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Alcohol drinking and all cancer mortality: a meta-analysis

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Background: Epidemiological studies have suggested an inconsistent relationship between alcohol drinking and risk of all cancer mortality. As far as we know, no meta-analysis has been conducted to explore this issue.
Patients and methods: We carried out a PubMed search to find relevant articles published before April 2012 in English. Categorical and dose–response meta-analyses were conducted to identify the impact of alcohol drinking on all cancer mortality. Potential sources of heterogeneity were detected by meta-regression and stratification analyses. Sensitivity and cumulative meta-analyses were also carried out.
Results: Eighteen independent cohort studies met the inclusion criteria. Compared with non/occasional drinkers, the pooled relative risks (RRs) were 0.91 [95% confidence interval (CI) 0.89–0.94] for light, 1.02 (95% CI 0.99–1.06) for moderate, and 1.31 (95% CI 1.23–1.39) for heavy drinkers. Former drinkers presented a higher risk (RR = 1.32, 95% CI 1.15–1.50) than current drinkers (RR = 1.06, 95% CI 0.98–1.16). There was a *J*-shaped relationship between all cancer mortality and alcohol consumption in males but not in females.
Conclusions: This meta-analysis confirms the health hazards of heavy drinking (≥50 g/day) and benefits of light drinking (≤12.5 g/day). Large-sample, well-designed, prospective epidemiological studies, especially on heavy drinking among women, should be developed in future.
Key words: alcohol drinking, all cancer, categorical meta-analysis, dose–response meta-analysis, mortality, systemic review

introduction

Cancer has been the leading cause of death in both developed and developing countries, and the rate of increase is faster than before in global population. The International Agency for Research on Cancer (IARC) estimated that ~7.6 million cancer deaths occurred in 2008, compared with 6.2 million in 2000 [1–3]. Alcohol drinking is one of the important known lifestyle-related risk factors. Evidence from humans for carcinogenicity of alcohol is considered to be conclusive, which has been confirmed as Group 1 'carcinogenic to humans' by IARC [4].

It is widely accepted that excessive alcohol consumption has an adverse effect on health and mortality [5]. However, several issues about the relationship between alcohol consumption and risk of cancer mortality are still under debate. First, the results from different epidemiological studies are inconsistent. Some studies suggest that only heavy alcohol drinkers display an elevated risk of cancer mortality but not light or moderate drinkers [6, 7], while others show that even light-to-moderate alcohol consumption is also positively associated with cancer mortality [8, 9]. There is no consensus on the 'safe' level of alcohol consumption in general population. Second, the effect of alcohol drinking on mortality shows different features for males and females, which seem to have negative association with mortality up to daily ethanol intake of 60 g for males and 50 g for females, respectively [10]. Moreover, previously published studies have shown a *J*-shaped relationship between alcohol drinking and risk of all-cause mortality [5, 10]. However, the exact dose–response relationship between alcohol drinking and all cancer mortality has not yet been reported in meta-analysis. To elucidate the association of alcohol drinking with all cancer mortality and the corresponding dose–response relationship, a meta-analysis of epidemiological studies published up to April 2012 was conducted.

materials and methods

search strategy and identification of eligible studies

A literature search was carried out in PubMed to find all relevant publications, which was carried out by one of the authors (MJ) and then confirmed by another author (SC). Figure 1 presents the flowchart of publication selection. Three of the authors (MJ, SC, and JG) retrieved and

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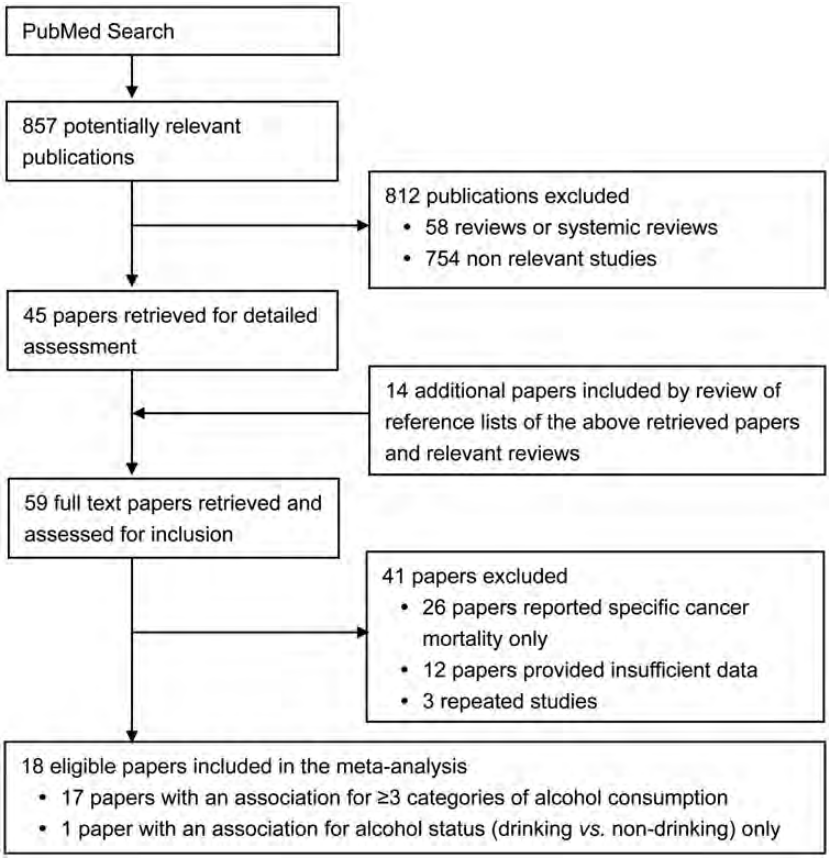

