Pre-Diagnostic Alcohol Consumption and Colorectal Cancer Survival: The Colon Cancer Family Registry

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Abstract

Background—Although previous studies have noted an increased risk of colorectal cancer (CRC) among moderate to heavy alcohol consumers relative to non-drinkers, the relationship between alcohol consumption and CRC survival remains unclear.

Methods—Cases of incident invasive CRC diagnosed between 1997-2007 were identified via population-based cancer registries at four study sites in the Colon Cancer Family Registry. Study participants completed a risk factor questionnaire on pre-diagnostic behaviors, including wine, beer, and liquor consumption, at baseline. Prospective follow-up for survival was conducted for 4966 CRC cases. Using Cox regression, we compared non-drinkers to individuals who consumed, on average, 1 serving/day of alcohol in the years preceding CRC diagnosis with respect to overall and disease-specific survival. Separate analyses by beverage type, and stratified by patient and tumor attributes, were also performed. All models were adjusted for age at diagnosis, sex, study site, year of diagnosis, smoking history, body mass index, and education.

Results—Pre-diagnostic beer and liquor consumption were not associated with CRC survival; however, higher levels of wine consumption were modestly associated with better prognosis

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overall [hazard ratio (HR)$_{CRC-specific}$=0.70, 95% confidence interval (CI): 0.48-1.03 and HR$_{overall}$=0.70, 95% CI: 0.53-0.94). Similar patterns were noted in stratified analyses.

Conclusions—These findings suggest that pre-diagnostic wine consumption is modestly associated with more favorable survival after CRC.

Keywords

colorectal cancer; survival; alcohol consumption; wine; tumor phenotype

Introduction

Colorectal cancer (CRC) remains a leading cause of cancer death in the United States.[1] Advances in early detection have contributed to favorable 5-year relative survival (90%) for patients with localized CRC; however, survival with distant-stage disease is only 13%.[1] Thus, it is important to identify factors contributing to CRC prognosis.

Alcohol has been classified as a Class I carcinogen, and the role of alcohol consumption as an etiologic risk factor for CRC has been well-characterized.[2-5] Previous studies have also noted a greater likelihood of advanced CRC at diagnosis and increased risk of liver metastases among heavy drinkers.[6-8] However, evidence for a possible relationship between alcohol and CRC survival has been minimal, with the few existing studies finding suggestive but not statistically significant evidence for an association between overall pre-diagnostic alcohol consumption and CRC prognosis.[9-12] Pelser and colleagues recently reported that moderate alcohol intake, in comparison to little or no alcohol consumption, was associated with lower risk of all-cause mortality among CRC patients.[12] Other studies have also observed patterns in the relationship between recent pre-diagnostic alcohol consumption and CRC outcomes that differ by beverage type.[9-11]

We conducted an analysis of data from the Colon Cancer Family Registry (C-CFR) to determine whether survival in individuals diagnosed with CRC varied according to patterns of pre-diagnostic alcohol consumption overall, by beverage type, and across case groups defined by patient and tumor attributes.

Materials and Methods

Study Population

The study sample included women and men diagnosed with incident invasive CRC between January 1997 and June 2007 who participated in the C-CFR. The C-CFR is an international collaborative effort between investigators in Australia, Canada, and the United States, with six contributing study centers. C-CFR recruitment protocols and eligibility criteria have been previously detailed.[13] We restricted our analysis to population-based cases, not selected on the basis of family history, recruited through cancer registries at one of four sites (University of Melbourne, Melbourne, Victoria, Australia; Cancer Care Ontario, Toronto, Ontario, Canada; Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; Mayo Clinic, Rochester, Minnesota, USA). All study participants provided informed consent. Institutional review boards from each center approved their respective studies.

