Research Article

Cancer Epidemiology, Biomarkers & Prevention

Alcohol Consumption and the Risk of Colorectal Cancer for Mismatch Repair Gene Mutation Carriers

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Abstract

Background: People with germline mutation in one of the DNA mismatch repair (MMR) genes have increased colorectal cancer risk. For these high-risk people, study findings of the relationship between alcohol consumption and colorectal cancer risk have been inconclusive.

Methods: 1,925 MMR gene mutations carriers recruited into the Colon Cancer Family Registry who had completed a questionnaire on lifestyle factors were included. Weighted Cox proportional hazard regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between alcohol consumption and colorectal cancer.

Results: Colorectal cancer was diagnosed in 769 carriers (40%) at a mean (SD) age of 42.6 (10.3) years. Compared with abstention, ethanol consumption from any alcoholic beverage up to 14 g/day and >28 g/day was associated with increased colorectal cancer risk (HR, 1.50; 95% CI, 1.09–2.07 and 1.69; 95% CI, 1.07–2.65, respectively; $P_{trend} = 0.05$), and colon cancer risk (HR, 1.78; 95% CI, 1.27–2.49 and 1.94; 95% CI, 1.19–3.18, respectively; $P_{trend} = 0.02$). However, there was no clear evidence for an association with rectal cancer risk. Also, there was no evidence for associations between consumption of individual alcoholic beverage types (beer, wine, spirits) and colorectal, colon, or rectal cancer risk.

Conclusions: Our data suggest that alcohol consumption, particularly more than 28 g/day of ethanol (~2 standard drinks of alcohol in the United States), is associated with increased colorectal cancer risk for MMR gene mutation carriers.

Impact: Although these data suggested that alcohol consumption in MMR carriers was associated with increased colorectal cancer risk, there was no evidence of a dose-response, and not all types of alcohol consumption were associated with increased risk.
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Introduction

Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC; ref. 1), is an autosomal-dominant disorder of cancer predisposition caused by heterozygous germline mutations in the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2* or a deletion in *EPCAM* (2). Approximately 1 in 300 to 370 people in the general population carry a mutation in an MMR gene (3, 4). MMR gene mutation carriers are at increased risk of colorectal cancer, with an estimated cumulative risk to age 70 years between 40% and 70% depending on sex and mutated MMR gene (5–9). Approximately 2%–4% of all colorectal cancers (10, 11) and 10%–15% of colorectal cancers diagnosed before age 50 years (12, 13) can be attributed to Lynch

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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syndrome. Personal and lifestyle factors could modify cancer risk for MMR gene mutation carriers (8). Identifying potentially protective or harmful risk factors for this high-risk group could assist with reducing their cancer risk, as well as understanding carcinogenesis.

For the general population, evidence from systematic reviews and meta-analyses supports a positive association between alcohol consumption and colorectal cancer risk, which is likely to be most evident at moderate to high levels of alcohol consumption (14–17). There is little evidence that this increased risk differs by alcoholic beverage types, sex, or the site of the colorectum (15, 17).

For MMR gene mutation carriers, only a few studies have investigated the association between alcohol consumption and colorectal cancer risk and their findings have been inconclusive (18–20). All these studies had small sample sizes, different selection criteria for participants (confirmed mutation carriers, those who met clinical criteria for HNPCC), different outcome measures (colorectal cancer, polyps, or both), and none investigated the association between lifetime alcohol consumption and colorectal cancer risk.

In this study, we estimated the associations between lifetime alcohol consumption and colorectal cancer risk for MMR gene mutation carriers using a large dataset from the Colon Cancer Family Registry. We also estimated the associations separately for different beverage types, for colon and rectal cancers, and for men and women.

Materials and Methods

Study sample

This study involved carriers of heterozygous germline pathogenic mutations in MMR genes who had been recruited by the Colon Cancer Family Registry. Detailed descriptions of study design and recruitment have been published (21) and are available at http://coloncfr.org (21). Between 1997 and 2012, the Colon Cancer Family Registry recruited and interviewed probands who were either recently diagnosed with colorectal cancer that was reported to state or regional population cancer registries in the United States (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria), and Canada (Ontario); or were from multiple-case families referred to family-cancer clinics in the United States (Mayo Clinic, Rochester, MN; and Cleveland Clinic, Cleveland, OH), Australia (Melbourne, Adelaide, Perth, Brisbane, and Sydney), Canada (Ontario), and New Zealand (Auckland). Permission was obtained from probands to contact their affected and unaffected relatives and seek their enrolment in the Colon Cancer Family Registry. For families recruited via population-based registries, first-degree relatives of probands were recruited by all centers. Recruitment was extended to more distant relatives by some centers. For families recruited via family-cancer clinics, attempts were made to recruit also second-degree relatives of affected individuals [details provided by Newcomb and colleagues (21)]. Informed consent was obtained from all participants and the study protocol was approved by research ethics review board at each recruitment center.

Data collection

At the time of baseline recruitment, standardized questionnaires were used to collect self-reported information on demographics, lifestyle factors including alcohol consumption, personal and family history of cancer, cancer-screening history, and history of polyps, polypectomy, and other surgeries from all participants via personal interviews, telephone interviews, or mailed questionnaires. The questionnaires used by the Colon Cancer Family Registry centers are available at http://coloncfr.org/questionnaires. Pathology reports, medical records, cancer registry reports, and death certificates were consulted, when possible, to confirm reported cancer diagnoses and age at diagnosis. Attempts were made to obtain blood samples from all participants and tumor tissue samples from all colorectal cancer-affected participants.

