review

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Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies

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Background: The International Agency for Research on Cancer (IARC) concluded that alcohol consumption is related to colorectal cancer (CRC). However, several issues remain unresolved, including quantification of the association for light (≤1 drink/day) and moderate (2–3 drinks/day) alcohol drinking, investigation of the dose–response relationship, and potential heterogeneity of effects by sex, colorectal site, and geographical region.

Methods: Twenty-seven cohort and 34 case–control studies presenting results for at least three categories of alcohol intake were identified from a PubMed search of articles published before May 2010. The summary relative risks (RRs) were estimated by the random effects model. Second-order fractional polynomials and random effects meta-regression models were used for modeling the dose–risk relation.

Results: The RRs were 1.21 [95% confidence interval (CI) 1.13–1.28] for moderate and 1.52 (95% CI 1.27–1.81) for heavy (≥4 drinks/day) alcohol drinking. The RR for moderate drinkers, compared with non-/occasional drinkers, was stronger for men (RR = 1.24, 95% CI 1.13–1.37) than for women (RR = 1.08, 95% CI 1.03–1.13; $P_{heterogeneity} = 0.02$). For heavy drinkers, the association was stronger in Asian studies (RR = 1.81, 95% CI 1.33–2.46; $P_{heterogeneity} = 0.04$). The dose–risk analysis estimated RRs of 1.07 (95% CI 1.04–1.10), 1.38 (95% CI 1.28–1.50), and 1.82 (95% CI 1.41–2.35) for 10, 50, and 100 g/day of alcohol, respectively.

Conclusions: This meta-analysis provides strong evidence for an association between alcohol drinking of >1 drink/day and colorectal cancer risk.

Key words: alcohol drinking, colorectal neoplasms, ethanol, meta-analysis

introduction

Based on the World Health Organization estimates, there are about two billion people worldwide who consume alcoholic beverages regularly [1], with an average of 6.2 l of ethanol per adult per year [2]. Alcohol consumption is one of the most important known risk factors for human cancers [3], and potentially, one of the largest avoidable factors. In has been estimated that in 2002, 5.1% and 1.3% of all cancer deaths were attributable to alcohol drinking worldwide in men and women, respectively; the corresponding figures for incidence were 5.2% of all cancers in men and 1.7% of all cancers in women [4]. Intake of alcohol is causally related to cancers of the oral cavity, pharynx, larynx, esophagus, liver, female breast, and colorectum [5, 6].

A pooled analysis of eight cohort studies from North America and Europe found a modestly increased colorectal cancer risk (45% for colon and 49% for rectal cancers) with regular high alcohol intake (≥45 g/day), compared with nondrinkers, in men and women combined [7]. Another pooled study by Mizoue et al. [8] analyzed original data from five Japanese cohort studies [9–12] and found an increased risk for colorectal cancer among men and women who regularly drink ≥23 g/day of ethanol, compared with nondrinkers. There were also several meta-analyses, and quantitative overviews [13–17], all of which have supported a positive association between alcoholic beverages consumption and colorectal cancer risk. However, several issues remained unresolved. First, the dose–risk relation of alcohol intake with colorectal cancer risk has not yet been investigated in detail. In particular, a more

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precise quantification of the association for light and/or moderate alcohol consumption and the identification of a possible threshold of effect remain to be determined. Secondly, it is still uncertain whether the effect of alcohol varies across colon and rectal anatomical subsites. Some studies have reported a stronger alcohol–cancer risk association in the colon than in the rectum [18–20], whereas others have found a stronger [21–25] or similar [7, 8, 11] association for the rectum. In addition, the few studies that have investigated the association between alcohol consumption and the risk for cancer in the proximal or distal colon showed a strong positive association in the latter and a weak or null association in the former [7, 11, 18, 22, 26–28]. Thirdly, the dose–response relationship is less apparent in women, probably because they tend to consume less alcohol than men. To date, the largest cohort study among women, with 6300 cases of colorectal cancer, has shown a small and statistically significantly increased risk for rectal, but not colon, cancer [23]. However, the range of alcohol consumption in this cohort was narrow. Finally, the association of alcohol drinking with colorectal cancer risk may be stronger among Asian populations as compared with Western populations, but this may also be due to random variation. Therefore, in order to address these issues we conducted a meta-analysis for any, light, moderate, and heavy alcohol drinking, and dose–risk meta-regression analysis of observational studies published before May 2010 on alcohol consumption and colorectal cancer.

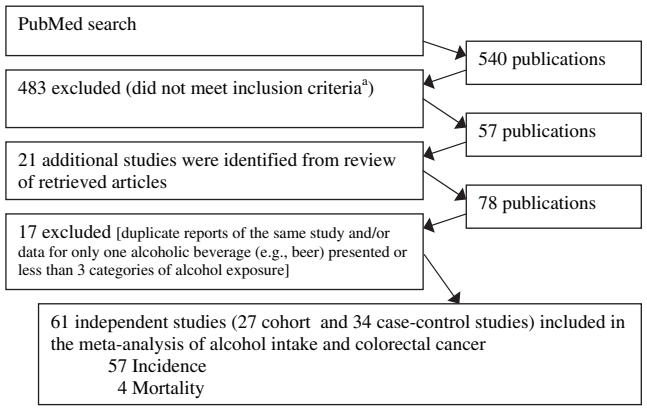
methods

search strategy and inclusion criteria

Publications were identified in PubMed using the Me SH terms 'alcohol', 'ethanol', 'alcoholic beverages', and 'colorectal neoplasms' as key words, following the MOOSE (Meta-analyses Of Observational Studies) guidelines [29]. Also, reference lists of the identified articles and previous literature reviews and meta-analyses were carefully examined for additional studies. The criteria for inclusion were as follows: (i) observational epidemiological studies (case–control, case–cohort, or cohort) on total alcohol intake and colorectal cancer incidence or mortality in general population, (ii) published in English before May 2010 (except for one article by Lim and Park [30] in Korean, in which all relevant data and tables were presented in English), (iii) reporting the odds ratio (OR) or relative risk (RR) estimates with the corresponding 95% confidence intervals (CI) or sufficient information to calculate them for each alcohol exposure level, and (iv) reporting an association for at least three categories of alcohol consumption. When several reports were published on the same study, only the most recent and informative one was included.

data abstraction

Figure 1 shows the flowchart for the selection of articles. For each study, the following information was extracted: study design, country, number of patients, duration of follow-up for cohort studies and type of controls for case–control studies, sex, variables adjusted for in the analysis, risk estimates for categories of alcohol drinking and the corresponding 95% CIs, and, when available, the number of cases and noncases or person-years for each level of alcohol consumption. A quality of each study was assessed according to the predefined criteria [31], which addressed study design, assessment of alcohol drinking, and data analysis.



