Annals of Oncology Advance Access published March 14, 2014

review

Annals of Oncology 00: 1–10, 2014
doi:10.1093/annonc/mdu020

Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies

F. Turati[1], C. Galeone[1], M. Rota[1,2], C. Pelucchi[1]*, E. Negri[1], V. Bagnardi[3,4], G. Corrao[3], P. Boffetta[5] & C. La Vecchia[1,6]

[1]*Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milan,;* [2]*Department of Health Sciences, Centre of Biostatistics for Clinical Epidemiology, University of Milan-Bicocca, Monza,;* [3]*Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan,;* [4]*Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy;* [5]*The Tisch Cancer Institute and Institute for Translational Epidemiology, Mount Sinai School of Medicine, New York, USA;* [6]*Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*

Received 24 October 2013; revised 4 December 2013; accepted 5 December 2013

Despite several studies support a positive association between heavy alcohol consumption and liver cancer risk, a consistent dose–risk relationship has not yet been established. We carried out a systematic review and a meta-analysis of the association between alcohol intake and liver cancer occurrence, following the Meta-analysis Of Observational Studies in Epidemiology guidelines. We searched for cohort and nested case–control studies on the general population published before April 2013, using PubMed and EMBASE. Summary meta-analytic relative risks (RRs) were estimated using random-effect models. We included 16 articles (19 cohorts) for a total of 4445 incident cases and 5550 deaths from liver cancer. Compared with non-drinking, the pooled RRs were 0.91 (95% confidence interval, CI, 0.81–1.02) for moderate drinking (<3 drinks per day) and 1.16 (95% CI, 1.01–1.34) for heavy drinking (≥3 drinks per day), with significant heterogeneity among studies. The dose–risk curve suggested a linear relationship with increasing alcohol intake in drinkers, with estimated excess risk of 46% for 50 g of ethanol per day and 66% for 100 g per day. This systematic review suggests a moderate detrimental role of consumption of 3 or more alcoholic drinks per day on liver cancer, and a lack of association with moderate drinking. Our results have to be taken with due caution on account of the possible limitations of the original studies included in the meta-analysis.

Key words: alcohol, liver cancer, epidemiology, meta-analysis, risk factors, systematic review

introduction

Worldwide, the major risk factors for hepatocellular carcinoma (HCC), the most frequent histological type of primary liver cancer, are persistent infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), both of which increase the risk of liver cancer some 20-fold [1]. Other established risk factors include non-alcoholic fatty liver disease, tobacco smoking, exposure to aflatoxine-contaminated food, and some rare inherited disorders, including hereditary hemochromatosis [2]. Most, but not all, HCCs occur in cirrhotic livers, and cirrhosis is a pathogenic step in liver carcinogenesis [3]. In alcoholics, prolonged, excessive alcohol consumption results in alcoholic cirrhosis. Moreover, alcohol may enhance and/or accelerate hepatocarcinogenesis in patients with HBV and/or HCV infection, hereditary hemochromatosis, or non-alcoholic fatty liver disease [4].

Alcohol has been associated with increased risk of primary liver cancer [5, 6], although not as strongly as for cancers of the upper aerodigestive tract [5]. Thereby, despite the high number of studies supporting an association between heavy alcohol consumption and liver cancer, a consistent dose–risk relationship has not yet been established. Moreover, most of the evidence is based on case–control studies, in which the association is likely to be underestimated, as most alcohol-related liver cancers follow liver diseases—and in particular cirrhosis—which leads to a reduction in alcohol drinking [3].

Therefore, we systematically reviewed prospective studies and quantitatively assessed the association between alcohol intake and liver cancer risk. Only studies with a prospective design, in which alcohol consumption was assessed at baseline, i.e. before liver cancer occurrence, were included, in order to avoid bias caused by alcohol cessation/reduction following clinical symptoms.

materials and methods

search strategy and data collection

In this meta-analysis, we followed the guidelines for reporting developed by the Meta-analysis Of Observational Studies in Epidemiology group [7]. In April 2013, two authors (FT and CG) carried out a systematic literature search in the Medline

*Correspondence to: Dr Claudio Pelucchi, Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, via Giuseppe La Masa 19, 20156 Milan, Italy. Tel: +39-02-39014577; Fax: +39-02-33200231; E-mail: claudio.pelucchi@marionegri.it

database, using PubMed, and in EMBASE for all prospective studies investigating the association between alcohol and liver cancer incidence or mortality.

Because the nested case–control study in a prospective cohort is just an efficient sampling of the same cohort study and thus retains the same prospective advantages of the cohort, including the fact that dietary information was collected among apparently healthy participants at baseline before the development of the outcome of interest, we also searched for nested case–control studies. We used the following search string in PubMed: (alcohol OR ethanol) AND (liver OR hepatocellular) AND (cancer OR neoplasm OR carcinoma) AND (cohort OR cohort studies[MeSH Terms] OR prospective). A similar strategy was used to search Embase. The searches were limited to studies written in English.