Figure 1. Flowchart of publication selection.

assessed potentially relevant publications, and the reference lists of the screened literatures as well as previous relevant reviews and meta-analyses were also checked to identify additional publications of interest. The criteria for paper inclusion were as follows: (i) case–control, case-cohort, or cohort studies focused on the association of alcohol drinking with all cancer mortality; (ii) presenting the odds ratio, risk ratio, or hazard ratio estimates with the corresponding 95% confidence intervals (CIs) or sufficient data to calculate; (iii) non/occasional drinking as the reference category; and (iv) published in English up to April 2012. The most informative (often the most recent) was selected in the circumstance of multiple papers published from the same population. Furthermore, as nondrinkers of specific kind of alcoholic beverage might consume others, studies only reported the estimates of specific kind of alcoholic beverage but not total alcohol drinking were excluded.

data extraction and methodological quality assessment

Two investigators (MJ and SC) independently carried out data extraction of following items: study design, publication year, country, study name, International Classification of Diseases code of cancers surveyed, the number of deaths caused by cancers, duration of follow-up, gender, age, variables adjusted for estimates, sample size (persons or person-years), alcohol exposure levels and corresponding estimates with 95% CIs. Data were extracted with the concealment of journals, authors, supporting funds, and organizations to avoid potential bias.

Two reviewers (YY and SZ) completed the quality assessment independently. A set of structured criteria (supplemental Table S1, available at *Annals of Oncology* online) modified from previous studies was used [11, 12]. The total score ranges from 0 to 10, and a higher score indicates higher quality. Discrepancies were resolved by consensus and discussion.

statistical analyses

The multivariate-adjusted risk estimates were selected. And the unadjusted were calculated using original data when the adjusted unavailable.

As alcohol consumption was reported in various measurement scales, we transferred the exposure data into a uniform measurement of grams (g) of ethanol per day. The convention was conducted based on the explanation of ethanol intake level in the article. If the information was not provided, the following equivalencies were used: 1 ml of alcohol as 0.8 g of ethanol, one drink as 12.5 g, and 1 ounce as 28 g. When a range of alcohol consumption was provided, the median was treated as the corresponding exposure dose. For the highest open-ended exposure data, the exposure dose was defined by the lower bound added to the three-quarters of the adjacent previous category [13]. Non/occasional drinkers were regarded as the reference group. And the alcohol drinkers were classified into three levels as light, moderate, and heavy drinkers, which were defined as ethanol intake of ≤12.5 g/day (≤1 drink/day), 12.6–49.9 g/day (2–3 drinks/day), and ≥50 g/day (≥4 drinks/day), respectively [12].

In the analysis of drinkers versus non/occasional drinkers, if the corresponding estimate had not been presented in a study, estimates associated with different alcohol exposure categories were synthesized into a single estimate among the combination of males and females (MF), males (M), and females (F), respectively. Similar methods were adopted for light, moderate, and heavy alcohol drinking when multiple exposure categories lay in one of these levels.

Cochran Q test [14] and I^2 index [15] were used to evaluate the heterogeneity across different studies. A random-effects model [16] was used when a notable heterogeneity (P of Q test ≤ 0.1 and/or I^2 index $\geq 50\%$) was presented; otherwise the fixed-effects model [17] was used. Subgroup analyses were carried out stratified by gender, source of cohort, geographic area, major confounders (age, gender, and cigarette smoking) adjusted, publication year, quality score, and ethnicity. We also attempted to ascertain the risk difference between the former and current drinkers, and the studies presenting these two estimates concurrently were selected. Restricted maximum likelihood-based random-effects meta-regression analysis was used to investigate the potential sources of heterogeneity. A univariate model was established, and then variables with P values ≥ 0.1 were entered into a multivariable model.

Cumulative meta-analysis in the order of publication year was conducted to find the starting point of risk estimate becoming statistically significant and clarify the variation tendency [18]. And we deleted each study in turn from the polled analysis to check its influence. Publication bias was assessed by Egger's linear regression [19] and Begg's rank correlation [20]. Begg's funnel plot was also drawn.

Nonlinearity in the relationship between alcohol consumption and all cancer mortality was assumed, and the flexible restricted cubic splines method was used in the dose–response analysis [21]. Briefly, varying location of four knots at fixed percentiles, 5%, 35%, 65% and 95%, of exposure level was used, which had negligible influence on the estimates [22]. Variances were calculated from the given confidence interval in papers. Covariances of the natural logarithm of the estimates for each dose were reconstructed using the method proposed by Hamling et al. [23]. A nonlinear fixed-effects model recommended by Orsini et al. [21] was used.

