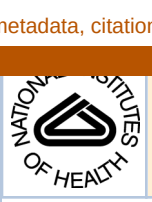

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Pre-diagnostic smoking history, alcohol consumption, and colorectal cancer survival: The Seattle Colon Cancer Family Registry

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Abstract

Background—Smoking and alcohol consumption are associated with an increased risk of developing colorectal cancer. However, it is unclear whether these exposures are associated with survival after colorectal cancer diagnosis.

Methods—Men and women diagnosed with incident colorectal cancer between 1998-2007 in 13 counties in western Washington State were identified using the Surveillance, Epidemiology, and End Results cancer registry. Information on smoking history and alcohol consumption was collected by telephone interview. Follow-up for mortality was completed through linkage to the National Death Index. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between smoking, alcohol consumption, and mortality after colorectal cancer diagnosis; stratified analyses were conducted by sex, age at diagnosis (<50, ≥50), tumor site (proximal, distal, rectal), stage (I-II, III-IV), and microsatellite instability status (stable/low, high).

Results—Disease-specific and all-cause mortality were significantly higher for smokers compared to never-smokers (HR=1.30, 95% CI: 1.09-1.74; HR=1.51, 95% CI: 1.24-1.83, respectively). However, this association was most prominent in those with tumors exhibiting high microsatellite instability (HR=3.83, 95% CI: 1.32-11.11) and did not extend to those with rectal cancer (HR=1.08, 95% CI: 0.72-1.61) or those diagnosed before age 50 (HR=0.99, 95% CI: 0.67-1.48). Alcohol consumption was not associated with disease-specific or all-cause mortality, regardless of patient or tumor characteristics.

Conclusion—In addition to an association with disease risk, smoking is associated with increased mortality after colorectal cancer diagnosis. This association is especially pronounced for colorectal cancer with high microsatellite instability.

Keywords

smoking; alcohol; colorectal cancer; survival; mortality; microsatellite instability

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INTRODUCTION

Colorectal cancer (CRC) is expected to contribute to over 51,000 deaths in the United States in 2010, making it the second most common cause of cancer-related mortality.[1] Estimated 5-year survival for CRC ranges from 91% for localized to only 11% for distant stage disease.[1] Despite this high burden, little is known about factors impacting survival after CRC diagnosis. Most studies of CRC survival have focused on the role of tumor characteristics such as stage at diagnosis,[1,2] tumor site,[3,4] and microsatellite instability (MSI) status.[5,6] Fewer studies have explored associations between risk factors for developing CRC and survival after diagnosis.[7-13] In particular, the role of potentially modifiable risk factors, such as smoking and alcohol consumption, in relation to survival, has not been well characterized.

Smoking and alcohol consumption have been widely studied as risk factors for incident CRC.[14-19] Recent meta-analyses suggest an almost 20% increased risk of CRC for current or former smokers compared to never-smokers,[15,16] and about a 50% higher risk of CRC for persons in the highest versus lowest categories of alcohol consumption.[14] However, these associations appear to differ across CRC tumor subtypes. In particular, smoking is most strongly associated with risk of CRC that exhibits high MSI (MSI-H);[18-20] smoking and alcohol consumption appear to be more strongly associated with rectal cancer than colon cancer.[15,17] These differences may have implications for CRC survival. Some studies have suggested that MSI-H CRC tumors are associated with a more favorable prognosis,[6] whereas rectal cancer has a less favorable prognosis than colon cancer.[21] Thus, to the extent that smoking and alcohol are associated with tumor characteristics,[18-20] these exposures could be associated with survival after CRC diagnosis.

Using data from the Seattle Colon Cancer Family Registry (S-CCFR), we examined the association between smoking history and alcohol consumption prior to CRC diagnosis, CRC-specific mortality, and all-cause mortality. Given potential differences in the distribution of tumor subtypes across these exposures, and the impact that such differences could have on mortality, we also stratified analyses by tumor site and MSI status, as well as by sex, age, and stage at diagnosis.