[a]The inclusion criteria were: original articles of case-control and cohort studies published in English language before May 2010 and reporting information on the association between alcohol consumption (at least 3 levels) and colorectal cancer risk.

Figure 1. Flowchart of publication selection for the meta-analysis.

The range of the quality score was between 0 (lowest) and 10 (highest) (Tables 1 and 2).

statistical methods

The multivariate-adjusted risk estimates were included in the meta-analyses; however, when unavailable, unadjusted RRs were computed from the exposure distributions for cases and controls as reported in the published article. When studies reported adjusted RR estimates without CIs, the 95% CI for the unadjusted RR estimate penalized by a factor of 1.5 was computed.

Different studies used different units to express alcohol intake. Therefore, alcohol consumption was converted into grams of ethanol per day using the following conversion factors: 1 drink = 12.5 g; 1 ounce = 28.35 g; and 1 ml = 0.8 g. The dose associated with each RR estimate was computed as the midpoint of the corresponding exposure category. When the highest category was open ended, the midpoint was calculated as 1.2 times its lower bound [77]. Nondrinkers or occasional alcohol drinkers were the reference category. Light alcohol drinking was defined as consumption of ≤1 drink/day (≤12.5 g/day of ethanol), moderate as 2–3 drinks/day (12.6–49.9 g/day of ethanol), and heavy as consumption of ≥4 drinks/day (≥50 g/day of ethanol). When more than one study category fell in the range considered for light, moderate, or heavy drinking, or when the same set of controls was used for colorectal cancer subsites (colon and rectum, proximal and distal colon), we combined the corresponding risk estimates using the method by Hamling et al. [78]. When a study reported risk estimates and 95% CI relative to a reference category other than nondrinkers or occasional drinkers, with available data for nondrinkers, the RRs were recalculated using the nondrinkers or occasional drinkers as reference by the method proposed by Greenland and Longnecker [79].

A random effects model was used to estimate pooled RRs in order to take into account the heterogeneity of the risk estimates and to provide more conservative estimates compared with the fixed effects model [80]. Forest plots were done for any, light, moderate, and heavy versus nonconsumption and occasional alcohol consumption. However, only two forest plots for moderate and heavy alcohol consumption are presented. Statistical heterogeneity between studies was assessed with the chi-square statistic and quantified by I^2, a statistic that represents the percentage of total variation contributed by between-study variation [80, 81]. A significant heterogeneity was defined as a P value <0.10. To investigate potential sources of between-study heterogeneity, subgroup analyses and meta-regression models were conducted. Also, sensitivity analyses were carried out to assess whether the

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Table 1. Characteristics of published case–control studies on alcohol intake and colorectal cancer risk

References	Country and name of the study	Sex strata explored in the analyses	Sites explored in the analyses	Period of enrolment	No. of cases	No. of controls	Quality score	Variables adjusted for (or matched on) in the regression models
Potter and McMichael [32]	Australia, South Australian Central Cancer Registry	M, W	C, R	1979–1981	419	732	3	Matched on age and sex
Kune et al. [33]	Australia, Melbourne Colorectal Cancer Study	M, W	C, R	–	715	727	3.5	Matched on age and sex
Peters et al. [34]	United States	M	C, R, CR	1974–1982	147	147	8.5	Matched on age, sex, race, and neighborhood; adjusted for education
Longnecker [35]	United States	M	C, R	1985–1988	644	992	5	Age, income, and smoking
Slattery et al. [36]	United States	M, W	C, CP, CD	1979–1983	231	391	5.5	Age, religion, BMI, and intakes of calories and fiber
Choi and Kahyo [25]	Korea, Korea Cancer Center Hospital	M	C, R	–	130	390	5	Matched on age, sex, and admission date; adjusted for marital status, education, diet, and smoking
Riboli et al. [37]	France	M, W	C, R	1979–1985	389	641	3.5	None
Barra et al. [38]	Italy	M, W, M + W	C, R	1985–1990	1470	2475	5.5	Age, sex, study center, BMI, education, and intake of total energy
Peters et al. [39]	United States	M, W, M + W	C	1983–1986	746	746	6.5	Matched on age, sex, and neighborhood; adjusted for family history, activity level, weight, and intakes of fat, protein, carbohydrates, calcium, and if female, pregnancies
Gerhardsson de Verdier et al. [40]	Sweden	M, W	C, R	1986–1988	569	512	7.5	Age, sex, BMI, physical activity, smoking, and intakes of total energy, protein, and fiber
Hoshiyama et al. [41]	Japan, Saitama Prefecture	M + W	CR	1984–1990	181	653	4	Age and sex
Newcomb et al. [42]	United States	W	C, R, CR	1990–1991	779	2315	8.5	Age, BMI, screening sigmoidoscopy history, and family history
Boutron et al. [43]	France	M, W	CR	1985	171	309	6	Age
Chyou et al. [44]	United States, Honolulu Heart Program	M	C, R	1965–1968	453	7945	5	Age
Murata et al. [19]	Japan, Chiba Cancer Registry	M	C, CP	1984–1993	887	1774	4.5	Matched on age and address code; no adjustment for other risk factors
Slattery [45]	United States, Kaiser Permanente	M + W	C, CP	1991–1994	1993	2410	5.5	Age at diagnosis, BMI, physical activity, smoking, and intakes of total energy, fiber and calcium
Yamada et al. [46]	Japan	M + W	CR	1991–1993	195	390	4.5	Age, sex, BMI, and smoking

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Table 1. (*Continued*)

References	Country and name of the study	Sex strata explored in the analyses	Sites explored in the analyses	Period of enrolment	No. of cases	No. of controls	Quality score	Variables adjusted for (or matched on) in the regression models
Tavani et al. [47]	Italy	M + W	C, R, CR	1991–1996	1953	4154	7	Age, sex, education, center, physical activity, smoking, family history, and intakes of beta-carotene, vitamin D, and total energy
Murata et al.[48]	Japan	M, W	C, R, CR	1989–1997	429	794	3	Age
Chen et al. [49]	United States, Physicians' Health Study	M	CR	1982–1995	211	1113	2	Matched on age and smoking status; adjusted for aspirin and multivitamin use
Ji et al. [50]	China	M, W	C, R	1990–1992	1805	1552	4.5	Matched on age and sex; adjusted for income and smoking
Sharpe et al. [28]	Canada	M	C, CP, CD, R	1979–1985	585	500	5.5	Matched on age; adjusted for respondent status, ethnicity, family income, education, marital status, and smoking
Ho et al. [51]	Hong Kong	M + W	C, R, CR	1998–2000	822	926	4.5	None
Kim et al. [52]	Korea	M + W	CR	1998–2000	243	225	4	None
Murtaugh et al. [53]	United States, Kaiser Permanente	M, W	R	1997–2001	952	1205	3.5	Age, physical activity, and intakes of energy, fiber, and calcium
Hu et al. [27]	Canada, NECSS	M, W	C, CP, CD	1994–1997	1723	3097	4	Matched on age and sex; adjusted for province, education, BMI, and physical activity
Stern et al. [54]	Singapore, Singapore Chinese Study	M + W	CR	1993–2002	310	1176	4	None
Gao et al. [55]	China	M	CR	2000–2002	190	223	7.5	Age and smoking
Lightfoot et al. [56]	UK	M + W	CR	1997–2000	500	742	5	Matched on age and sex
Benedetti et al. [57]	Canada	M	C, R	mid-1980s	666	507	8.5	Age, smoking, respondent status, ethnicity, census tract income, and education
Kim et al. [58]	Korea	M, W, M + W	CR	2001–2004	596	509	4.5	None
Morita et al. [59]	Japan, Fukuoka Colorectal Cancer Study	M + W	CR	2000–2003	685	778	4.5	None
Wernli et al. [60]	United States	W	C, R, CR	1998–2002	1014	1064	4	None
Yamamoto et al. [61]	Japan, Hitachi Health Center	M + W	CR	2004–2007	22	66	2	None