All statistical analyses were carried out by STATA version 11.0 (STATA Corp, College Station, Texas) and SAS version 9.2 (SAS Institute Inc., Cary, NC).

results

characteristics of included studies

Finally, 18 prospective cohort studies [7–9, 24–38] met the inclusion criteria and were included, among which only one study [36] just provided an overall RR of drinkers versus non/occasional drinkers. The quality scores ranged from 3.5 to 8.5 with a median of 6.5 for methodological assessment (supplementary Table S1, available at *annals of oncology* online). Seven cohorts [9, 24, 32–36] were constructed and followed-up in Asia, four [8, 27, 29, 37] in Europe, and seven [7, 25, 26, 28, 30, 31, 38] in North America. Thirteen studies [7–9, 24, 25, 27, 28, 30, 32–35, 38] presented the estimates for M, eleven [7–9, 26, 28, 31, 32, 34, 35, 37, 38] for F, and four [8, 29, 36, 38] for MF. Five studies [33–36, 38] provide the estimates for the former and current drinkers simultaneously. Detailed characteristics of the studies included are shown in Table 1. A total of 48 178 deaths from all cancers were observed among all these cohort studies.

categorical meta-analysis

Figure 2 is the forest plots that provide study-specific and pooled RRs (95% CIs) of all cancer mortality for any, light, moderate, and heavy drinkers. When compared with non/occasional drinkers, the pooled RRs were 1.05 (95% CI 1.00–1.10; P for heterogeneity = 0.008) for any, 0.91 (95%CI 0.89–0.94; P for heterogeneity = 0.449) for light, 1.02 for (95%CI 0.99–1.06; P for heterogeneity = 0.105) for moderate, and 1.31 (95%CI 1.23–1.39; P for heterogeneity = 0.442) for heavy drinkers.

Table 2 presents the pooled RRs (95% CIs) of all cancer mortality for any, light, moderate, and heavy drinkers among different subgroups stratified by relevant factors. For drinkers versus non/occasional drinkers, significant differences were found between studies with population-based (RR = 1.06, 95% CI 1.02–1.11) and occupation-specific cohort (RR = 1.01, 95% CI 0.89–1.14; P for heterogeneity = 0.020); and between studies with $\geq$ median (RR = 1.08, 95% CI 1.02–1.14) and < median (RR = 1.02, 95% CI 0.96–1.08; P for heterogeneity = 0.043) of quality score. While considering different drinking levels, significant heterogeneity was demonstrated only at a moderate drinking level. And the meaningful stratified factors included gender, geographic area, publication year, quality score, and ethnicity. A significant difference was also found between the former (RR = 1.32, 95% CI 1.15–1.50) and current drinkers (RR = 1.06, 95% CI 0.98–1.16, P for heterogeneity <0.001).

testing the heterogeneity

The between-study heterogeneity of any versus non/occasional drinking was significant, while it became nonsignificant when the specific drinking levels were taken into consideration (supplementary Table S2, available at *Annals of Oncology* online). In addition, nine factors (gender, source of cohort, geographic area, major confounders adjusted, publication year, quality score, ethnicity, exposure level, and sample size), which may be potential sources of heterogeneity, were tested by a meta-regression method. Only the exposure level had statistical significance in a multivariate model ($P < 0.001$).

cumulative meta-analysis and sensitivity analysis

Cumulative meta-analyses show that the estimates gradually became consistent, and the corresponding CIs narrowed down with the increase of the number of included studies in the order of publication year (Figure 3). We also carried out sensitivity analysis, and the pooled results did not change evidently even if the most influential study was omitted (supplemental Figure S1, available at *Annals of Oncology* online).

dose–response meta-analysis

In this stage, 13 studies [7, 8, 25–28, 31–35, 37, 38] including 37 554 all cancer deaths were eligible. Figure 4 gives the dose–response relationship between alcohol consumption and all cancer mortality among MF, M, and F. When compared with non/occasional drinkers, the average ethanol intake of 12.5 g/day increased 6.2% of the risk of all cancer mortality for MF. As shown in Figure 4A, the nadir indicated that the most protective effect (RR = 0.97, 95% CI 0.94–1.00) was observed at a dose of 12.7 g/day. And a borderline increased risk (RR = 1.00, 95% CI 0.97–1.04) was detected at a daily dose of 22.3 g followed by a continuously increasing risk with an increase in the exposure level. The risk became statistically significant (RR = 1.04, 95% CI 1.00–1.08) at a daily intake of 27.2 g. The overall dose–response relationship approximated to a J-shaped curve.

Table 1. Characteristics of cohort studies included in the meta-analysis on alcohol consumption and all cancer mortality

