Effect modification of the alcohol – colorectal cancer association

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Abstract

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Introduction: 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 meta-analysis of 16 studies of CRC to examine the shape of the alcohol-CRC association, investigate potential effect modifiers of the association between alcohol consumption and CRC, and examine differential effects of alcohol consumption by cancer anatomic site and cancer stage.
Methods: We collected information on alcohol consumption for 13,248 cases and 14,430 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. Potential effect modifiers were evaluated using multiplicative interaction terms. Results were also stratified by cancer anatomic site and stage.

Results: Compared to non-/occasional drinking, light/moderate drinking (up to 2 drinks/day) was associated with a decreased risk of CRC (OR: 0.92, 95% CI: 0.87-0.98, p<0.007), while very heavy drinking (more than 3 drinks/day) was associated with an increased risk (OR: 1.26, 95% CI: 1.11-1.42, P<0.001). While the risk associated with very heavy alcohol consumption was elevated among men (OR: 1.33, p<0.001) and among distal colon (OR: 1.41, p<0.001) and rectal cancers (OR 1.53, p<0.001), the protective effect of light/moderate drinking was observed across both sexes and all tumor sites and there was no evidence of significant interaction in any of the stratified analyses.

Discussion: These results support a J-shaped association between alcohol consumption and CRC risk. This overall pattern, particularly the protective effect of light/moderate drinking, was not significantly modified by other CRC risk factors or tumor site.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, and the second leading cause of cancer-related deaths in the United States [1], [2]. Alcohol consumption is an established risk factor for CRC [3]–[11]. Several mechanisms have been suggested for the association between alcohol consumption and risk of developing CRC, including the metabolism of acetaldehyde, increased degradation of folate, modulation of folate uptake, mucosal and DNA damage, and modulation of gene expression [4], [10], [12]–[14].

While studies have consistently reported elevated risk of CRC among heavy drinkers, associations at moderate levels of alcohol consumption are less clear. Some studies have identified a J-shaped association between alcohol consumption and CRC, where moderate alcohol consumption is protective compared to individuals who consume no alcohol [15]–[17]. However, others have reported a positive dose-response relationship [5], [9]–[11], [18] or non-significant 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 [19]–[22]. A few studies have observed that the association between alcohol consumption and CRC differs by other factors including sex [7], [16], [17], family history of CRC [3], and obesity [6]. However, further research 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 association, identify potential effect modifiers of the association between alcohol consumption and CRC, and examine differential effects of alcohol consumption by colorectal cancer anatomic site and cancer stage.

Methods

Study design and data collection

We conducted a meta-analysis of 5 case-control and 11 nested case-control studies of CRC. Data on basic demographics and environmental risk factors were collected through interviews or self-administered questionnaires. We used risk factor information at the reference time, which varied across studies. A multi-step data harmonization process was applied to reconcile differences in individual study questionnaires [23]. 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. Data and relevant documentation were obtained from each study and an iterative harmonization and quality control process was applied to transform and combine study-specific data into a single data set with common definitions, standardized permissible values, and standardized coding [23]. Data for all studies were centrally harmonized at the Fred Hutchinson Cancer Research Center.

Study Subjects

Case participants were diagnosed with invasive CRC. Appendix or non-invasive (stage 0 or in situ) CRC cases were excluded. Control participants were required to be free of invasive CRC and non-invasive 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. The number of cases and controls per study are included in Appendix 1.

Alcohol consumption and key covariates

The primary exposure is alcohol consumption, 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 beverage consumed per day. When studies reported alcohol consumption in terms of servings, we converted this using a ratio of 14 g/serving. A summary of the study-specific questions used to collect information on alcohol consumption is included in Appendix 2.

We considered the following potential confounders: age at reference time, race, sex, education (less than high school graduate, high school graduate or GED, some college or technical school, college graduate or graduate school), body mass index (BMI), physical activity (≥1 hour of vigorous/moderate physical activity vs <1 hour), smoking (never vs ever smoker and pack-years), regular use of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) at reference time, regular use of any post-menopausal hormone therapy (PMH) at reference time (collected only for post-menopausal women), red/processed meat intake, fruit and vegetable intake, folate intake, calcium intake, dietary fiber intake, screening history (history of sigmoidoscopy or colonoscopy), family history of CRC, 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)]. Pack-years were calculated by multiplying the average number of cigarettes per day by the number of years smoked for former or current smokers 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 (Appendix 3), and for associations between each potential confounder and CRC risk among those who reported no alcohol consumption (Appendix 4).

Covariates that were significantly associated ($p<0.05$) with both exposure and outcome were adjusted for in the final models as confounders.

Missingness

Subjects with missing data on alcohol consumption were excluded from the analysis. A sensitivity analysis was conducted to evaluate the impact of high-levels of missingness 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.

Missingness of key covariates was evaluated separately for each study (Appendix 5). 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. 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.

Analysis

Modeling the shape of the alcohol-CRC 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.), as one standard drink is approximately equal to 14 grams of alcohol. 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 multivariate 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. To evaluate effect modification, 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 [24]. 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 multivariate logistic regression 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 to distal colon or rectal cancers. A joint test of coefficients was preformed 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.

IRB

Participants or next of kin 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.

Results

This study included 5 case-control studies and 11 case-control studies nested within cohorts of colorectal cancer (CRC). Basic characteristics of the participants are shown in Table 1. We were able to harmonize measures of alcohol consumption for 13,248 cases and 14,430 controls. Overall, the majority of participants reported light or moderate alcohol consumption

(1.1-28 g/day or up to 2 drinks/day). Average alcohol consumption for subjects reporting any alcohol consumption was 10.6 g/day.

We observed a J-shaped association between alcohol consumption and CRC risk across multiple spline and restricted cubic-spline models (Figure 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 low levels of alcohol consumption. However, later 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 (38217) and BIC (38267) compared to the corresponding linear spline model (AIC: 38231, BIC: 38281) and the model that included the continuous variable (AIC: 38254, BIC: 38287).

Using fixed-effects meta-analysis, light/moderate alcohol consumption was significantly associated with a decreased risk of CRC (OR: 0.92, 95% CI: 0.87-0.98, p<0.007) (Figure 2A) while very heavy alcohol consumption was significantly associated with an increased risk of CRC (OR: 1.26, 95% CI: 1.11-1.42, P<0.001) (Figure 2C), compared with non-/occasional drinkers. We observed a non-significant increased risk associated with heavy alcohol consumption (OR: 1.10, 95% CI: 0.97-1.23, p=0.13), compared with non-drinkers (Figure 2B). Similar effect estimates were observed in separate sub-analyses of case control and cohort studies (Table 2). There was no evidence of heterogeneity across studies at any of the levels of alcohol consumption.

Meta 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 genders, although effect was stronger in females (OR: 0.89, 95% CI: 0.82-0.96, p=0.002) than males (OR: 0.96, 95% CI: 0.88, 1.05, p=0.338) (Table 2). Very heavy alcohol consumption was only associated with increased risk of CRC among males (OR 1.33, 95% CI: 1.03-1.84, p<0.001), however there was no evidence of significant effect modification by sex (interaction p=0.379).

Associations with low levels of alcohol consumption differed slightly when stratified by BMI. In contrast to associations in the overall study population, light/moderate alcohol consumption (compared to non-/occasional consumption) was not associated with reduced risk among obese individuals (OR: 1.11, 95% CI: 0.96-1.28, p=0.166). However, despite the observed difference in stratified ORs among light/moderate drinkers, there was no evidence of significant overall effect modification by BMI (interaction p=0.746). Age, smoking (evaluated as ever vs never and pack-years), and family history of CRC were not found to significantly modify the alcohol-CRC association.

When analyses were stratified by cancer site, similar protective associations for light/moderate alcohol consumption were observed across proximal colon, distal colon, and rectal cancer sites (Table 3). Heavy alcohol consumption, however, was associated with risk of distal colon (OR: 1.22, 95% CI: 1.02-1.45, p<0.031) and rectal cancer (OR: 1.20, 95% CI: 0.99-1.46, p=0.065), but not with risk of proximal colon cancer (OR: 1.01, 95% CI: 0.85-1.19, p=0.941). Very heavy alcohol consumption was associated with increased risk across all cancer sites. A J-shaped association was also observed when analyses were stratified by cancer stage. Stronger associations were observed between very heavy alcohol and stage 1 and stage 4 cancers, but overall associations did not differ dramatically by cancer stage.

