

Meta-analysis of 16 studies of the association of alcohol with colorectal cancer

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Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BMI: body mass index; CI: confidence interval; CORECT: Colorectal Transdisciplinary; CRC: colorectal cancer; GECCO: Genetics and Epidemiology of Colorectal Cancer Consortium; NSAIDs: nonsteroidal anti-inflammatory drugs; OR: odds ratio; RR: relative risk

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Alcohol consumption is an established risk factor for colorectal cancer (CRC). However, while studies have consistently reported elevated risk of CRC among heavy drinkers, associations at moderate levels of alcohol consumption are less clear. We conducted a combined analysis of 16 studies of CRC to examine the shape of the alcohol–CRC association, investigate potential effect modifiers of the association, and examine differential effects of alcohol consumption by cancer anatomic site and stage. We collected information on alcohol consumption for 14,276 CRC cases and 15,802 controls from 5 case-control and 11 nested case-control studies of CRC. We compared adjusted logistic regression models with linear and restricted cubic splines to select a model that best fit the association between alcohol consumption and CRC. Study-specific results were pooled using fixed-effects meta-analysis. Compared to non-/occasional drinking (≤ 1 g/day), light/moderate drinking (up to 2 drinks/day) was associated with a decreased risk of CRC (odds ratio [OR]: 0.92, 95% confidence interval [CI]: 0.88–0.98, $p = 0.005$), heavy drinking (2–3 drinks/day) was not significantly associated with CRC risk (OR: 1.11, 95% CI: 0.99–1.24, $p = 0.08$) and very heavy drinking (more than 3 drinks/day) was associated with a significant increased risk (OR: 1.25, 95% CI: 1.11–1.40, $p < 0.001$). We observed no evidence of interactions with lifestyle risk factors or of differences by cancer site or stage. These results provide further evidence that there is a J-shaped association between alcohol consumption and CRC risk. This overall pattern was not significantly modified by other CRC risk factors and there was no effect heterogeneity by tumor site or stage.

What's new?

Heavy drinking is associated with increased colorectal cancer (CRC) risk, but there's debate about the impact of moderate drinking. Here, the authors conducted a combined analysis of 16 studies comprising 14,276 cases and 15,802 controls. By their analysis, drinking 1-2 alcoholic beverages per day was associated with a reduced risk of CRC, compared with rare or no alcohol consumption. With 3 or more drinks per day, CRC risk rises. The authors suggest that moderate alcohol consumption may reduce inflammation and DNA damage, although they acknowledge that more research is needed to understand the biochemical mechanism at work.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, and the second leading cause of

cancer-related death in the United States.^{1,2} Alcohol consumption is an established risk factor for CRC.^{3–12} Several mechanisms have been suggested for the association between alcohol

consumption and risk of developing CRC, including the metabolism of alcohol to acetaldehyde, the carcinogenic effect of nitrosamines, increased degradation of folate, modulation of folate uptake, mucosal and DNA damage, and modulation of gene expression.^{4,10,13–15}

While studies have consistently reported elevated risk of CRC among heavy drinkers, associations at light and moderate levels of alcohol consumption are less clear. Both cohort and case control studies have identified a J-shaped association between alcohol consumption and CRC, where moderate alcohol consumption is protective compared to no alcohol consumption.^{16–18} However, other studies have reported a positive dose–response relationship^{5,9–11,19} or nonsignificant positive associations at moderate levels of alcohol consumption.^{3,6}

Several other risk factors for CRC have been identified, including smoking, obesity, high consumption of red meat, physical inactivity, and family history of CRC.^{12,20–23} A few studies have observed the association between alcohol consumption and CRC to differ by other factors including sex,^{7,12,17,18} family history of CRC³, and obesity,^{6,24} but further research in statistically well-powered study settings is needed to explore potential interactions between alcohol consumption and other CRC risk factors.

We conducted a meta-analysis of 16 studies of CRC to examine the shape of the alcohol-CRC dose–response association, identify potential effect modifiers of the association between alcohol consumption and CRC, and examine effects of alcohol consumption by CRC anatomic site and disease stage.

Materials and Methods

Study design and data collection

We conducted a meta-analysis of 5 case-control studies and 11 case-control studies nested within prospective cohorts. Information on basic demographics, lifestyle, and environmental risk factors was collected by self-report using in-person interviews and/or self-administered structured questionnaires. We used risk factor information at the reference time, which was defined as study entry or blood collection for nested case-control studies and 1–2 years before diagnosis for case-control studies to ensure exposures were assessed before cancer diagnoses.

Individual level data from all studies were centrally harmonized. We carried out a multistep data harmonization procedure, reconciling each study's unique protocols and data-collection instruments.²⁵ First, common data elements were defined for key demographic and environmental risk factors. Next, questionnaires and data dictionaries from each study were examined to identify study-specific data elements that could be mapped to the common data elements. Through an iterative process, we communicated with each data contributor to obtain relevant data and coding information. The data elements were written to a common data platform, transformed, and combined into a single dataset with common

definitions, standardized permissible values, and standardized coding.²⁵ The mapping and resulting data were reviewed for quality assurance, and range and logic checks were performed to assess data and data distributions within and between studies. Outlying measures were truncated to the minimum or maximum value of the established range for each variable.

