Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association between Alcohol Consumption and Survival in Colorectal Cancer: A Meta-analysis

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Abstract

Background: Although an association between alcohol consumption and risk of colorectal cancer is well established, little is known about the association between alcohol consumption and colorectal cancer survival. We conducted a meta-analysis of prospective cohort studies to quantitatively assess this association.

Methods: Data searches were performed using PubMed and ISI Web of Science databases through December 2018. We estimated pooled RRs with 95% confidence intervals (CI) using random-effects models.

Results: Twelve studies with 32,846 patients with colorectal cancer were included in the meta-analysis. Compared with no alcohol consumption, light (RR = 0.87; 95% CI, 0.81–0.94) and moderate (RR = 0.92; 95% CI, 0.85–1.00) prediagnostic alcohol consumption were associated with lower risk of all-cause mortality. Light prediagnostic alcohol consumption was associated with lower risk of colorectal cancer–specific mortality (RR = 0.87; 95% CI, 0.78–0.98). However, heavy prediagnostic alcohol consumption was not significantly associated with colorectal cancer survival. In a dose–response analysis, a nonlinear association between prediagnostic alcohol consumption and all-cause mortality was observed ($P_{\text{nonlinearity}} = 0.0025$), showing the reduction in RR at <30 g/day of alcohol consumption. By type of alcohol, wine consumption was associated with lower risk of mortality from all-causes and colorectal cancer, but a positive association was observed between moderate liquor consumption and all-cause mortality. There was no association between postdiagnostic alcohol consumption and colorectal cancer survival.

Conclusions: Light and moderate prediagnostic alcohol consumption were associated with better survival in colorectal cancer.

Impact: Our findings suggest that light and moderate alcohol consumption may be associated with better survival in colorectal cancer, but further studies are warranted.

Introduction

According to the report of the WHO, colorectal cancer is the third most common cause of cancer-related deaths worldwide, accounting for 862,000 deaths in 2018 (1). Despite early detection and advances in therapeutic methods, the 5-year survival rate for colorectal cancer still remains below 70%, even in developed countries (2, 3). Given the global burden of death from colorectal cancer, it is necessary to identify lifestyle factors associated with prognosis and survival in colorectal cancer. Accumulating evidence from previous studies suggested that smoking may have detrimental effects on survival after colorectal cancer (4) whereas physical activity may have beneficial effects on colorectal cancer survival (5).

Previous researches on alcohol consumption and colorectal cancer have mostly focused on the incidence of colorectal cancer, and reported that higher alcohol consumption was positively associated with increased risk of colorectal cancer (6–8). However, the association between alcohol consumption and survival in colorectal cancer remains unclear. Although there were several prospective cohort studies which investigated the association between alcohol intake and mortality among patients with colorectal cancer (9–22), the results were not consistent, and diversity in categorization of alcohol consumption made it difficult to determine the relationship between alcohol intake and mortality. To date, alcohol consumption guidelines for colorectal cancer survival are not well-established.

To assess quantitatively the association between pre- and postdiagnostic alcohol consumption and colorectal cancer survival, we performed a systematic review and meta-analysis of prospective cohort studies at various levels of alcohol consumption. In addition, we assessed a potential nonlinear association between alcohol consumption and survival in colorectal cancer through dose–response meta-analysis.

Materials and Methods

Literature search and selection

The electronic databases PubMed and ISI Web of Science were searched for inclusion of eligible studies published as full-length articles and written in English through December 2018. The following key words were used: "(alcohol or ethanol or alcoholic or wine or beer or liquor) and (colorectal or colon or rectal) and (survival or recurrence or prognosis)." All relevant studies from

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the lists of references of retrieved articles were manually searched and reviewed to include additional eligible studies. The studies included in this meta-analysis met the following criteria: (i) the study had a prospective design; (ii) the exposure was alcohol consumption; (iii) the outcomes were all-cause mortality or colorectal cancer–specific mortality; (iv) the study reported RR of mortality and its 95% confidence intervals (CI); and (v) the subjects were patients with colorectal cancer. If 2 different articles provided the results from same cohort (12, 23), we selected the article that included a large number of participants (12).

Data extraction

Two authors (Y.K. and Y.J.) independently extracted data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (24). When there were any disagreements in data extraction, we addressed this through checking the original publications and discussion. From each study, the following data were extracted: the last name of first author, study name, publication year, country name or geographical region, study period or follow-up time, baseline age, number of patients and deaths, stage of cancer, categories of alcohol consumption, RRs and 95% CIs for association between each alcohol consumption category and mortality, and adjustment factors. If the study reported several RRs, we used the RRs which were maximally adjusted for confounding factors.

Quality assessment

The Newcastle-Ottawa quality assessment scale (25) was used to evaluate the quality of the studies included in meta-analysis. Two authors (Y.K. and Y.J.) independently assessed the quality of each study for the following subscales: representativeness of the exposed cohort; the methods of alcohol consumption measurement; adjustment for important confounders [age, body mass index (BMI), stage, etc.]; assessment of outcome; follow-up time; and adequacy of follow-up of cohorts. Any discrepancies between the investigators were resolved through discussion and consensus. We considered a study with a score of 10 or higher (out of 13) as a high-quality study. The studies with scores of 7 to 9 and a score of 6 or less were considered as a good and low quality, respectively.