MATERIALS AND METHODS

Study Population

Detailed descriptions of S-CCFR protocols have been published elsewhere.[22,23] Briefly, eligible participants for the first phase of the S-CCFR included men and women diagnosed between January 1998 and June 2002 with incident invasive CRC who, at the time of diagnosis, were aged 20-74 years and resided within King, Pierce, or Snohomish counties in Washington State. The second phase of recruitment covered a broader geographic region (13 counties in Washington State) and narrower age range (18-49 years), with diagnosis dates from April 2002 through July 2007. All cases were identified via the Cancer Surveillance System, a population-based cancer registry affiliated with the Surveillance, Epidemiology, and End Results (SEER) program. Case eligibility was limited to English-speakers with available telephone numbers. Of 2,933 individuals contacted and identified as eligible, 211 (7%) were deceased, 348 (12%) refused participation, 88 (3%) were lost to follow-up prior to interview, and 22 (1%) completed only a partial interview; thus, the present analysis includes 2,264 incident CRC cases.

Vital status was determined via linkage to the National Death Index (NDI). Through NDI linkage, we obtained information on the date and cause of death, classified according to ICD-10 conventions.[24] CRC-specific deaths included those with an underlying cause

attributed to ICD-10 codes C18.0-C20.0 or C26.0. Vital status linkage was performed periodically, with the most recent linkage occurring in July 2010.

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services.

Exposure and Covariate Assessment

Participants completed a structured telephone interview at the time of enrollment. Interviews were conducted an average of 8.0 months post-diagnosis (median=6.9 months). Participants were asked to provide information on exposures prior to diagnosis, including smoking, alcohol consumption, family and personal history of CRC, CRC screening history, and use of selected medications. Participants were classified as 'ever-smokers' if they reported having ever smoked at least one cigarette a day for a continuous duration of at least three months prior to the reference date; the reference date was defined as two years prior to interview and, therefore, preceded CRC diagnosis for the vast majority of participants. Ever-smokers were asked to report how much they typically smoked in a day, the age at which they started smoking, whether they were still smoking at the reference date and at the time of the interview, and, as applicable, the age they stopped smoking. Participants also reported their typical alcohol consumption between ages 20-30, 30-50, and after age 50. Within each age interval, participants were asked whether they had consumed at least one alcoholic beverage per week for a duration of at least six months and, separately, whether they had consumed beer or cider, wine or sake, and liquor at least once a week for at least six months. For each beverage type, participants were asked to recall the number of drinks they typically consumed each week and the number of years within the age interval during which they consumed that beverage. We restricted our analyses to alcohol consumption during the age interval that included the age at diagnosis, to estimate recent consumption.

Tumor Site and Microsatellite Instability Assessment

Information on tumor site was available from SEER. Tumors located in the cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure were grouped together as proximal colon cancers (ICD-O-3 codes C180, C182, C183, C184, and C185).[25] Tumors in the descending (C186) and sigmoid colon (C187) were classified as distal colon cancers, and tumors in the rectosigmoid junction (C199) and rectum (C209) were grouped together as rectal cancers.

MSI status was evaluated in two ways for cases with available tumor tissue (N=1809). MSI was determined via genetic analysis for most cases (N=1364), based on a 10-marker panel (BAT25, BAT26, BAT40, MYCL, D5S346, D17S250, ACTC, D18S55, D10S197, and BAT34C4) as previously described.[22,26] Briefly, tumors were classified as MSI-H if instability was observed for ≥30% of markers (N=212), and as MSS/MSI-L if instability was observed for <30% of markers (N=1138). For other cases (N=371), MSI was approximated based on immunohistochemistry testing of four markers: hMLH1, hMSH2, hMSH6, and hPMS2.[27,28] Cases who exhibited positive staining for all markers were considered MSS/MSI-L (N=324); cases who were negative on at least one marker were considered MSI-H (N=43). Cases for whom results were equivocal (N=5) or for whom testing could not be completed (N=87) were classified as having unknown MSI status (N=92). Thus, the present analysis includes 1462 MSS/MSI-L and 255 MSI-H cases.