Study subjects

Case participants were diagnosed with invasive CRC. Appendix or noninvasive (stage 0 or *in situ*) CRC cases were excluded. Control participants were required to be free of invasive CRC and noninvasive CRC at the time of selection into the study. Case and control participants were excluded if they had prior history of CRC at baseline. CRC cases were confirmed by medical records, pathologic reports, or death certificates. Participants provided consent for participation in each of the included studies. The overall project was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Alcohol consumption and key covariates

The primary exposure was alcohol consumption during the referent time, measured in grams of alcohol per day (g/day). As part of the data harmonization process, we converted consumption of alcoholic beverages into grams of alcohol per day by summing the alcohol content of each type of beverage consumed per day. When studies reported alcohol consumption in terms of servings, we converted this assuming an alcohol content of 14 g/serving.^{6,16,26}

We considered the following potential confounders, measured at reference time: age, ethnic group, sex, educational attainment (less than high school graduate, high school graduate or GED, some college or technical school, college graduate or graduate school), body mass index (BMI: kg/m²), physical activity (≥ 1 hr/week of vigorous/moderate physical activity vs. < 1 hr/week), smoking (never vs. ever smoker and pack-years), regular use of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), regular use of postmenopausal hormone therapy (collected only for postmenopausal women), red/processed meat intake, fruit and vegetable intake, folate intake (including dietary and supplements), calcium intake (including dietary and supplements), dietary fiber intake, screening history (history of sigmoidoscopy or colonoscopy), family history of CRC in first-degree relatives, and history of diabetes. BMI was derived using pre-diagnosis (cases) or referent (controls) weight and height and analyzed as both a continuous and categorical variable (underweight or normal [< 24.9], overweight,^{25–30} obese [≥ 30]). Smoking pack-years were calculated for former or current smokers by multiplying the average number of cigarettes per day by the number of years smoked and dividing by 20 (number of cigarettes in a pack). Pack-years and all dietary variables were collapsed into study- and sex-specific quartiles for analysis. These covariates were identified as potential confounders because prior

research has shown that they are potentially associated with both alcohol consumption and CRC. To evaluate confounding within our study, we conducted chi-square, ANOVA, and *t*-tests to test for associations between each potential confounder and alcohol consumption among study controls and for associations between each potential confounder and CRC risk among those who reported no alcohol consumption. Covariates that were significantly associated ($p < 0.05$) with both exposure and outcome were adjusted for in the final models as confounders.

Missing data

Subjects with missing data on alcohol consumption ($n = 2,375$) were excluded from the analysis. A sensitivity analysis was conducted to evaluate the impact of high levels of missing data in alcohol consumption on effect estimates. A meta-analysis of only those studies that were missing alcohol information on less than 10% of participants (11 studies) produced similar effect estimates and inference as the full meta-analysis with all 16 studies. Cases missing information on cancer anatomic site or cancer stage were excluded from the respective stratified analyses.

The influence of missing data for key covariates was evaluated separately for each study. Covariates that were missing for more than 25% of subjects were excluded from the model for that study.

Single regression imputation was used to impute values for potential effect modifiers to ensure consistency across imputations for calculating stratified effect estimates. Study-specific single imputation models included alcohol consumption, case-control status, and any identified confounders (age, sex, education, BMI, smoking, aspirin, NSAIDs, red/processed meat intake, fruit and vegetable intake, folate intake, calcium intake, screening history, and history of diabetes) that were available for all study subjects. We then used multiple imputation by chained equations to impute values for all other covariates that were missing for less than 25% of subjects.²⁷ Alcohol consumption, case-control status, and all identified confounders were included in the multiple imputation models. Imputation and data analysis were performed using STATA 14.2 (College Station, Texas, USA).

Analysis

Modeling the shape of the alcohol-CRC dose-response association. To evaluate the association between alcohol and CRC, we used minimally adjusted (sex and age) logistic regression to model alcohol as a continuous variable and explored the use of splines and higher level terms. We created linear splines at intervals of 14 g/day (1–14 g/day, 15–28 g/day, 29–42 g/day, etc.), based on the definition of a standard drink as equaling 14 g of alcohol.^{6,16,26} We also created splines at the 25th, 50th, and 75th percentiles of alcohol consumption among subjects with any alcohol consumption. We sequentially added linear splines to the model and also modeled restricted cubic

splines with varying numbers of nodes. We used Akaike information criterion (AIC) and Bayesian information criterion (BIC) to compare each model and selected the models that minimized AIC and BIC. We then created categories of alcohol consumption based on the splines from the models with the lowest AICs and BICs and selected the categorical model that minimized AIC and BIC.

Each study was analyzed separately using multivariable logistic regression models. A Cochran's *Q* test was used to evaluate heterogeneity between studies. Study-specific results were combined using fixed-effects meta-analysis methods to obtain summary odds ratios (ORs) and 95% confidence intervals (CIs) across studies. We also conducted separate meta-analyses for case-control and cohort studies.