BMI, body mass index; C, colon; CD, distal colon; CP, proximal colon; CR, colorectal; M, men; M + W, men and women combined; R, rectal; W, women.

summary estimates are robust to inclusion of studies (i) with a reference category for alcohol exposure different from nondrinkers, (ii) reporting estimates not adjusted for the main risk factors (age, sex, body fatness, smoking, and physical activity), and (iii) not reporting 95% CI for adjusted risk estimates. Publication bias was assessed using the tests by Egger [82], Begg and Mazumdar [83], the trim and fill method [84], and the contour-enhanced funnel plots [85].

A dose–response analysis was carried out using both linear and nonlinear random effects models on the natural logarithm of the RR using the method by van Houwelingen [86], which was modified by our group [87]. This method accounts for correlation between reported risk estimates within the same study, heterogeneity between the studies, and nonlinear dose–risk relation. Thirty-six second-order fractional polynomial random effects models and linear random effect models were tested. The

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Table 2. Characteristics of published cohort studies on alcohol intake and colorectal cancer risk

References	Country and name of the study	Sex strata explored in the analyses	Sites explored in the analyses	Duration of follow-up (years)	No. of cases	No. of noncases/ person-years	Quality score	Variables adjusted for in the regression models
Wu et al. [62]	United States	M, W	C, CR	5	126	11 888	3	Age
Klatsky et al. [63]	United States, Kaiser Permanente	M, W, M + W	C, R	6	230	106 203	7.5	Age, smoking, sex, race, BMI, coffee, cholesterol, and education
Stemmermann et al. [64]	United States, Iowa Women's Health Study	M	C, R	–	312	–	4	Age at exam, smoking
Gapstur et al. [65]	United States	W	C, CP, CD, R	5	312	41 837	6	Age
Goldbohm et al. [66]	Netherlands	M, W, M + W	C, R	3.3	330	120 852	7	Age, smoking, BMI, history of gall bladder surgery, education, energy intake, and energy-adjusted intakes of fat, meat protein and dietary fiber
Flood et al. [67]	United States	W	CR	8.5	490	45 264	5.5	Intakes of energy, dietary folate, and methionine and smoking
Otani et al. [9]	Japan, Japan Public Health Center-based Prospective Study	M	C, R, CR	7–10	457	42 540	8	Age, family history, BMI, smoking, physical activity, and study center
Pedersen et al. [68]	Denmark	M + W	C, R	15	613	29 132	5.5	Age, sex, smoking, BMI, and study
Shimizu et al. [12]	Japan, Takayama study	M, W	C, R	7	295	29 051	5	Age, height, BMI, smoking, and education
Sanjoaquin et al. [69]	UK	M, W, M + W	CR	17	95	10 998	2	Age, sex, and smoking
Su and Arab [70]	United States, NHANES, NHEFS	M + W	C	2	111	10 418	7.5	Age, sex, race, BMI, education, history of colonic polyps, smoking, multivitamins, and intakes of non-poultry meat, poultry meat, and seafood
Wei et al. [71]	United States, Nurses' Health Study (NHS)	W	C, R	14–20	1478	134 365	5.5	Age, sex, family history, BMI, physical activity, height, smoking, history of endoscopy, and consumption of beef, pork or lamb, processed meat, calcium, and folate
Chen et al. [24]	China, Jiashan County	M, W, M + W	CR, C, R	11	242	64 343	4	Age, sex, smoking, occupation, education, and marital status
Wakai et al. [10]	Japan, Japan Collaborative Cohort Study	M, W	R, C	7.69	629	57 736	5	Age, area, education, family history of colorectal cancer, BMI, smoking, walking time, sedentary work, and consumption of green leafy vegetables and beef
Akhter et al. [11]	Japan, Miyagi cohort study	M	C, CP, CD, R, CR	11	307	21 199	8	Age, family history, education, BMI, walking time, smoking, and intakes of meat, green and yellow vegetables, and fruits

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Table 2. (*Continued*)

References	Country and name of the study	Sex strata explored in the analyses	Sites explored in the analyses	Duration of follow-up (years)	No. of cases	No. of noncases/ person-years	Quality score	Variables adjusted for in the regression models
Ferrari et al. [26]	Europe, EPIC	M + W	C, CP, CD, R, CR	6.2	1833	478 732	8	Age, sex, center, physical activity, smoking, education, weight, height, and intake of energy from nonalcohol sources
Tsong et al. [72]	China, Singapore Chinese Study	M + W	C, R, CR	11	845	63 257	7	Age, sex, year of recruitment, education, BMI, history of diabetes, family history, smoking, and physical exercise
Thygesen et al. [18]	United States, Health Professionals Follow-up study (HPFS)	M	C, CP, CD, R, CR	16	868	47 432	8	Stratified by age in 1-year groups; adjusted for family history, aspirin use, smoking, physical activity, BMI, colonoscopy, sigmoidoscopy, and intakes of folate, methionine, vitamin D, calcium, total calories, multivitamins, and processed and red meat
Toriola et al. [73]	Finland, Findrink study	M	CR	16.7	59	2682	7.5	Age, examination year, vegetable consumption, fiber intake, family history of cancer, smoking, socioeconomic status, and leisure time physical activity
Bongaerts et al. [22]	The Netherlands, the Netherlands Cohort Study	M + W	C, CP, CD, R, CR	13.3	2323	120 852	9	Age, sex, family history, BMI, physical activity, and intakes of total energy, energy-adjusted fat, fiber, and calcium
Kabat et al. [74]	Canada, Canadian National Breast Screening Study	W	CR	16.4	617	89 835	6.5	Age, BMI, smoking, education, menopausal status, oral contraceptive use, hormone replacement therapy, and total calories
Lim and Park [30]	Korea, Korea Elderly Pharmacoepidemiologic Cohort (KEPEC)	M + W	CR	4.8	112	14 304	5	Age and sex
Allen et al. [23]	UK, Million Women Study	W	C, R	10	6298	1 280 296	6.5	Age, region of residence, socioeconomic status, BMI, smoking, physical activity, oral contraceptives, and hormone replacement therapy
Mortality								
Kono et al. [75]	Japan, Male Japanese Physician's study	M	CR	19	39	5135	5	Age and smoking
Camargo et al. [76]	United States, US Male Physicians	M	CR	10.7	80	22, 071	6	Age, smoking, and treatment groups