MMR gene mutation testing

Testing for germline mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* was performed for all population-based probands who had a colorectal tumor that showed impaired MMR function, as evidenced by tumor microsatellite instability (MSI) or absence of MMR protein expression in immunohistochemical analysis. Testing was also performed for the colorectal cancer–affected participants from clinic-based families regardless of tumor MSI or MMR protein expression status. Sanger sequencing or denaturing high-performance liquid chromatography, followed by confirmatory DNA sequencing, was performed to screen for mutations in the *MLH1*, *MSH2*, and *MSH6* genes. Large duplication and deletion mutations were detected by Multiplex Ligation Dependent Probe Amplification (MLPA) according to the manufacturer's instructions (MRC Holland; refs. 21–23). *PMS2* mutation testing involved a modified protocol from Senter and colleagues (7), in which exons 1–5, 9, and 11–15 were amplified with 3 long-range PCRs followed by nested exon-specific PCR and sequencing. The remaining exons (7, 8, and 10) were amplified and sequenced directly from genomic DNA. Large-scale deletions in *PMS2* were detected using the P008-A1 MLPHA kit (MRC Holland; ref. 24). Relatives of probands with a pathogenic MMR germline mutation (25) who provided a blood sample were tested for the specific mutation identified in the proband.

Definitions of exposure and outcome

The primary outcome was self-reported diagnosis of colorectal cancer. The primary exposure was grams of ethanol consumption per day from alcoholic beverages from age 20 years to age at colorectal cancer diagnosis or age at censoring.

At baseline, participants were asked to report the number of 12-oz servings of beer or alcoholic cider (included as beer in the remainder of this article), 4-oz servings of wine or 1-oz servings of sake (included as wine), and 1-oz servings of spirits that they had consumed daily or weekly in their 20s, 30s and 40s, and 50s and older, as well as the number of years they had consumed the alcoholic beverages at least once a week for 6 months or longer during each of these periods.

Grams of ethanol in alcoholic beverages (14 g in 12-oz serving of beer, 11.2 g in 4-oz serving of wine, 3.5 g in 1-oz serving of sake, and 9.3 g in 1-oz serving of spirits) were calculated on the basis of average alcohol content in each drink (5% in beer, 12% in wine, 15% in sake, and 40% in spirits), density of ethanol (0.79 g/mL), and converting United States/British Imperial measurements of volume to metric (1-oz equivalent to 29.57 mL).

Grams of ethanol consumption per day from alcoholic beverages when drinking beer, wine, and spirits were calculated on the basis of self-reported number of alcoholic

beverages consumed and years of alcohol consumption from age 20 years to age at colorectal cancer diagnosis or age at censoring. Abstainers were defined as carriers who had not consumed alcohol for at least once a week for 6 months or longer throughout this period.

Statistical analysis

Cox proportional regression analyses, with age as the time scale, were used to estimate the association between alcohol consumption and the risk of colorectal cancer for MMR gene mutation carriers. Time at risk started at age 20 years and ended at age of first colorectal cancer diagnosis, any other cancer diagnosis, polypectomy, or age at baseline interview, whichever occurred first. Observation time ended at age of diagnosis of any other cancer, because subsequent cancer treatment and surveillance could have altered later colorectal cancer risk and MMR gene mutations carriers might have changed their behavior following cancer diagnosis.

Because colorectal cancer cases from multiple-cancer families and cases with early-onset colorectal cancer were preferentially tested for MMR gene mutations, selection of carriers was not random with respect to their disease status. This non-random ascertainment was adjusted for in the analysis by applying probability weights to carriers based on the weighted cohort approach developed by Antoniou and colleagues (26). Age-specific incidences of colorectal cancer for MMR gene mutation carriers (27) were used to calculate statistical weights for colorectal cancer–affected and -unaffected carriers for each age-stratum so the proportion of affected carriers in each age-stratum was equal to the proportion of affected carriers in the general population.

Variables that were considered as potential confounders are listed in Table 1. When applicable, all variables, including the alcohol consumption variables, were treated as time-varying covariates. We were not able to generate time-varying variables for consumption of aspirin or ibuprofen, and multivitamin, calcium, and folic acid supplements because we did not have information on carriers' age at first exposure to regular consumption of these medications and supplements. For investigating the associations between consumption of specific types of alcoholic beverages with colorectal cancer risk, after confirming that these variables were not strongly correlated (all correlation coefficients were $\leq$0.25) and running collinearity diagnostic tests, consumption of the other two sources of ethanol were included as potential confounders in the multivariable models. The proportional hazards assumption was tested with the Schoenfeld and scaled Schoenfeld residuals (28). The confounding variables that did not meet the proportional hazards assumption were stratified for in the final models. The overall model fit was assessed using Cox–Snell residuals as the time variable and plotting them against the Nelson–Aalen cumulative hazard function (29). For continuous variables, deviation from linearity was tested using the likelihood ratio test in comparison between models with the original variable and models that included the original and quadric transformation of the variable. To test for interaction, the difference in the log-likelihood ratio was assessed after adding a cross-product term between each exposure variable and the potential effect modifiers identified *a priori*. The numbers of missing values for all variables are reported in Tables 1–2. All univariable analyses were complete case analyses. In the multivariable models, all confounder variables were fitted as categorical variables with their missing values (all <8%) coded as an additional category.

We estimated associations by each colorectal cancer site, sex and cancer site, smoking status, body mass index (BMI) at age 20 years, and history of having received sigmoidoscopy or colonoscopy. The following additional analyses were also conducted: analyses with colorectal polyp or cancer as the outcome; and analyses restricted to carriers who received a colorectal cancer diagnosis or were censored within 5 years before interview to reduce survival bias. To take into account the potential correlation in risk between family members, we used the Huber–White robust variance estimation by clustering on family membership (30, 31). All statistical tests were two-sided. All statistical analyses were performed using STATA statistical software, version 13.0 (Stata Corp LP).