Statistical Analysis

We used Cox proportional hazards regression to evaluate associations between smoking, alcohol consumption, and survival after CRC diagnosis, where the time axis was defined as

days since CRC diagnosis. CRC-specific mortality was the primary outcome of interest, although we also constructed models for all-cause mortality. We conducted analyses for all exposures in the full cohort and stratified by sex, tumor site (proximal colon / distal colon / rectal), SEER summary stage (I-II / III-IV), age at diagnosis (<50 / ≥50 years), and MSI status (MSS or MSI-L / MSI-H). Participants still alive at their last vital status assessment were censored at that date. In analyses of CRC-specific mortality, persons who died due to causes other than CRC were censored at the time of death. Proportional hazards assumptions were verified by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times.[29]

We fit regression models adjusted for age (ten-year strata), time from diagnosis to interview (<6 / 6-9 / >9 months), history of preventive screening (yes / no endoscopy screening ≥2 years before diagnosis), and other factors that altered main effect estimates by ≥10%. Confounding by CRC family history, body mass index, NSAID use, race, sex, and education level was examined; only the latter two of these variables influenced estimates sufficiently to be included in the final model. To account for the possibility that smoking and alcohol have an association with survival by way of an impact on stage at diagnosis, we adjusted for stage[30] in exploratory analyses (not shown).

Based on reported smoking history at the reference date, we compared mortality in smokers to that in never-smokers by current smoking status (smoker / former smoker) and pack-years (<20 / 20-40 / >40). For former smokers, we evaluated the association between time since smoking cessation (≥25 / 10-24 / <10 years) and mortality risk. Tests for linear trend were performed by modeling exposure categories with a continuous variable, excluding never-smokers. We also assessed the association between changes in smoking status from the reference to interview dates and mortality risk (remained a never-smoker / remained a former smoker / remained a smoker / quit smoking / initiated or resumed smoking). For analyses of alcohol consumption, we evaluated average weekly consumption for all beverage types combined, and for wine, beer, and liquor separately (none / 1-6 / ≥7 drinks per week).

RESULTS

Characteristics of the study population are presented in Table 1. Most participants were aged ≥50 (65%) and had education beyond high school (67%). Cases who died during follow-up were more likely to have had stage IV disease (33% versus 16% for alive cases) and less likely to have MSI-H tumors (12% versus 17%).

Compared to cases with no smoking history, cases who were ever-smokers experienced significantly greater CRC-specific and all-cause mortality (Table 2). Associations were most pronounced for cases who were smokers at the reference date [$HR_{CRC\text{-}specific}$=1.30, 95% confidence interval (CI): 1.09-1.74; $HR_{all\text{-}cause}$=1.51, 95% CI: 1.24-1.83], and cases with >40 pack-years of smoking history ($HR_{CRC\text{-}specific}$=1.31, 95% CI: 1.00-1.70; $HR_{all\text{-}cause}$=1.53, 95% CI: 1.24-1.90). There was no gradient of increasing or decreasing risk with decreasing time since smoking cessation for former smokers. The majority of cases who were smokers at the reference date had quit smoking by the interview date (63%). Associations with all-cause mortality were almost identical for cases who quit smoking between the reference and interview dates (HR=1.52, 95% CI: 1.20-1.90) and those who remained smokers (HR=1.50, 95% CI: 1.14-1.97); cases who quit smoking had only a slightly lower risk of CRC-specific mortality (HR_{quit}=1.32, 95% CI: 1.00-1.74; $HR_{continued}$=1.47, 95% CI: 1.07-2.03). Alcohol consumption was not associated with CRC-specific or all-cause mortality, regardless of beverage type. Overall alcohol consumption

was not associated with CRC-specific or all-cause mortality within subgroups defined by sex, tumor site, stage, age at diagnosis, or MSI (not shown).