Alcohol Consumption Assessment

Study participants completed a standardized risk factor questionnaire regarding pre-diagnostic exposures via telephone interviews or mail at the time of enrollment (http://www.coloncfr.org/questionnaires). Interviews were administered an average of 11.4 months (median: 9.4 months) after diagnosis. Participants recalled their alcohol consumption prior to CRC diagnosis for (as applicable) the intervals between ages 20-30, 30-50, and after age 50. Participants were queried as to whether they had consumed 1 serving/week of alcohol for a period of 6 months, and were separately asked if they had consumed 1 serving/week of beer or hard cider, wine or fortified wines, or hard liquor for 6 months. A serving was defined as a 12-ounce can/bottle of beer/cider, a 4-ounce glass of wine / 1-ounce glass of fortified wine, or a 1-ounce shot of hard liquor. For each beverage category, participants reported their average servings/week and the number of years within the age interval during which they drank that beverage. To reflect recent pre-diagnostic consumption, we restricted our analysis to intake during the age interval including the age at diagnosis (referred to here as "pre-diagnostic alcohol consumption").[14] We further categorized alcohol intake as "average alcohol use overall" and by alcoholic beverage type.

Tumor Characteristics

Cancers arising from the cecum through the splenic flexure (ICD-O-3 codes C180, C182-C185) were grouped together as right-sided colon cancers, while neoplasms in the descending or sigmoid colon (C186-C187) were defined as left-sided colon cancers. Tumors originating in the rectosigmoid junction (C199) or rectum (C209) were classified as rectal cancers.[15]

We assessed mismatch repair status (MMR) status using one of two methods.[13] The first method was genetic analysis for microsatellite instability (MSI) based on a 10-marker panel using tumor DNA and DNA from normal surrounding tissue.[10] We categorized tumors as MMR deficient (i.e., high MSI) if instability was observed for 30% of markers and as MMR proficient (i.e., microsatellite stable) if instability was seen in <30% of markers. For a subset of cases, we evaluated MMR status using immunohistochemistry of four markers.[16] Cases with tumors where all markers exhibited positive staining were categorized as proficient (pMMR); tumors with 1 negative marker were classified as deficient (dMMR). We assayed tumors for the presence of the V600E *BRAF* mutation using a fluorescent allele-specific PCR.[17] CIMP testing was based on a validated, five-gene panel quantitative DNA methylation assay, and was completed for cases, with complete MMR information, diagnosed before July 2002. Cases were classified as CIMP-high if the percentage of methylated reference (PMR) ratio was 10 for 3 of 5 markers in a tumor and as non-CIMP if the PMR ratio was 10 for <3 markers.[18]

Vital Status and Cause of Death

We ascertained vital status, date and cause of death via linkage to population-based registries, contact with relatives, and collection of death certificates. For a small number of cases, we determined vital status through other means (e.g., obituaries).[19] We categorized a death as CRC-specific when the underlying cause of death was classified as C18.0-C20.0 or

C26.0 (ICD-10). Vital status information was available through December 2013. Cases who were alive through the most recent evaluation of vital status were censored at that date.

Statistical Analysis

We employed Cox proportional hazards regression to assess the relationship of pre-diagnostic alcohol consumption with overall and CRC-specific survival. Our time scale was defined as days since CRC diagnosis, with left censoring to account for the time-lag between diagnosis and C-CFR enrollment. Separate analyses were conducted for each outcome. In analyses of CRC-specific survival, we censored participants who died from causes other than CRC. Proportional hazards assumptions were supported by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times.

We conducted separate analyses for alcohol overall and by beverage type. We used non-drinkers as the reference category, including those who consumed an average of <1 serving of alcohol/week. We also conducted analyses stratified by sex, age at diagnosis, smoking history, tumor site, *BRAF*-mutation status, MMR status, and CIMP status.

We adjusted all regression models for age at diagnosis, year of diagnosis, sex, study site, and several self-reported pre-diagnostic exposures ascertained in the baseline interview: smoking history, body mass index, educational attainment, and use of non-steroidal anti-inflammatory drugs (NSAIDs). All covariates were categorized as shown in Table 1. We conducted all analyses in STATA SE 14 (College Station, Texas).