Statistical analysis

The pooled RRs of mortality for alcohol consumption were estimated through combining the natural logarithm of the RR from each study. The DerSimonian and Laird random-effects models, which incorporate both within-study and between-study variations were used to calculate the pooled RRs (26). We performed stratified meta-analyses by the level of alcohol consumption, taking into account the variances of the highest category of alcohol consumption among studies. To unify the unit of alcohol consumption, we defined one drink as 12.5 g of ethanol, as in previous studies (27). Alcohol consumption category was classified into light ($\leq$12.5 g/day of ethanol), moderate (>12.5–<37.5 g/day of ethanol), and heavy ($\geq$37.5 g/day of ethanol). Each category of alcohol consumption was assigned according to its calculated median. The reference category was defined as nondrinkers. Then the pooled RRs and 95% CIs for light, moderate, and heavy alcohol consumption were calculated, compared with no drink. We also conducted meta-analyses for type of alcohol (wine/beer/liquor) consumption and mortality from all-causes and colorectal cancer. Heterogeneity between studies included in meta-analysis was evaluated using the Q statistic (28) and I^2 statistics (29). Sensitivity analyses were performed by removing each study at a time, and estimated the pooled RR for the rest of the studies to investigate its influence on the pooled RR.

Dose–response analysis was conducted for studies that provided the information on the distributions of deaths, participants, or person-years in each alcohol consumption category (10, 12, 14–16, 19–21). A dose–response curve was created using restricted cubic splines with 3 knots at fixed percentiles (25%, 50%, and 75%) of the exposure distribution (30–32). The P value for nonlinearity was calculated by testing against the null hypothesis that the coefficient of the second spline is equal to 0 (32). Publication bias was assessed through Begg (33) and Egger (34) statistical test. A 2-sided $P < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using STATA/SE version 14.2 software (Stata Corp.).

Results

Study characteristics

Detailed information about selection process for studies used in meta-analysis is presented in Figure 1. A total of 12 prospective cohort studies with 32,846 patients were included for mortality from all-causes and colorectal cancer among patients with colorectal cancer (9–17, 19–21). The characteristics of prospective cohort studies included in meta-analysis are shown in Table 1. Among 12 studies, 7 studies reported RRs for mortality from all-causes and colorectal cancer (10, 12, 14–16, 20, 21), 4 studies reported RRs for all-cause mortality only (9, 13, 17, 19), and 1 study provided RR for colorectal cancer–specific mortality only (11). Nine studies provided RRs on prediagnostic alcohol consumption (10, 11, 13–17, 19, 20), 2 studies provided RRs on postdiagnostic alcohol consumption (9, 12), and 1 study provided RRs on pre- and postdiagnostic alcohol consumption (21). Eight studies reported data on total alcohol consumption (9–14, 19, 21), 1 study reported data on type of alcohol consumption (wine, beer, and liquor; ref. 16), and 3 studies reported data on both total alcohol and type of alcohol consumption (15, 17, 20). All the studies provided RRs, which adjusted for age, and most studies adjusted for BMI (9–14, 16, 17, 21), smoking (10–12, 14, 16, 17, 20, 21), or tumor stage (9–12, 14, 20, 21). As a result of quality assessment, 9 studies got a score of 10 or more, indicating high quality (10, 12–17, 20, 21) and 3 studies got scores of 8 or 9, indicating good quality (9, 11, 19).

Prediagnostic alcohol consumption and mortality

Nine studies including 28,544 patients with colorectal cancer examined the association between prediagnostic alcohol consumption and overall survival (10, 13–17, 19–21). The pooled RRs of all-cause mortality with light, moderate, and heavy prediagnostic alcohol consumption categories compared with no alcohol consumption category are presented in Fig. 2. Compared with no alcohol consumption, light (RR = 0.87; 95% CI, 0.81–0.94) and moderate prediagnostic alcohol consumption (RR = 0.92; 95% CI, 0.85–1.00) were inversely associated lower risk of all-cause mortality, and there was no significant heterogeneity among studies ($P = 0.40$, $I^2 = 3.8\%$ for light prediagnostic alcohol consumption; $P = 0.66$, $I^2 = 0.0\%$ for moderate prediagnostic alcohol consumption). However, there was no significant association between heavy prediagnostic alcohol consumption and