Differences in the association between smoking status at the reference date and CRC-specific mortality emerged in analyses stratified by patient and tumor characteristics (Table 3). There was elevated mortality in smokers versus never-smokers for both men and women, although this association was slightly greater in women (p-interaction=0.65). The increased CRC-specific mortality risk associated with smoking was limited to cases aged ≥50 (p-interaction=0.20), and those with proximal or distal colon cancer. With respect to stage at diagnosis, confidence intervals were wide but suggested a slightly stronger associated with smoking in stage I-II cases (p-interaction=0.53). CRC-specific mortality risk was not significantly elevated for former smokers, regardless of subgroup. There were no significant trends of increasing risk with increasing pack-years or decreasing time since smoking cessation across these strata (not shown).

There were pronounced differences in the association between smoking and CRC-specific mortality by MSI status (Table 4). In MSI-H cases, smokers had a 3.83-fold (95% CI: 1.32-11.11) higher risk of CRC-specific mortality than never-smokers; no such association was observed for MSS/MSI-L cases (HR=1.17, 95% CI: 0.87-1.57; p-interaction=0.07). Even for MSS/MSI-L cases with a smoking history >40 pack-years, there was no increased CRC-specific mortality (HR=1.17, 95% CI: 0.84-1.63); MSI-H cases with this level of smoking exposure experienced a 5.19-fold increased risk (95% CI: 1.64-16.45, p-interaction=0.02). Numbers were limited in other analyses, but suggested that cases who quit smoking <10 years prior to the reference date had a risk similar to cases who were still smokers at the reference date and suggested little difference in effect estimates for cases who quit smoking between the reference and interview dates versus those who continued smoking, regardless of MSI status.

Similar subgroup-specific results were obtained from analyses of all-cause mortality (not shown). Cases who were smokers at the reference date had an increased risk of all-cause mortality across all subgroups, although the magnitude of this association varied. In particular, the increased mortality risk for smokers versus never-smokers was greater for MSI-H than MSS/MSI-L cases ($HR_{MSI\text{-}H}$=3.40, 95% CI: 1.59-7.29; $HR_{MSS/MSI\text{-}L}$=1.33, 95% CI: 1.03-1.70; p-interaction=0.02), and was again restricted to proximal and distal colon cancer cases ($HR_{proximal}$=1.72, 95% CI: 1.25-2.37; HR_{distal}=1.62, 95% CI: 1.12-2.32; HR_{rectal}=1.18, 95% CI: 0.83-1.68) and cases aged ≥50 years at diagnosis ($HR_{<50}$=1.01, 95% CI: 0.71-1.45; $HR_{\geq 50}$=1.74, 95% CI: 1.74, 95% CI: 1.37-2.20). Men and women who were smokers at the reference date had a similarly increased risk of all-cause mortality (HR_{men}=1.48, 95% CI: 1.13-1.94; HR_{women}=1.55, 95% CI: 1.17-2.05). Smokers with stage I-II CRC experienced a significantly increased risk of all-cause mortality relative to never-smokers (HR=1.79, 95% CI: 1.27-2.51), but this association was weaker for stage III-IV cases (HR=1.31, 95% CI: 0.93-1.85, p-interaction=0.13). As in unstratified analyses, there was a modest increased risk of all-cause mortality in former smokers relative to never-smokers across all subgroups.

Associations were slightly attenuated when adjusted for stage at diagnosis, especially in analyses of CRC-specific survival (not shown). The increased CRC-specific mortality risk in cases who were smokers at the reference date (relative to never-smokers) declined to 1.16 (95% CI: 0.84-1.60) in the full population and 1.74 (95% CI: 0.52-5.78) among individuals with MSI-H disease (not shown).

DISCUSSION

In this cohort of persons with incident CRC, we found significantly elevated rates of CRC-specific and all-cause mortality for smokers versus never-smokers, limited primarily to MSI-H cases. Across sex, tumor site, stage, and MSI status, and for both all-cause and CRC-specific mortality, the increased risk of death was greater in cases who were smokers at the reference date than in former smokers, and was strongest for cases with a smoking history >40 pack-years. We found no difference in CRC-specific or all-cause mortality by alcohol consumption.