Results

Compared to individuals who consumed <1 serving of alcohol/week, individuals in the upper alcohol consumption category (>1 serving/day) were more likely to be male (78% vs. 38%), to have a history of smoking (74% vs. 48%), and to have a primary tumor in the rectum (40% vs. 33%), and were less likely to be obese (23% vs. 31%), or to have a primary tumor that was MMR deficient (12% vs. 16%) or CIMP-high (10% vs. 17%) (Table 1). The distribution of participant characteristics was similar among persons in the middle versus upper consumption categories, except for sex (53% vs. 78% male) and smoking status (15% vs. 28% current smokers).

After adjustment for patient and tumor characteristics, there was no evidence of a relationship between overall pre-diagnostic alcohol consumption and survival (Table 2). With respect to specific alcohol types, evidence of a modest but not statistically significant poorer overall survival was noted in those who consumed >1 serving of liquor/day versus <1 serving/week (HR$_{overall}$: 1.12, 95% CI: 0.92-1.36). Conversely, there was evidence of an inverse association of wine consumption with survival. This relationship was primarily evident in the upper category of wine consumption (HR$_{CRC-specific}$: 0.70, 95% CI: 0.48-1.03 and HR$_{overall}$: 0.70, 95% CI: 0.53-0.94).

When analyses focused on pre-diagnostic wine consumption, we observed generally similar findings within case subgroups (Tables 3-4). This association, strongest in the upper wine consumption category, was only statistically significant in men (HR$_{CRC-specific}$: 0.57, 95%

CI: 0.34-0.97 and $HR_{overall}$: 0.61, 95% CI: 0.42-0.90) and in former smokers ($HR_{CRC-specific}$: 0.59, 95% CI: 0.36-0.98 and $HR_{overall}$: 0.62, 95% CI: 0.42-0.91). There was some difference in the association depending on CRC site, with the strongest inverse relationship noted among cases with left-sided colon tumors ($HR_{CRC-specific}$: 0.44, 95% CI: 0.20-0.963 and $HR_{overall}$: 0.59, 95% CI: 0.33-1.02). Conversely, we noted that current smokers who were modest wine drinkers displayed a poorer prognosis than individuals who consumed <1 serving/week ($HR_{CRC-specific}$: 1.80, 95% CI: 1.21-2.67 and $HR_{overall}$: 1.41, 95% CI: 1.00-1.98).

Discussion

In this prospective analysis of invasive CRC, there was no evidence for an association between overall pre-diagnostic alcohol consumption and disease survival. When considering different types of beverage types, however, our findings suggested slightly better survival with higher levels of pre-diagnostic wine consumption, especially in men and former smokers.

Consistent with the results presented here, the majority of previous studies have found no evidence for a relationship between pre-diagnostic alcohol consumption overall and CRC outcomes. In the largest evaluation of this association to-date, Pelser et al reported similar findings to ours in that they found a suggestively, but not significantly lower risk of all-cause mortality when comparing moderate drinkers to non-drinkers ($RR_{colon\ cancer}$: 0.86, 95% CI: 0.73-1.01 and $RR_{rectal\ cancer}$: 0.84, 95% CI: 0.62-1.14).[12] Among colon cancer cases specifically, this observed relationship was likely primarily driven by the association between pre-diagnostic alcohol intake and lower cardiovascular disease (CVD) mortality ($RR_{colon\ cancer}$: 0.47, 95% CI: 0.31-0.73). In a previous analysis of a subset of the data included in the present analysis, Phipps et al similarly found no association between overall alcohol consumption and CRC outcomes;[10] although that study also considered separate associations with pre-diagnostic wine, beer, and liquor consumption, results were inconclusive due to small numbers.