Results

A total of 2,031 MMR gene mutation carriers were identified from the Colon Cancer Family Registry. Of these, the 53 (2.6%) who were younger than 20 years old at the time of colorectal cancer diagnosis ($n = 11$) or censoring ($n = 42$) were excluded. We also excluded 16 colorectal cancer–affected and 36 unaffected carriers for whom no data on alcohol consumption were available, and one carrier whose reported average ethanol consumption from alcoholic beverages was more than 200 g/day. Excluded carriers had similar characteristics compared with those who were included in this study (details not shown).

The final sample comprised 1,925 MMR gene mutation carriers (920 were recruited as colorectal affected cases and 1,005 as unaffected) from 761 families. Of these, 1,077 (56%) were female; 1,425 (74%) were recruited through family-cancer clinics; and 714 carried a mutation in *MLH1*, 898 in *MSH2*, 215 in *MSH6*, and 98 in *PMS2*. Time at risk ended at age at colorectal cancer diagnosis for 769 carriers (643 located in the colon, 116 in the rectum, and 10 in both the colon and rectum), polypectomy for 338, other cancer diagnosis for 224, and interview for 594. The time interval (SD) between age at colorectal cancer diagnosis and age at interview for affected carriers was 9.1 (9.8) years, and between censored age and age at interview for unaffected carriers was 5.1 (8.8) years ($P = 0.20$). Colorectal cancer incidence from age 20 was 1.8 [95% confidence interval (CI), 1.68–1.93] per 100 person-years and mean (SD) age at diagnosis was 42.6 (10.3) years. Colorectal cancer diagnosis was confirmed for 704 affected carriers (92%) by pathology reviews or reports, cancer registries, or hospital records.

Characteristics of MMR gene mutation carriers included in the current study are summarized in Table 1. On average, men had higher consumption of ethanol from any alcoholic beverage than women [mean (SD) in unaffected carriers: 15.9 (21.1) vs. 4.2 (9.6) g/day] as well as from beer and spirits. Average ethanol consumption per day from any alcoholic beverage and from beer were higher in colorectal cancer–affected carriers compared with unaffected carriers [12.9 (21.4) vs. 8.6 (16.0) g/day and 8.7 (19.3) vs. 4.9 (11.1) grams per day, respectively; Table 2].

Compared with abstention, consumption of ethanol from any alcoholic beverage both up to 14 g/day and >28 g/day were associated with an increased risk of colorectal cancer (HR, 1.50; 95% CI, 1.09–2.07 and 1.69; 95% CI, 1.07–2.65 respectively). There was evidence for a linear dose-dependent relationship between ethanol intake from any alcoholic beverage and colorectal cancer risk in the univariable model (HR per 14 g/day, 1.07;

Table 1. Characteristics[a] of DNA MMR gene germline mutation carriers

	No colorectal cancer *N* = 1,156 (60%)	Colorectal cancer *N* = 769 (40%)	Total *N* = 1,925
Sex			
Female	725 (62.7)	352 (45.8)	1,077 (56.0)
Male	431 (37.3)	417 (54.2)	848 (44.1)
Study centers, *n* (%)			
Australia or New Zealand	670 (58.0)	365 (47.5)	1,035 (53.8)
USA	326 (28.2)	286 (37.2)	612 (31.8)
Canada	160 (13.8)	118 (15.3)	278 (14.4)
Race			
Caucasian	1,093 (94.6)	693 (90.1)	1,786 (92.8)
Other	41 (3.6)	64 (8.3)	105 (5.5)
Missing	22 (1.9)	12 (1.6)	34 (1.8)
Ascertainment method			
Clinic	915 (79.2)	510 (66.3)	1,425 (74.0)
Population	241 (20.9)	259 (33.7)	500 (26.0)
Age (year)[b]			
Mean (SD)	41.9 (12.8)	42.6 (10.3)	42.2 (11.9)
Median (range)	41 (20–85)	43 (20–75)	42 (20–85)
Year of birth, *n* (%)			
1914–1945	256 (22.2)	234 (30.4)	490 (25.5)
1946–1955	283 (24.5)	234 (30.4)	517 (26.9)
1956–1965	259 (22.4)	192 (25.0)	451 (23.4)
1966–1990	258 (31.0)	109 (14.2)	467 (24.3)
Education level, *n* (%)			
Some high school or less	237 (20.5)	180 (23.4)	417 (21.7)
Completed high school/some tertiary study	387 (33.5)	259 (33.7)	646 (33.6)
Vocational/technical school	209 (18.1)	127 (16.5)	336 (17.5)
University degree	318 (27.5)	196 (25.5)	514 (26.7)
Missing	5 (0.4)	7 (0.9)	12 (0.6)
MMR gene mutated, *n* (%)			
MLH1	381 (33.0)	333 (43.3)	714 (37.1)
MSH2	571 (49.4)	327 (42.5)	898 (46.7)
MSH6	151 (13.1)	64 (8.3)	215 (11.2)
PMS2	53 (4.6)	45 (5.9)	98 (5.1)
BMI at age 20,[c]*n* (%)			
Normal	788 (68.2)	489 (63.6)	1,277 (66.3)
Overweight	183 (15.8)	149 (19.4)	332 (17.3)
Obese	46 (4.0)	42 (5.5)	88 (4.6)
Underweight	101 (8.7)	61 (7.9)	162 (8.4)
Missing	38 (3.3)	28 (3.6)	66 (3.4)
BMI 2 years before diagnosed/censored age,[c,d]*n* (%)			
Normal	338 (29.2)	91 (11.8)	429 (22.3)
Overweight	224 (19.4)	114 (14.8)	338 (17.6)
Obese	113 (9.8)	60 (7.8)	173 (9.0)
Underweight	21 (1.8)	7 (0.9)	28 (1.5)
Missing	460 (39.8)	497 (64.6)	957 (49.7)
Number of received sigmoidoscopy or colonoscopy, *n* (%)			
0	380 (32.9)	185 (24.1)	565 (29.4)
1	266 (23.0)	227 (29.5)	493 (25.6)
2	128 (11.1)	31 (4.0)	159 (8.3)
3 or more	138 (11.9)	49 (6.4)	187 (9.7)
Missing	244 (21.1)	277 (36.0)	521 (27.1)
Diabetes, *n* (%)			
No	1,117 (96.6)	727 (94.5)	1,844 (95.8)
Yes	33 (2.9)	34 (4.4)	67 (3.5)
Missing	6 (0.5)	8 (1.0)	14 (0.7)