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Table 2. (*Continued*)

References	Country and name of the study	Sex strata explored in the analyses	Sites explored in the analyses	Duration of follow-up (years)	No. of cases	No. of noncases/ person-years	Quality score	Variables adjusted for in the regression models
Ozasa [21]	Japan, Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	M, W	C, R	13–15	692	109 778	4	Age and area of study
Yi et al. [20]	Korea, Kangwha Cohort Study	M	C, R, CR	20.8	26	6291	6.5	Age, smoking, ginseng use, education, and pesticide use

BMI, body mass index; C, colon; CD, distal colon; CP, proximal colon; CR, colorectal; M, men; M + W, men and women combined; R, rectal; W, women.

best-fitting model, defined as the one with the lowest Akaike's information criterion, a model fit statistic, was selected as the final dose–risk relation model.

All statistical tests were two-sided, and all statistical analyses were carried out with SAS (version 9.2; SAS Institute Inc., Cary, NC) and Stata Statistical Software (version 10; StataCorp LP, College Station, TX).

results

alcohol intake and CRC incidence

A total of 57 studies on colorectal cancer incidence and alcohol intake published between 1986 and 2010 were identified, among which 22 studies were from Asia (Japan, Korea, China, Hong Kong, and Singapore), 2 from Australia, 13 from Western Europe, and 24 from North America (Canada and United States). Of all these studies, 22 reported fully adjusted risk estimates and 36 reported risk estimates adjusted for tobacco smoking (Tables 1 and 2).

The pooled random effects RRs for comparison with nondrinkers were as follows: any drinkers, 1.12 (95% CI 1.06–1.19); light drinkers, 1.00 (95% CI 0.95–1.05); moderate drinkers, 1.21 (95% CI 1.13–1.28); and heavy drinkers, 1.52 (95% CI 1.27–1.81) (Table 3). The relative risks were higher for rectal than for colon cancer among any drinkers ($P = 0.03$) and light drinkers ($P = 0.05$), but about the same among moderate and heavy drinkers. There was no significant heterogeneity of effect estimates by colon subsites among any and light drinkers. However, there was a nonsignificant increased risk for cancer of the distal colon compared with the proximal colon among moderate ($P = 0.12$) and heavy ($P = 0.18$) drinkers. Men had statistically significantly higher risk than women among any drinkers ($P = 0.001$) and moderate drinkers ($P = 0.02$). Geographical region, type of study, study quality, adjustment for main confounders (age, sex, smoking, body mass index, and physical activity), and year of publication were not significant sources of heterogeneity. For colorectal cancer, a potential heterogeneity by geographical location was observed only among heavy drinkers ($P = 0.04$), with the highest risk summary estimate of 1.81 (95% CI 1.33–2.46) for studies conducted in Asia and the lowest risk summary estimate of 1.16 (95% CI 0.95–1.43) for studies conducted in Europe (supplemental Figure S1, available at *Annals of Oncology* online). RRs were systematically higher in hospital-based case–control studies than in population-based case–controls; however, the difference was not statistically significant.

Figure 2A presents RRs for colorectal cancer incidence and moderate alcohol intake, compared with no alcohol intake in men and women from 31 case–control and 22 cohort studies. Combined, the 53 studies included more than 20 700 colorectal cancer cases. There was a statistically significant heterogeneity among studies ($I^2 = 60\%$, $P < 0.001$). Summary results did not materially change when studies with no adjustment for potential confounders were excluded (Table 3). Because there was a significant heterogeneity by sex ($P = 0.02$), the forest plots are also presented by sex (Figure 2B and C). The nine cohort and 12 case–control studies that investigated the association between moderate alcohol intake and colorectal cancer risk among women (involving 6084 cases) did not show heterogeneity ($I^2 = 0\%$, $P = 0.50$; Figure 2B), whereas 11 cohort and 21 case–control studies among men showed substantial heterogeneity ($I^2 = 55\%$, $P < 0.001$; Figure 2C). The summary RRs of colorectal cancer were 1.08 (95% CI 1.03–1.13) and 1.24 (95% CI 1.13–1.37) for women and men, respectively, for moderate alcohol consumption, compared with nondrinkers.

Figure 3 presents RR estimates for colorectal cancer incidence for heavy alcohol drinkers, compared with nondrinkers or occasional drinkers from seven cohort and 12 case–control studies involving 6653 colorectal cancer cases ($I^2 = 76\%$, $P < 0.001$). The summary RR for heavy drinking was 1.52 (95% CI 1.27–1.81), compared with nondrinkers or occasional drinkers. The majority of studies reported results for men or for men and women combined. Only two studies reported results for women (summary RR = 1.54, 95% CI 1.04–2.29; Table 3). Exclusion of studies with no adjustment for potential confounders ($N = 12$) slightly attenuated the summary RR (1.42, 95% CI 1.13–1.80; Table 3).

Detailed evaluation of publication bias suggested that the presence of publication bias is unlikely (supplemental Figures S2 and S3, available at *Annals of Oncology* online). Furthermore, several sensitivity analyses showed that the summary estimates are robust to inclusion of studies with certain methodological limitations and are not substantially influenced by definition of the highest alcohol intake category (supplemental material, available at *Annals of Oncology* online). Results for alcohol intake and CRC mortality were consistent with the results for CRC incidence and are presented in the supplemental material (available at *Annals of Oncology* online).

