pipe a month?
• yes • no → Please go to #65f • don't know → Please go to #65f
- Q3e. When did you stop smoking at least one pipe a month (meaning stop smoking permanently)?
____ age at first use or ____ year of first use • don't know
- Q3f. How many years, in total, did you smoke at least one pipe a month for 3 months or longer? (If you have stopped and restarted at least once, count only the time when you were smoking.)
____ total number of years • don't know

enhancing motility in the colon, but not in the rectum.²¹ Tobacco carcinogens may be more concentrated in the rectum than in the colon.^{69,70}

Possible biological mechanisms relating to the cause of CRC may involve the exposure of the epithelium of the large bowel to carcinogens either via the blood circulation after absorption of these chemicals in the lung, or after ingestion of saliva contaminated by tobacco smoke.^{29,71} Tobacco smoke contains at least 50 carcinogenic components, the most genotoxic of which are thought to be the

polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and N-nitroso compounds.⁷² These compounds require bioactivation before they can form adducts with DNA. Polycyclic aromatic hydrocarbons are activated mainly by extra-hepatic enzymes [e.g., cytochrome P450 (CYP1A1) and microsomal epoxide hydrolase (mEH)], whereas heterocyclic aromatic amines are activated in the liver by CYP1A2, and N-nitroso compounds are activated by hepatic CYP2E1 and CYP2A6.⁷² Polymorphisms in mEH have been associated with CRC in the presence of smoking.^{73,74} The MspI CYP1A1 variant rare allele gives rise to increased levels of the main enzyme involved in the activation of polycyclic aromatic hydrocarbons and was found to be related to higher risk for colon or rectum cancer.^{74,75}

This study is subject to several limitations. First, despite our best efforts, the participation rates of both cases and control subjects were relatively low (59.6% and 44.7%, respectively), in particular that of the controls. It is possible that study respondents and non-respondents differed by certain characteristics (e.g., smoking and drinking). However, our analysis (another prepared paper) on non-participation bias of the cases did not show evidence that non-participation greatly affects the results of the study. An evaluation of the low participation rate in controls in this study suggested that participating controls tended to have a higher socio-economic status and lower smoking prevalence than the province's general population, which may have led to an overestimation of the true effects of smoking.⁴¹ Second, our study was not free from recall bias. Cases may have been more likely than controls to recall smoking behaviour, trying to attribute their diagnosis to their past behaviour. The main protection against this was the standardization of methods, therefore the questions were identical and were presented in an identical fashion to both cases and controls. Analyses (another prepared paper) conducted to assess the validity and reliability of self-reporting lifetime tobacco use for this study did not suggest that inaccurate or differential reporting of smoking for cases and controls may have biased the association greatly. Third, our study included 258 deceased cases; of these, 143 died before the survey was conducted. The response from proxies of these deceased cases might differ from those of living cases, possibly biasing the results. However, examination of the estimates of the risk of living and deceased cases did not show any difference. Finally, while our study could not assess how other unknown confounders affected the observed association, a recent review suggests that confounding is not important.⁷⁶

In conclusion, this study found that there was a higher risk of CRC among former and current smokers than non-smokers. The association showed a clear dose-response relationship with the risk of CRC increasing with cigarette smoking years, the number of cigarettes smoked daily, and cigarette pack years, and a decrease in risk with more years of abstinence from smoking. This association was stronger among drinkers and in men. In addition, this effect was observed to be slightly stronger for rectum compared to colon cancer.

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RÉSUMÉ

Objectif : C'est à Terre-Neuve-et-Labrador (T.-N.-L.) que l'on observe les plus hauts taux d'incidence du cancer colorectal (CCR) et de prévalence du tabagisme au Canada. Nous avons cherché à déterminer si le CCR était associé au tabagisme dans cette population.

Méthode : Les cas nouvellement diagnostiqués déclarés entre 1999 et 2003 ont été assortis par fréquence selon le groupe d'âge (intervalles de cinq ans) et le sexe; les témoins ont été sélectionnés par composition aléatoire parmi les résidents de T.-N.-L. En tout, 702 cas et 717 témoins ont consenti à participer à l'étude et ont répondu à un ensemble de questionnaires à remplir soi-même. Les indicateurs de tabagisme étaient le genre de tabac, l'âge d'initiation au tabac, les années de tabagisme, les années écoulées depuis l'initiation au tabac, le nombre de cigarettes fumées par jour, le nombre de paquets par année et le nombre d'années d'abstention du tabagisme. Nous avons estimé les rapports de cotes par régression logistique multivariée.

Résultats : Par comparaison avec les non-fumeurs, les anciens fumeurs et les fumeurs actuels présentaient un risque significativement élevé de CCR avec des rapports de cotes de 1,36 et de 1,96, respectivement. Le risque augmentait de façon significative avec les années de tabagisme, le nombre de cigarettes fumées par jour et le nombre de paquets de cigarette par année. Le risque diminuait de façon significative avec les années d'abstention du tabagisme. Cette association était plus prononcée chez les consommateurs d'alcool et les hommes. De plus, cet effet était légèrement plus prononcé pour le cancer du rectum que pour le cancer du côlon.

Discussion : Pour résumer, l'usage de la cigarette accroît le risque de CCR dans la population de T.-N.-L. Le risque de CCR associé à l'usage de la cigarette varie selon le sexe, la consommation d'alcool et le site de CCR.

Mots clés : tumeurs colorectales; tabagisme; rapport de cotes; études cas-témoins

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