Of the three prior studies to perform separate evaluations by beverage type, two observed statistically significant findings indicating more favorable prognosis in those with higher pre-diagnostic wine intake.[9-11] Zell and colleagues reported a significant association between overall survival and regular (1-3 glasses/month) versus infrequent wine intake (<1 glass/month) among CRC patients with a family history of CRC (HR: 0.50, 95% CI: 0.25-0.99).[11] Additionally, a recent study by Phipps and colleagues found significantly better overall survival among stage III colon cancer cases reporting 30 servings of wine/ month in the year prior to cancer diagnosis (HR: 0.51, 95% CI: 0.30-0.85, versus never consumers),[9] and found no evidence for variations in the effect of pre-diagnostic alcohol use on CRC outcomes according to evaluated tumor characteristics.[9] This result, and our similar findings, could be impacted by low numbers, especially within wine-only analyses, but may also suggest that the impact of alcohol consumption on disease progression or development does not depend on known molecular pathways of disease process.

Consistent with recent meta-analyses indicating a positive association between alcohol consumption and CRC risk,[3,4] in vitro evidence suggests that high alcohol consumption, perhaps via its mechanism as a local solvent, plays a role in early tumorigenesis in the colon and rectum.[20] Alcohol damages the epithelial cells of the intestinal tract through direct and indirect means, assisting the absorption of acetaldehyde, a recognized carcinogen, and facilitating the production of species that proliferate DNA damage, oxidative stress, and lipid peroxidation in the intestinal lumen.[20] Increased alcohol intake can also lead to a suppression of immune surveillance, which could impact both CRC risk and progression.[20] Our results indicated no association between overall pre-diagnostic alcohol consumption and survival, but also hinted at a potentially less favorable prognosis given higher daily liquor intake.

Conversely, recent evidence suggests that moderate wine consumption may elicit benefits not only for CVD survival, but also for CRC prognosis.[21] With respect to cardiovascular outcomes, moderate wine consumption has been linked to lower levels of inflammatory markers.[22] Red wine also contains resveratrol and polyphenols – elements that appear to exhibit anti-coagulatory,[23] anti-oxidant,[24] and anti-platelet traits.[21] However, whether and how these properties contribute to CRC survival is unclear.[11,25] Studies using mice found that resveratrol triggers apoptosis in cancer cell lines,[26] downregulated intestinal genes involved in cell proliferation or cell cycle progression,[27] interrupted growth of transplanted human primary gastric cancer cells,[28] and intensified the anti-tumor effect of 5-fluorouracil.[29] Thus, it is plausible that our findings reflect some CRC-specific effects of wine.

Interpretation of these findings is subject to some limitations. Our measure of alcohol consumption required self-reported recall for a time period prior to CRC diagnosis. By relying on this variable, we assumed that patient recall was accurate. Furthermore, because our measure of alcohol intake could reflect an averaged consumption level over an extended time (e.g., ages 30-50 for someone diagnosed at age 50), there is potential for misclassification of the relevant exposure. Additionally, despite the large size of our overall study, wine-specific analyses stratified by tumor markers lacked the statistical precision necessary to conclude differences between MMR, CIMP, and *BRAF*-mutation strata. We also had limited information on stage at diagnosis in our sample; however, when we performed a sensitivity analysis stratified by tumor stage among those with these data, our findings and interpretations did not change. Finally, our findings may be partially attributable to lifestyle differences between individuals who regularly consume wine and non-consumers. Past evidence indicates that wine consumption is positively associated with healthier diet,[30] physical activity,[30] educational attainment,[31] and income,[31] all of which may also be associated with CRC survival. While we did adjust for several patient characteristics, residual confounding is possible.

This study is among the first to focus on the relationship between pre-diagnostic alcohol consumption, overall and by type, and CRC outcomes using population-based data. In line with past findings, we observed that overall pre-diagnostic alcohol use was not associated with overall or disease-specific survival, but also that higher levels of pre-diagnostic wine consumption were associated with a more favorable prognosis. Because the mechanistic

action of wine on CRC prognosis is not understood, further study is merited to better elucidate biological pathways and explore possible alternative explanations.