Study (reference)	Country and name of the study	Quality score	No. of deaths	No. at risk	Duration of follow-up (years)	Gender	Age	Variables adjusted for in the regression models
Kono et al. [24]	Japan, male physicians in western Japan	7	380	4643 (PR)	19	M	27–89	Age and smoking
Boffetta and Garfinkel [25]	USA, men enrolled in a large American Cancer Society prospective study	7	9293	2 907 872 (PY)	12	M	40–59	Age and smoking
Berberian et al. [8]	Netherland, Epidemiological Prevention Study of Zoetermeer follow-up study	7.5	57	1620 (PR)	10	M, F, MF	≥20	Age, BMI, serum cholesterol, systolic blood pressure, diastolic blood pressure, pulse rate, cigarette smoking, and history of antihypertension drug use
Fuchs et al. [26]	USA, The Nurses' Health Study	5	1495	1 010 209 (PY)	12	F	35–59	Age, smoking status, BMI, regular aspirin use, regular vigorous exercise, high plasma cholesterol level, diabetes, hypertension, myocardial infarction in a parent at 60 years of age, past or present oral-contraceptive use, menopausal status, past or present postmenopausal hormone use, and energy-adjusted intake of dietary fiber and saturated fat
Thun et al. [7]	USA, Cancer Prevention Study II	7	12 363	490 000 (PR)	9	M, F	30–104	Education, BMI, smoking, a crude index of fat consumption, and the use or nonuse of estrogen-replacement therapy
Maskarinec et al. [28]	USA, multiethnic cohort in Hawaii	5,5	1155	423 655 (PY)	19	M, F	≥30	Age, ethnicity, smoking, BMI, and years of education
Renaud et al. [27]	France, Centre de Medecine Preventive de Nancy for health examination	6	795	418 068 (PY)	10–15	M	40–60	Age, education, smoking, serum total cholesterol, systolic blood pressure, and BMI
Gaziano et al. [30]	USA, Physicians' Health Study	3.5	944	89 299 (PR)	5.5	M	40–84	Age and other coronary risk factors, including smoking, diabetes, exercise, and BMI
Grønbæk et al. [29]	Denmark, Copenhagen Centre for Prospective Population Studies	6.5	1552	257 859 (PY)	9	MF	20–98	Age, sex, smoking habits, educational level, physical activity, and BMI
Inoue and Tsugane [32]	Japan, Japan Public Health Center-based Prospective Study	7.5	1208	721 302.5 (PY)	9.8	M, F	40–59	Age, study area, pack-years of smoking, green vegetable intake, and leisure-time physical activity
Ebbert et al. [31]	USA, Iowa Women's Health Study	6.5	1607	404 377(PY)	14	F	55–69	Hypertension, diabetes, education, marital status, physical activity, BMI, waist-to-hip ratio, hormone-replacement therapy, vitamin supplement use, fruit/vegetable consumption, red meat consumption, total caloric intake, whole-grain intake, cholesterol intake, vitamin E intake, and pack-years
Ozasa [34]	Japan, Japan Collaborative Cohort Study for Evaluation of Cancer	5.5	6219	1 291 361(PY)	/	M, F	/	Age and area
Xu et al. [33]	China, Shanghai Women's Health Study	8.5	982	297 396 (PY)	4.6	M	30–89	Age, education, BMI, and history of any cancer, chronic bronchitis, diabetes, hypertension, coronary heart disease, and stroke, number of cigarettes smoked per day, and tea consumption
Sadakane et al. (2009) [35]	Japan, The Jichi Medical School Cohort Study	6.5	246	107 385 (PY)	12	M, F	56.3 (M) 56.4 (F)	Age, tobacco smoking, education level, marital status, BMI, and physical activity index
Kim et al. [9]	Korea, Korea National Health Insurance Corporation's Health Examinee Cohort in 2000 (HEC 2000)	6	8407	1 341 393 (PY)	5	M, F	40–69	Age, residential, smoking status exercise, BMI, systolic and diastolic blood pressure, and fasting blood sugar

Ramadas et al. [36]	India, cluster-randomized community-based cohort	6	1092	1 060 067 (PY)	6.5	MF	≥34		Sex, age, chewing habits, smoking habits, alcohol consumption, occupation, education, vegetables intake, fruits intake, equipment, study group, religion
Behrens et al. [37]	Swedish, Swedish Women's Lifestyle and Health Study	8.5	673	713 295 (PY)	15	F	30–49		Age, BMI, saturate fat intake, smoking status, smoking intensities, physical activity, and education
Breslow et al. [38]	USA, National Health Interview Survey	6	362	82 716 472 (PY)	11	M, F, MF	≥18		Race/ethnicity, education, region, marital status, smoking status, BMI, and sex

PR, person at risk; PY, person-year; M, male; F, female; MF, male and female; BMI, body-mass index.

The gender-specific dose–response relationship was also explored. A *J*-shaped trend was observed among M (Figure 4B), and the risk estimate increased by 6.3% for every 12.5 g daily ethanol intake. The ethanol consumption of 12.8 g/day and 20.1 g/day produced the nadir (RR = 0.99, 95% CI 0.96–1.02) and a marginal increased risk (RR = 1.00, 95% CI 0.96–1.04), respectively. The risk elevated significantly at the exposure level of 28.7 g/day (RR = 1.04, 95% CI 1.00–1.09). For females, every daily ethanol intake of 12.5 g would lead to an average risk increase by 3.9%. Figure 4C shows that the most significant negative association (RR = 0.92, 95% CI 0.86–0.98) occurred at a dose of 9.1 g/day. The elevated risk (RR = 1.00, 95% CI 0.94–1.07) initiated at the exposure level of 17.4 g/day. Then, with the increase of ethanol intake, the risk increased sharply to a peak (RR = 1.27, 95% CI 1.12–1.43) at a dose of 43.6 g/day. However, an inverse risk with wide CI was observed at a daily ethanol intake of ≥75.9 g.