The results presented here are consistent with previous reports of an increased risk of CRC mortality for smokers relative to never-smokers.[15,16] In separate meta-analyses, Botteri et al. reported an absolute risk increase of 6.0 CRC deaths per 100,000 person-years (95% CI: 4.2-7.6) for smokers versus non-smokers and Liang et al. reported 1.27-fold (95% CI: 1.05-1.53) increased risk of CRC mortality in current smokers relative to never-smokers. In contrast to our findings, some studies within these meta-analyses reported associations with smoking that were stronger for rectal cancer than colon cancer.[31-33] These studies and the others upon which the meta-analyses were based, however, employed cohort designs wherein study participants were enrolled prior to cancer diagnosis and followed only for mortality. Under such a design it is not possible to distinguish between the influence of smoking on disease incidence and the influence of smoking on survival after diagnosis.

There is limited literature exploring the relationship between smoking and survival after CRC diagnosis.[7-9,12] One hospital-based study found no association between smoking and all-cause mortality in 2,337 CRC patients.[7] Park et al. found significantly increased all-cause mortality associated with smoking for all cancer cases combined, but this association did not persist in analyses restricted to CRC.[9] In contrast, one small case-series of patients receiving curative surgery for CRC found significantly poorer CRC-specific survival in patients who were actively smoking at the time of their first post-operative visit as compared to former or never-smokers (HR=2.6, 95% CI: 1.4-4.6).[8] Most recently, an analysis within a treatment trial for stage III CRC revealed a modest increased risk of all-cause mortality among patients who reported being current smokers halfway through adjuvant therapy (HR=1.38, 95% CI: 0.87-2.18), but revealed no association with disease-free survival (HR=1.10, 95% CI: 0.73-1.64).[12]

To our knowledge, this analysis is the first to report on the increased risk of CRC-specific and all-cause mortality for smokers with MSI-H CRC. Several studies have indicated the association between smoking and CRC incidence is most pronounced, if not restricted to MSI-H tumors.[18-20,34] In studies not assessing smoking, MSI is strongly associated with prognosis: a recent meta-analysis reported that MSI-H patients have significantly better overall survival than MSS patients (OR=0.60, 95% CI: 0.53-0.69).[6] We also observed a more favorable distribution of vital status for MSI-H than MSS/MSI-L cases (Table 1); however, our results suggest that the survival benefit associated with MSI-H status is diminished for smokers.

The biological basis for the observed increased risk of CRC-specific mortality in smokers is unclear. It has been suggested that smoking induces gene-expression that could confer a growth advantage via resistance to chemotherapy or promotion of angiogenesis,[35] and that smoking contributes to abnormal promoter methylation resulting in regulatory gene silencing.[36] Thus, this association could reflect an adverse contribution of smoking to treatment response, or a more aggressive pathology of smoking-associated CRC. In the absence of treatment data, we were unable to explore the former of these possibilities. We did find that ever-smokers were more likely than never-smokers to be diagnosed at an early

stage (66% versus 60% stage I-II) and to have MSI-H tumors (17% versus 12%), which is inconsistent with a more aggressive pathology of smoking-associated CRC.

We found no association between alcohol consumption and mortality, regardless of sex, age, tumor site, stage, or MSI status. As with smoking, repeated studies have indicated a modest increased risk of CRC incidence associated with alcohol consumption.[14] Studies looking alcohol consumption in relation to CRC mortality and survival are limited.[9,10,37] One study reported modestly increased CRC mortality for regular versus rare drinkers for men (HR_{colon}=1.16, HR_{rectum}=1.33).[37] Two studies looking at alcohol and CRC survival have been largely null:[9,10] one found no association between overall alcohol consumption and all-cause mortality in CRC cases,[9] and another found no association with beer or liquor but a borderline-significant decreased risk of all-cause mortality associated with wine consumption for familial cases (HR=0.50, 95% CI: 0.25-0.99).[10] Other studies have suggested a decreased risk of cancer death for light consumers of wine, but not beer or liquor.[38] This pattern was not evident in our data.