Discussion

In this large meta-analysis, we observed a J-shaped pattern of association between alcohol consumption and CRC risk. Light to 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 significantly greater risk than observed in non-drinkers. While this pattern of association varied slightly according to participant sex, BMI, and tumor site, there was no evidence of significant interaction by any of the covariates we evaluated.

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], [15], [16], [18]. While there are mixed findings regarding CRC risk at lower levels of alcohol consumption, we observed a significant protective association for participants who reported light/moderate alcohol consumption (up to 2 drinks/day) compared to non-drinkers, consistent with previous findings [15], [17]. Both linear and restricted spline models with nodes at varying cut-points demonstrated a J-shaped association, further supporting this finding. A 2014 meta-analysis of 9 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 [16].

The mechanisms by which alcohol consumption impacts CRC risk are still being explored [12], [13], [25]. 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 [13], [26], [27]. Chronic alcohol consumption has also been shown to disrupt folate metabolism, and folate deficiency is an established risk factor for CRC [8], [12], [14], [26], [28]. 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 [26]. A better understanding of these mechanisms is necessary to interpret observed protective effects of

light/moderate alcohol consumption and inform CRC prevention recommendations. 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 [25].

It has been suggested that the association between alcohol and colorectal cancer may differ by sex, in part due to differences in alcohol metabolism between men and women. Although we did not observe sex to significantly modify the risk of CRC, we did observe some differences in associations with alcohol by sex. 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 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], [17]. 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=283) in our analysis reported very heavy alcohol consumption, compared to over 10% (n=1,435) of men, which limited our power to 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 8 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 (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 very heavy alcohol consumption was associated with a higher risk of distal colon cancer and rectal cancer, compared to proximal colon cancer, however there was no evidence of significant interaction 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 (MSI-high) phenotype have been observed more frequently in proximal colon tumors compared to distal colon tumors [29], [30]. A case-unaffected sibling study observed that alcohol consumption was associated with increased risk of CRC tumors characterized by MSI-low phenotype but not MSI-high phenotype [31]. These findings suggest that pathways may vary by cancer anatomic site and that the role of alcohol may differ by pathway. Further evaluation of alcohol risk by site may provide additional insight regarding the biological mechanisms through which alcohol impacts CRC risk, and provide more precise estimates of risk for specific anatomic sites.

We are mindful of limitations in our study. Recall bias is a common challenge when collecting dietary information, particularly within studies that asked subjects to report alcohol consumption from several years ago. Some studies defined serving size in terms of ounces, while others defined in terms of bottles, glasses, or shots/drinks. Subjects may have different concepts of what constitutes a glass of wine, for example, and may not have an accurate sense of the size of their alcoholic drinks. Additionally, a few studies allowed subjects to specify an exact number of drinks in a given time period, but most asked subjects to select from a series of listed frequencies (2-3 per month, 1 per week, 4-6 per week, etc.). Some participants may not have been provided a frequency option that reflected their true alcohol consumption, and thus had to select the best available approximation. Additional precision of measurement was lost when converting frequency ranges to grams of alcohol consumed per day. These sources of

measurement error potentially contributed to misclassification of participants in terms of alcohol consumption.

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], [32]. 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. However, a pooled analysis of 4 cohort studies observed a similar J-shaped alcohol-CRC association when former drinkers were included and excluded from the non-drinker reference group [10].

While overall missingness of key covariates was low, there were a few variables that were not collected by certain studies or only collected for subset of the study population (Appendix 5). We evaluated the alcohol-CRC association separately within each study and excluded confounders with high levels of missingness (>25%) from that study's model. As a result, estimates from some studies may be subject to additional bias due to unmeasured confounding. While missing data resulted in slightly different models across studies, 8 of the 16 studies included all identified confounders in their models and the most confounders excluded from a model was three (Sweden-Wolk). Multiple imputation by chained equations was used to impute missing values which allowed for specification of different imputation models for each variable and is less prone to underestimated variance compared to single imputation methods. However, in order to evaluate smoking and BMI as effect modifiers, we had to use single imputation regression to ensure consistency across imputations for calculating stratified effect estimates. As a result, the variance in the distribution of smoking and BMI is underestimated in our study, which increased

the likelihood of type 1 error. However, given the low levels of missingness of smoking (pack-years: 4%, ever/never: 1%) and BMI (2%), the likely impact of the reduced variance is minimal. Finally, the study population was very racially homogenous with over 98% of participants reporting white race. Thus study findings may not be generalizable to more diverse populations or settings outside of North America and Europe.

This study also had several strengths, including a large sample size and availability of key environmental exposure and other risk factor variables across 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, multi-step 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 across studies, which indicates that our results represent evidence across all studies and were not dominated by one or a few studies.

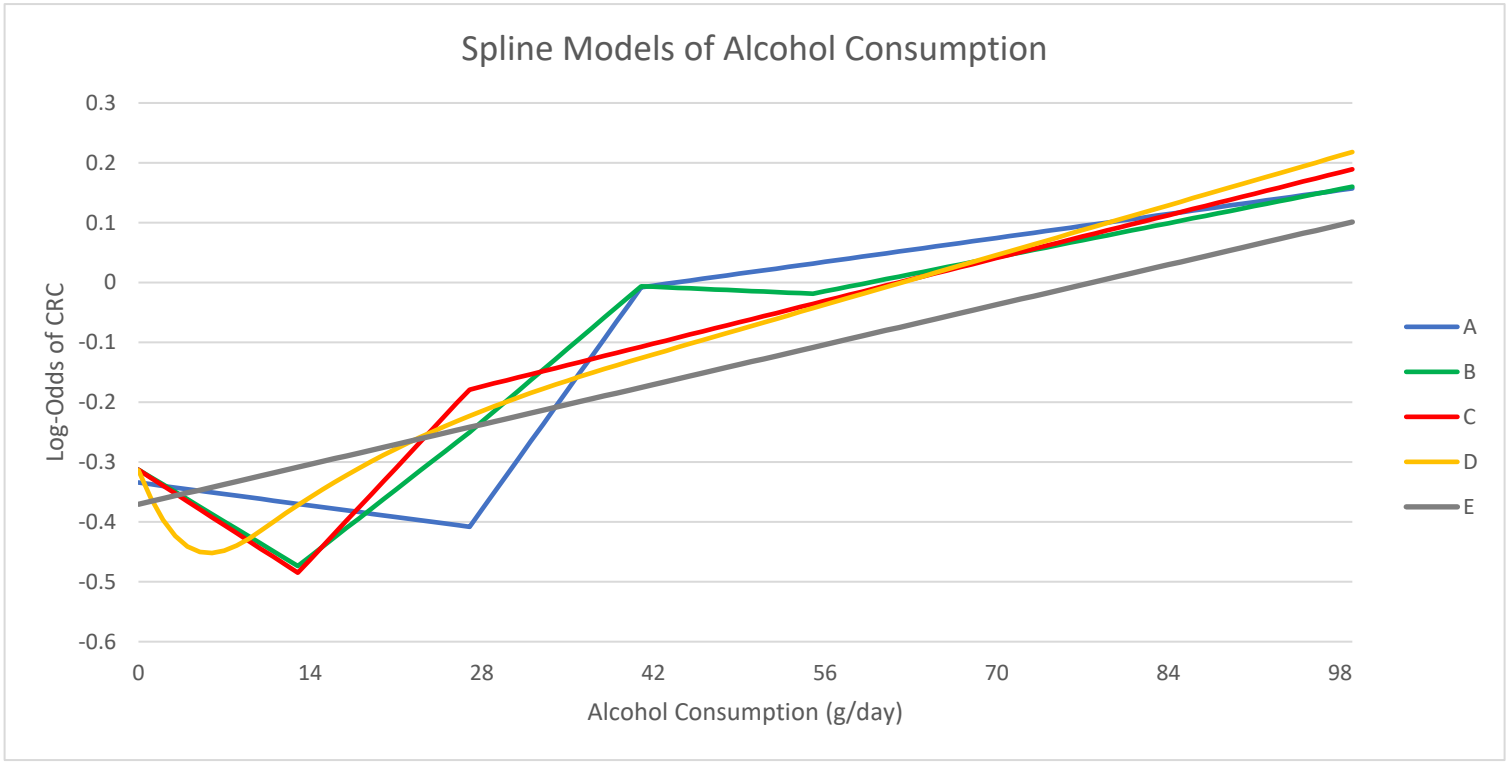
Finally, there are no standard definitions of light, moderate, or heavy alcohol intake that are used consistently in CRC literature. A strength of this study is that the cut-points we selected minimized AIC and BIC, reflect similar ranges to those reported in the literature, and are practically applicable 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 colorectal cancer 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. We observed a J-shaped association between alcohol and CRC, which may indicate that light/moderate drinkers have a reduced risk of CRC compared to non-/occasional drinkers. While the J-shaped association was observed across all cancer anatomic sites, we observed stronger associations between heavy alcohol consumption and distal colon and rectal cancers, compared to proximal colon cancers. These findings can inform future studies of the mechanisms through which alcohol impacts CRC risk.