Acknowledgments

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Table 1

Study population characteristics

	Pre-diagnostic alcohol consumption:			
	Non-drinker *or* <1 drink / week N (%)	1 drink / week *but* 1 drink / day N (%)	>1 drink / day N (%)	Chi-square *P*-value
Age at diagnosis:				<0.01
<40	233 (10)	166 (12)	119 (10)	
40-49	759 (32)	518 (37)	438 (36)	
50-59	545 (23)	316 (23)	282 (23)	
60-69	530 (22)	276 (20)	251 (21)	
70	298 (13)	123 (9)	112 (9)	
Median age (SD)	53 (11.7)	50 (11.4)	51 (11.2)	
Study center:				<0.01
Ontario, Canada	603 (26)	477 (34)	415 (35)	
Melbourne, Australia	251 (11)	296 (21)	251 (21)	
Minnesota, USA	273 (12)	140 (10)	113 (9)	
Seattle-Puget Sound, USA	1238 (52)	486 (35)	423 (35)	
Sex:				<0.01
Male	896 (38)	748 (53)	938 (78)	
Female	1469 (62)	651 (47)	264 (22)	
Cigarette smoking history:				<0.01
Never smoker	1229 (52)	587 (42)	321 (27)	
Former smoker	769 (33)	588 (42)	545 (46)	
Current smoker	357 (15)	216 (15)	331 (28)	
Missing	10	8	5	
Body mass index (kg/m^2):				<0.01
<25.0	786 (34)	556 (40)	381 (32)	
25.0-29.9	826 (35)	557 (39)	535 (45)	
30.0	718 (31)	284 (20)	275 (23)	
Missing	35	12	11	
Pre-diagnostic NSAID use:				0.59
No	1837 (80)	1092 (80)	925 (79)	
Yes	461 (20)	268 (20)	250 (21)	
Missing	64	38	23	
Educational attainment:				<0.01
High school graduate or less	900 (38)	471 (34)	475 (40)	
Some college / vocational school	784 (33)	439 (32)	404 (34)	
College graduate	664 (28)	480 (35)	318 (27)	
Missing	17	9	5	
Tumor site:				<0.01
Right-sided	878 (37)	484 (35)	357 (30)	

	Pre-diagnostic alcohol consumption:			
	Non-drinker *or* <1 drink / week N (%)	1 drink / week *but* 1 drink / day N (%)	>1 drink / day N (%)	Chi-square *P*-value
Left-sided	703 (30)	371 (27)	355 (30)	
Rectal	765 (33)	524 (38)	475 (40)	
Missing	19	20	15	
Mismatch repair status:				<0.01
Proficient	1562 (84)	997 (88)	872 (90)	
Deficient	307 (16)	139 (12)	101 (10)	
Unknown	496	263	229	
BRAF-mutation status:				0.01
Wildtype	1324 (87)	861 (90)	706 (90)	
Mutated	206 (13)	97 (10)	77 (10)	
Missing	835	441	419	
CIMP status:				<0.01
CIMP-high	207 (17)	75 (10)	53 (9)	
Non-CIMP	1009 (83)	612 (90)	525 (91)	
Missing	1149	712	624	

Table 2

Pre-diagnostic alcohol consumption and survival after colorectal cancer diagnosis

		Total N	# deaths	Overall Survival HR (95% CI)*	P	# deaths	CRC-Specific Survival HR (95% CI)*	P
Alcohol type (not mutually exclusive among drinkers)	Non-drinker / <1 drink/week	2245	869	1.0 (ref)		519	1.0 (ref)	
	Beer / hard cider	1360	476	0.93 (0.80-1.08)	0.36	312	1.01 (0.84-1.22)	0.96
	Wine / fortified wines	1267	418	0.81 (0.65-1.02)	0.07	264	0.90 (0.68-1.2)	0.39
	Liquor	1138	453	0.89 (0.74-1.09)	0.30	249	0.94 (0.73-1.21)	0.66
	Drinker – type unspecified	16	11			6		
Beer servings:	No beer / <1 serving/week	3070	1181	1.0 (ref)		691	1.0 (ref)	
	1 serving/day (1 serving/week)	874	279	0.89 (0.76-1.05)	0.17	185	1.01 (0.83-1.23)	0.93
	>1 serving/day	486	197	1.01 (0.83-1.21)	0.89	127	1.17 (0.92-1.48)	0.20
Wine servings:	No wine / <1 serving/week	3272	1298	1.0 (ref)		772	1.0 (ref)	
	1 serving/day (1 serving/week)	1038	348	0.96 (0.83-1.12)	0.62	222	0.95 (0.79-1.15)	0.62
	>1 serving/day	229	70	0.70 (0.53-0.94)	0.02	42	0.70 (0.48-1.03)	0.07
Liquor servings:	No liquor / <1 serving/week	3242	1197	1.0 (ref)		744	1.0 (ref)	
	1 serving/day (1 serving/week)	838	310	0.94 (0.81-1.09)	0.40	170	0.88 (0.72-1.08)	0.23
	>1 serving/day	281	137	1.12(0.92-1.36)	0.25	76	1.09 (0.82-1.44)	0.46