In addition, evidences of nonlinearity as well as between-study heterogeneity were detected. All *P* values for nonlinear assessment were <0.05. We also did not find any significant difference among study-specific slopes in any of the dose–response fitting model ($P > 0.10$).

publication bias analysis

No evident publication bias was detected by Egger's and Begg's tests for all, light, moderate, and heavy drinking. All *P* values for a two-sided test were >0.05 (supplementary Table S2, available at *Annals of Oncology* online). Besides, Begg's funnel plots did not reveal remarkable asymmetry (supplementary Figure S2, available at *Annals of Oncology* online).

The PRISMA checklist [39] for present meta-analysis is given in supplementary Table S3 (available at *Annals of Oncology* online).

discussion

In this meta-analysis, 18 prospective studies and 48 178 deaths from all cancers were included. A *J*-shaped relationship between alcohol consumption and all cancer mortality was found, indicating an inverse association at a light exposure level (≤12.5 g/day), while a positive association at a heavy exposure level (≥50 g/day). As for gender-specific dose–response association, a *J*-shaped curve was found in males but not in females, which are consistent with those of a pooled analysis of six large-scale cohort studies in Japan [40]. Similar negative effects were observed for both the genders when alcohol exposure is light, in agreement with previous findings in all cancer [40] and all-cause mortality [5]. However, with an increase in alcohol consumption, the dose–risk relation differs evidently, and a positive association occurs at dose lower in females than in males. An updated meta-analysis of 34 prospective studies [5] also shows a similar phenomenon in the association between alcohol dosing and total mortality. And the authors suggest that women are more exposed than men to all-cause death at moderate-to-high levels of alcohol consumption, probably owing to increasing risk of cancer [5, 41].

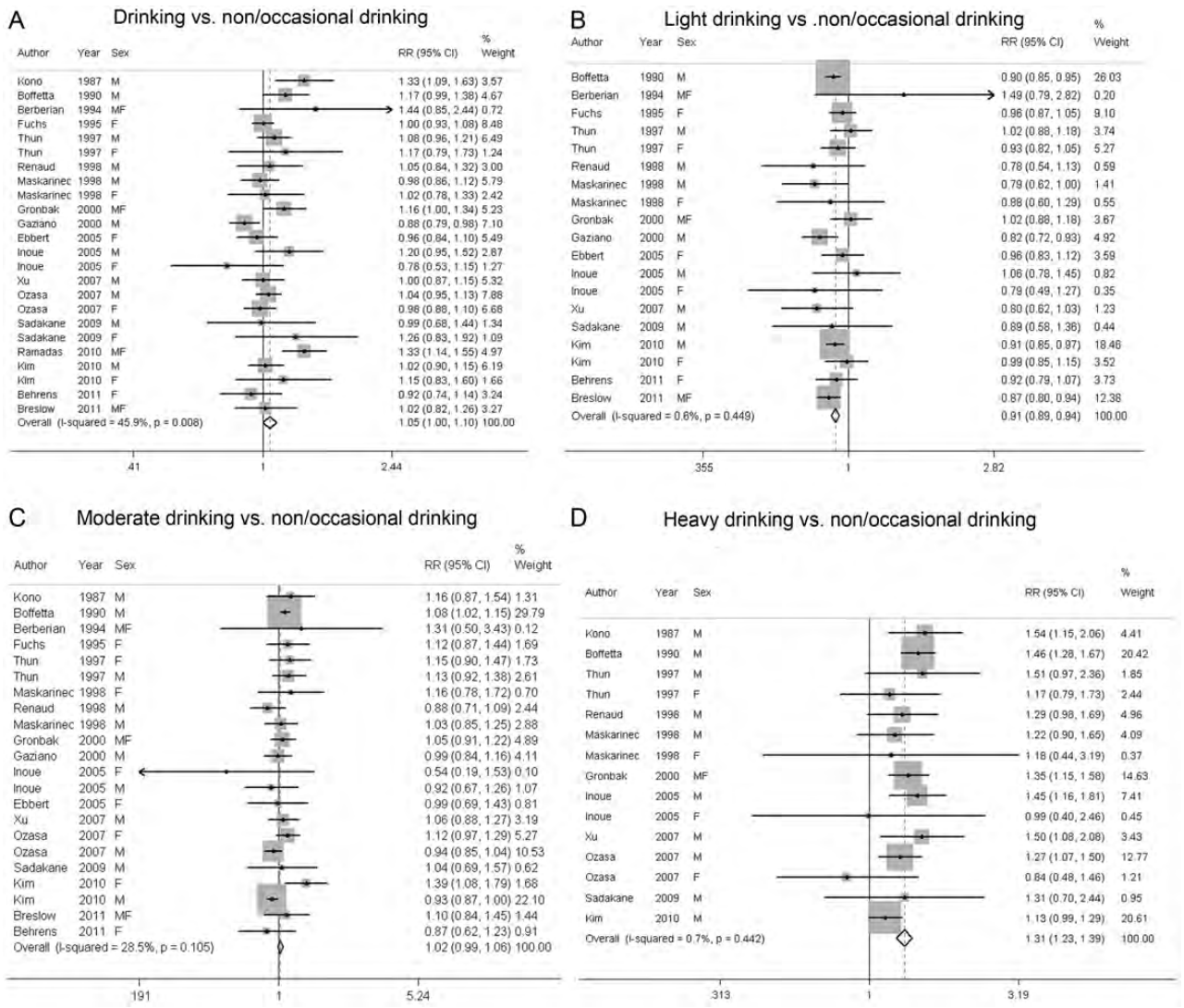

Figure 2. Forest plots for pooled relative risks (RRs) and the corresponding 95% confidence intervals (CIs) of all cancer mortality for all (A), light (B), moderate (C), and heavy (D) drinking.