Table 1: Characteristics of Study Population

								Alcohol consumption									
					Age (years)		Female	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)		Alcohol consumption (g/day) among drinkers	
Study	**Study Design**	**Cases**	**Controls**	**Total**	**Mean**	**SD**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**M**	**SD**
DALS	Case-control	1,453	1,475	2,928	63.7	9.9	43.9	1,524	52.1	1031	35.2	164	5.6	209	7.1	11.0	22.7
PLCO	Cohort	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
WHI	Cohort	1,427	1,527	2,954	66.4	6.6	100	1,636	55.4	1178	39.9	97	3.3	43	1.5	5.3	10.3
DACHS	Case-control	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
COLO2&3	Case-control	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
HPFS	Cohort	828	1,149	1,977	64.3	8.8	0	498	25.2	1187	60.0	163	8.2	129	6.5	12.5	15.8
MEC	Cohort	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
NHS	Cohort	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
VITAL	Cohort	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
CPS-II	Cohort	1,224	984	2,208	68.7	5.6	50.8	913	41.4	1105	50.1	109	4.9	81	3.7	7.9	13.0
SELECT	Cohort	308	308	616	65.3	6.7	0	221	35.9	304	49.4	38	6.2	53	8.6	13.1	22.6
MCCS	Cohort	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
Kentucky	Case-control	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
NFCCS	Case-control	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
ATBC	Cohort	221	141	362	57.6	4.7	0	52	14.4	228	63.0	40	11.1	42	11.6	18.3	20.2
Sweden-Wolk	Cohort	566	868	1,434	63.2	8.2	39.1	142	9.9	1189	82.9	65	4.5	38	2.7	11.1	13.0
Total		**13,248**	**14,430**	**27,678**	**64.4**	**9.0**	**50.5**	**11,328**	**40.9**	**13,079**	**47.3**	**1,573**	**5.7**	**1,698**	**6.1**	**10.6**	**18.5**

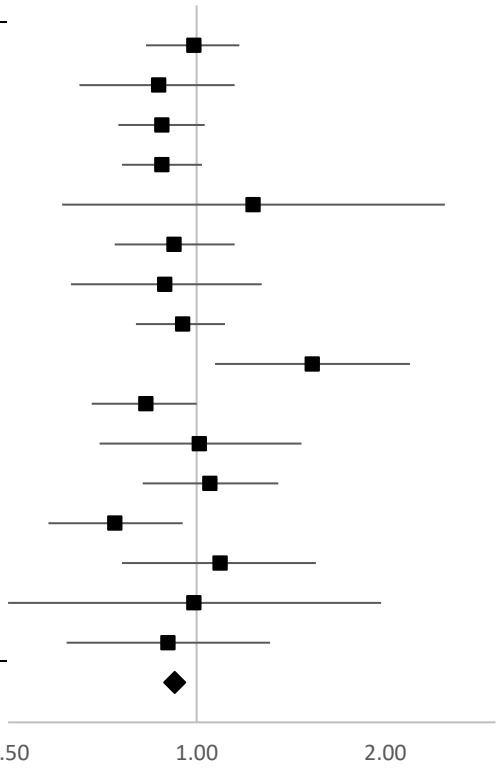
Figure 1: Spline Models of Alcohol Consumption



			Change in log-odds of CRC per 1 g/day increase in alcohol consumption						Spline model		Categorical model based on splines	
Model	**Type**	**Nodes**	**SP1**	**SP2**	**SP3**	**SP4**	**SP5**	**Intercept**	**AIC**	**BIC**	**AIC**	**BIC**
A	Linear spline	28, 42	-0.003	0.029	0.003			-0.332	38231	38281	38217	38267
B	Linear spline	14, 28, 42, 56	-0.012	0.016	0.017	-0.001	0.004	-0.300	38219	38285	38219	38285
C	Linear spline	14, 28	-0.013	0.022	0.005			-0.300	38219	38268	38223	38273
D	Cubic spline	0, 0.02, 3, 12.3, 46.8	-0.050	1.355	0.000	-1.797		-0.265	38214	38263	38236	38302
E	Linear	None	0.005					-0.375	38254	38287	n/a	n/a

Figure 2A. Light/moderate (1.1-28 g/day) vs Non/occasional Alcohol Consumption

Study	N	Cases	OR[1]	Weight	p-value
DALS[2]	2,928	1,475	0.99	130	0.902
PLCO	1,118	684	0.87	47	0.322
WHI[3]	2,954	1,527	0.88	151	0.112
DACHS[4]	5,204	2,325	0.88	183	0.096
COLO2&3[5]	223	129	1.23	8	0.560
HPFS[3]	1,977	1,149	0.92	80	0.465
MEC[5]	700	355	0.89	31	0.524
NHS[3]	2,792	1,685	0.95	142	0.506
VITAL	721	363	1.53	30	**0.019**
CPS-II	2,208	984	0.83	107	**0.049**
SELECT[6]	616	308	1.01	27	0.948
MCCS[7]	1,479	699	1.05	61	0.690
Kentucky	1,957	1,052	0.74	65	**0.016**
NFCCR[8]	1,005	686	1.09	31	0.639
ATBC[3]	362	141	0.99	8	0.978
Sweden-Wolk[9]	1,434	868	0.90	27	0.582
Meta	**27,677**	**14,430**	**0.92**		**0.007**
Q=16.67	Heterogeneity p=0.339				



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

Figure 2B. Heavy (28.1-42 g/day) vs Non/occasional Alcohol Consumption

Study	OR[1]	Weight	p-value
DALS[2]	1.11	32	0.544
PLCO	1.13	9	0.713
WHI[3]	0.87	21	0.528
DACHS[4]	1.00	58	0.991
COLO2&3[5]	1.08	2	0.907
HPFS[3]	0.92	27	0.646
MEC[5]	0.85	11	0.578
NHS[3]	1.52	23	**0.047**
VITAL	2.70	7	**0.008**
CPS-II	0.85	21	0.463
SELECT[6]	1.47	7	0.311
MCCS[7]	1.04	26	0.841
Kentucky	1.42	6	0.410
NFCCR[8]	1.86	9	0.066
ATBC[3]	1.03	4	0.944
Sweden-Wolk[9]	1.36	10	0.341
Meta	**1.10**		**0.134**
Q=16.67	Heterogeneity p=0.339		

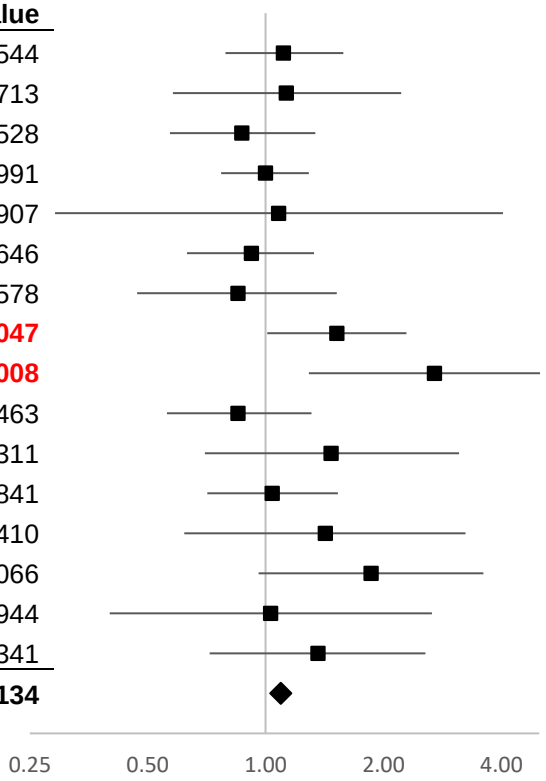


Figure 2C. Very heavy (>42 g/day) vs Non/occasional Alcohol Consumption

Study	OR[1]	Weight	p-value
DALS[2]	1.19	39	0.273
PLCO	1.57	19	**0.050**
WHI[3]	1.18	10	0.617
DACHS[4]	1.19	71	0.135
COLO2&3[5]	1.30	2	0.707
HPFS[3]	1.22	23	0.342
MEC[5]	1.02	14	0.945
NHS[3]	0.85	7	0.666
VITAL	2.10	6	0.062
CPS-II	1.11	15	0.679
SELECT[6]	0.97	9	0.930
MCCS[7]	1.69	22	**0.014**
Kentucky	0.85	10	0.608
NFCCR[8]	1.61	11	0.115
ATBC[3]	1.81	4	0.236
Sweden-Wolk[9]	1.74	6	0.162
Meta	**1.26**		**<0.001**
Q=10.751	Heterogeneity p=0.770		