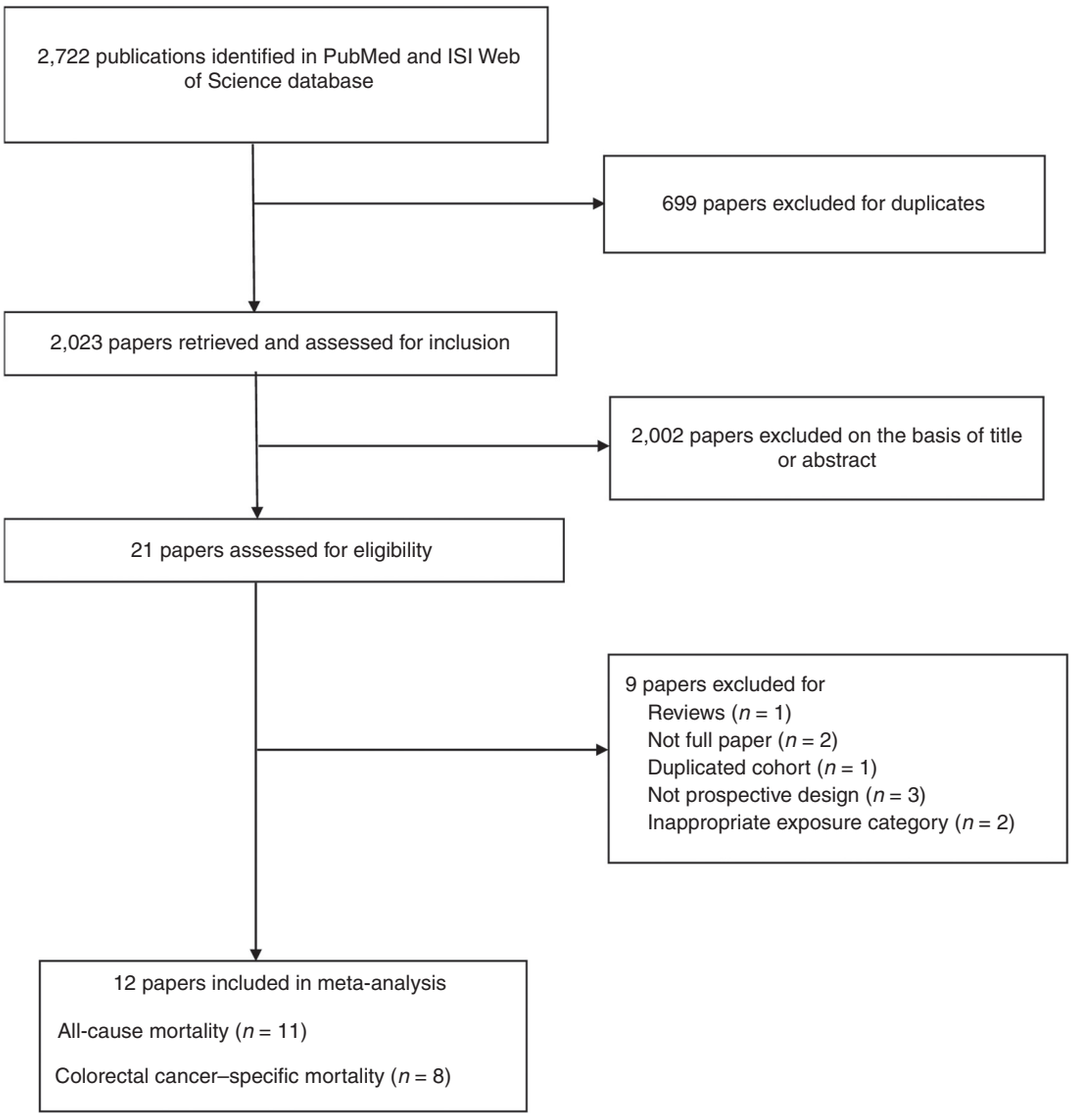

Figure 1.
Flow chart of study selection. The flow chart shows a process used to select prospective cohort studies for meta-analysis of the association between alcohol consumption and survival in colorectal cancer.

all-cause mortality (RR = 0.95; 95% CI, 0.77–1.18), compared with no alcohol consumption.

Six studies including 18,814 patients with colorectal cancer examined the association between prediagnostic alcohol consumption and colorectal cancer–specific survival (10, 14–16, 20, 21). The pooled RRs of colorectal cancer–specific mortality with light, moderate, and heavy prediagnostic alcohol consumption categories compared with no alcohol consumption category are presented in Fig. 3. Light prediagnostic alcohol consumption was inversely associated with lower colorectal cancer–specific mortality (RR = 0.87; 95% CI, 0.78–0.98), compared with no alcohol consumption, and there was no significant heterogeneity among studies ($P = 0.26$; $I^2 = 22.7\%$). However, we found no significant association between moderate (RR = 0.95; 95% CI, 0.82–1.11) and heavy prediagnostic alcohol consumption (RR = 0.89; 95% CI, 0.62–1.27), compared with no alcohol consumption.

The pooled RRs of mortality with light and moderate prediagnostic alcohol consumption categories compared with no alcohol consumption category by type of alcohol are presented in Table 2. Regarding all-cause mortality, light (RR = 0.85; 95% CI, 0.75–0.96) and moderate (RR = 0.79; 95% CI, 0.63–0.99) wine consumption was inversely associated with reduced risk of all-cause death, compared with no wine consumption. Moderate liquor consumption was positively associated with increased risk of all-cause death, compared with no liquor consumption (RR = 1.15; 95% CI, 1.00–1.32). Light wine consumption was inversely associated with reduced colorectal cancer–specific mortality, compared with no wine consumption (RR = 0.82; 95% CI, 0.69–0.97). Consumption of beer or liquor was not significantly

Table 1. Characteristics of the prospective studies included in the present meta-analysis