The World Health Organization IARC on the Cancer Monograph Working Group puts forward causal relations between alcohol consumption and the occurrence of oral cavity, pharynx, larynx, esophagus, liver, colorectal, and female breast cancers, possible increased risk of lung and stomach cancers, 'evidence suggesting lack of carcinogenicity' for renal-cell cancer and non-Hodgkin's lymphoma, and uncertain association for other cancers [42]. A series of meta-analyses provide more evidence for inconsistent correlations between different types of cancer and alcohol consumption [11, 12, 43–45]. The risk difference between the genders might be due to the discrepancy in cancer spectrum, the body composition of lower water in females, different biological characteristics of alcohol metabolism, or other unknown potential factors [46, 47]. The nonsignificant increased risk at heavy exposure levels for females might derive from relatively small sample size but not real effect.

Significant differences were also observed across subgroups stratified by geographic area, publication year, quality score, and ethnicity at moderate exposure levels. A positive relation demonstrated in the pooled result from studies with higher quality indicates the importance of the quality of study. As for the geographic area and ethnicity, the results of different types of cancer and different studies are inconsistent, which should be further explored. The group information of the former and current drinkers was quoted directly from five eligible studies [33–36, 38]. The former drinkers show higher risk of all cancer mortality than the current drinkers, in accordance with the previous finding [40]. This discrepancy could be interpreted as 'healthy drinkers effect' that former drinkers ceased drinking because of health problems certainly including cancer lesion [48].

Several strengths could be highlighted in this study. First, all included studies were prospective cohort studies with less information bias. Second, the combined use of categorical and dose–response meta-analyses can provide more information [49]. Third, though marked between-study heterogeneity was observed in categorical meta-analysis as drinkers versus non/

Table 2. Pooled and subgroup analyses stratified by gender, source of cohort, geographic area, and potential-related factors

	Drinking versus non/occasional			Light versus non/occasional			Moderate versus non/occasional			Heavy versus non/occasional		
	N^a	Relative risk (RR, 95% CI)	P value [b]	N^a	RR (95%CI)	P value[b]	N^a	RR (95%CI)	P value [b]	N^a	RR (95%CI)	P value[b]
Overall	18	1.05(1.00–1.10)	–	15	0.91(0.89–0.94)	–	17	1.02(0.99–1.06)	–	11	1.31(1.23–1.39)	–
Gender[c]												
Male	13	1.05(0.99–1.11)	0.214	11	0.91(0.87–0.94)	0.270	13	1.01(0.97–1.05)	0.005	10	1.32(1.23–1.43)	0.134
Female	11	0.99(0.94–1.04)		9	0.94(0.89–0.99)		10	1.14(1.05–1.24)		4	1.05(0.79–1.40)	
Source of cohort												
Population-based	14	1.06(1.02–1.11)	0.020	12	0.91(0.88–0.94)	0.840	13	1.03(0.98–1.09)	0.732	10	1.30(1.22–1.38)	0.263
Occupation-specific	4	1.01 (0.89–1.14)		3	0.91 (0.82–1.01)		4	1.04 (0.93–1.17)		1	1.54 (1.15–2.06)	
Geographic area												
Asia	7	1.09 (1.00–1.17)	0.075	4	0.92 (0.87–0.97)	0.499	6	1.03 (0.94–1.13)	0.024	6	1.25 (1.15–1.37)	0.306
Europe	4	1.08 (0.98–1.20)		4	0.96 (0.87–1.06)		4	0.98 (0.88–1.10)		2	1.33 (1.16–1.53)	
North America	7	1.00 (0.95–1.04)		7	0.91 (0.87–0.94)		7	1.08 (1.02–1.13)		3	1.40 (1.25–1.56)	
Major confounders adjusted[d]												
Adjusted	12	1.06 (0.99–1.13)	0.917	10	0.91 (0.88–0.94)	0.771	11	1.03 (0.96–1.09)	0.821	8	1.33 (1.23–1.44)	0.434
Unadjusted/partly adjusted	6	1.03 (0.98–1.08)		5	0.92 (0.87–0.97)		6	1.03 (0.96–1.10)		3	1.25 (1.09–1.43)	
Publication year												
<2000	7	1.05 (1.00–1.10)	0.323	6	0.91 (0.87–0.94)	0.597	7	1.08 (1.02–1.13)	0.009	5	1.40 (1.27–1.54)	0.095
≥2000	11	1.03 (0.97–1.10)		9	0.91 (0.87–0.94)		10	0.99 (0.94–1.03)		6	1.26 (1.17–1.36)	
Quality score												
≥Median	10	1.08 (1.02–1.14)	0.043	9	0.93 (0.89–0.97)	0.297	10	1.07 (1.02–1.12)	0.010	7	1.42 (1.31–1.54)	0.694
<Median	8	1.02 (0.96–1.08)		6	0.90 (0.86–0.94)		7	1.02 (0.95–1.10)		4	1.19 (1.08–1.30)	
Ethnicity[e]												
Asian	6	1.04 (0.99–1.09)	0.770	4	0.92 (0.87–0.97)	0.913	6	1.03 (0.94–1.13)	0.023	6	1.25 (1.15–1.37)	0.108
Caucasian	11	1.06 (0.98–1.14)		10	0.91 (0.88–0.94)		10	1.06 (1.01–1.11)		4	1.39 (1.27–1.52)	

[a]The number of studies included.