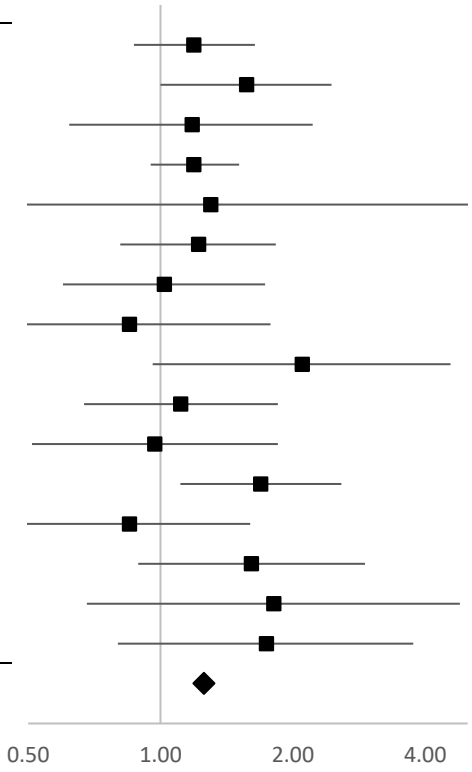


Table 2: Stratified Odds Ratios for Alcohol Consumption and CRC by Key Covariates

		Alcohol consumption											
		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				
Meta Analyses	**N**	**OR[1]**	**95% CI**		**p-value**	**OR[1]**	**95% CI**		**p-value**	**OR[1]**	**95% CI**		**p-value**	**Interaction p-value**
Overall	**27,678**	**0.92**	**0.87**	**0.98**	**0.007**	**1.10**	**0.97**	**1.23**	**0.134**	**1.26**	**1.11**	**1.42**	**<0.001**	
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	16,361	0.93	0.87	1.00	0.055	1.09	0.93	1.27	0.283	1.32	1.11	1.56	**0.001**	
Sex														0.379
Female	13,688	0.89	0.82	0.96	**0.002**	1.05	0.85	1.30	0.657	1.04	0.79	1.36	0.806	
Male	13,704	0.96	0.88	1.05	0.338	1.11	0.95	1.29	0.195	1.33	1.15	1.53	**<0.001**	
BMI														0.746
Normal or Underweight	10,289	0.88	0.80	0.97	**0.012**	1.06	0.87	1.30	0.573	1.17	0.94	1.47	0.164	
Overweight	11,692	0.87	0.79	0.95	**0.003**	1.05	0.88	1.26	0.585	1.26	1.05	1.50	**0.014**	
Obese	5,561	1.11	0.96	1.28	0.166	1.06	0.76	1.48	0.742	1.38	1.03	1.84	**0.032**	

[1] All estimates calculated by fixed effect meta-analysis

Table 3: Stratified Odds Ratios for Alcohol Consumption and CRC by Cancer Anatomic Site

		Alcohol consumption											
		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				
Meta Analyses	**N**	**OR[1]**	**95% CI**		**p-value**	**OR[1]**	**95% CI**		**p-value**	**OR[1]**	**95% CI**		**p-value**	**Interaction p-value[2]**
Overall	**27,678**	**0.92**	**0.87**	**0.98**	**0.007**	**1.10**	**0.97**	**1.23**	**0.134**	**1.26**	**1.11**	**1.42**	**<0.001**	
Cancer Site														0.142
Proximal	5,140	0.93	0.86	1.00	0.059	1.01	0.85	1.19	0.941	1.12	0.95	1.32	0.196	
Distal	3,700	0.92	0.84	1.01	0.078	1.22	1.02	1.45	**0.031**	1.41	1.19	1.68	**<0.001**	
Rectal	2,830	0.92	0.82	1.02	0.107	1.20	0.99	1.46	0.065	1.53	1.26	1.85	**<0.001**	

[1] All estimates calculated by fixed effect meta-analysis
[2] Interaction was evaluated from a case-only logistic regression comparing proximal colon cancers to distal colon and rectal cancers (combined).

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Appendix 1: Description of Study Populations Included in the Meta-analysis

Study	Study Abbreviation	Study Design	Cases	Controls	Total
Alpha-Tocopherol, Beta-Carotene Cancer Prevention	ATBC	Cohort	221	141	362
Cancer Prevention Study II	CPS-II	Cohort	1,224	984	2,208
Colorectal Cancer Studies 2 & 3	COLO2&3	Case-control	94	129	223
Diet, Activity and Lifestyle Study	DALS	Case-control	1,453	1,475	2,928
German Population-based Case-control Study of CRC	DACHS	Case-control	2,879	2,325	5,204
Health Professionals Follow-up Study	HPFS	Cohort	828	1,149	1,977
Kentucky	Kentucky	Case-control	905	1,052	1,957
Melbourne Collaborative Cohort Study	MCCS	Cohort	780	699	1,479
Multiethnic Cohort Study	MEC	Cohort	345	355	700
Newfoundland Familial Colorectal Cancer Registry	NFCCS	Case-control	319	686	1,005
Nurses' Health Study	NHS	Cohort	1,107	1,685	2,792
Prostate, Lung, Colorectal, & Ovarian Cancer Screening Trial	PLCO	Cohort	434	684	1,118
Selenium and Vitamin E Prevention Trial	SELECT	Cohort	308	308	616
Swedish Mammography Cohort and COSMs	Sweden-Wolk	Cohort	566	868	1,434
VITamin And Lifestyle Study	VITAL	Cohort	358	363	721
Women's Health Initiative	WHI	Cohort	1,427	1,527	2,954
Total			**13,248**	**14,430**	**27,678**

Appendix 2: Definitions of Alcohol Consumption by Study

Study	Questions	Data Harmonization
DALS	Did you ever drink an average of one or more alcoholic beverages a month for a year or longer? 1) YES 3) NO 8) DK 10 years ago, did you drink an average of one or more alcoholic beverages a month? 1) YES 3) NO 8) DK 10 years ago, how many 12-ounce cans or bottles of beer did you usually drink per week or month? (value) 0) None ____NUMBER 98)DK 10 years ago, how many 12-ounce cans or bottles of beer did you usually drink per week or month? (unit) 1) WEEK 3) MONTH 8) DK 10 years ago, how many 4-ounce glasses of wine did you usually drink per week or month? (value) 0) None ____NUMBER 98)DK 10 years ago, how many 4-ounce glasses of wine did you usually drink per week or month? (unit) 1) WEEK 3) MONTH 8) DK 10 years ago, how many 1 1/2-ounce shots of hard liquor did you usually drink per week or month? (value) 0) None ____NUMBER 98)DK 10 years ago, how many 1 1/2-ounce shots of hard liquor did you usually drink per week or month? (unit) 1) WEEK 3) MONTH 8) DK [During referent year] Did you drink beer? [During referent year] Did you drink wine? [During referent year] Did you drink liqueurs, mixed drinks, cocktails or liquor?	Used study-derived dietary alcohol (g/day)
PLCO	Over the past 12 months, did you drink beer? No, Yes How often did you drink beer in the Summer? Never, 1 time per month or less, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 times per day, 2-3 times per day, 4-5 times per day, 6 or more times per day How often did you drink beer during the rest of the year? Never, 1 time per month or less, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 times per day, 2-3 times per day, 4-5 times per day, 6 or more times per day Each time you drank beer, how much did you usually drink? Less than a 12-ounce can or bottle, 1 to 3 12-ounce cans or bottles, More than 3 12-ounce cans or bottles Over the past 12 months, how often did you drink wine or wine coolers? Never, 1 time per month or less, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 times per day, 2-3 times per day, 4-5 times per day, 6 or more times per day Each time you drank wine or wine coolers, how much did you usually drink? Less than 5 ounces or less than one glass, 5 to 12 ounces or 1 to 2 glasses, More than 12 ounces or more than 2 glasses Over the past 12 months, how often did you drink liquor or mixed drinks? Never, 1 time per month or less, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 times per day, 2-3 times per day, 4-5 times per day, 6 or more times per day Each time you drank liquor or mixed drinks, how much did you usually drink? Less than 1 shot of liquor, 1 to 3 shots of liquor, More than 3 shots of liquor (in past year) How often: beer Never or less than once per month, 1-2 times per month, 1 time per week, 2-4 times per week, 5-6 times per week, 1 time per day, 4-6 times per day, 6+ times per day How much : beer smaller, 12-oz can or bottle, larger (in past year) How often: wine or wine coolers Never or less than once per month, 1-2 times per month, 1 time per week, 2-4 times per week, 5-6 times per week, 1 time per day, 4-6 times per day, 6+ times per day How much : wine or wine cooler smaller, 1 medium glass, larger (in past year) How often: Liquor, such as whiskey, vodka, gin, or rum Never or less than once per month, 1-2 times per month, 1 time per week, 2-4 times per week, 5-6 times per week, 1 time per day, 4-6 times per day, 6+ times per day (in past year) How much : Liquor, such as whiskey, vodka, gin , or rum smaller, 1 shot, larger	Used study-derived alcohol from diet (g/day)