First author, year	Country	Cohort name	Follow-up period	Age at baseline	Exposure category	Stage	Study size: Patients	Study size: Number of death	Adjustment for covariates
Park, 2006 (13)	Korea	National Health Insurance Corporation Study	3.78 years	≥20 years	Prediagnostic 0 (ref) 0–124.1 g/week 124.2 g/week	All	1,882	538 all	Age, alcohol consumption, BMI, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease)
Phipps, 2011 (15)	USA	Surveillance, Epidemiology and End Results program	1998–2010	18–74 years	Prediagnostic None (ref) 1–6 drinks/week ≥7 drinks/week	I–IV	1,818	644 all 444 crc	Age at diagnosis, time from diagnosis to interview, history of preventive CRC screening, sex, and education
Pelser, 2014 (14)	USA	NIH-AARP Diet and Health study	5 years	50–71 years	Prediagnostic Nondrinker (ref) Moderate drinking: <2 drinks/day (M) <1 drink/day (F) Heavier drinking: >2 drinks/day (M) >1 drink/day (F)	I–IV	5,727 (cc, 4,213; rc, 1,514)	cc: 1,273 all, 856 cc rc: 454 all, 301 rc	Age, lag time, sex, education, family history of colon cancer, cancer stage, first course of treatment (surgery, radiation, chemotherapy), HEI-2005 scores, BMI, physical activity, smoking
Walter, 2016 (20)	Germany	DACHS study (Darmkrebs: Chancen der Verhütung durch Screening)	4.8 years	30–96 years	Prediagnostic Abstainers Light drinkers: 0–24 g/d (M) 0–12 g/d (F) (ref) Moderate drinkers: 24–50 g/d (M) 12–25 g/d (F) Heavy drinkers: 50 g/d (M) 25 g/d (F)	I–IV	3,121	868 all 635 crc	Age, sex, stage, smoking status, use of statins, use of nonsteroidal anti-inflammatory drugs, use of b-blockers, diabetes mellitus, history of heart failure, myocardial infarction, angina pectoris, or stroke, history of Ca age 3 log(time) and Ca 3 log(time) to account for time-dependent effects
Phipps, 2016 (17)	USA	Phase III trial N0147	6.5 years	19–86 years	Prediagnostic Never Ever Former Current	III	1,984	NA	Age at diagnosis, ECOG performance score, sex, frequency of vigorous physical activity, BMI, smoking history at enrolment, race and treatment assignment
Phipps, 2017 (16)	Australia, Canada, USA	Colon Cancer Family Registry	1997–2013	51 years	Prediagnostic <1 serving/week (ref) ≥1 serving/week ≤1 serving/day >1 serving/day	All	4,966	2,216 all 1,344 crc	Age at diagnosis, year of diagnosis, sex, smoking history, BMI, education, study site
Tamakoshi, 2017 (19)	Japan	BioBank Japan	7.4 years	≥25 years	Prediagnostic Never-drinker (ref) Ex-drinker 0–15 g/d 15–30 g/d >30 g/d	All	5,864	540 all	Age, sex, institutions, entry year

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Table 1. Characteristics of the prospective studies included in the present meta-analysis (Cont'd)

First author, year	Country	Cohort name	Follow-up period	Age at baseline	Exposure category	Stage	Study size		Adjustment for covariates
							Patients	Number of death	
Yang, 2017 (21)	USA	The Cancer Prevention Study II Nutrition Cohort	1992–2012 (8.3 years)	64.2 y	Pre- and postdiagnostic Never (ref) Former <2 2 to <3 ≥3 drinks/day	All	2,458	Pre: 1,156 all, 449 crc Post: 732 all, 235 crc	Age at diagnosis, sex, tumor stage at diagnosis, smoking status, BMI, physical activity, education, preexisting diseases in 1982/1992 (chronic obstructive pulmonary disease, liver disease, or kidney disease)
Kwak, 2017 (11)	Korea	The Busan Regional Cancer Registry	2011–2014	63.3 years	Prediagnostic No (ref) Yes	All	1,533	475 crc	Age, sex, BMI, area-level deprivation index, tumor stage, smoking, diagnosis path
Jayasekara, 2018 (10)	Australia	Melbourne Collaborative Cohort Study	9 years	44–87 y	Prediagnostic Lifetime abstention (ref) Former drinkers >0–19 20–39 40 g/d	I–III	724	339 all 170 crc	Age at diagnosis, year of diagnosis, sex, country of birth, American Joint Committee on Cancer stage, degree of differentiation, smoking, physical activity, BMI, waist circumference
Asghari-Jafarabadi, 2009 (9)	Iran	Research Center of Gestroenterology and Liver Disease	2.2 years	53.6 years	Postdiagnostic Never used (ref) Past or current	I–IV	1,219	NA	Age at diagnosis, sex, race, marital status, education, BMI, smoking, alcohol history, personal and familial history (familial adenomatous polyposis, hereditary nonpolyposis colon cancer, inflammatory bowel disease), mucin production, tumor grade, tumor size, pathologic stage, the kind of first treatment
Lochhead, 2015 (12)	USA	Nurses' Health Study and Health Professionals Follow-Up Study	14.9 years	53–77 y	Postdiagnostic No alcohol (ref) 0.1–14.9 ≥15 g/d	I–III	1,550	641 all 176 crc	Age at diagnosis, year of diagnosis, BMI, prediagnostic alcohol consumption, family history of colorectal cancer in any first-degree relative, postdiagnostic aspirin use, postdiagnostic multivitamin use, postdiagnostic smoking status, postdiagnostic physical activity, postdiagnostic folate, vitamin B-12, methionine, and vitamin B-6 intakes, tumor location, tumor differentiation, the time from diagnosis to questionnaire return, stage, sex