*
Adjusted for age at diagnosis, year of diagnosis, sex, smoking history, body mass index, education, study site

†
Counts exclude those with missing data on adjustment variables (N=130)

Table 3

Pre-diagnostic wine consumption and overall survival after colorectal cancer diagnosis by patient and tumor attributes

	No wine (<1 serving/week)†		1 serving/day of wine (≥1 serving/week)†			>1 servings/day of wine†		
	N (deaths)	HR (95% CI)*	N (deaths)	HR (95% CI)*	P	N (deaths)	HR (95% CI)*	P
Sex								
Male	1674 (725)	1.0 (ref)	554 (196)	0.87 (0.71-1.05)	0.15	138 (46)	0.61 (0.42-0.90)	0.01
Female	1598 (573)	1.0 (ref)	484 (152)	1.07 (0.85-1.33)	0.57	91 (24)	0.81 (0.52-1.24)	0.32
Age at diagnosis								
50	1562 (506)	1.0 (ref)	509 (149)	0.95 (0.77-1.18)	0.66	89 (20)	0.63 (0.38-1.03)	0.07
>50	1710 (792)	1.0 (ref)	529 (199)	0.97 (0.80-1.18)	0.77	140 (50)	0.73 (0.51-1.03)	0.07
Smoking history								
Never smoker	1449 (472)	1.0 (ref)	453 (139)	1.03 (0.82-1.29)	0.73	65 (14)	0.73 (0.39-1.37)	0.27
Former smoker	1185 (527)	1.0 (ref)	459 (151)	0.77 (0.62-0.97)	0.02	114 (38)	0.62 (0.42-0.91)	0.02
Current smoker	638 (299)	1.0 (ref)	126 (58)	1.41 (1.00-1.98)	0.05	50 (18)	0.77 (0.44-1.37)	0.42
Tumor site								
Right-sided	1133 (485)	1.0 (ref)	342 (122)	1.01 (0.79-1.28)	0.96	65 (19)	0.66 (0.39-1.13)	0.13
Left-sided	970 (350)	1.0 (ref)	272 (83)	1.14 (0.85-1.52)	0.39	67 (18)	0.59 (0.33-1.02)	0.06
Rectal	1139 (447)	1.0 (ref)	410 (137)	0.91 (0.72-1.17)	0.47	97 (33)	0.81 (0.54-1.21)	0.30
MMR status								
Proficient	2210 (889)	1.0 (ref)	775 (269)	0.97 (0.82-1.14)	0.69	172 (58)	0.76 (0.55-1.05)	0.10
Deficient	377 (113)	1.0 (ref)	96 (15)	0.54 (0.29-1.02)	0.06	22 (4)	--	
BRAF-mutation status								
Wildtype	1852 (716)	1.0 (ref)	696 (226)	1.03 (0.85-1.23)	0.78	162 (56)	0.82 (0.59-1.14)	0.25
Mutated	251 (107)	1.0 (ref)	73 (24)	1.24 (0.70-2.20)	0.47	19 (3)	--	
CIMP status								
Non-CIMP	1371 (581)	1.0 (ref)	484 (172)	0.91 (0.73-1.13)	0.39	116 (39)	0.70 (0.47-1.02)	0.07
CIMP-high	246 (114)	1.0 (ref)	54 (19)	1.05 (0.58-1.90)	0.52	11 (3)	--	