WHI	During your entire life, have you had at least 12 drinks of any kind of alcoholic beverage? No, Yes Do you still drink alcohol? No, Yes How often: Beer Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day How much: Beer S, M, L (medium=12 ounces or 1 can) How often: Wine Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day How much: Wine S, M, L (medium=1 medium glass 6 oz)) How often: Liquor Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day How much: Liquor S, M, L (medium=1 shot (1 1/2 oz))	Convert from study-derived servings/week to grams/day. Assume 1 serving=14 g. (svg/week)*(14g/svg)*(week/7days)*2 = g/day
DACHS	Kontrollteilnehmer v.2 Page 34; 75 Bitte sagen Sie mir, an wie vielen Tagen pro Woche Sie in den letzten 12 Monaten üblicherweise Alkohol getrunken haben? (On how many days in the last week did you drink alcohol?) 0 1 2 3 4 5 6 7 Kontrollteilnehmer v.2 Page 34; 76 Wie viel Alkohol haben Sie in verschiedenen Lebensaltern im Durchschnitt pro Woche getrunken? (How much did you drink of each type of alcohol?) in den letzten 12 Monaten |__|__| Flaschen/Woche Bier (Flaschen zu 0,33 l) |__|__| Gläser/Woche Wein (Gläser zu ¼ l) |__|__| Gläschen/Woche Schnaps (Gläschen zu 2 cl)	Used study-derived average daily ethanol consumption in the last 12 months in grams
COLO2&3	Regular and draft beer (asks for serving size and frequency) Light beer (asks for serving size and frequency) Red wine (asks for serving size and frequency) White wine (asks for serving size and frequency) Hard liquor, such as Scotch, Bourbon, gin and cocktails (asks for serving size and frequency)	Used study-derived alcohol (g/day) Includes dietary alcohol
HPFS	Beverages Average use, during the past year: Beer (1 glass bottle, 1 can) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day Beverages Average use, during the past year: Red wine (4 oz glass) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day Beverages Average use, during the past year: White wine (4 oz glass) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day Beverages Average use, during the past year: Liquor e.g. whiskey, gin, etc. (1 drink or shot) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 4-6 per day, 6+ per day	Used study-derived alcohol (g/day)
MEC	Average use during last year: Regular or Draft Beer Never or hardly ever, once a month, 2-3 times a month, Once a week, 4 to 6 times a week, Once a day, 2-3 times a day, 4 or more times a day Your usual serving size: Beer 1 can or bottle or less, 2 cans or bottles, 3 cans or bottles, 4 cans or bottles or more Average use during last year: Light Beer Never or hardly ever, once a month, 2-3 times a month, Once a week, 4 to 6 times a week, Once a day, 2-3 times a day, 4 or more times a day Your usual serving size: Light Beer 1 can or bottle or less, 2 cans or bottles, 3 cans or bottles, 4 cans or bottles or more Average use during last year: White or Pink wine (includes champagne and sake) Never or hardly ever, once a month, 2-3 times a month, Once a week, 4 to 6 times a week, Once a day, 2-3 times a day, 4 or more times a day Your usual serving size: White or Pink Wine 1 glass or less, 2 glasses, 3 glasses, 4 glasses or more Average use during last year: Red wine Never or hardly ever, once a month, 2-3 times a month, Once a week, 4 to 6 times a week, Once a day, 2-3 times a day, 4 or more times a day Your usual serving size: Red wine 1 glass or less, 2 glasses, 3 glasses, 4 glasses or more Average use during last year: Hard liquor (such as bourbon, scotch, gin, vodka, tequila, rum, cocktails Never or hardly ever, once a month, 2-3 times a month, Once a week, 4 to 6 times a week, Once a day, 2-3 times a day, 4 or more times a day Your usual serving size: Hard Liquor 1 drink or less, 2 drinks, 3 drinks, 4 drinks or more	Used study-derived alcohol (g/day)

NHS	Beverages For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year. Beer (1 glass, bottle, can) Never, or less than once per month, 1-3 per mo, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day 9 Beverages For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year. Red wine (4 oz glass) Never, or less than once per month, 1-3 per mo, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day Beverages For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year. White wine (4 oz glass) Never, or less than once per month, 1-3 per mo, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day Beverages For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year. Liquor, e.g. whiskey, gin, etc. (1 drink or shot) Never, or less than once per month, 1-3 per mo, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day	Used study-derived alcohol (g/day)
VITAL	How often did you drink these beverages in the last year? Beer (all types) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day How often did you drink these beverages in the last year? Beer (all types) Serving size: Medium=12-ounce can or bottle S, M, L How often did you drink these beverages in the last year? Red wine Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day How often did you drink these beverages in the last year? Red wine Serving size: Medium=4 oz S, M, L How often did you drink these beverages in the last year? White or rose wine (all types) Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day How often did you drink these beverages in the last year? White or rose wine Serving size: Medium=4 oz S, M, L How often did you drink these beverages in the last year? Liquor and mixed drinks Never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day How often did you drink these beverages in the last year? Liquor and mixed drinks wine Serving size: Medium=1 shot (1 1/2 oz) or 1 mixed drink S, M, L	Used study-derived alcohol (g/day)
CPS-II	On average, how frequency did you drink any alcoholic beverage (beer, win, or liquor) in the last year? Never or less than 1 day per month, 1-3 days per month, 1 day per week, 2-3 days per week, 4-5 days per week, 6-7 days per week On days that you drink, how many drinks of alcohol (beer, wine, or liquor) do you have on average? I don't drink alcohol, 1 drink, 2 drinks, 3 drinks, 4 drinks, 5 drinks, 6 or more drinks Please fill in your average total use, during the past year, of each specified food? Beer, regular (1 glass, bottle, can) never, less than once per month, 1-3 cans per month, 1 can per week, 2-4 cans per week, 5-6 cans per week, 1 can per day, 2-3 cans per day, 4-5 cans per day, 6+ cans per day Please fill in your average total use, during the past year, of each specified food? Light beer, e.g., Bud Light, (1 glass, bottle, can) never, less than once per month, 1-3 cans per month, 1 can per week, 2-4 cans per week, 5-6 cans per week, 1 can per day, 2-3 cans per day, 4-5 cans per day, 6+ cans per day Please fill in your average total use, during the past year, of each specified food? Red wine (4 oz. glass) never, less than once per month, 1-3 glasses per month, 1 glass per week, 2-4 glasses per week, 5-6 glasses per week, 1 glass per day, 2-3 glasses per day, 4-5 glasses per day, 6+ glasses per day Please fill in your average total use, during the past year, of each specified food? White wine (4 oz. glass) never, less than once per month, 1-3 glasses per month, 1 glass per week, 2-4 glasses per week, 5-6 glasses per week, 1 glass per day, 2-3 glasses per day, 4-5 glasses per day, 6+ glasses per day Please fill in your average total use, during the past year, of each specified food? Liquor, e.g., vodka, gin, etc. (1 drink or shot) never, less than once per month, 1-3 drinks per month, 1 drink per week, 2-4 drinks per week, 5-6 drinks per week, 1 drink per day, 2-3 drinks per day, 4-5 drinks per day, 6+ drinks per day	Used study-derived alcohol (g/day). Does not include dietary alcohol
SELECT	Not currently available	Used study-derived alcohol (g/day)