Abbreviations: cc, colon cancer; crc, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; rc, rectal cancer; NA, not available; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

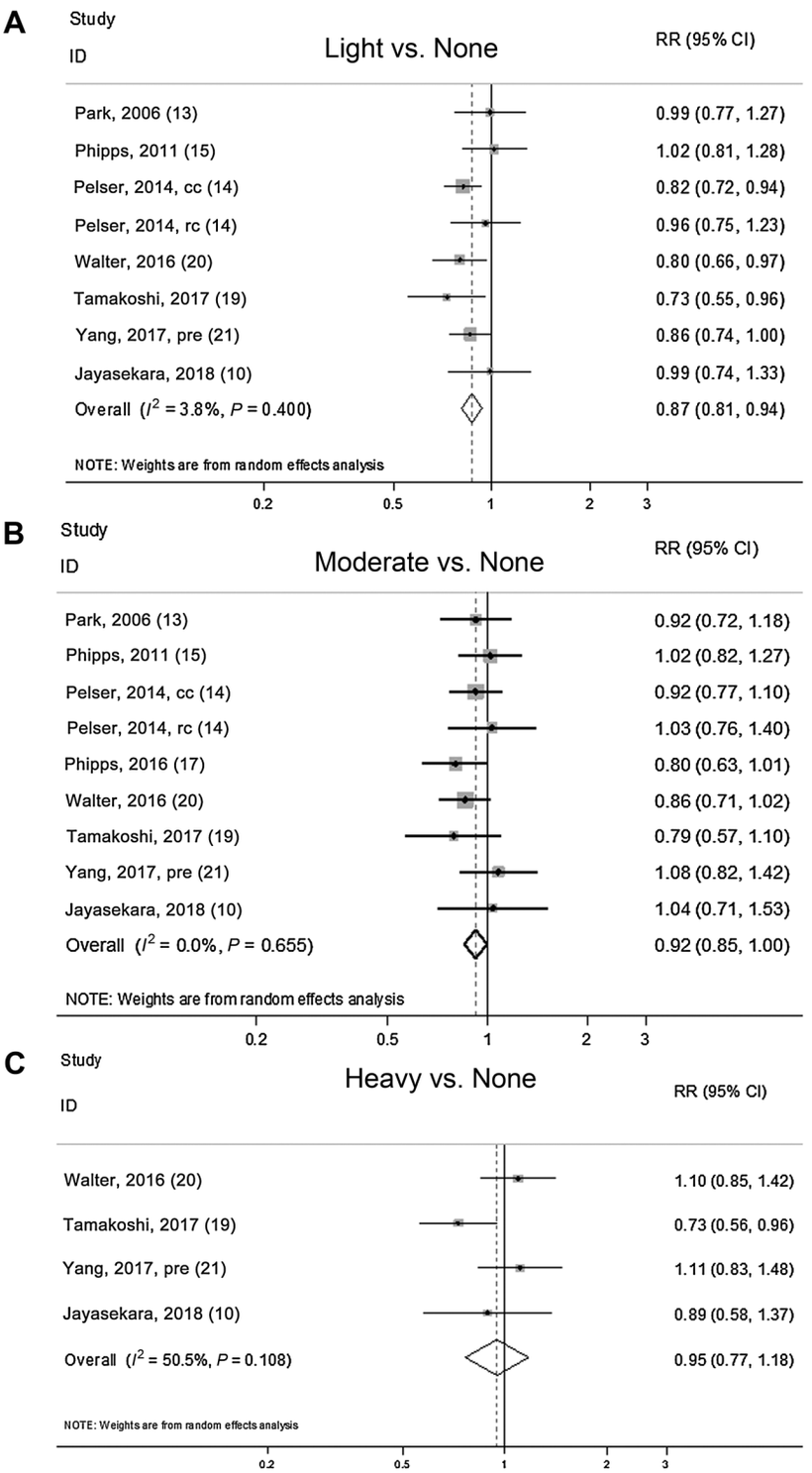

Figure 2.
Forest plot of the prospective cohort studies of all-cause mortality for prediagnostic alcohol consumption. RRs for light (**A**), moderate (**B**), and heavy (**C**) prediagnostic alcohol consumption and all-cause mortality compared with no alcohol consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from each prospective cohort study, and the diamond indicates the pooled RR.

associated with colorectal cancer–specific mortality, compared with no drink.