[a]At the time of colorectal cancer diagnosis or age of another cancer, or polypectomy, or interview for colorectal cancer-unaffected participants (whichever came first).

[b]Age of diagnosis of colorectal cancer for affected participants; age of diagnosis of another cancer or polypectomy or interview for colorectal cancer-unaffected participants (whichever came first).

[c]Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. Underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), obese (≥30).

[d]Carriers who were diagnosed with colorectal cancer or censored more than 2 years before interview had missing for this variable.

(Continued on the following page)

95% CI, 1.01–1.14), but not in the multivariable model (HR per 14 g/day, 1.02; 95% CI, 0.94–1.09). Similarly, there were associations between beer and spirit consumption and colorectal cancer risk in the univariable models, but no clear association between the consumption of any alcohol type (beer, wine, or spirits) and colorectal cancer risk in the multivariable models (Table 3).

Table 1. Characteristics[a] of DNA MMR gene germline mutation carriers (Cont'd)

	No colorectal cancer *N* = 1,156 (60%)	Colorectal cancer *N* = 769 (40%)	Total *N* = 1,925
Aspirin and/or ibuprofen intake,[b] *n* (%)			
<1 month	903 (78.1)	632 (82.2)	1,535 (79.7)
≥1 month	190 (16.4)	95 (12.4)	285 (14.8)
Missing	63 (5.5)	42 (5.5)	105 (5.5)
Multivitamin supplement intake,[b] *n* (%)			
<1 month	789 (68.3)	584 (75.9)	1,373 (71.3)
≥1 month	309 (26.7)	141 (18.3)	450 (23.4)
Missing	58 (5.0)	44 (5.7)	102 (5.3)
Calcium supplement intake,[b] *n* (%)			
<1 month	991 (85.7)	702 (91.3)	1,693 (88.0)
≥1 month	121 (10.5)	48 (6.2)	169 (8.8)
Missing	44 (3.8)	19 (2.5)	63 (3.3)
Folic acid supplement intake,[b] *n* (%)			
<1 month	1,012 (87.5)	709 (92.2)	1,721 (89.4)
≥1 month	112 (9.7)	39 (5.1)	151 (7.8)
Missing	32 (2.8)	21 (2.7)	53 (2.8)
Cigarette smoking,[c] *n* (%)			
Never	624 (54.0)	345 (44.9)	969 (50.3)
Former	262 (22.7)	160 (20.8)	422 (21.9)
Current	267 (23.1)	262 (34.1)	529 (27.5)
Missing	3 (0.3)	2 (0.3)	5 (0.3)
Regular physical activity,[d] *n* (%)			
<3 months	51 (4.4)	47 (6.1)	98 (5.1)
≥3 months	1,074 (92.9)	691 (89.9)	1,765 (91.7)
Missing	31 (2.7)	31 (4.0)	62 (3.2)
Fruit and vegetable intake (servings/day) 2 years before diagnosed/censored age,[e,f] *n* (%)			
<2	190 (16.4)	111 (14.4)	301 (15.6)
2.01–3	129 (11.2)	45 (5.9)	174 (9.0)
3.01–4	134 (11.6)	47 (6.1)	181 (9.4)
≥4.01	256 (22.2)	67 (8.7)	323 (16.8)
Missing	447 (38.7)	499 (64.9)	946 (49.1)
Red meat intake (servings/day 2 years before diagnosed/censored age),[f,g] *n* (%)			
<0.30	211 (18.3)	88 (11.4)	299 (15.5)
0.31–0.60	240 (20.8)	83 (10.8)	323 (16.8)
0.61–0.90	102 (8.8)	45 (5.9)	147 (7.6)
≥0.91 or more	153 (13.2)	55 (7.2)	208 (10.8)
Missing	450 (38.9)	498 (64.8)	948 (49.3)
Number of live births,[h] *n* (%)			
No	198 (27.3)	66 (18.8)	264 (24.5)
1	76 (10.5)	51 (14.5)	127 (11.8)
2	204 (28.1)	96 (27.3)	300 (27.9)
≥3	227 (31.3)	126 (35.8)	353 (32.8)
Missing	20 (2.8)	13 (3.7)	33(3.1)
Hormonal contraception use,[h] *n* (%)			
<1 year	187 (25.8)	100 (28.4)	287 (26.7)
≥1 year	527 (72.7)	240 (68.2)	767 (71.2)
Missing	11 (1.5)	12 (3.4)	23 (2.1)
Menopause status,[h] *n* (%)			
Pre-menopause	481 (66.3)	230 (65.3)	711 (66.0)
Pre-menopause	213 (29.3)	112 (31.9)	325 (30.2)
Missing	31 (4.3)	10 (2.8)	41 (3.8)