Evaluation of effect modification. We assessed the following CRC risk factors as potential modifiers of the alcohol-CRC association, identified from the literature: age, sex, BMI, smoking, and family history of CRC. Multiplicative interaction terms were included in the study-specific logistic regression models and a joint test of coefficients was performed to test if the interaction coefficients were equal to 0. Study-specific *p*-values from the joint test of coefficients test were pooled using Fisher's combination method to evaluate overall interaction.²⁸ Models were adjusted for any potential confounders that were not observed to modify the association between alcohol and CRC.

Differential effects by CRC anatomic site and cancer stage. Polytomous logistic regression adjusted for confounders was used to evaluate the alcohol-CRC association by cancer anatomic site and by cancer stage. Study-specific results were combined using fixed-effects meta-analysis. Models were adjusted for identified confounders, and stratified ORs and 95% CIs were reported for each anatomic site and cancer stage. Interaction between alcohol and anatomic site was evaluated by conducting a case-only analysis comparing proximal colon cancer (ICD-9: 153.0, 153.1, 153.4, 153.6) to distal colon (ICD-9: 153.2, 153.3, 153.7) or rectal cancers (ICD-9: 154.0, 154.1). A joint test of coefficients was performed to test if the coefficients for each level of alcohol consumption were equal to 0, and *p*-values were pooled across studies using Fisher's combination method.

Results

Basic characteristics of the participants are shown in Table 1. We were able to harmonize measures of alcohol consumption for 14,276 cases and 15,802 controls. Overall, 47% of participants reported light or moderate alcohol consumption (1.1–28 g/day or up to 2 drinks/day), 6% of participants reported heavy alcohol consumption (28.1–42 g/day or 2–3 drinks/day), 6% reported very heavy alcohol consumption (>42 g/day or more than 3 drinks/day) and 41% reported no alcohol

Table 1. Characteristics of study population

Study	Study design	Country	Cases	Controls	Total	Age (Years)		Female %	Alcohol consumption				Alcohol consumption (g/day) among drinkers					
						Mean	SD		Non/occasional drinkers (≤1 g/day)		Light/moderate drinkers (1.1–28 g/day)		Heavy drinkers (28.1–42 g/day)		Very heavy drinkers (>42 g/day)		M	SD
									N	%	N	%	N	%	N	%		
ATBC	Cohort	Finland	221	141	362	57.6	4.7	0	52	14.4	228	63.0	40	11.1	42	11.6	18.3	20.2
COLO2&3	Case-control	US	94	129	223	65.0	11.3	43.5	96	43.1	98	44.0	16	7.2	13	5.8	12.4	21.6
CPS-II	Cohort	US	2,252	2,356	4,608	67.9	5.9	48.1	2,016	43.8	2,179	47.3	230	5.0	183	3.97	8.3	14.9
DACHS	Case-control	Germany	2,879	2,325	5,204	68.7	10.4	39.6	1,500	28.8	2,773	53.3	383	7.4	548	10.5	15.3	20.6
DALS	Case-control	US	1,453	1,475	2,928	63.7	9.9	43.9	1,524	52.1	1,031	35.2	164	5.6	209	7.1	11.0	22.7
HPFS	Cohort	US	828	1,149	1,977	64.3	8.8	0	498	25.2	1,187	60.0	163	8.2	129	6.5	12.5	15.8
Kentucky	Case-control	US	905	1,052	1,957	62.8	9.4	51.6	1,364	69.7	508	26.0	30	1.5	55	2.8	4.6	13.5
MCCS	Cohort	Australia	780	699	1,479	59.5	7.6	47.9	537	36.3	638	43.1	156	10.6	148	10.0	15.0	21.1
MEC	Cohort	US	345	355	700	63.0	8.0	48.0	268	38.3	284	40.6	62	8.9	86	12.3	17.6	30.9
NFCCS	Case-control	Canada	319	686	1,005	59.3	9.5	28.5	452	45.0	431	42.9	55	5.5	67	6.7	11.6	22.6
NHS	Cohort	US	1,107	1,685	2,792	58.7	6.7	100	1,341	48.0	1,313	47.0	106	3.8	32	1.2	5.4	9.7
PLCO	Cohort	US	434	684	1,118	64.5	5.1	39.2	468	41.9	491	43.9	43	3.9	116	10.4	13.0	24.7
SELECT	Cohort	US	308	308	616	65.3	6.7	0	221	35.9	304	49.4	38	6.2	53	8.6	13.1	22.6
SMC & COSM	Cohort	Sweden	566	868	1,434	63.2	8.2	39.1	142	9.9	1,189	82.9	65	4.5	38	2.7	11.1	13.0
VITAL	Cohort	US	358	363	721	66.3	6.3	45.1	316	43.8	321	44.5	46	6.4	38	5.3	9.8	17.5
WHI	Cohort	US	1,427	1,527	2,954	66.4	6.6	100	1,636	55.4	1,178	39.9	97	3.3	43	1.5	5.3	10.3
Total			14,276	15,802	30,078	64.7	8.9	50.1	12,431	41.3	14,153	47.1	1,694	5.6	1,800	6.0	10.5	18.4