† Unadjusted 5-year survival %: <1 serving/week (74.6%), ≥1 serving/day (≥1 serving/week) (77.7%), >1 serving/day (82.1%)

* Adjusted for age at diagnosis, year of diagnosis, sex, smoking history, body mass index, education, study site

-- Result based on <5 deaths in one comparison group

Table 4

Pre-diagnostic wine consumption and disease-specific survival after colorectal cancer diagnosis by patient and tumor attributes

	No wine (<1 serving/week)†		1 serving/day of wine (≥1 serving/week)†			>1 servings/day of wine†		
	N (deaths)	HR (95% CI)*	N (deaths)	HR (95% CI)*	P	N (deaths)	HR (95% CI)*	P
Sex								
Male	1622 (423)	1.0 (ref)	527 (121)	0.85 (0.66-1.10)	0.22	131 (24)	0.57 (0.34-0.97)	0.04
Female	1552 (349)	1.0 (ref)	468 (101)	1.10 (0.83-1.46)	0.50	88 (18)	0.92 (0.56-1.52)	0.76
Age at diagnosis								
≤50	1499 (363)	1.0 (ref)	485 (109)	1.01 (0.78-1.30)	0.94	82 (13)	0.63 (0.34-1.18)	0.15
>50	1675 (409)	1.0 (ref)	510 (113)	0.93 (0.71-1.22)	0.59	137 (29)	0.74 (0.46-1.18)	0.20
Smoking history								
Never smoker	1408 (302)	1.0 (ref)	432 (92)	1.01 (0.76-1.34)	0.88	64 (9)	0.82 (0.39-1.73)	0.59
Former smoker	1159 (300)	1.0 (ref)	441 (86)	0.70 (0.51-0.96)	0.01	108 (21)	0.59 (0.36-0.98)	0.04
Current smoker	607 (170)	1.0 (ref)	122 (44)	1.80 (1.21-2.67)	0.004	47 (12)	0.82 (0.40-1.68)	0.64
Tumor site								
Right-sided	1100 (260)	1.0 (ref)	330 (86)	1.31 (0.98-1.76)	0.07	63 (14)	0.92 (0.48-1.75)	0.79
Left-sided	943 (201)	1.0 (ref)	256 (42)	0.76 (0.49-1.20)	0.24	62 (9)	0.44 (0.20-0.96)	0.04
Rectal	1103 (302)	1.0 (ref)	397 (91)	0.89 (0.66-1.20)	0.45	94 (19)	0.72 (0.42-1.22)	0.22
MMR status								
Proficient	2154 (558)	1.0 (ref)	740 (172)	0.91 (0.73-1.13)	0.39	164 (35)	0.76 (0.51-1.15)	0.19
Deficient	374 (44)	1.0 (ref)	96 (7)	0.56 (0.24-1.33)	0.19	21 (2)	--	
BRAF-mutation status								
Wildtype	1816 (435)	1.0 (ref)	666 (138)	0.90 (0.71-1.14)	0.39	156 (35)	0.80 (0.53-1.23)	0.32
Mutated	243 (44)	1.0 (ref)	72 (20)	1.76 (0.93-3.33)	0.08	19 (3)	--	
CIMP status								
Non-CIMP	1346 (356)	1.0 (ref)	464 (106)	0.82 (0.62-1.09)	0.18	115 (25)	0.71 (0.44-1.16)	0.18
CIMP-high	242 (51)	1.0 (ref)	54 (13)	0.96 (0.46-1.99)	0.91	11 (3)	--	

† Unadjusted 5-year survival %: <1 serving/week (80.2%), ≥1 serving/week (≤1 serving/day) (81.4%), >1 serving/day (84.7%)

* Adjusted for age at diagnosis, year of diagnosis, sex, smoking history, body mass index, education, study site

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-- Result based on <5 deaths in one comparison group

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