Certain limitations should be considered in interpreting our findings. Inclusion in the study population was contingent on surviving long enough after diagnosis to enroll in the S-CCFR and complete the interview. Selection bias is possible if eligible cases who died before they could be interviewed differed from included cases with respect to exposures. However, the median lag-time between diagnosis and interview was less than seven months, limiting the potential for such bias. Missing MSI data resulted in reduced power in MSI-specific analyses. However, cases missing MSI data were similar to other cases in their distribution of exposures. Misclassification of underlying cause of death is also possible. We classified cases as having experienced CRC-specific death if their underlying cause of death was listed as CRC, per ICD-10,[24] but recognize that certain comorbidities may influence this classification. Additionally, we were unable to evaluate treatment variables as confounders or effect modifiers since we did not have this information. Lastly, although the exposures assessed in this analysis primarily reflect behaviors prior to CRC diagnosis, it is possible that early life exposure to smoking or alcohol, consumption after diagnosis, and/or changes in consumption after diagnosis are also relevant to survival. We did find that 37% (N=152) of participants who were smokers at the reference date had quit smoking by the time of the interview, but that these individuals did not differ from other smokers with respect to risk of overall and CRC-specific mortality.

There are also several important strengths of this analysis. The population-based design of the S-CCFR makes the results described here broadly generalizable. The size of the study population also allowed us to perform stratified analyses and to consider CRC-specific and all-cause mortality. The availability of information on tumor site, MSI status, and type of alcohol also allowed us to evaluate potential sources of heterogeneity.

Given the high burden associated with CRC, it remains important to identify factors associated with CRC survival. Smoking and alcohol consumption are modestly associated with CRC incidence.[14-16] We found that smoking, but not alcohol, is also associated with mortality after CRC diagnosis. Our results indicate a particularly strong effect of smoking on mortality for MSI-H cases and a difference in effect by MSI status that merits further study.

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TABLE 1

Selected characteristics of CRC cases, by vital status

	Alive *N (%)*	Deceased *N (%)*	
		All causes	CRC death
Sex			
Male	739 (52)	470 (57)	308 (55)
Female	694 (48)	361 (43)	254 (45)
Age at diagnosis			
<40	147 (10)	43 (5)	38 (7)
40-49	416 (29)	183 (22)	151 (27)
50-59	322 (22)	164 (20)	131 (23)
60-69	369 (26)	258 (31)	157 (28)
70-79	179 (12)	183 (22)	85 (15)
Education			
< High school	85 (6)	87 (11)	51 (9)
High school graduate	342 (24)	222 (27)	134 (24)
Some college	486 (34)	301 (36)	216 (39)
College graduate	519 (36)	219 (26)	160 (29)
Unknown	1	2	1
History of preventive CRC screening*			
No	1143 (80)	643 (78)	447 (80)
Yes	285 (20)	184 (22)	111 (20)
Unknown	5	4	4
Tumor site			
Proximal	513 (36)	325 (40)	215 (39)
Distal	401 (28)	224 (27)	139 (25)
Rectal	502 (35)	270 (33)	200 (36)
Unknown	17	12	8
Microsatellite instability (MSI) status			
MSS / MSI-L	913 (83)	549 (88)	375 (92)
MSI-H	181 (17)	74 (12)	33 (8)
Unknown†	45	45	17
Stage at diagnosis			
I	679 (50)	185 (33)	49 (15)
II	253 (19)	113 (20)	62 (19)
III	209 (15)	83 (15)	62 (19)
IV	225 (16)	189 (33)	151 (47)
Unstaged / unknown	67	261	238

*Screening history defined as receipt of endoscopic screening ≥2 years prior to diagnosis.

†Excludes cases for whom tumor tissue was not obtained (N=294 alive; 163 deceased).