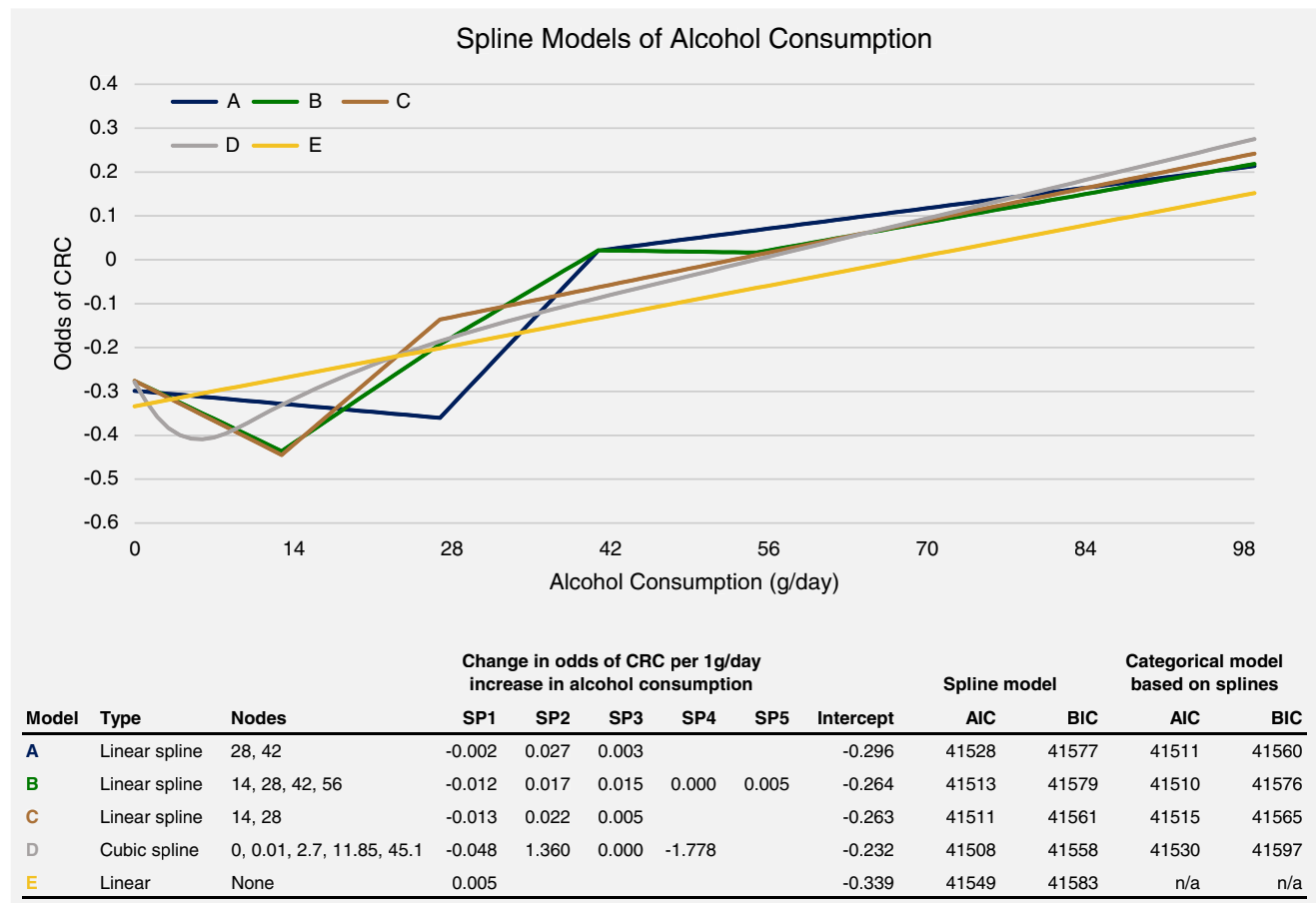


Figure 1. Spline models of alcohol consumption. [Color figure can be viewed at wileyonlinelibrary.com]

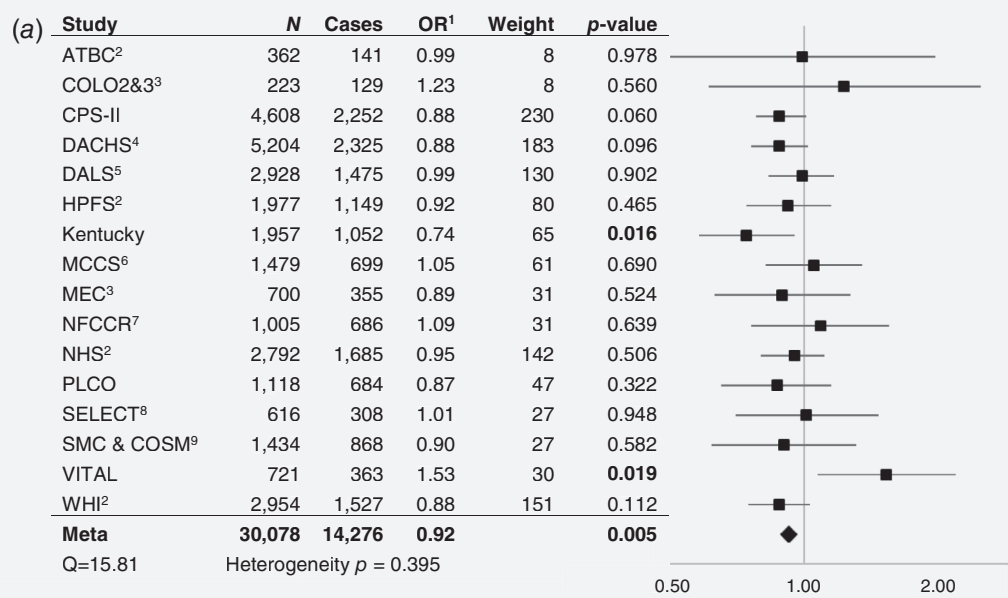
consumption (≤ 1 g/day). The average alcohol consumption for subjects reporting any alcohol consumption was 10.5 g/day.