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Table 3. Pooled RR estimates for colorectal cancer incidence stratified by colon site, sex, geographical region, and potential modifying factors

Factors stratified	Drinkers versus non-/occasional drinkers[a]					Light versus non-/occasional drinkers[a]					Moderate versus non-/occasional drinkers[a]					Heavy versus non-/occasional drinkers[a]				
	No. of studies[b]	RR	LCI	UCI	*P* value[c]	No. of studies[b]	RR	LCI	UCI	*P* value[c]	No. of studies[b]	RR	LCI	UCI	*P* value[c]	No. of studies[b]	RR	LCI	UCI	*P* value[c]
All studies	57	1.12	1.06	1.19		49	1.00	0.95	1.05		53	1.21	1.13	1.28		19	1.52	1.27	1.81	
Site																				
Colon	42	1.05	0.99	1.12	0.03	36	0.96	0.90	1.02	0.05	39	1.15	1.06	1.24	0.27	16	1.43	1.23	1.67	0.56
Rectum	38	1.19	1.09	1.31		32	1.06	0.98	1.14		35	1.23	1.13	1.35		15	1.59	1.18	2.15	
Colon site																				
Proximal	10	1.02	0.91	1.14	0.66	9	1.01	0.88	1.16	0.30	8	1.01	0.86	1.17	0.12	3	1.38	0.96	1.98	0.18
Distal	8	1.07	0.90	1.28		8	0.91	0.80	1.05		7	1.22	1.02	1.47		3	2.46	1.38	4.40	
Sex[d]																				
Female	26	1.00	0.94	1.07	0.001	25	0.95	0.89	1.01	0.27	21	1.08	1.03	1.13	0.02	2	1.54	1.04	2.29	0.82
Male	33	1.25	1.13	1.39		27	1.02	0.92	1.14		32	1.24	1.13	1.37		15	1.62	1.31	2.01	
Geographical region																				
Asia	19	1.21	1.03	1.43	0.67	14	0.97	0.83	1.14	0.82	19	1.27	1.09	1.49	0.80	8	1.81	1.33	2.46	0.04
Australia	2	1.04	0.76	1.44		2	0.98	0.69	1.38		2	1.10	0.82	1.49				N/A		
Europe	14	1.09	1.01	1.18		12	1.03	0.97	1.11		13	1.17	1.06	1.29		6	1.16	0.95	1.43	
North America	22	1.08	1.01	1.15		21	0.99	0.92	1.05		19	1.18	1.08	1.30		5	1.59	1.25	2.01	
Type of study																				
Cohort	23	1.12	1.03	1.22	0.87	23	1.02	0.96	1.08	0.43	22	1.24	1.13	1.28	0.38	7	1.57	1.38	1.80	0.74
Case–control	34	1.11	1.04	1.19		26	0.98	0.90	1.06		31	1.18	1.07	1.29		12	1.49	1.13	1.96	
Source of controls[e]																				
Population based	25	1.08	0.99	1.17	0.24	20	0.98	0.90	1.07	0.85	23	1.15	1.03	1.29	0.15	7	1.43	1.15	1.79	0.82
Hospital based	9	1.26	1.01	1.58		6	0.96	0.78	1.17		8	1.29	1.16	1.44		5	1.54	0.89	2.67	
Quality score																				
Above median	29	1.08	1.02	1.14	0.31	25	0.99	0.95	1.04	0.71	27	1.21	1.08	1.35	0.91	10	1.42	1.15	1.75	0.46
Below median	28	1.15	1.04	1.28		24	1.01	0.92	1.11		26	1.20	1.10	1.29		9	1.65	1.20	2.26	
Adjustment for main confounders[f]																				
Adjusted	22	1.08	1.02	1.18	0.39	20	1.01	0.97	1.05	0.69	22	1.20	1.11	1.30	0.90	7	1.42	1.13	1.80	0.54
Unadjusted	35	1.14	1.04	1.26		29	0.99	0.91	1.09		31	1.21	1.09	1.34		12	1.59	1.21	2.08	
Publication year																				
<2000	24	1.10	0.99	1.23	0.67	20	0.97	0.88	1.07	0.46	22	1.17	1.05	1.30	0.45	10	1.49	1.06	2.09	0.89
≥2000	33	1.13	1.07	1.20		29	1.01	0.96	1.05		31	1.23	1.14	1.33		9	1.53	1.33	1.76	

[a]Nondrinkers category included nondrinkers and occasional drinkers; light drinking was defined as ≤12.5 g/day of alcohol (≤1 drink/day), moderate drinking as 12.6-49.9 g/day (2–3 drinks/day), and heavy drinking as ≥50 g/day (≥4 drinks/day).

[b]Strata-specific results from the same study were counted as one study.

[c]*P* values from the test of homogeneity between strata.

[d]Studies reporting estimates separately for men and women were selected.

[e]Among case–control studies only.

[f]Age, sex, body mass index, and/or physical activity.

LCI, lower confidence interval; RR, relative risk; UCI, upper confidence interval.

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review

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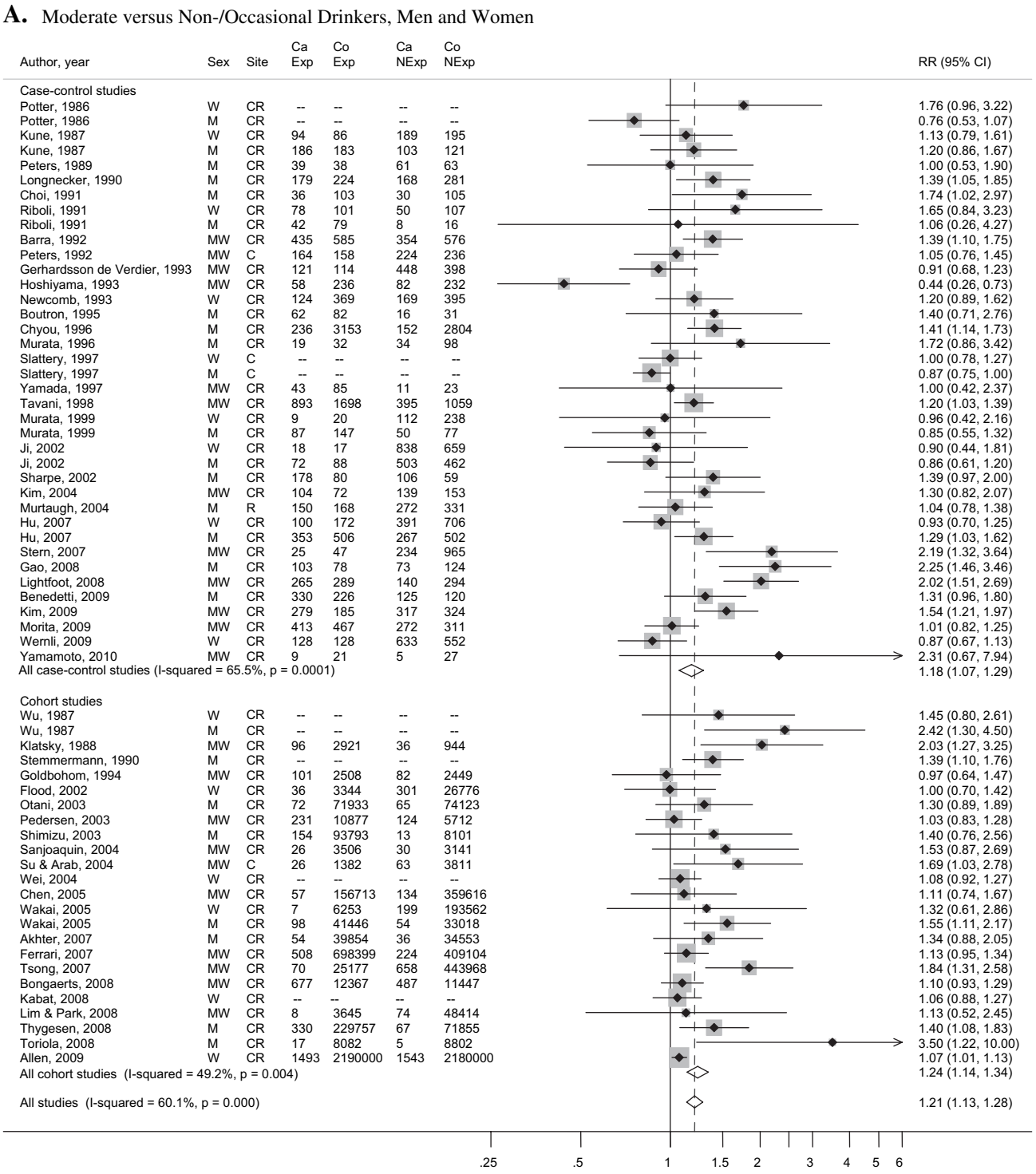