TABLE 2

History of smoking and alcohol consumption prior to CRC diagnosis and CRC-specific and all-cause mortality risk

		CRC-specific mortality		All-cause mortality	
	No. at risk	**No. deaths**	**HR (95% CI)***	**No. deaths**	**HR (95% CI)***
SMOKING HISTORY*					
Never-smoker	920	203	1.0	269	1.0
Ever-smoker:	1341	359	1.21 (1.01-1.45)	562	1.33 (1.14-1.55)
Former smoker	931	236	1.14 (0.93-1.38)	379	1.26 (1.07-1.49)
Smoker	410	123	1.30 (1.09-1.74)	183	1.51 (1.24-1.83)
Pack-years of smoking					
Never-smoker	920	203	1.0	269	1.0
<20	658	175	1.19 (0.97-1.46)	241	1.23 (1.03-1.47)
20 – 40	350	89	1.13 (0.87-1.46)	150	1.33 (1.08-1.63)
>40	311	86	1.34 (1.01-1.76)	158	1.56 (1.26-1.93)
p-trend†			0.54		0.05
Time since quit smoking (years)‡					
Never-smoker	920	203	1.0	269	1.0
≥25	330	94	1.33 (1.03-1.74)	145	1.34 (1.08-1.66)
10 – 24	376	85	0.97 (0.87-1.26)	137	1.10 (0.89-1.36)
<10	212	53	1.14 (0.84-1.55)	91	1.48 (1.16-1.89)
p-trend†			0.57		0.13
CHANGE IN SMOKING STATUS (Between reference and interview dates)					
Remained never-smoker	919	203	1.0	269	1.0
Remained former smoker	919	233	1.14 (0.93-1.38)	374	1.26 (1.07-1.48)
Remained a smoker	152	48	1.47 (1.07-2.03)	67	1.50 (1.14-1.97)
Quit smoking	258	75	1.32 (1.00-1.74)	116	1.52 (1.21-1.90)
Initiated/resumed smoking	13	3	--	5	--
ALCOHOL CONSUMPTION (drinks per week)*					

		CRC-specific mortality		All-cause mortality	
	No. at risk	No. deaths	HR (95% CI)*	No. deaths	HR (95% CI)*
Overall					
None	1167	294	1.0	427	1.0
1 – 6	316	68	0.89 (0.68-1.17)	101	1.02 (0.81-1.28)
≥7	335	82	1.02 (0.78-1.32)	116	1.02 (0.82-1.27)
Wine					
None	1650	434	1.0	637	1.0
1 – 6	352	69	0.77 (0.59-1.00)	105	0.83 (0.67-1.03)
≥7	102	27	1.08 (0.73-1.60)	36	0.97 (0.69-1.36)
Beer					
None	1482	364	1.0	538	1.0
1 – 6	297	65	0.90 (0.69-1.19)	90	0.91 (0.72-1.15)
≥7	183	44	0.96 (0.69-1.34)	63	0.95 (0.72-1.25)
Liquor / Spirits					
None	1639	422	1.0	604	1.0
1 – 6	362	80	0.94 (0.74-1.20)	131	1.05 (0.87-1.27)
≥7	168	50	1.20 (0.89-1.62)	80	1.18 (0.93-1.50)

*Adjusted for age at diagnosis, time from diagnosis to interview, history of preventive CRC screening, sex, and education.

**Smoking history assessed as of the reference date (i.e., 2-years prior to interview). Alcohol consumption assessed within the age interval of diagnosis (i.e., 20-30, 30-50, >50 years).

†P-trend in smokers only.

‡Excludes current smokers.