We observed a J-shaped association between alcohol consumption and CRC risk across multiple spline and restricted cubic-spline models (Fig. 1). In each model, the slope of the first spline was negative, indicating a negative association between alcohol consumption and log-odds of CRC at lower levels of alcohol consumption. Subsequent splines had positive slopes, representing an increase in the log-odds of CRC as alcohol consumption increases past light/moderate consumption levels. The categorical model that minimized AIC and BIC had four categories of alcohol consumption: non-/occasional drinkers (≤ 1 g/day), light/moderate drinkers (1.1–28 g/day or up to 2 drinks/day), heavy drinkers (28.1–42 g/day or 2–3 drinks/day) and very heavy drinkers (>42 g/day or more than 3 drinks/day). This model also had smaller AIC (41,510) and BIC (41,576) compared to the corresponding linear spline model (AIC: 41,528; BIC: 41,577) and the model that included the continuous variable as a single linear term (AIC: 41,549; BIC: 41,583).

Using fixed-effects meta-analysis, compared to non-/occasional drinkers, light/moderate alcohol consumption was

associated with a decreased risk of CRC (OR: 0.92, 95% CI: 0.88–0.98, $p = 0.005$) (Fig. 2a) while very heavy alcohol consumption was associated with an increased risk of CRC (OR: 1.25, 95% CI: 1.11–1.40, $p < 0.001$) (Fig. 2c). We observed much weaker evidence of increased risk associated with heavy alcohol consumption (OR: 1.11, 95% CI: 0.99–1.24, $p = 0.077$), compared to non-/occasional drinkers (Fig. 2b). A sub-analysis within the light/moderate alcohol consumption group found similar effect estimates across each of four sub-groups. Similar effect estimates were also observed in separate sub-analyses of case-control and nested case-control studies (Table 2). There was no evidence of heterogeneity across studies at any of the levels of alcohol consumption.

Analyses were also conducted separately for men and women. Light/moderate alcohol consumption was associated with decreased risk of CRC compared to non-/occasional consumption among both sexes, although the effect estimate was greater for women (OR: 0.88, 95% CI: 0.82–0.95, $p = 0.001$) than men (OR: 0.96, 95% CI: 0.88, 1.05, $p = 0.351$) (Table 2). Very heavy alcohol consumption was only associated with increased risk of CRC among men (OR 1.32, 95% CI: 1.15–1.51, $p < 0.001$), however there was no evidence of effect modification by sex (interaction $p = 0.204$).



¹All analyses adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake unless otherwise noted. ²Adjusted for age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake. ³Adjusted for sex; age; education; smoking; aspirin; NSAIDS; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake. ⁴Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI; and calcium, fruit, vegetable, processed meat, and red meat intake. ⁵Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake. ⁶Adjusted for sex; age; education; smoking; history of endoscopy; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake. ⁷Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI; and folate, calcium, fruit, vegetable, and red meat intake. ⁸Adjusted for age; education; smoking; aspirin; NSAIDS; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake. ⁹Adjusted for sex; age; education; smoking; diabetes; BMI; and folate, calcium, fruit, vegetable, processed meat, and red meat intake.

Figure 2. (a) Light/moderate (1.1–28 g/day) vs. non/occasional alcohol consumption. (b) Heavy (28.1–42 g/day) vs. non/occasional alcohol consumption. (c) Very heavy (>42 g/day) vs. non/occasional alcohol consumption. ¹All analyses adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake unless otherwise noted. ²Adjusted for age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake. ³Adjusted for sex; age; education; smoking; aspirin; NSAIDS; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake. ⁴Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI and calcium, fruit, vegetable, processed meat and red meat intake. ⁵Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake. ⁶Adjusted for sex; age; education; smoking; history of endoscopy; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake. ⁷Adjusted for sex; age; education; smoking; aspirin; NSAIDS; history of endoscopy; diabetes; BMI and folate, calcium, fruit, vegetable and red meat intake. ⁸Adjusted for age; education; smoking; aspirin; NSAIDS; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake. ⁹Adjusted for sex; age; education; smoking; diabetes; BMI and folate, calcium, fruit, vegetable, processed meat and red meat intake.

Associations with low levels of alcohol consumption differed slightly when stratified by BMI. Compared to non-/occasional consumption, light/moderate alcohol consumption was not associated with reduced risk among obese individuals (OR: 1.07, 95% CI: 0.93–1.22, $p = 0.366$). However, there was no evidence overall of effect modification by BMI (interaction $p = 0.736$). Additionally, age, smoking (evaluated as ever vs. never and pack-years), and family history of CRC were not found to modify the alcohol–CRC association.