[a]At the time of colorectal cancer diagnosis or age of another cancer, or polypectomy, or interview for colorectal cancer–unaffected participants (whichever came first).
[b]At least twice a week.
[c]Former smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and had quit more than 2 years before age at colorectal cancer or censored age; current smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and continued within 2 years of age at colorectal cancer or censored age.
[d]Regular physical activity defined as any physical activity for at least 30 minutes per week for at least 3 months.
[e]A serving of fruit defined as 1 medium fresh fruit, or ½ cup of chopped, cooked, or canned fruit, or ¼ cup of dried fruit, or 6 ounce of fruit juice; a serving of vegetable defined as 1 cup raw leafy vegetables, or ½ cup of other vegetables, or cooked or chopped raw, 6 ounces of vegetable juice.
[f]Carriers who were diagnosed with colorectal cancer or censored more than 2 years before interview had missing for this variable.
[g]A serving of red meat defined as 2–3 ounces of red meat, or a piece of meat about the size of a deck of cards.
[h]Limited to women (725 unaffected and 352 colorectal cancer affected).

An increased risk of colon, but not rectal, cancer was associated with ethanol consumption from any alcoholic beverage of up to 14 g/day (HR, 1.78; 95% CI, 1.27–2.49) and >28 g/day (HR, 1.94; 95% CI, 1.19–3.18) in multivariable models (Table 4). Similar results were seen in analyses when the outcome was defined as colorectal polyp or cancer (HR for ethanol >28 g/day vs.

Table 2. Alcohol consumption[a] in DNA MMR gene germline mutation carriers

	Women			Men			Overall		
	No colorectal cancer *N* = 725 (67%)	Colorectal cancer *N* = 352 (33%)	Total *N* = 1,077	No colorectal cancer *N* = 431 (51%)	Colorectal cancer *N* = 417 (49%)	Total *N* = 848	No colorectal cancer *N* = 1,156 (60%)	Colorectal cancer *N* = 769 (40%)	Total *N* = 1,925
Average daily ethanol intake from any alcoholic beverage (g/day),									
Mean (SD)	4.2 (9.6)	3.9 (7.7)	4.1 (9.1)	15.9 (21.1)	20.4 (25.9)	18.1 (23.7)	8.6 (16.0)	12.9 (21.4)	10.3 (18.5)
Median (range)	1.1 (0–176.8)	0.6 (0–63.8)	0.9 (0–176.8)	9.2 (0–157.9)	11.9 (0–172.0)	9.9 (0–172.0)	3.1 (0–176.8)	3.5 (0–172.0)	3.2 (0–176.8)
Missing (%)	80 (11.0)	41 (11.6)	121 (11.2)	42 (9.7)	47 (11.3)	89 (10.5)	122 (10.6)	88 (11.4)	210 (10.9)
Average daily ethanol intake from beer (g/day),									
Mean (SD)	1.3 (4.1)	1.2 (4.0)	1.2 (4.0)	10.9 (15.5)	15.1 (24.1)	13.0 (20.3)	4.9 (11.1)	8.7 (19.3)	6.4 (15.0)
Median (range)	0 (0–43.9)	0 (0–38)	0 (0–44)	5.3 (0–93.3)	6.7 (0–168)	6 (0–168)	0 (0–93.3)	0.7 (0–168)	0 (0–168)
Missing (%)	44 (6.1)	25 (7.1)	69 (6.4)	25 (5.8)	29 (7.0)	54 (6.4)	69 (6.0)	54 (7.0)	123 (6.4)
Average daily ethanol intake from wine (g/day),									
Mean (SD)	1.8 (4.4)	1.4 (3.5)	1.6 (4.1)	2.2 (5.6)	1.8 (4.3)	2.0 (5.0)	1.9 (4.9)	1.6 (4.0)	1.8 (4.5)
Median (range)	0 (0–71.2)	0 (0–29.6)	0 (0–71.2)	0 (0–69.3)	0 (0–30.1)	0 (0–69.3)	0 (0–71.2)	0 (0–30.1)	0 (0–71.2)
Missing (%)	40 (7.6)	23 (6.5)	63 (5.8)	21 (4.9)	18 (4.3)	39 (4.6)	61 (5.3)	41 (5.3)	102 (5.3)
Average daily ethanol intake from spirits (g/day),									
Mean (SD)	1.1 (4.6)	1.1 (2.8)	1.1 (4.1)	2.5 (6.1)	2.9 (9.3)	2.7 (7.8)	1.6 (5.3)	2.0 (7.2)	1.8 (6.1)
Median (range)	0 (0–105.6)	0 (0–22.1)	0 (0–105.6)	0 (0–50.8)	0 (0–111.6)	0 (0–111.6)	0 (0–105.6)	0 (0–111.6)	0 (0–111.6)
Missing (%)	55 (5.5)	27 (7.7)	82 (7.6)	31 (7.2)	30 (7.2)	61 (7.2)	86 (7.4)	57 (7.4)	143 (7.4)

Abbreviation: g/day, grams per day.

[a]At the time of colorectal cancer diagnosis or age of another cancer, or polypectomy, or interview for colorectal cancer–unaffected participants (whichever came first).

abstention, 1.46; 95% CI, 1.15–1.86; Supplementary Table S1), and in analyses restricted to carriers who were diagnosed with colorectal cancer or censored within 5 years before interview (HR for ethanol >28 g/day vs. abstention, 1.29; 95% CI, 0.65–2.53; Supplementary Table S2).