Dose–response analysis

Six studies including 19,712 patients with colorectal cancer were included in dose–response meta-analysis of prediagnostic alcohol consumption and mortality (10, 14, 15, 19–21). As presented in Fig. 4, an evidence of nonlinear association between pre-diagnostic alcohol consumption and all-cause mortality was found ($P_{\text{nonlinearity}}$ = 0.0025). Prediagnostic alcohol consumption of <30 g/day was associated with a lower risk of all-cause mortality, compared with no alcohol

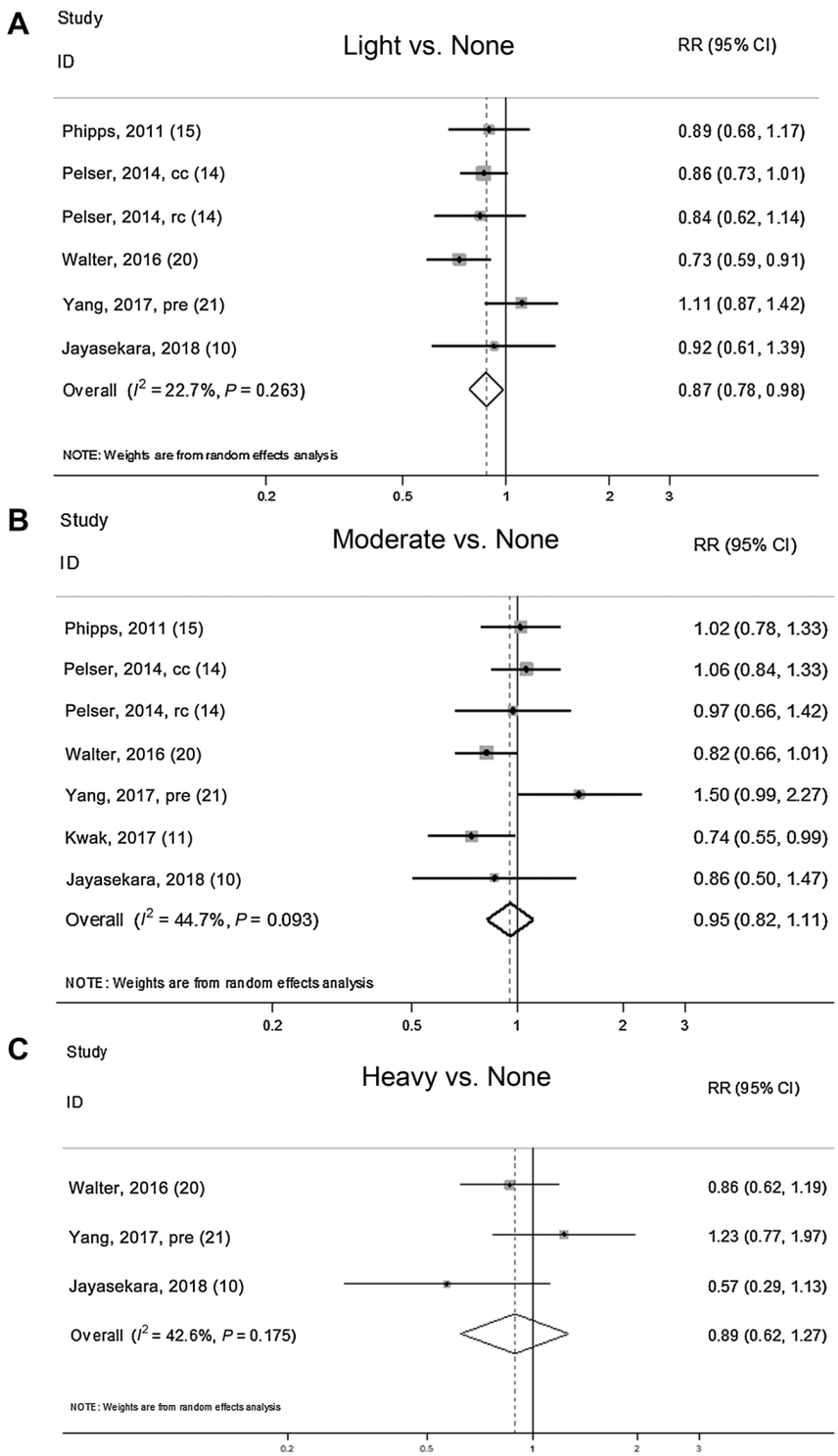

Figure 3.
Forest plot of the prospective cohort studies of colorectal cancer–specific mortality for prediagnostic alcohol consumption. RRs for light (**A**), moderate (**B**), and heavy (**C**) prediagnostic alcohol consumption and colorectal cancer–specific mortality compared with no alcohol consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from each prospective cohort study, and the diamond indicates the pooled RR.

consumption. No significant association between prediagnostic alcohol consumption and colorectal cancer–specific mortality was found for nonlinearity ($P = 0.12$) or linearity ($P = 0.81$; Supplementary Table S1). By type of alcohol, the pooled RR of all-cause mortality for 10 g/day increment of wine consumption was 0.92 (95% CI, 0.85–0.99). Consumption of beer or liquor did not show any significant associations in dose–response analyses.