Similar protective associations for light/moderate alcohol consumption were observed across proximal colon, distal colon, and rectal cancer sites (Table 2). Heavy alcohol consumption, however, was associated with increased risk of distal colon (OR: 1.19, 95% CI: 1.01–1.45, $p = 0.004$), with a

consistent result observed for rectal cancer (OR: 1.17, 95% CI: 0.97–1.41, $p = 0.099$), but not proximal colon cancer (OR: 1.05, 95% CI: 0.90–1.23, $p = 0.511$). Very heavy alcohol consumption was associated with increased risk across all cancer sites. A J-shaped dose–response association was also observed when analyses were stratified by cancer stage. Stronger associations were observed between very heavy alcohol consumption and Stage 1 and Stage 4 cancers, but overall associations did not differ substantially by cancer stage.

Discussion

In this large meta-analysis, we observed a J-shaped dose–response pattern of association between alcohol consumption and CRC risk. Compared to non-/occasional drinking, light to

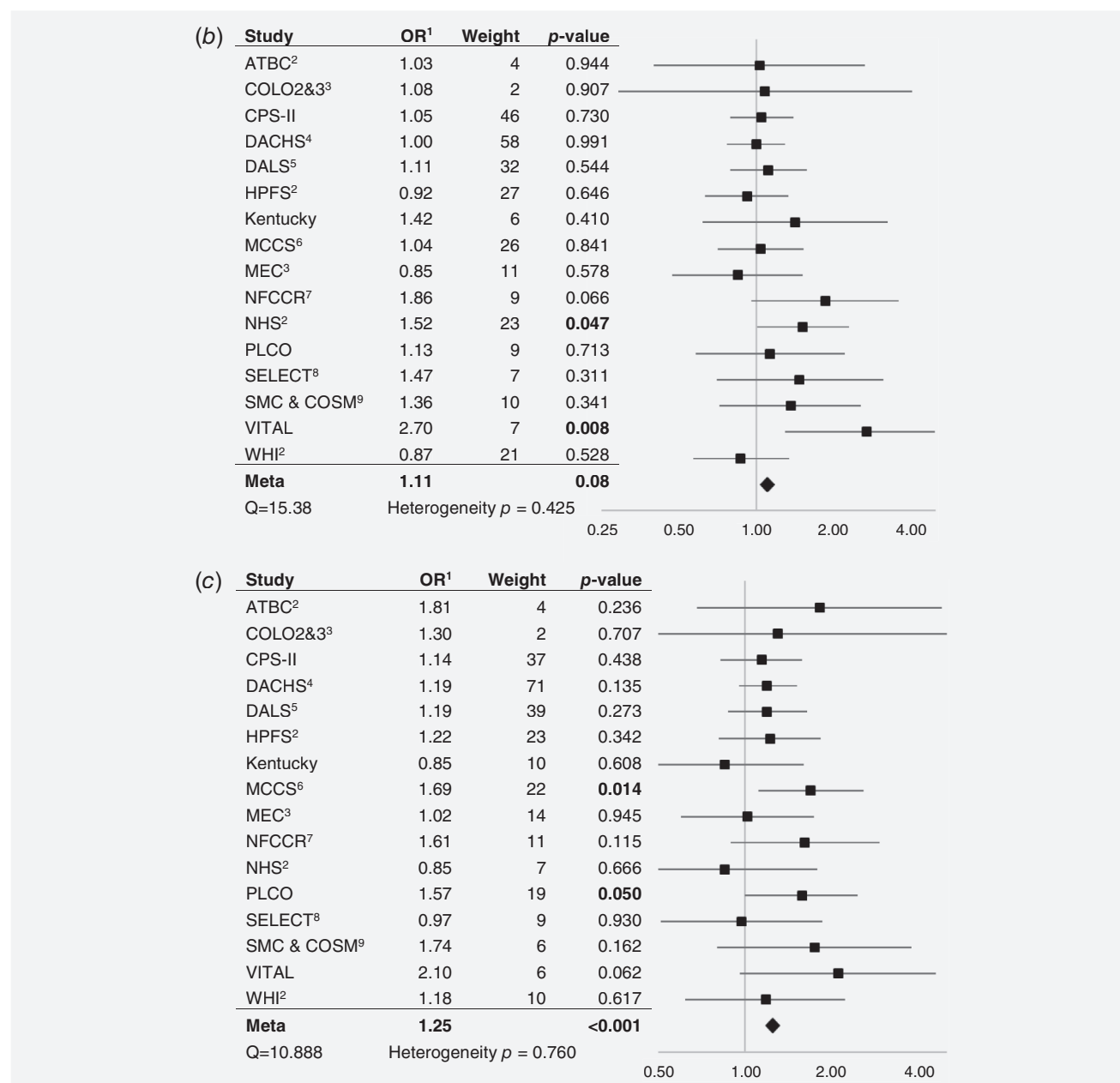


Figure 2. (Continued)

moderate alcohol consumption (up to 2 drinks/day) was inversely associated with CRC risk, while very heavy consumption (more than 3 drinks/day) was associated with greater risk. While effect estimates varied slightly according to participant sex, BMI, and tumor site, there was no evidence of interaction or of heterogeneity by tumor site. The J-shaped association was consistently observed among both case-control and nested case-control studies.