There was no evidence for an interaction between alcohol consumption and sex ($P = 0.78$; Fig. 1), cigarette smoking status ($P = 0.61$), BMI at age 20 ($P = 0.88$), history of having received sigmoidoscopy or colonoscopy ($P = 0.43$; Supplementary Table S3), the specific mutated MMR gene ($P = 0.99$), country of recruitment ($P = 0.99$), ascertainment method ($P = 0.11$), or folic acid supplement intake ($P = 0.37$; Supplementary Table S4). There was no evidence of nonlinearity for continuous variables, or of violation of the proportional hazards assumption by any of the

Table 3. HRs for associations between alcohol consumption and the risk of colorectal cancer for DNA MMR gene germline mutation carriers

			Univariable model		Multivariable model[a]		Multivariable model[a,b]	
	Cases	Person-years	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Average daily ethanol intake from any alcoholic beverage								
Abstainer	195	13,258.5	1 (Reference)		1 (Reference)		1 (Reference)	
Ever user	486	24,702	1.47 (1.13–1.90)	0.003	1.49 (1.09–2.03)	0.01	1.55 (1.11–2.15)	0.01
>0–≤14 g	294	15,340.5	1.39 (1.04–1.86)	0.03	1.50 (1.09–2.07)	0.01	1.56 (1.11–2.18)	0.01
>14–≤28 g	87	4,662.5	1.29 (0.88–1.90)	0.19	1.23 (0.78–1.94)	0.37	1.25 (0.77–2.04)	0.37
>28 g	105	4,699	1.95 (1.36–2.79)	<0.001	1.69 (1.07–2.65)	0.02	1.79 (1.12–2.87)	0.02
Average daily ethanol intake from any alcoholic beverage (per 14 g/day)	681	37,960.5	1.07 (1.01–1.14)	0.03	1.02 (0.94–1.09)	0.66	1.02 (0.95–1.10)	0.52
Average daily ethanol intake from beer[c]								
Abstainer	330	21,864	1 (Reference)		1 (Reference)		1 (Reference)	
Ever user	385	18,012.5	1.55 (1.24–1.94)	<0.001	1.27 (0.94–1.73)	0.11	1.23 (0.90–1.70)	0.19
Average daily ethanol intake from beer (per 14 g/day)	715	39,876.5	1.10 (1.02–1.19)	0.01	1.02 (0.92–1.13)	0.72	1.02 (0.92–1.12)	0.75
Average daily ethanol intake from wine[d]								
Abstainer	475	27,673	1 (Reference)		1 (Reference)		1 (Reference)	
Ever user	253	12,565.5	0.97 (0.76–1.24)	0.80	1.01 (0.76–1.34)	0.96	1.06 (0.78–1.43)	0.71
Average daily ethanol intake from wine (per 14 g/day)	728	40,238.5	0.78 (0.54–1.11)	0.18	0.79 (0.54–1.15)	0.22	0.87 (0.61–1.24)	0.45
Average daily ethanol intake from spirits[e]								
Abstainer	435	26,204	1 (Reference)		1 (Reference)		1 (Reference)	
Ever user	277	13,331.5	1.30 (1.02–1.66)	0.04	1.21 (0.91–1.61)	0.19	1.27 (0.94–1.70)	0.12
Average daily ethanol intake from spirits (per 14 g/day)	712	39,535.5	1.19 (1.00–1.41)	0.04	1.07 (0.85–1.36)	0.57	1.15 (0.97–1.36)	0.10

Abbreviation: g/day, grams per day.

[a]All multivariable models were adjusted for country (categorical, time-fixed), education (categorical, time-fixed I), ascertainment (binary, time-fixed), sex (binary, time-fixed), BMI at age 20 (categorical, time-fixed), diabetes status (binary, time-varying), regular physical activity (binary, time-varying), and smoking status (categorical, time-varying).

[b]All models were additionally adjusted for aspirin or ibuprofen intake (binary, time-fixed), multivitamin intake (binary, time-fixed), calcium intake (binary, time-fixed), and folic acid intake (binary, time-fixed).

[c]Multivariable models additionally adjusted for average daily ethanol intake from wine (binary, time-varying) and from spirits (binary, time-varying).

[d]Multivariable models additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from spirits (binary, time-varying).

[e]Multivariable models additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from wine (binary, time-varying).

Table 4. HRs for associations between alcohol consumption and the risk of colorectal cancer for DNA MMR gene germline mutation carriers by cancer site