[b]P for heterogeneity between strata.

[c]Studies which reported or could calculate the gender-specific estimates were selected.

[d]Age, gender, and cigarette smoking;

[e]Study reported by Maskarinec et al. [28] containing multiple ethnicities was not included in the subgroup analysis of ethnicity.

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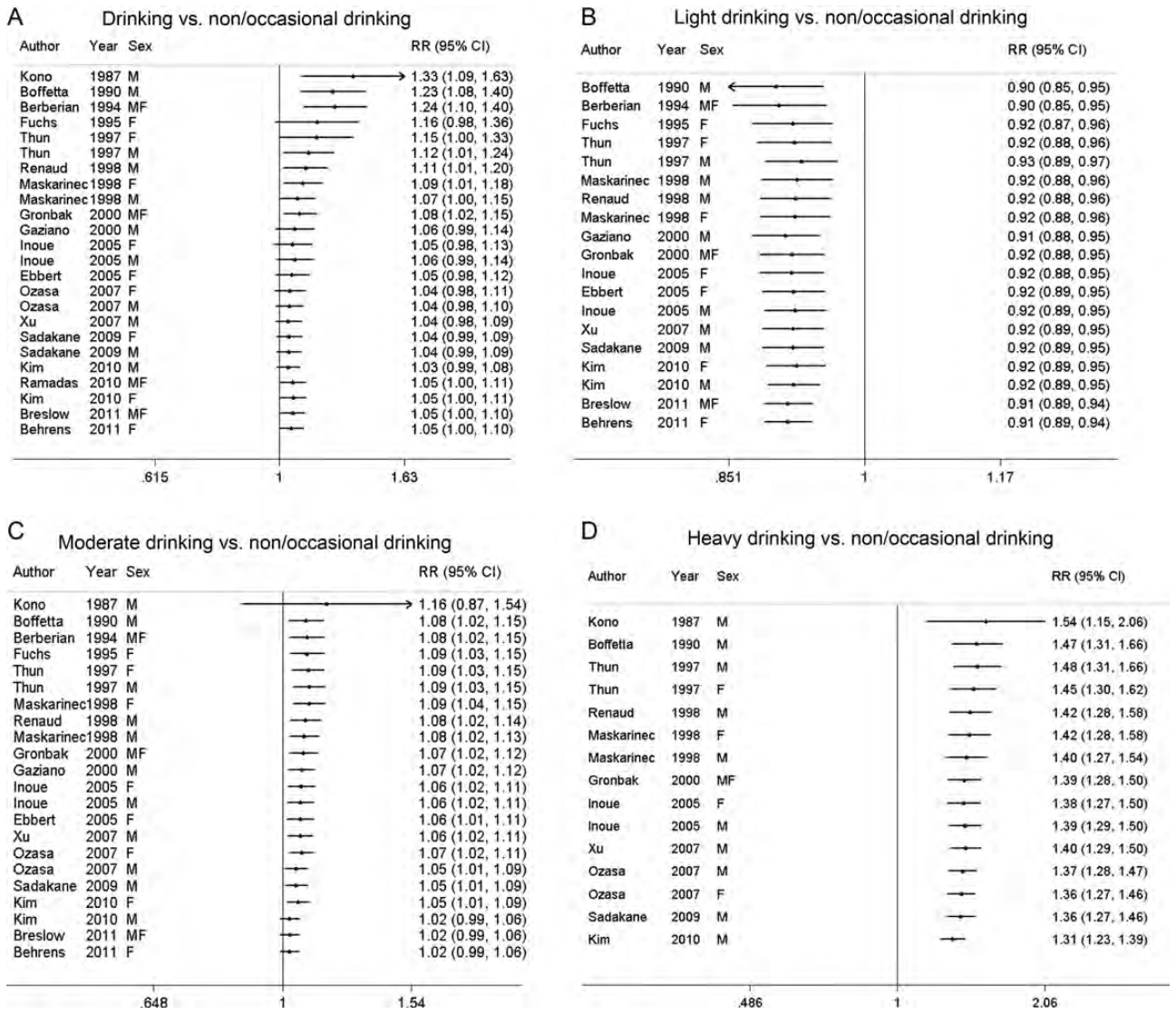

Figure 3. Cumulative meta-analysis for all (A), light (B), moderate (C), and heavy (D) drinking. Each study was put into the pooled analysis one by one according to the publication year.

occasional drinkers, it became nonsignificant after the dose grouping. Robust results were also obtained from cumulative meta-analysis and sensitivity analysis. Moreover, the results of Begg's test, Egger's test, and Begg's funnel plots did not support the existence of major publication bias.