MCCS	In the past 12 months, how often did you drink any kind of alcoholic drink? This includes beer, wine, spirits, port, sherry or any drink containing alcohol. 1 day per month or less often, 2 to 3 days per month, 1 day per week, 2 days per week, 3-4 days per week, 5-6 days per week, 7 days per week, never In the last 12 months, how often did you drink beer? 1 day per month or less often, 2 to 3 days per month, 1 day per week, 2 days per week, 3-4 days per week, 5-6 days per week, 7 days per week, never On the days when you drank beer during the last 12 months, how much did you usually drink in a single day? (asks for amount and unit) In the last 12 months, how much of the beer you drank was light beer? Light beer is sometimes called low alcohol beer. All or almost all, more than half, about half, less than half, none or almost none In the last 12 months, how often did you drink wine? 1 day per month or less often, 2 to 3 days per month, 1 day per week, 2 days per week, 3-4 days per week, 5-6 days per week, 7 days per week, never On the days when you drank wine during the last 12 months, how much did you usually drink in a single day? (asks for amount and unit) In the last 12 months, how much of the wine you drank was red wine? All or almost all, more than half, about half, less than half, none or almost none In the last 12 months, how often did you drink spirits? Spirits include whisky, gin, vodka, brandy, grappa, rum, on their own or as mixed drinks. 1 day per month or less often, 2 to 3 days per month, 1 day per week, 2 days per week, 3-4 days per week, 5-6 days per week, 7 days per week, never On the days when you drank spirits during the last 12 months, how much did you usually drink in a single day? (asks for amount and unit) What size was the bottle?	Used study-derived alcohol (g/day)
Kentucky	Average use - light beer: serving size (S/M/L), average use (6+ times a day, 3-5 times a day, twice a day, once a day, 5-6 times a week, 2-4 times a week, once a week, 1-3 times a month, rarely/never) Average use - beer: serving size (S/M/L), average use (6+ times a day, 3-5 times a day, twice a day, once a day, 5-6 times a week, 2-4 times a week, once a week, 1-3 times a month, rarely/never) Average use - wine serving size (S/M/L), average use (6+ times a day, 3-5 times a day, twice a day, once a day, 5-6 times a week, 2-4 times a week, once a week, 1-3 times a month, rarely/never) Average use - liquor: serving size (S/M/L), average use (6+ times a day, 3-5 times a day, twice a day, once a day, 5-6 times a week, 2-4 times a week, once a week, 1-3 times a month, rarely/never)	Used study-derived alcohol (g/day)
NFCCR	Not currently available	Used study-derived alcohol (g/day)
ATBC	Light beer (asked frequency and portion size) Medium beer (asked frequency and portion size) Strong beer (asked frequency and portion size) Gin and grapefruit drink (asked frequency and portion size) Spirits and other distilled liquors (vodka, rum, bitters, brandy, whisky) (asked frequency and portion size) Liqueurs (asked frequency and portion size)	Used study-derived alcohol (g/day)

Sweden-Wolk	How often do you drink alcohol? I have never had alcohol, I stoppped drinking alcohol at the age of ___ I usually drink beer (2.8% alc): never, 0-1 times per mot, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3+ times per day I usually drink beer (4.5% alc): never, 0-1 times per mot, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3+ times per day I usually drink wine: never, 0-1 times per mot, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3+ times per day I usually drink wine (>18% alc): never, 0-1 times per mot, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3+ times per day I usually drink spirits (40% alc): never, 0-1 times per mot, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3+ times per day Beer: how much do you drink on each occasion (Cl)? (1 can of beer =33/50 cl) Wine: how much do you drink on each occasion (Cl)? (bottle of win/spirits=75 cl, 1 dl==10) Spirits: how much do you drink on each occasion (Cl)? (bottle of win/spirits=75 cl, 1 dl==10)	Used study-derived alcohol (g/day)

Appendix 3: Characteristics of Controls by Level of Alcohol Consumption

	Alcohol consumption											
	Non/ occasional (≤1 g/day)		Light/ moderate (1.1-28 g/day)		Heavy (28.1-42 g/day)		Very heavy (>42 g/day)			Alcohol consumption (g/day)		
	N	%	N	%	N	%	N	%	P-value[1]	M	SD	P-value[2]
Overall	**5,843**	**40.5**	**7,107**	**49.3**	**751**	**5.2**	**729**	**5.1**		**9.8**	**16.9**	
Sex									<0.001			<0.001
Female	3,797	51.1	3,313	44.6	206	2.8	121	1.6		5.5	10.2	
Male	2,046	29.3	3,794	54.3	545	7.8	608	8.7		14.5	20.9	
Race									0.017			0.1258
Am. Indian or Alaska Native	2	100	0	0.0	0	0.0	0	0.0		0.01	0.01	
Asian	12	57.1	9	42.9	0	0.0	0	0.0		3.8	5.9	
Black or African-American	32	64.0	15	30.0	2	4.0	1	2.0		5.2	13.4	
Other	22	29.7	47	63.5	3	4.1	2	2.7		9.8	14.3	
White	5,757	40.4	7,018	49.3	745	5.2	723	5.1		9.9	16.9	
Education									<0.001			0.1769
Less than high school grad	901	40.8	1,115	50.5	87	3.9	104	4.7		9.7	18.2	
High school grad or GED	1,296	44.2	1,306	44.6	147	5.0	181	6.2		10.2	17.8	
Some college or tech. school	1,405	44.7	1,438	45.7	158	5.0	146	4.6		9.3	17.4	
College grad/grad school	2,221	36.4	3,229	52.9	358	5.9	296	4.9		10.0	15.6	
Aspirin Use									0.012			0.001
Yes	1,756	41.9	1,943	46.3	249	5.9	245	5.8		10.5	18.0	
No	3,780	42.7	4,203	47.4	433	4.9	443	5.0		9.5	16.8	
NSAID Use									<0.001			<0.0001
Yes	1,058	47.4	984	44.1	98	4.4	94	4.2		8.2	15.3	
No	4,498	41.3	5,204	47.8	588	5.4	591	5.4		10.1	17.5	
Aspirin or NSAID Use									0.171			0.1025
Yes	2,336	42.7	2,528	46.2	305	5.6	302	5.5		10.0	17.4	
No	3,290	42.3	3,704	47.7	388	5.0	392	5.0		9.6	17.0	
Postmenopausal Hormone Therapy[3]									<0.001			0.0103
Yes	1,466	48.7	1,395	46.3	97	3.2	55	1.8		5.7	10.4	
No	2,068	54.5	1,585	41.7	91	2.4	54	1.4		5.1	10.0	
Smoking Status									<0.001			<0.0001
Never Smoker	3,215	49.2	2,970	45.4	180	2.8	173	2.7		6.6	13.0	
Ever Smoker	2,536	33.1	4,019	52.5	563	7.4	544	7.1		12.6	12.2	
Pack Years (Quartiles)[4]									<0.001			<0.0001
Non-smokers	3,215	49.2	2,970	45.4	180	2.8	173	2.7		6.6	13.0	
1	609	31.8	1,097	57.2	115	6.0	96	5.0		11.0	17.0	
2	564	30.6	1,009	54.8	134	7.3	136	7.4		13.0	18.7	
3	596	32.5	946	51.6	152	8.3	139	7.6		13.2	19.0	
4	616	35.1	827	47.1	145	8.3	167	9.5		14.3	22.7	