	Colon[a]				Rectum[b]			
			Multivariable model[c]				Multivariable model[c]	
	Cases	Person-years	HR (95% CI)	*P*	Cases	Person-years	HR (95% CI)	*P*
Average daily ethanol intake from any alcoholic beverage								
Abstainer	157	12,455.5	1 (Reference)		35	9,002.5	1 (Reference)	
Ever user	410	23,048	1.76 (1.27–2.46)	0.001	69	15,741	0.79 (0.41–1.53)	0.49
>0–≤14 g	252	14,459.5	1.78 (1.27–2.49)	0.001	38	10,123	0.79 (0.39–1.59)	0.50
>14 g–≤28 g	75	4,338.5	1.51 (0.91–2.49)	0.11	10	2,862	0.51 (0.19–1.40)	0.19
>28 g	83	4,250	1.94 (1.19–3.18)	0.01	21	2,756	1.14 (0.45–2.89)	0.79
Average daily ethanol intake from any alcoholic beverage (per 14 g/day)	567	35,503.5	1.01 (0.94–1.09)	0.76	104	24,743.5	1.08 (0.88–1.31)	0.47
Average daily ethanol intake from beer[d]								
Abstainer	275	20,705	1 (Reference)		51	15,245	1 (Reference)	
Ever user	321	16,579.5	1.36 (0.97–1.91)	0.08	58	10,759.5	1.03 (0.60–1.78)	0.91
Average daily ethanol intake from beer (per 14 g/day)	596	37,284.5	0.99 (0.89–1.10)	0.90	109	26,004.5	1.16 (0.91–1.48)	0.24
Average daily ethanol intake from wine[e]								
Abstainer	386	25,671	1 (Reference)		82	17,604.5	1 (Reference)	
Ever user	221	11,959.5	1.09 (0.80–1.48)	0.59	29	8,609	0.63 (0.29–1.36)	0.24
Average daily ethanol intake from wine (per 14 g/day)	607	37,630.5	0.79 (0.53–1.18)	0.26	111	26,213.5	0.74 (0.29–1.87)	0.52
Average daily ethanol intake from spirits[f]								
Abstainer	362	24,531	1 (Reference)		67	17,020.5	1 (Reference)	
Ever user	234	12,510.5	1.27 (0.93–1.73)	0.13	39	8,615	0.94 (0.48–1.84)	0.86
Average daily ethanol intake from spirits (per 14 g/day)	596	37,041.5	1.11 (0.89–1.39)	0.34	106	25,635.5	0.63 (0.24–1.66)	0.35

Abbreviation: g/day, grams per day.

[a]Number of colon cancers: 643; participants with synchronous colon and rectal cancers ($n = 10$) were excluded from analysis.

[b]Number of rectal cancers: 116; participants with colorectal cancer synchronous colon and rectal cancers ($n = 10$) were excluded from analysis.

[c]All multivariable models were adjusted for country (categorical, time-fixed), education (categorical, time-fixed), ascertainment (binary, time-fixed), sex (binary, time-fixed), BMI at age 20 (categorical, time-fixed), diabetes status (binary, time-varying), regular physical activity (binary, time-varying), and smoking status (categorical, time-varying).

[d]Models additionally adjusted for average daily ethanol intake from wine (binary, time-varying) and from spirits (binary, time-varying).

[e]Models additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from spirits (binary, time-varying).

[f]Models additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from wine (binary, time-varying).

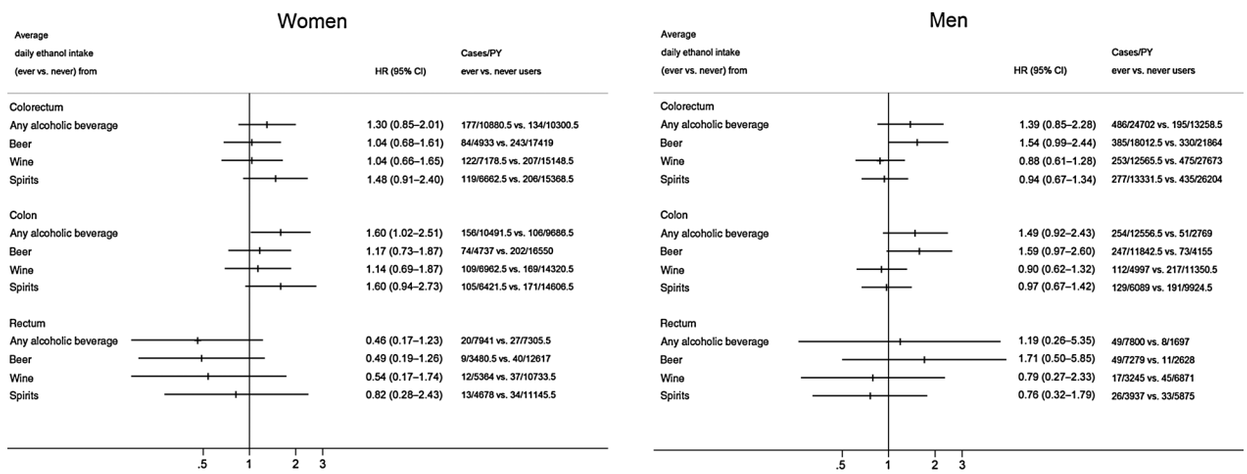

Figure 1.

HRs for associations between alcohol consumption and the risk of colon, rectum, and colorectal cancer for DNA mismatch repair gene germline mutation carriers by sex. All models were multivariable and adjusted for country (categorical, time-fixed), education (categorical, time-fixed), ascertainment (binary, time-fixed), BMI at age 20 (categorical, time-fixed), diabetes status (binary, time-varying), regular physical activity (binary, time-varying), and smoking status (categorical, time-varying). NOTE: models for women were additionally adjusted for number of live births (categorical, time-varying), and years of hormonal contraceptive use (categorical, time-varying). Models for beer were additionally adjusted for average daily ethanol intake from wine (binary, time-varying) and from spirits (binary, time-varying). Models for wine were additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from spirits (binary, time-varying). Models for sake were additionally adjusted for average daily ethanol intake from beer (binary, time-varying) and from wine (binary, time-varying). CI, confidence interval; HR, hazard ratio; PY, person-years.

main alcohol variables in any of the final models. The unweighted and weighted analyses yielded similar results, although the weighted analyses gave larger SEs and wider CIs (details not shown).