Figure 2. Pooled risk estimates for colorectal cancer incidence for moderate alcohol drinkers versus nondrinkers or occasional drinkers from case–control and cohort studies reporting estimates for men and women (A), for women (B), and for men (C). Moderate alcohol consumption was defined as 12.6-49.9 g of alcohol per day (>1–3 drinks/day).

dose–response meta-analyses

Among the second-order fractional polynomial random effects models, the best-fitting dose–response relationship between alcohol intake and colorectal cancer risk was $\ln(RR) = 0.006992 \times dose - 0.00001 \times dose^2$ (Figure 4). Compared with nondrinkers, the fractional polynomial model estimates of the RR were 1.07 (95% CI 1.04–1.10), 1.18 (95% CI 1.12–1.25), 1.38 (95% CI 1.28–1.50), and 1.82 (95% CI 1.41–2.35) for 10, 25, 50, and 100 g/day of alcohol, respectively.

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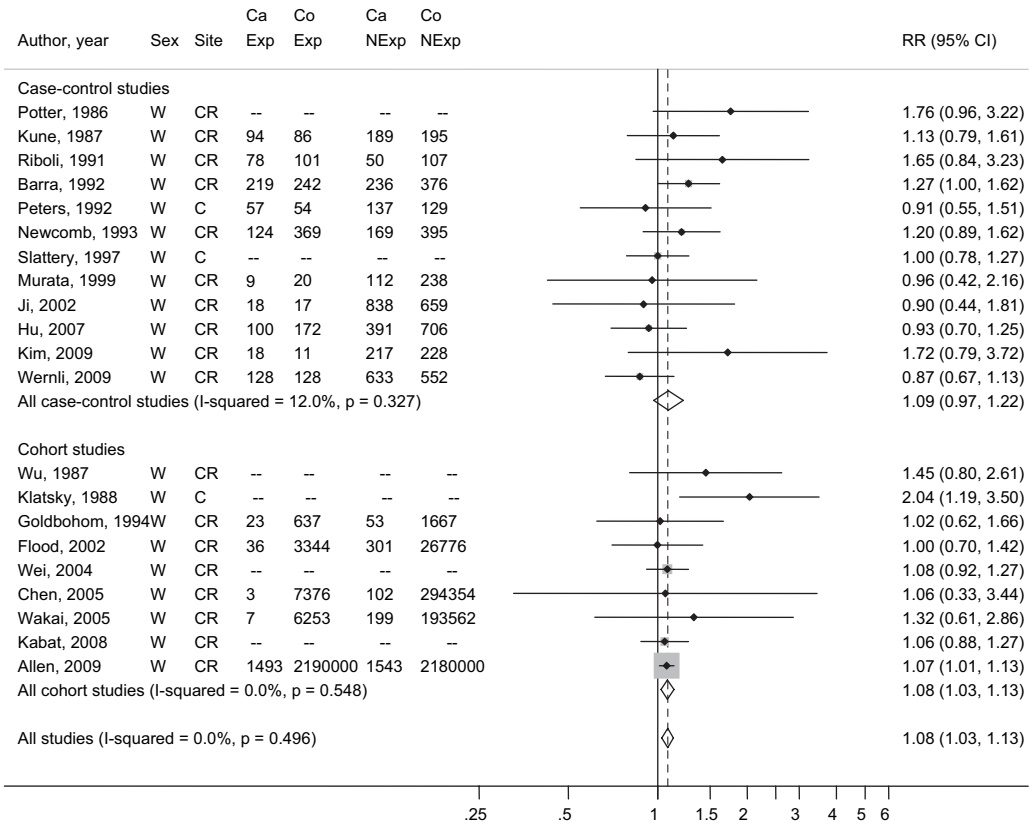

Figure 2. (continued)

discussion

The results of this meta-analysis support the evidence for a causal relation between high intakes of alcohol and increased risk for colorectal cancer, and provide additional evidence of an association for moderate intakes of alcohol and a shape for the dose–risk relationship. Compared with nondrinkers or occasional alcohol drinkers, moderate drinking (>1–4 drinks/day, equivalent to 12.6–49.9 g/day of ethanol) was associated with a 21% and heavy drinking (≥4 drinks/day, equivalent to ≥50 g/day of ethanol) with a 52% increased risk for colorectal cancer, whereas light alcohol consumption (≤1 drink/day, equivalent to ≤12.5 g/day of ethanol) was not associated with an increased risk. However, results of the dose–risk analysis showed a statistically significant 7% increased colorectal cancer risk for 10 g/day of alcohol intake, which includes light alcohol consumers.

The results for heavy and moderate drinking are consistent with previous pooled [7, 8] and meta-analyses [14, 15, 17]; however, the results for light drinking in these studies were either not reported or statistically nonsignificant. In our categorical meta-analysis, there was no association between light alcohol intake and colorectal cancer risk; however, the dose–response analysis found a 7% increase in colorectal cancer risk for low doses. The differences between the dose–response analysis and meta-analysis for light drinkers may likely be explained by the different methods used. The dose–response analysis of aggregate data with the use of fractional polynomial allows investigation of functional relations but does not overcome the general limitations of modeling because the risk estimates for low alcohol doses may be influenced by the function used and affected by observations in high-dose categories and by exposure misclassification in general [87].