Alcohol is an established risk factor for CRC and heavy alcohol consumption has been shown to be associated with increased risk of CRC.^{3,6,8,10,12,16,17,19} Findings are inconsistent

for lower levels of alcohol consumption, with some studies reporting minimal or nonsignificant associations^{3,6,10,19} and others reporting a reduced risk of CRC for low or moderate drinkers.^{16,18} We observed a protective association with light/moderate alcohol consumption (up to 2 drinks/day) compared to non- or occasional consumption. A sub-analysis of four subgroups within the light/moderate alcohol consumption group gave similar effect estimates across each of the subgroups, indicating that the observed protective effect is consistent within the low/moderate level of alcohol consumption. Both linear and restricted spline models with

Table 2. Stratified odds ratios for alcohol consumption and CRC by key covariates¹

Alcohol consumption													
Meta analyses	N	Light/moderate (1.1–28 g/day) vs. non/occasional			Heavy (28.1–42 g/day) vs. non/occasional			Very heavy (>42 g/day) vs. non/occasional			Interaction p-value		
		OR ²	95% CI	p-value	OR ²	95% CI	p-value	OR ²	95% CI	p-value			
Overall	30,078	0.92	0.88	0.98	0.005	1.11	0.99	1.24	0.077	1.25	1.11	1.40	<0.001
Study design													
Case control	11,317	0.91	0.83	1.00	0.056	1.11	0.92	1.34	0.29	1.20	1.01	1.42	0.04
Cohort	18,761	0.93	0.87	1.00	0.04	1.11	0.96	1.28	0.157	1.29	1.11	1.51	0.001
Sex													
Female	15,067	0.88	0.82	0.95	0.001	1.12	0.91	1.37	0.289	1.01	0.77	1.32	0.967
Male	15,011	0.96	0.88	1.05	0.351	1.09	0.94	1.26	0.243	1.32	1.15	1.51	<0.001
BMI													
Normal or underweight	11,254	0.88	0.80	0.96	0.005	1.11	0.91	1.34	0.301	1.13	0.91	1.40	0.275
Overweight	12,876	0.89	0.81	0.97	0.007	1.06	0.89	1.26	0.18	1.25	1.05	1.49	0.011
Obese	5,928	1.07	0.93	1.22	0.366	1.04	0.76	1.43	0.812	1.38	1.04	1.83	0.025
Cancer site													
Proximal	5,562	0.94	0.87	1.01	0.094	1.05	0.90	1.23	0.511	1.13	0.96	1.32	0.145
Distal	4,000	0.91	0.83	0.99	0.026	1.19	1.01	1.41	0.004	1.39	1.18	1.64	<0.001
Rectal	3,109	0.91	0.82	1.01	0.063	1.17	0.97	1.41	0.099	1.46	1.22	1.76	<0.001

¹See footnotes in Figure 2 for adjustment factors.

²All estimates calculated by fixed effect meta-analysis.

nodes at varying cut points were consistent with a J-shaped association, further supporting this finding. A 2014 meta-analysis of nine studies also reported a J-shaped dose-response relationship between alcohol and CRC mortality, indicating that trends in CRC risk may also be reflected in CRC mortality.¹⁷

The mechanisms by which alcohol consumption influences CRC risk are still being explored.^{13,14,29} The breakdown of alcohol to acetaldehyde, a carcinogen that has been shown to disrupt DNA replication and repair, is widely believed to play a role in CRC risk.^{14,30,31} Chronic alcohol consumption has also been shown to disrupt folate metabolism, and folate deficiency is an established risk factor for CRC.^{8,13,15,30,32} Alcohol consumption can also interfere with the breakdown and absorption of other nutrients, and alcohol metabolism generates reactive oxygen species which can damage DNA, proteins, and lipids.³⁰ Moderate alcohol empirically lowers inflammatory markers and C-peptide,^{33–35} and a short-term randomized clinical trial observed a benefit of alcohol on insulin parameters.³⁶ A 2017 study of the effects of moderate alcohol consumption in rats observed that moderate levels of alcohol intake did not elevate biological risk factors for CRC development and may provide beneficial effects through reduced inflammation and lower DNA damage.²⁹ As we cannot rule out that the inverse association may be explained by residual confounding or chance, a better understanding of the underlying mechanism is necessary to interpret observed protective effects of light/moderate alcohol consumption and inform CRC prevention recommendations.

It has been suggested that the association between alcohol and CRC may differ by sex, in part due to differences in alcohol metabolism between men and women.³⁷ Although we did not observe sex to significantly modify the association between alcohol and CRC, we did observe some differences in estimated effect sizes. In particular, the protective effect associated with light/moderate alcohol intake was observed among both sexes; this association was most pronounced among women, and the positive association with very heavy alcohol consumption was restricted to men. The potential benefit of moderate alcohol consumption on insulin parameters has been observed to be stronger in women than men,³⁸ which could contribute to the stronger protective effect for CRC observed among women in our analysis. The observed increased risk of CRC associated with very heavy alcohol consumption among men is consistent with other studies that have reported increased risk with heavy drinking among men but not among women.^{7,18} Studies of the effect of higher levels of alcohol consumption among women are often limited due to the low prevalence of heavy alcohol consumption among women. For example, less than 2% of women ($n = 275$) in our analysis reported very heavy alcohol consumption, compared to over 10% ($n = 1,525$) of men, which limited our power to detect effect modification or identify associations with high levels of alcohol consumption among women.