Discussion

We found that alcohol consumption particularly more than 28 g/day of ethanol (~2 standard drinks of alcohol in the United States) was associated with an increased risk of colorectal cancer for MMR gene mutation carriers. The direction and strength of associations that we estimated for carriers were similar to those reported by a meta-analysis of 7 studies on associations between long-term alcohol consumption and colorectal cancer (relative risk for highest vs. lowest category, 1.49; 95% CI, 1.27–1.74; ref. 14), and meta-analyses of associations between current alcohol consumption and colorectal cancer risk (16, 17, 32), estimated for the general population. For the general population, alcohol consumption has been reported to increase the risk of both colon and rectal cancer (15, 17). In this study, however, we did not find evidence for a positive association between alcohol consumption and rectal cancer. While our overall results were not contrary to findings for the general population (ref. 15; 95% CIs were compatible), the small number of rectal cancer cases with available data on alcohol consumption ($n = 104$) could possibly explain the lack of evidence for an association between alcohol consumption and rectal cancer in our study (in MMR gene mutation carriers, proximal colon is the predominant site for colorectal cancers (33)). Similarly, our study provided no clear evidence for an association between individual beverage types and colorectal, colon, or cancer risk and in separate analyses for men and women. This might be due to limited statistical power given the limits of CIs for estimates from these subanalyses. The reason for absence of a clear dose-dependent relationship between alcohol consumption and colorectal cancer risk in our study is not clear. However, in part, it might be because the majority of this cohort ($n = 831$) were light alcohol drinkers (0 to 14 g/day), a limited number of carriers ($n = 188$; 16 women and 172 men) were in our highest category of alcohol consumption (more than 28 g/day), and our study was under powered to assess dose-dependent relationship, particularly at high levels of alcohol consumption.

A few previous studies have investigated the association between alcohol consumption and the risk of colorectal cancer (18), colorectal polyp or cancer (19), and colorectal adenoma (20), for MMR gene mutation carriers. In a retrospective cohort study of 271 MMR gene mutation carriers, Watson and colleagues reported no evidence for an association between alcohol use and colorectal cancer risk ($P > 0.4$; estimates not reported; ref. 18). In a Dutch case–control study of suspected and confirmed MMR gene mutation carriers [145 cases with colorectal cancer ($n = 36$) or polyps ($n = 119$) vs. 103 controls], Diergaarde and colleagues did not find evidence for an association between alcohol consumption and the risk of colorectal polyp or cancer (OR $\geq$12.8 g/day vs. $\leq$2.6 g/day, 1.0; 95% CI, 0.5–2.0; ref. 19). However, as here, those authors reported greater alcohol consumption by cases than controls [mean (SD) 14.0 (15.2) vs. 9.8 (10.9); ref. 19]. In a prospective cohort study of 386 MMR gene mutation carriers (58 diagnosed with colorectal adenoma over a median follow-up of 10 months), Winkels and colleagues reported an HR of 1.56 (95% CI, 0.71–3.43) for the association between highest versus lowest tertiles of alcohol consumption and the risk of colorectal adenoma. This is similar to our estimate from analysis in which the outcome was defined as either colorectal polyp or cancer (HR > 28 g/day vs. abstention, 1.60; 95% CI, 1.16–2.20; ref. 20). The smaller sample sizes of those studies relative to ours could explain their lack of evidence for associations between alcohol consumption and the risk of colorectal polyp or cancer.

The mechanisms of alcohol-related carcinogenesis specifically for MMR gene mutation carriers are not known. For the general population, it has been suggested that acetaldehyde, a metabolite of ethanol found in high concentrations in the colon following alcohol consumption, has a carcinogenic role. Acetaldehyde affects DNA synthesis and repair, alters the structure and function of glutathione (an anti-oxidative peptide), and increases mucosal proliferation in the colon (34). There is also evidence that ethanol could have carcinogenic effects by altering methyl group transfer (34).

To the best of our knowledge, this is the largest study to date examining the association between alcohol consumption and colorectal cancer risk for MMR gene mutation carriers. Data for this study came from the Colon Cancer Family Registry, which used standardized and uniform questionnaires and conducted standardized genetic screening for MMR gene mutations (21). To handle the fact that selection of carriers was on the basis of their disease status, we used a weighted cohort analyses to produce unbiased estimates (26).

One of the limitations of our study is potential for imprecision in estimates, and attenuation toward the null due to nondifferential errors in the measurement of alcohol consumption and other variables because they were based on self-reported questionnaires. In addition, the assumptions that underpinned our calculation of average alcohol consumption between the age of 20 years and age at colorectal cancer diagnosis or censored age might have overestimated alcohol consumption for both colorectal affected and unaffected MMR gene mutation carriers. Because affected carriers were interviewed after having been diagnosed with colorectal cancer, disease status might have influenced their recall of exposures, introducing recall bias. In addition, there may have been residual confounding by factors that we were not able to take into account in our analyses. BMI is a known risk factor for colorectal cancer (35) and might have confounded the association between alcohol consumption and colorectal cancer. We were not able to adjust for recent BMI because this variable was available for only 50% of carriers in this study. Because we did not have data on age at first regular consumption of aspirin or ibuprofen, or of multivitamin, calcium, and folic acid supplements, we were not able to treat them as time-varying variables in our analyses. When included as time-fixed variables in the models, the strength and direction of estimated alcohol associations did not change. Finally, survival bias might have influenced our analysis as affected carriers with better survival were more likely to have been recruited into the Colon Cancer Family Registry. However, a supplementary analysis limited to carriers who were censored or diagnosed with colorectal cancer within 5 years before the interview gave similar results to our main analysis.

For MMR gene mutation carriers, alcohol consumption, particularly more than 28 g/day of ethanol, was associated with an increased risk of colorectal cancer. However, there was no clear evidence for a dose-dependent relationship or increased risks associated with individual beverage types. These findings need further confirmation, particularly using large prospective cohort studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government or the CCFR. Authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

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