The association of alcohol drinking with colorectal cancer risk did not differ by colon and rectal anatomic subsites, consistent with previous meta-analysis [13–15] and pooled analysis [7, 8]. The findings according to proximal and distal colon subsites were consistent with the previous observational studies and one pooled analysis [7, 11, 18, 22, 26–28]. Our results suggested a stronger positive association of moderate and heavy alcohol drinking with cancer in the distal colon compared with cancer in the proximal colon, but the difference was not statistically significant.

The results for alcohol drinking and colorectal cancer risk appeared to be similar between men and women for any and light drinkers. There was a suggestion that the colorectal cancer–moderate alcohol drinking association is stronger among men than among women. This can be explained by the limited number of studies reporting data on high alcohol intake among women, by lower average alcohol consumption in women as compared with men, and/or by possible effect modification of the association by sex.

A large number of studies in our meta-analysis allowed us to investigate whether the association between alcohol drinking

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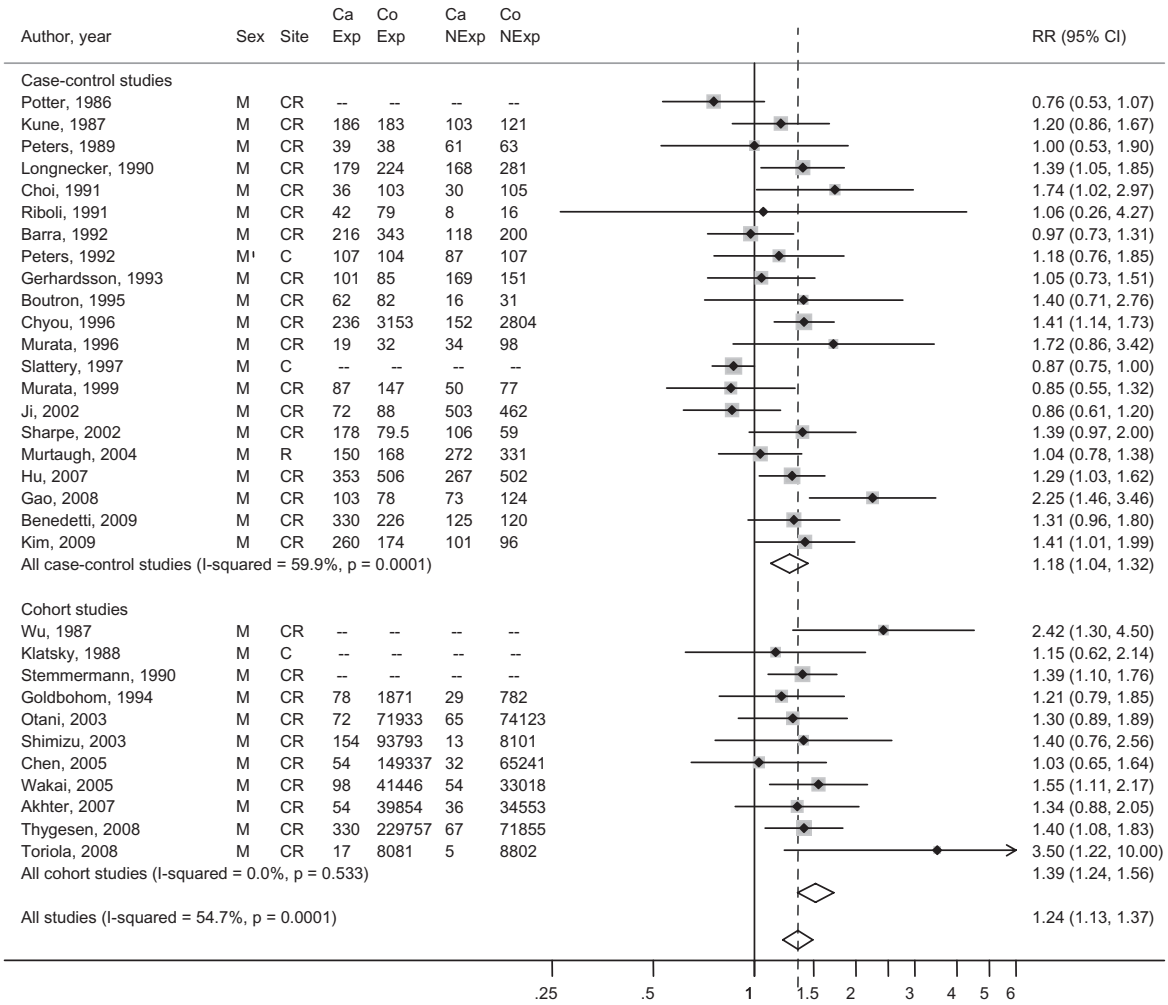
C. Moderate versus Non-/Occasional Drinkers, Men



The size of each grey square is proportional to the study's weight calculated as inverse of variance.
RR, relative risk; 95%CI, 95% confidence intervals; M, men; W, women; MW, both men and women.
C, colon; R, rectum; CR, colorectal.
Ca Exp, number of exposed cases; Co Exp, number of exposed controls; Ca NExp, number of non-exposed cases; Co NExp, number of non-exposed controls.
Weights are from random effects analysis.

Figure 2. (continued)

and colorectal cancer risk is stronger among Asian populations. Consistent with the previous pooled analyses of prospective studies from North America and Europe [7] and Japan [8], our study has found a slightly stronger association between alcohol drinking and colorectal cancer risk among studies from Asia when compared with studies from other geographical regions. Potential explanations for these findings include (i) a high prevalence (up to 30%) of the slow-metabolizing variant of aldehyde dehydrogenase enzyme, which is associated with increased blood levels of acetaldehyde after alcohol ingestion [88], and (ii) other nongenetic factors, e.g. body composition [8]. No studies were published on colorectal cancer–alcohol intake association among South American and African populations; therefore, further research in these populations is required.

Our meta-analysis had several strengths, including an extensive search of literature on the association between colorectal cancer risk and alcohol drinking that was conducted to identify all published articles before May 2010. Furthermore, the associations for colon and rectal cancers were evaluated separately, as well as the associations by sex, geographical region, and other factors. Finally, two different methods were used to investigate the association between colorectal cancer risk and alcohol consumption, which allowed us to conduct traditional meta-analysis by categories of alcohol drinking and dose–response analysis.