TABLE 3

History of smoking prior to CRC diagnosis and CRC-specific mortality risk,* by sex, age at diagnosis, tumor site, and stage at diagnosis

	Never-Smoker		Former Smoker		Smoker	
	No. deaths / No. at risk	**HR (95% CI)†**	**No. deaths / No. at risk**	**HR (95% CI)†**	**No. deaths / No. at risk**	**HR (95% CI)†**
By Sex:						
Men	98 / 432	1.0	146 / 559	1.11 (0.84-1.45)	64 / 217	1.27 (0.92-1.76)
Women	105 / 488	1.0	90 / 372	1.16 (0.87-1.55)	59 / 193	1.51 (1.08-2.11)
By Age At Diagnosis:						
<50	90 / 424	1.0	64 / 237	1.13 (0.81-1.59)	42 / 165	0.99 (0.67-1.48)
≥50	113 / 496	1.0	172 / 694	1.14 (0.89-1.45)	81 / 245	1.59 (1.19-2.13)
By Tumor Site:						
Proximal	75 / 348	1.0	94 / 339	1.25 (0.90-1.73)	46 / 150	1.59 (1.08-2.35)
Distal	50 / 255	1.0	54 / 253	1.05 (0.70-1.58)	35 / 117	1.53 (0.98-2.70)
Rectal	73 / 303	1.0	87 / 329	1.08 (0.78-1.50)	40 / 139	1.08 (0.72-1.61)
By Stage At Diagnosis:						
I / II	34 / 470	1.0	52 / 548	1.11 (0.71-1.74)	25 / 210	1.40 (0.82-2.39)
III / IV	81 / 317	1.0	93 / 263	1.18 (0.86-1.61)	39 / 125	1.21 (0.82-1.80)

*Smoking history assessed as of the reference date (i.e., 2-years prior to interview).

†Adjusted for age at diagnosis, time from diagnosis to interview, history of preventive CRC screening, sex, and education.

TABLE 4

History of smoking prior to CRC diagnosis and CRC-specific mortality risk, by MSI status

	MSS / MSI-L		MSI-H	
	No. deaths / No. at risk	**HR (95% CI)***	**No. deaths / No. at risk**	**HR (95% CI)***
SMOKING HISTORY*				
Never-smoker	146 / 599	1.0	6 / 81	1.0
Ever-smoker:	229 / 862	1.06 (0.85-1.31)	27 / 173	2.33 (0.92-5.91)
Former smoker	159 / 618	1.01 (0.80-1.28)	15 / 116	1.79 (0.66-4.85)
Smoker	70 / 244	1.17 (0.87-1.57)	12 / 57	3.83 (1.32-11.11)
Pack-years of smoking				
Never-smoker	146 / 599	1.0	6 / 81	1.0
<20	99 / 395	0.99 (0.76-1.28)	12 / 84	2.06 (0.74-5.73)
20 – 40	64 / 239	1.07 (0.79-1.45)	4 / 46	1.46 (0.37-5.82)
>40	61 / 216	1.17 (0.84-1.63)	11 / 42	5.19 (1.64-16.45)
p-trend†		0.35		0.09
Time since quit smoking (years)‡				
Never-smoker	146 / 599	1.0	6 / 81	1.0
≥10	126 / 489	1.02 (0.79-1.31)	8 / 75	1.41 (0.47-4.34)
<10	32 / 121	1.06 (0.72-1.57)	7 / 40	2.53 (0.80-7.95)
p-trend†		0.71		0.33
CHANGE IN SMOKING STATUS (Between reference and interview dates)				
Remained never-smoker	146 / 598	1.0	6 / 81	1.0
Remained former smoker	158 / 610	1.03 (0.81-1.30)	15 / 115	2.01 (0.74-5.40)
Remained a smoker	27 / 96	1.13 (0.74-1.71)	4 / 19	4.12 (1.07-15.88)
Quit smoking	43 / 148	1.19 (0.84-1.70)	8 / 38	3.41 (1.11-10.54)
Initiated/resumed smoking	1 / 9	--	0 / 1	--

*Adjusted for age at diagnosis, time from diagnosis to interview, history of preventive CRC screening, sex, and education.

**Smoking history assessed as of the reference date (i.e., 2-years prior to interview).

†P-trend in smokers only.

‡Excludes current smokers.