Postdiagnostic alcohol consumption and mortality

Three studies including 4,368 patients with colorectal cancer reported the association between postdiagnostic alcohol

Table 2. Summary of pooled RR for all-cause and colorectal cancer mortality according to different type of alcohol consumption

	Light vs. none			Moderate vs. none		
Type	**No. of studies**	**RR (95% CI)**	***P* for difference**	**No. of studies**	**RR (95% CI)**	***P* for difference**
All-cause mortality						
Wine	4	0.85 (0.75–0.96)		4	0.79 (0.63–0.99)	
Beer	4	0.94 (0.80–1.10)	0.28[a]	4	1.03 (0.91–1.18)	0.05[a]
Liquor	4	0.95 (0.86–1.06)	0.23[b]	4	1.15 (1.00–1.32)	0.02[b]
Colorectal cancer–specific mortality						
Wine	3	0.82 (0.69–0.97)		3	0.86 (0.70–1.06)	
Beer	3	1.03 (0.90–1.18)	0.05[a]	3	1.14 (0.98–1.32)	0.05[a]
Liquor	3	0.90 (0.80–1.01)	0.34[b]	3	1.15 (0.94–1.41)	0.08[b]

[a]*P* value difference in RR for studies of beer versus wine.
[b]*P* value difference in RR for studies of liquor versus wine.

consumption and mortality (9, 12, 21). The pooled RRs of mortality from all-causes and colorectal cancer with light and moderate postdiagnostic alcohol consumption categories compared with no alcohol consumption category was shown in Supplementary Table S2. Nonsignificant inverse associations between light and moderate postdiagnostic alcohol consumption and mortality from all-causes and colorectal cancer were found.

Publication bias

We found no evidence of publication bias for the meta-analysis of all-cause mortality (Begg $P > 0.5$; Egger $P > 0.2$ in all analyses) and colorectal cancer–specific mortality (Begg $P > 0.7$; Egger $P > 0.6$ in all analyses).

Discussion

The current meta-analysis of 12 prospective cohort studies including 32,846 patients with colorectal cancer indicated that light and moderate prediagnostic alcohol consumption were inversely associated with lower risk of all-cause mortality compared with no alcohol consumption by 13% and 8%, respectively. There was no statistically significant association between heavy prediagnostic alcohol consumption and risk of all-cause mortality. Regarding colorectal cancer-specific mortality, moderate and heavy prediagnostic alcohol consumption were not significantly associated with risk of colorectal cancer–specific mortality compared with no alcohol consumption, but light prediagnostic alcohol consumption was inversely associated with 13% lower risk of colorectal cancer–specific mortality, compared with no alcohol consumption. We found no significant association between postdiagnostic alcohol consumption and risk of mortality from all-causes and colorectal cancer.

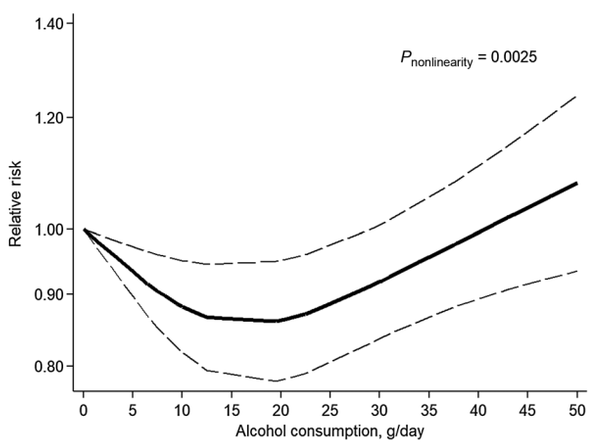

Figure 4.
Dose–response relation between prediagnostic alcohol consumption and RRs of all-cause mortality. Data were modeled with random-effects restricted cubic spline models with 3 knots. The vertical axis is on a log scale.

Previous meta-analyses which investigated the association between alcohol consumption and risk of colorectal cancer reported that moderate and heavy alcohol consumption (>1 drink/day) were associated with increased incidence of colorectal cancer (6) and a 7% higher risk of colorectal cancer per 10 g/day of alcohol intake was observed (8). However, we found an increased overall survival in patients with colorectal cancer with light and moderate prediagnostic alcohol consumption compared with nondrinking patients, and a nonlinear association between alcohol consumption and all-cause mortality was observed among patients with colorectal cancer in dose–response meta-analysis, showing better survival in <30 g/day of alcohol consumption compared with no alcohol consumption. A beneficial association of light and moderate alcohol consumption on other health outcomes was also reported from previous studies. A recent dose–response meta-analysis from 26 prospective studies indicated that low to moderate (<30 g/day) alcohol consumption was associated with lower risk of type 2 diabetes (35), and the other meta-analysis of 14 intervention studies found that moderate alcohol consumption was associated with decreased fasting insulin and HbA1c levels among nondiabetic women (36). The summary results from 45 prospective studies also suggested that low-volume drinkers (<25 g/day) had reduced coronary heart disease mortality than abstainers (37). However, it should be careful to draw conclusions because other studies reported that the sick-quitter phenomenon caused the poor health of the nondrinker (38) and the safe level of alcohol intake for health is none (39). Differences in the effects of alcohol consumption on cancer development and cancer survival have also been reported in relation to breast cancer. The accumulating evidence showed a positive association between alcohol consumption and increased risk of breast cancer incidence (40–42), but the results from 11 studies showed better overall survival in women with moderate prediagnostic alcohol consumption than nondrinkers among patients with breast cancer (43).