Our meta-analysis also had some limitations. A statistically significant heterogeneity between the studies for moderate and high alcohol doses, including open-ended categories, was observed, which was likely to be attributed to the variation in

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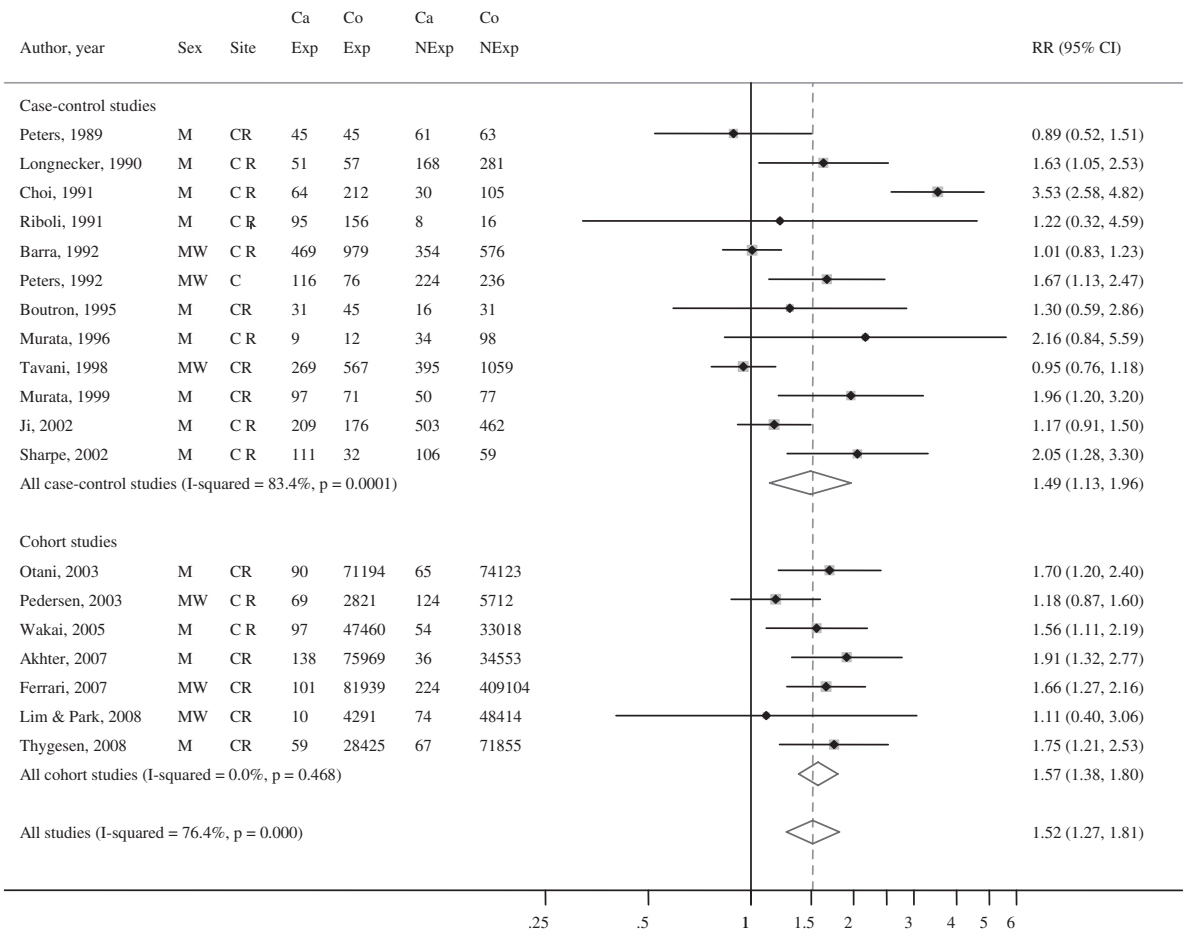

The size of each grey square is proportional to the study's weight calculated as inverse of variance.
RR, relative risk; 95%CI, 95% confidence intervals; M, men; W, women; MW, both men and women.
C, colon; R, rectum; CR, colorectal.
Ca Exp, number of exposed cases; Co Exp, number of exposed controls; Ca NExp, number of non-exposed cases; Co NExp, number of non-exposed controls.
Weights are from random effects analysis.

Figure 3. Pooled risk estimates for colorectal cancer incidence for heavy alcohol drinkers versus nondrinkers or occasional drinkers from case–control and cohort studies reporting estimates for men and women. Heavy alcohol consumption was defined as ≥50 g of alcohol per day (≥4 drinks/day).

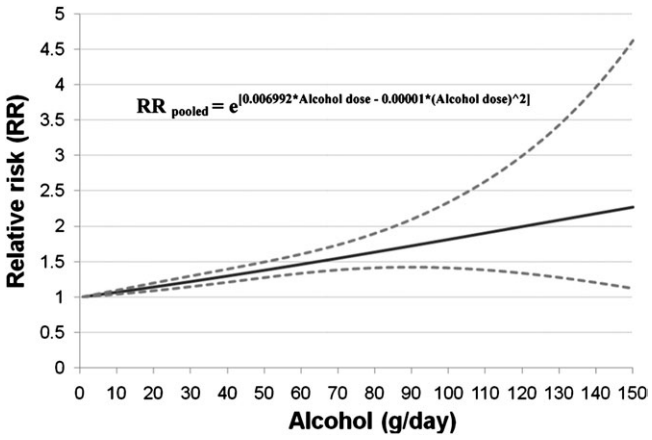

Figure 4. Relative risk function and the corresponding 95% confidence interval estimated by van Houwelingen approach, describing the best-fitting dose–response association of alcohol drinking (in grams per day) and colorectal cancer risk.

study design and quality. The type of alcoholic beverage, as well as lifetime exposure to alcohol, and drinking patterns were not included in the meta-analysis because very few studies investigated them. Furthermore, high alcohol intake may be associated with behaviors that predispose to colorectal cancer, such as smoking, unhealthy diet, and low physical activity [89–92]; however, exclusion of studies with no adjustment for main risk factors resulted in no substantial change of summary estimates. Another limitation was that we did not examine whether the association of alcohol with colorectal cancer risk varied by folate status, smoking, or other potential modifying factors because very few studies investigated these associations. Furthermore, our results are likely to be affected by some degree of alcohol exposure misclassification. However, studies with a high-quality score, which have a better collection of alcohol exposure data, found results similar to those reported by the studies with low-quality score. Finally, the evaluation of contour-enhanced funnel plots

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and other methods suggested minor evidence of publication bias.

The results from this large meta-analysis have important public health implications, given the large number of women and, especially, men consuming alcohol and the high incidence of colorectal cancer worldwide and in developed countries in particular. Our results have shown that alcohol consumption was associated with an increase in risk for colorectal cancer, for intakes of >1 drink/day (>12.5 g/day of ethanol). Thus, public health recommendations for colorectal cancer prevention should consider limiting intake of alcoholic beverages.

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PB, CLV, and MJ conceived and coordinated the study; VF and LS carried out literature search, selected the articles for this meta-analysis, and extracted the data; VB and MR developed the statistical analyses methods; IT, VB, and MR provided assistance in data analyses; and VF conducted the statistical analyses and drafted the paper. All authors contributed substantially to interpreting the data, writing of the manuscript, and critically reviewing the manuscript.

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disclosure

The authors declare no conflict of interest. The funding sources had no influence on the design of the study; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

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