Few studies have evaluated the alcohol–CRC association by cancer anatomic site. A large-scale cohort study in a Korean population observed that frequent alcohol consumption was associated with increased risk of distal colon cancer but not with proximal colon or rectal cancer.⁷ A pooled analysis of eight cohort studies from North America and Europe observed elevated risk associated with increased alcohol intake across proximal colon, distal colon, and rectal cancers.¹⁰ The highest level of alcohol consumption (≥ 45 g/day) was associated with a higher risk of distal colon cancer (relative risk [RR]: 1.66, 95% CI: 1.17–2.36) and rectal cancer (RR: 1.49, 95% CI: 1.04–2.12) compared to proximal colon cancer (RR: 1.35, 95% CI: 0.97–1.89).¹⁰ We observed a similar trend, where heavy and very heavy alcohol consumption were associated with a higher risk of distal colon cancer and rectal cancer, compared to proximal colon cancer; however, there was no evidence of significant heterogeneity by cancer site. There is some evidence of biological and clinical differences between proximal and distal colon cancer. For example, the *BRAF* mutation and microsatellite instability-high phenotype have been observed more frequently in proximal colon tumors compared to distal colon tumors.^{39,40} A case-affected sibling study observed that alcohol consumption was associated with increased risk of CRC tumors characterized by microsatellite instability-low phenotype but not microsatellite instability-high phenotype.⁴¹ These findings suggest that etiological pathways may vary by cancer anatomic site and that the role of alcohol may differ by pathway. Further evaluation of alcohol risk by site and tumor characteristics may provide additional insight regarding the biological mechanisms through which alcohol affects CRC risk, and provide more precise estimates of risk for specific anatomic sites.

We are mindful of limitations in our study. Each contributing study used a different questionnaire to obtain information on alcohol consumption and other key covariates. While our centralized data harmonization process improved consistency in measuring these variables across studies, our data are still subject to recall bias, measurement error, and misclassification. Additionally, because we analyzed current alcohol consumption rather than lifetime consumption, former drinkers were included with never drinkers in the referent category of non-/occasional drinkers. There is some evidence that longer duration of alcohol consumption is associated with elevated CRC risk and that past drinkers have a higher risk of CRC compared to non-drinkers.^{7,42} Thus, inclusion of former drinkers in the referent category could attenuate observed associations and contribute to the observed protective effect associated with light/moderate alcohol consumption. Reassuringly, a pooled analysis of four cohort studies observed a similar J-shaped alcohol–CRC association when former drinkers were included and excluded from the non-drinker reference group.¹⁰

Overall, the majority of key covariates were missing for less than 5% of subjects. However, there were a few variables that were not collected by certain studies or were only collected for

subsets of the study sample. We evaluated the alcohol–CRC association separately within each study and adjusted for all available known and suspected environmental and lifestyle risk factors as potential confounders, thus estimates from some studies may be subject to additional bias due to other confounders, such as screening. However, some large-scale studies have examined the association between alcohol consumption and CRC screening showing opposite results,^{43,44} suggesting that it is less likely that screening is a confounder. It should also be noted that adjusting for screening is not without problems that cannot be easily addressed. For example, adjusting for screening could remove at least part of the effect of alcohol by removing the adenoma precursor and truncating the disease process, and also lowers the absolute risk of CRC by removing precursors. Finally, the study sample was racially homogenous with over 98% of participants reporting white ethnic group; thus, our study findings may not be generalizable to more diverse populations.

Our study also had several strengths, including a large sample size and availability of key environmental exposure and other risk factor variables across its contributing studies. This enabled us to adjust for multiple key confounders across studies. Additionally, because we had access to individual-level data from all studies and could select which variables to include in the study-specific multivariate analyses, this allowed for the use of much more consistent models than are typically available for a meta-analysis.

Additionally, a standardized harmonization of data across studies was used to reconcile each study's unique protocols and data collection instruments. This rigorous, multistep process contributed to improved data quality and more consistent measures across studies. The use of study- and sex-specific quartiles for smoking (pack-years) and dietary variables also supported improved comparability across studies. There was no evidence of heterogeneity of the alcohol–CRC association across studies, which indicates that our results were not dominated by one or a few studies.

Finally, there are no standard definitions of light, moderate, or heavy alcohol intake that are used consistently in CRC literature. A strength of our study is that the cut points we selected are based on individual-level data that minimized AIC and BIC, reflect similar ranges to those reported in the literature, and are practically applicable as they can be easily interpreted as a number of drinks per day (light/moderate: up to 2 drinks/day, heavy: 2–3 drinks/day, very heavy: >3 drinks/day).

Improving our understanding of the association between alcohol and CRC is particularly important because alcohol consumption is a modifiable behavioral risk factor that has the potential to be influenced by medical recommendations or behavioral interventions. Our findings indicate that light/moderate drinkers may have a reduced risk of CRC compared to non-/occasional drinkers, but that heavier drinkers are at increased risk. These findings can inform future

studies of the mechanisms through which alcohol affects CRC risk.

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