	Non/ occasional (≤1 g/day)		Light/ moderate (1.1-28 g/day)		Heavy (28.1-42 g/day)		Very heavy (>42 g/day)			Alcohol consumption (g/day)		
	N	%	N	%	N	%	N	%	P-value[1]	M	SD	P-value[2]
Family History of CRC									0.15			0.0119
Yes	746	43.0	827	47.6	87	5.0	77	4.4		10.0	16.9	
No	4,909	40.4	5,968	49.1	645	5.3	637	5.2		9.0	16.5	
CRC Screening									0.036			0.0015
Yes	2,386	42.9	2,657	47.8	275	5.0	239	4.3		9.0	8.6	
No	2,884	42.4	3,190	46.9	363	5.3	364	5.4		9.8	17.4	
History of Diabetes									<0.001			0.0001
Yes	549	51.1	439	40.8	47	4.4	40	3.7		10.0	9.7	
No	4,479	38.1	6,075	51.6	618	5.3	593	5.0		8.0	7.0	
Sedentary									<0.001			<0.0001
Yes	918	47.6	799	41.4	99	5.1	114	5.9		9.9	19.3	
No	2,054	36.2	2,861	50.4	366	6.5	392	6.9		11.9	18.6	
BMI									<0.001			<0.0001
Normal or Underweight	2,111	36.8	3,081	53.8	289	5.0	250	4.4		9.7	15.7	
Overweight	2,252	38.3	2,957	50.2	343	5.8	336	5.7		10.6	17.3	
Obese	1,384	53.9	946	36.8	104	4.1	135	5.3		8.4	18.7	
Total Folate Intake (Quartiles)[4]									0.006			0.1019
1	1,372	45.3	1,379	45.6	136	4.5	140	4.6		8.8	17.1	
2	1,319	43.6	1,436	47.5	154	5.1	114	3.8		8.7	16.0	
3	1,280	42.5	1,478	49.1	128	4.3	124	4.1		8.6	16.0	
4	1,243	40.8	1,489	48.9	168	5.5	144	4.7		9.6	16.2	
Total Calcium Intake (Quartiles)[4]									0.001			0.0126
1	1,501	41.6	1,702	47.1	199	5.5	209	5.8		10.2	17.5	
2	1,466	40.6	1,777	49.2	181	5.0	190	5.3		10.0	17.2	
3	1,384	38.2	1,852	51.2	204	5.6	180	5.0		10.1	16.3	
4	1,490	41.7	1,768	49.5	164	4.6	149	4.2		9.0	16.6	
Fiber Intake (Quartiles)[4]									<0.001			<0.0001
1	1,261	43.9	1,300	45.2	156	5.4	159	5.5		9.8	17.8	
2	1,196	41.6	1,400	48.8	152	5.3	124	4.3		9.3	16.7	
3	1,214	42.7	1,378	48.5	132	4.6	120	4.2		8.8	16.3	
4	1,322	46.2	1,339	46.8	106	3.7	94	3.3		7.6	14.9	
Fruit Intake (Quartiles)[4]									<0.001			<0.0001
1	1,388	44.3	1,389	44.3	172	5.5	186	5.9		10.2	19.0	
2	1,765	35.7	2,574	52.1	284	5.8	315	6.4		11.3	17.5	
3	1,346	39.2	1,781	51.9	178	5.2	130	3.8		9.1	15.0	
4	1,293	45.7	1,334	47.1	113	4.0	92	3.3		7.6	14.4	

	Non/ occasional (≤1 g/day)		Light/ moderate (1.1-28 g/day)		Heavy (28.1-42 g/day)		Very heavy (>42 g/day)			Alcohol consumption (g/day)		
	N	%	N	%	N	%	N	%	P-value[1]	M	SD	P-value[2]
Vegetable Intake (Quartiles)[4]									<0.001			<0.0001
1	1,522	48.4	1,362	43.3	137	4.4	124	3.9		7.8	16.1	
2	1,747	36.2	2,506	51.9	265	5.5	313	6.5		11.4	18.1	
3	1,395	39.8	1,733	49.5	203	5.8	173	4.9		9.8	15.3	
4	1,147	39.6	1,492	51.5	143	4.9	118	4.1		9.5	17.2	
Processed Meat Intake (Quartiles)[4]									<0.001			<0.0001
1	1,368	44.8	1,404	46.0	136	4.5	144	4.7		9.1	16.1	
2	1,893	37.3	2,679	52.8	284	5.6	220	4.3		9.7	16.0	
3	1,177	39.5	1,508	50.7	143	4.8	149	5.0		9.6	16.8	
4	1,027	40.0	1,201	46.8	155	6.0	183	7.1		11.5	18.9	
Red Meat Intake (Quartiles)[4]									<0.001			<0.0001
1	1,651	44.0	1,786	47.6	147	3.9	166	4.4		8.5	15.4	
2	1,492	37.8	2,050	51.9	225	5.7	182	4.6		10.2	16.7	
3	1,318	37.6	1,797	51.2	199	5.7	195	5.6		10.4	16.7	
4	1,346	42.6	1,452	46.0	178	5.6	184	5.8		10.3	18.7	
	M	SD	M	SD	M	SD	M	SD	P-value[2]	Mean	SD	P-value[5]
Age (years)	64.6	8.8	64.1	9.0	64.3	8.9	64.1	9.0	0.018	64.4	9.0	0.334
BMI	27.2	5.1	26.0	3.9	26.1	3.8	26.7	3.9	<0.0001	26.9	4.6	<0.001

[1] P-value from chi-square test
[2] P-value from one-sided t-test or one-way ANOVA
[3] Percents calculated only among post-menopausal women
[4] Quartiles are study- and sex-specific
[5] P-value from linear regression

Appendix 4: Characteristics of Non-drinkers by CRC Status

	Overall		CRC Case		Control		
	N	%	N	%	N	%	P-value[1]
Sex							0.551
Female	7,332	64.7	3,535	64.5	3,797	65.0	
Male	3,996	35.3	1,950	35.6	2,046	35.0	
Race							0.923
American Indian or Alaska Native	3	0.0	1	0.0	2	0.0	
Asian	25	0.2	13	0.2	12	0.2	
Black or African-American	66	0.6	34	0.6	32	0.6	
Other	46	0.4	24	0.4	22	0.4	
White	11,159	98.8	5,402	98.7	5,757	98.8	
Education							<0.001
Less than high school graduate	1,926	17.1	1,025	18.7	901	15.5	
High school graduate or GED	2,702	23.9	1,406	25.7	1,296	22.3	
Some college or technical school	2,716	24.1	1,311	24.0	1,405	24.1	
College graduate/graduate school	3,948	35.0	1,727	31.6	2,221	38.1	
Aspirin Use							<0.001
Yes	3,137	29.3	1,381	26.6	1,756	31.7	
No	7,587	70.8	3,807	73.4	3,780	68.3	
NSAID Use							<0.001
Yes	1,859	17.3	801	15.4	1,058	19.0	
No	8,911	82.7	4,413	84.6	4,498	81.0	
Aspirin or NSAID Use							<0.001
Yes	4,174	38.3	1,838	34.8	2,336	41.5	
No	6,730	61.7	3,440	65.2	3,290	58.5	
Postmenopausal Hormone Therapy[2]							<0.001
Yes	2,517	24.6	1,051	21.2	1,466	27.9	
No	7,704	75.4	3,906	78.8	3,798	72.2	
Smoking Status							<0.001
Never Smoker	5,995	53.8	2,780	51.5	3,215	55.9	
Ever Smoker	5,157	46.2	2,621	48.5	2,536	44.1	
Pack Years (Quartiles)[3]							<0.001
Non-smokers	5,995	55.2	2,780	52.9	3,215	57.4	
1	1,122	10.3	513	9.8	609	10.9	
2	1,135	10.5	571	10.9	564	10.1	
3	1,197	11.0	601	11.4	596	10.6	
4	1,409	13.0	793	15.1	616	11.0	
Family History of CRC							<0.001
Yes	1,618	14.8	872	16.5	746	13.2	
No	9,327	85.2	4,418	83.5	4,909	86.8	