In our meta-analysis, postdiagnostic alcohol consumption showed null associations, although this finding was based only on 3 studies and we may have been underpowered; thus, more studies for this topic are warranted. However, pre- and postdiagnostic alcohol consumption are likely to be correlated, and thus prediagnostic alcohol consumption might be a substitute of postdiagnostic alcohol consumption. Previous studies on

patients with cancer reported that the majority of cancer patients did not change their alcohol consumption or dietary intake after diagnosis (43, 44). Thus, we cannot exclude the possibility that the apparent benefit of prediagnostic light and moderate drinking could have resulted because similar drinking patterns extended to the postdiagnostic period.

In the stratified analysis by type of alcohol, significant inverse associations between light and moderate prediagnostic alcohol consumption and lower mortality were found among people who consumed wine. The inverse association between wine consumption and lower risk of mortality among patients with colorectal cancer was also shown in the study that could not be included in our meta-analysis due to atypical alcohol consumption category (infrequent/regular; ref. 22). This study examined the association between beer, liquor, and wine consumption and overall survival among colorectal cancer patients, and found 50% lower all-cause mortality in people with regular wine consumption than those with infrequent wine consumption (22). Wine consumption may be beneficial to patients with colorectal cancer because resveratrol and anthocyanin have antiproliferative effects on the growth of colorectal cancer cells (45, 46). Alternatively, the pattern of moderate wine drinking with meals rather than binge drinking patterns may be relevant. However, the observed inverse association between wine consumption and colorectal cancer survival requires further verification through additional studies.

The strengths of the present meta-analysis were as follows. First, to the best of our knowledge, this is the first dose–response meta-analysis that investigated the association between prediagnostic alcohol consumption and survival among patients with colorectal cancer. The results of this meta-analysis can provide useful information on the guideline for improving the prognosis of patients with colorectal cancer, and help to establish hypotheses for future studies. Second, this meta-analysis included a large number of patients with colorectal cancer. A large sample size increased the statistical power, and enabled us to conduct analyses by timing of alcohol consumption assessment (prediagnostic/postdiagnostic) or type of alcohol (wine/beer/liquor). Third, the results of study quality assessment showed that all of the studies included in the meta-analysis had high or at least good quality, and most of the studies controlled for important potentially confounding factors such as BMI, smoking, and tumor stage.

Several limitations of the current meta-analysis should be acknowledged. First, the cut-offs for alcohol consumption categories differed among the studies included in the meta-analysis. However, we analyzed alcohol consumption in light, moderate, and heavy levels to compensate for differences in alcohol consumption categories between the studies. In addition, we conducted a dose–response meta-analysis which showed the effects of increments of alcohol consumption. Second, the results of this meta-analysis are susceptible to misclassification as most of the studies included in the meta-analysis assessed alcohol intake through self-reported questionnaires. However, a previous study has suggested that a self-administered questionnaire can reflect relatively accurate alcohol intake even with a single measurement for alcohol (47). Even if there was misclassification in alcohol consumption, it may be random for prediagnostic alcohol consumption, which would have likely weakened the association between prediagnostic alcohol consumption and survival, rather than strengthened the association. Third, alcohol drinking habits are likely to be related to other lifestyle factors such as smoking or physical activity. Although we included the estimates which reflected the greatest degree of control for confounders from each study in the meta-analysis, we cannot rule out the possibility of residual or unmeasured confounding by additional potential confounding factors. Finally, the nondrinking group may have included people who quit drinking recently, and this could affect the results. Overall, 6 (9, 10, 17, 19–21) of 12 studies included never drinkers in nondrinking group separated from former drinkers. When we conducted an additional analysis limited to these studies, the observed inverse association between prediagnostic alcohol consumption and overall survival became slightly stronger (RR = 0.84; 95% CI, 0.76–0.93 for light vs. none; RR = 0.88; 95% CI, 0.79–0.99 for moderate vs. none). For colorectal cancer-specific survival, the direction of the association between light prediagnostic alcohol consumption and colorectal cancer–specific mortality was not changed, but the significance disappeared (RR = 0.90; 95% CI, 0.68–1.20). In spite of all these facts, the measurement of alcohol consumption was mainly made by self-report, so there is the possibility of potential bias. Self-reported alcohol intake is likely to be underestimated due to design of questionnaire (48) or response biases (49).

In conclusion, the results of the current meta-analysis indicated that light and moderate prediagnostic alcohol consumption were associated with better overall survival in colorectal cancer, and light prediagnostic alcohol consumption was associated with decreased colorectal cancer–specific mortality. Heavy prediagnostic alcohol consumption showed no significant association in relation to survival in patients with colorectal cancer. Considering the totality of our findings, light and moderate alcohol consumption are unlikely to have a critical harmful effect on survival of people with colorectal cancer. Further large and well-designed prospective studies which assessed the association between survival and pre- and postdiagnostic alcohol consumption among patients with colorectal cancer should be performed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Kim, Y. Je, E.L. Giovannucci
Development of methodology: Y. Kim
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Kim
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Kim, Y. Je, E.L. Giovannucci
Writing, review, and/or revision of the manuscript: Y. Kim, Y. Je, E.L. Giovannucci
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