Several limitations should be also noticed. The first is, when the multivariate-adjusted estimates were unavailable, that the calculated estimates without adjustment are likely to have potential confounding. Nevertheless, the results were consistent between subgroups stratified by 'major confounders adjusted (age, gender, and cigarette smoking)'. Second, most studies (16/18) collected information by self-reporting questionnaires, which might lead to information bias. Lastly, the results were prone to be influenced by possible exposure misclassification as the exposure dose was estimated with median for interval exposure, and the lower bound added to the three-quarters of the adjacent previous category for the highest open-ended exposure.

A community-based cross-sectional study suggests that heavy and frequent/episodic drinking is strongly associated with health problems [50]. Besides, the consumption of different kinds of alcohol beverage (beer, wine, liquor, spirit etc.) is related to certain dietary patterns [51, 52] and other health-related lifestyles [49]. It was also reported that the antioxidative compounds rich in wine and the carcinogens (such as nitrosamines and polycyclic aromatic hydrocarbon) rich in beer and liquors might play a role in carcinogenesis [53]. However, the cumulative time, frequency, and pattern of alcohol drinking were not analyzed comprehensively in the present study due to insufficient data.

In summary, this meta-analysis shows a *J*-shaped relationship between alcohol consumption and all cancer mortality, which confirms the health hazards of heavy drinking (≥50 g/day) and benefits of light drinking (≤12.5 g/day). As for the gender-specific dose–risk relation, special attention should be paid to the impact of heavy drinking in females.

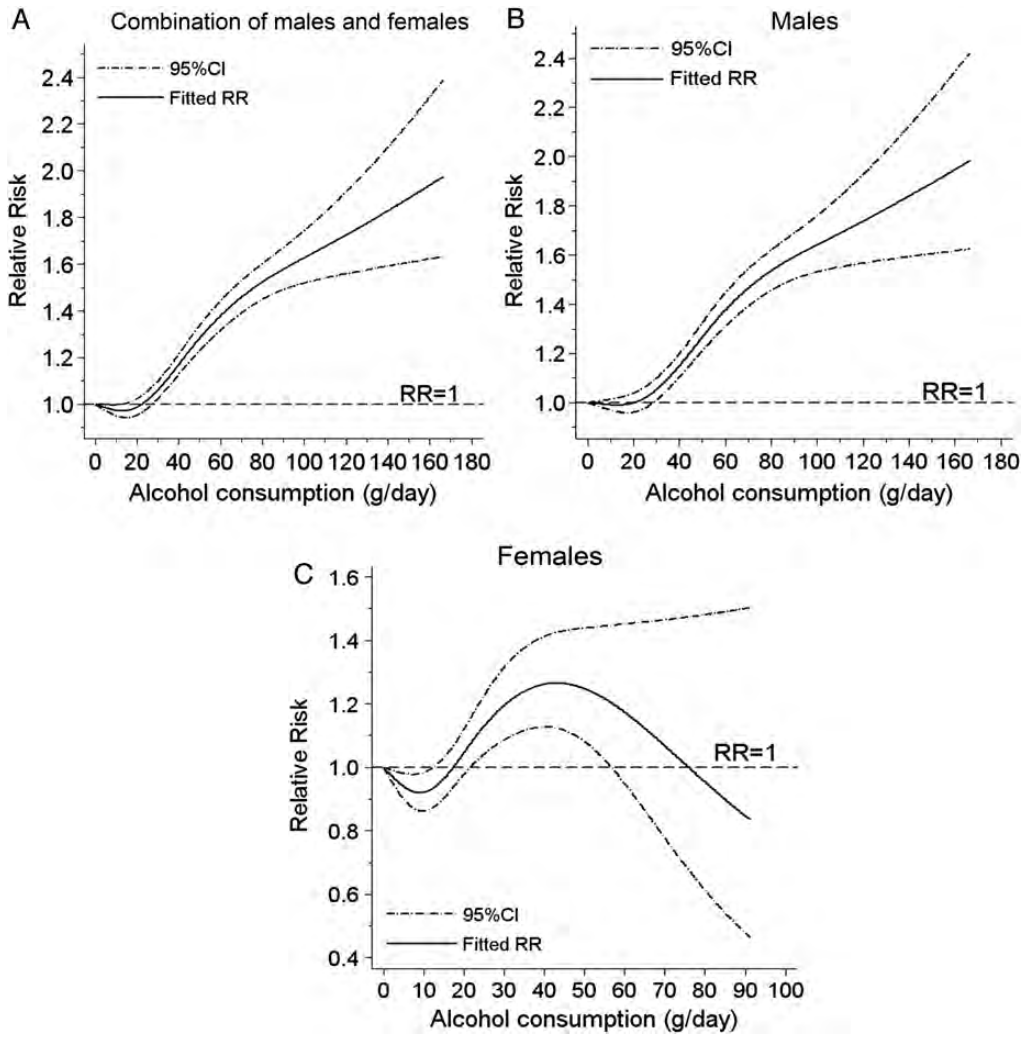

Figure 4. Relative risks (RRs) and the corresponding 95% confidence intervals (CIs) for the dose–response relationship between alcohol consumption (grams per day) and all cancer mortality among the combination of males and females (A), males (B), and females (C). The *P* values for the nonlinearity test were all <0.001. Data fitting was based on fixed-effects restricted cubic spline models using the fixed percentiles 5%, 35%, 65%, and 95% as knot locations.

Large-sample, well-designed, prospective epidemiological studies, especially on heavy drinking among women, should be developed in future.

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disclosure

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