	Overall		CRC Case		Control		
	N	%	N	%	N	%	P-value[1]
CRC Screening							0.018
Yes	4,506	44.2	2,120	43.0	2,386	45.3	
No	5,700	55.9	2,816	57.1	2,884	54.7	
History of Diabetes							<0.001
Yes	1,217	12.6	668	14.4	549	10.9	
No	8,463	87.4	3,984	85.6	4,479	89.1	
Sedentary							0.336
Yes	1,868	30.3	950	29.8	918	30.9	
No	4,296	69.7	2,242	70.2	2,054	69.1	
BMI							<0.001
Normal or Underweight	3,853	34.6	1,742	32.3	2,111	36.7	
Overweight	4,358	39.1	2,106	39.1	2,252	39.2	
Obese	2,926	26.3	1,542	28.6	1,384	24.1	
Total Folate Intake Quartiles)[3]							0.004
1	2,727	27.8	1,355	29.4	1,372	26.3	
2	2,403	24.5	1,084	23.5	1,319	25.3	
3	2,414	24.6	1,134	24.6	1,280	24.6	
4	2,283	23.2	1,040	22.5	1,243	23.8	
Total Calcium Intake (Quartiles)[3]							<0.001
1	3,099	27.4	1,598	29.2	1,501	25.7	
2	2,891	25.5	1,425	26.0	1,466	25.1	
3	2,629	23.2	1,245	22.7	1,384	23.7	
4	2,703	23.9	1,213	22.1	1,490	25.5	
Fiber Intake (Quartiles)[3]							0.100
1	2,491	26.1	1,230	27.1	1,261	25.3	
2	2,308	24.2	1,112	24.5	1,196	24.0	
3	2,256	23.7	1,042	23.0	1,214	24.3	
4	2,476	26.0	1,154	25.4	1,322	26.5	
Fruit Intake (Quartiles)[3]							<0.001
1	2,639	23.5	1,251	22.9	1,388	24.0	
2	3,660	32.5	1,895	34.7	1,765	30.5	
3	2,594	23.1	1,248	22.9	1,346	23.2	
4	2,354	20.9	1,061	19.5	1,293	22.3	
Vegetable Intake (Quartiles)[3]							<0.001
1	2,920	25.9	1,398	25.6	1,522	26.2	
2	3,609	32.0	1,862	34.1	1,747	30.1	
3	2,595	23.0	1,200	22.0	1,395	24.0	
4	2,147	19.1	1,000	18.3	1,147	19.7	

	Overall		CRC Case		Control		
	M	**SD**	**M**	**SD**	**M**	**SD**	**P-value[4]**
Processed Meat Intake (Quartiles)[3]							<0.001
1	2,636	24.4	1,268	23.7	1,368	25.0	
2	3,558	32.9	1,665	31.2	1,893	34.6	
3	2,442	22.6	1,265	23.7	1,177	21.5	
4	2,170	20.1	1,143	21.4	1,027	18.8	
Red Meat Intake (Quartiles)[3]							<0.001
1	3,004	26.7	1,353	24.8	1,651	28.4	
2	2,865	25.4	1,373	25.1	1,492	25.7	
3	2,727	24.2	1,409	25.8	1,318	22.7	
4	2,672	23.7	1,326	24.3	1,346	23.2	
	M	**SD**	**M**	**SD**	**M**	**SD**	**P-value[4]**
Age (years)	64.8	9.0	65.0	9.2	64.6	8.8	0.004
BMI	27.6	5.3	27.9	5.5	27.2	5.1	<0.001

[1] P-value from chi-square test
[2] Percents calculated only among post-menopausal women
[3] Quartiles are study- and sex-specific
[4] P-value from one-sided t-test

Appendix 5: Missingness of Key Covariates by Study

		Percent Missing																
Study	**N**	**Age**	**Sex**	**Education**	**Smoking Status**	**Pack Years**	**Aspirin**	**NSAIDs**	**HRT**	**Endoscopy**	**Diabetes**	**BMI**	**Folate**	**Calcium**	**Fruit**	**Vegetables**	**Processed Meat**	**Red Meat**
DALS	2,928	0	0	<1	<1	<1	<1	<1	<1	11	100	<1	0	0	0	0	0	0
PLCO	1,118	0	0	<1	0	1	<1	<1	2	1	<1	1	0	0	0	0	0	0
WHI	2,954	0	0	<1	1	4	0	0	0	5	<1	<1	0	0	0	0	0	0
DACHS	5,204	0	0	<1	<1	<1	2	2	2	<1	<1	2	100	<1	<1	<1	<1	<1
COLO2&3	223	0	0	<1	0	0	<1	<1	2	100	<1	13	0	0	0	0	0	0
HPFS	1,977	<1	0	0	4	7	0	0	0	2	0	3	0	0	0	0	<1	0
MEC	700	0	0	<1	<1	2	2	4	3	100	0	<1	0	0	0	0	0	0
NHS	2,792	0	0	0	<1	2	0	0	0	<1	0	2	0	0	<1	<1	<1	0
VITAL	721	<1	0	<1	<1	2	19	3	3	1	0	4	0	0	7	7	7	7
CPS-II	2,208	0	0	<1	<1	1	9	4	1	8	9	<1	0	0	0	0	0	0
SELECT	616	0	0	1	<1	<1	0	<1	0	100	0	<1	0	0	<1	<1	0	<1
MCCS	1,479	0	0	0	0	<1	40	44	<1	6	0	0	<1	<1	<1	<1	<1	<1
Kentucky	1,957	0	0	<1	12	20	1	3	<1	<1	<1	0	0	0	1	<1	2	1
NFCCS	1,005	0	0	<1	<1	8	<1	2	2	0	<1	2	0	0	7	2	100	1
ATBC	362	0	0	0	0	0	2	2	0	2	0	0	0	0	0	0	0	0
Sweden-Wolk	1,434	0	0	<1	1	4	100	100	<1	100	0	4	0	0	<1	<1	1	<1
Total	**27,678**	**<1**	**0**	**<1**	**1**	**4**	**9**	**9**	**<1**	**14**	**12**	**2**	**19**	**<1**	**<1**	**<1**	**4**	**<1**

Appendix 6: The Association between Alcohol Consumption and CRC

			Alcohol Consumption														
			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				
Study	**N**	**Cases**	**OR[1]**	**95% CI**		**Weight**	**p-value**	**OR[1]**	**95% CI**		**Weight**	**p-value**	**OR[1]**	**95% CI**		**Weight**	**p-value**
DALS[2]	2,928	1,475	0.99	0.83	1.17	130	0.902	1.11	0.79	1.58	32	0.544	1.19	0.87	1.64	39	0.273
PLCO	1,118	684	0.87	0.65	1.15	47	0.322	1.13	0.58	2.22	9	0.713	1.57	1.00	2.45	19	**0.050**
WHI[3]	2,954	1,527	0.88	0.75	1.03	151	0.112	0.87	0.57	1.34	21	0.528	1.18	0.62	2.22	10	0.617
DACHS[4]	5,204	2,325	0.88	0.76	1.02	183	0.096	1.00	0.77	1.29	58	0.991	1.19	0.95	1.51	71	0.135
COLO2&3[5]	223	129	1.23	0.61	2.49	8	0.560	1.08	0.29	4.04	2	0.907	1.30	0.33	5.06	2	0.707
HPFS[3]	1,977	1,149	0.92	0.74	1.15	80	0.465	0.92	0.63	1.33	27	0.646	1.22	0.81	1.83	23	0.342
MEC[5]	700	355	0.89	0.63	1.27	31	0.524	0.85	0.47	1.52	11	0.578	1.02	0.60	1.73	14	0.945
NHS[3]	2,792	1,685	0.95	0.80	1.11	142	0.506	1.52	1.01	2.29	23	**0.047**	0.85	0.41	1.78	7	0.666
VITAL	721	363	1.53	1.07	2.19	30	**0.019**	2.70	1.29	5.63	7	**0.008**	2.10	0.96	4.57	6	0.062
CPS-II	2,208	984	0.83	0.68	1.00	107	**0.049**	0.85	0.56	1.31	21	0.463	1.11	0.67	1.85	15	0.679
SELECT[6]	616	308	1.01	0.70	1.47	27	0.948	1.47	0.70	3.12	7	0.311	0.97	0.51	1.85	9	0.930
MCCS[7]	1,479	699	1.05	0.82	1.35	61	0.690	1.04	0.71	1.53	26	0.841	1.69	1.11	2.58	22	**0.014**
Kentucky	1,957	1,052	0.74	0.58	0.95	65	**0.016**	1.42	0.62	3.24	6	0.410	0.85	0.45	1.60	10	0.608
NFCCR[8]	1,005	686	1.09	0.76	1.55	31	0.639	1.86	0.96	3.60	9	0.066	1.61	0.89	2.92	11	0.115
ATBC[3]	362	141	0.99	0.50	1.97	8	0.978	1.03	0.40	2.66	4	0.944	1.81	0.68	4.80	4	0.236
Sweden-Wolk[9]	1,434	868	0.90	0.62	1.31	27	0.582	1.36	0.72	2.56	10	0.341	1.74	0.80	3.76	6	0.162
Meta	**27,678**	**14,430**	**0.92**	**0.87**	**0.98**		**0.007**	**1.10**	**0.97**	**1.23**		**0.13**	**1.26**	**1.11**	**1.42**		**<0.001**

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