The same authors retrieved and assessed potentially relevant articles; abstracts and unpublished studies were not included. No studies were excluded a priori for weakness of design or data quality. Each publication identified was reviewed and included in the analysis if the following criteria were met: cohort or nested case–control study conducted on the general population, considering at least three levels of alcohol consumption, and reporting the estimates of the relative risk (RR)/odds ratio/hazard ratio for primary liver cancer or HCC and the corresponding confidence interval (CI)—or information sufficient to calculate them—for each exposure level. Studies on special populations (e.g. cohorts of cirrhotic patients, patients HBV/HCV infected, or alcoholics), studies considering liver cholangiocarcinoma [8], studies analyzing alcohol consumption by combining in a unique variable information on dose and duration (e.g. cumulative lifetime alcohol intake) [9], or studies that met the inclusion criteria but reported information only on specific types of alcoholic beverages [10, 11] were not included. One nested case–control study reporting odds ratios for HCC mortality according to tertiles of consumption, without providing category boundaries was also excluded [12]. When multiple reports were published on the same study population, we included in the meta-analysis only the most informative one. In particular, we included a pooled analysis of four Japanese cohorts [13], rather than separate publications from the single studies, since one of these cohorts did not publish results on alcohol. By checking the reference list of all papers of interest, we identified three additional publications [14–16].

Two of the authors (FT and MR) independently reviewed all the studies and abstracted the following information in a standard format: study design, country, period of enrolment and/or follow-up, number of subjects (cases, controls or non-cases or cohort size), gender, covariates adjusted for in the analysis, RR estimates (odds ratios or RRs or hazard ratios, collectively referred to as RRs) for categories of alcohol consumption and the corresponding 95% CIs, and, when available, the number of cases and non-cases for each level of alcohol consumption considered.

statistical analysis

In the analyses on amount of alcohol drinking, we used the midpoint of each category of alcohol consumption for each study. For upper, open-ended exposure categories, we used 1.2-fold its lower bound [17]. Grams of ethanol were used as measure for the analyses, defining one drink as 12.5 g of ethanol, if not otherwise specified in the original report, and 1 ml as 0.79 g of ethanol. We used the lowest category of exposure in each study (mostly, non-drinking) as reference category (i.e. non-drinking, hereafter). When original reports provided RRs using a different reference category (e.g. moderate drinking), the new RRs were calculated dividing each RR by the RR for non-drinking, and the corresponding CIs were calculated using the standard errors of the corresponding crude RR estimates, penalized by a factor of 1.5 [13, 16]. One study using moderate drinking as reference category which did not provide information sufficient for estimating CIs for different alcohol doses when compared with non-drinking was not included [18]. In the Million Women Study [19] and in a cohort study from China [20], we derived the floated variances from the 95% floated CIs provided by the authors, to obtain RRs and 95% CIs for different categories of alcohol consumption compared with non-drinking [21]. In a study reporting multivariate RRs but not the corresponding CIs [15], the standard error of the adjusted estimate was obtained by penalizing the standard error of the crude RR by a factor of 1.5. We summarized decisions and operations on original data for each study in the column 'notes' of Table 1.

We defined moderate alcohol drinking as <3 drinks per day, i.e. <37.5 g of ethanol per day, and heavy drinking as ≥3 drinks per day. When more than one estimate in a study fell in the range considered for moderate or heavy drinking, we pooled the corresponding estimates using, whenever possible, the Hamling et al. method [22], thus taking into account their correlation. Otherwise, we used fixed-effects models.

We calculated summary estimates of the RR using random-effects models [i.e. as weighed averages using the inverse of the sum of the variance of the log(RR) and the moment estimator of the variance between studies as weight] [23]. Heterogeneity between studies was assessed using the χ^2 test, defined as a $P < 0.10$, and inconsistency was measured using also the I^2 statistic [24].

We conducted sensitivity analyses by excluding each study at a time from the meta-analysis. In order to investigate possible sources of heterogeneity among studies, we also conducted subgroups analyses according to potentially relevant factors.

For the dose–response analysis, we used a random-effect meta-regression model in a non-linear dose–response relationship framework, providing the best fitting two-term fractional-polynomial model [25]. The presence of publication bias was assessed by examination of funnel plot [26] and by applying the tests proposed by Begg and Mazumdar [27], and by Egger et al. [28]. All the statistical analyses were carried out using the STATA software (version 11; StataCorp, College Station, TX).

results

The present meta-analysis included 16 publications (19 cohorts): 5 publications gave results from nested case–control studies [14, 15, 29–31], 10 from cohort studies [16, 19, 20, 32–38], and 1 from a pooled analysis of 4 cohorts [13], for a total of 4445 incident cases and 5550 deaths from liver cancer (Table 1). Fifteen cohorts were from Asia, two from Europe, and one from the United States; one cohort from Hawaii (United States) included men of Japanese ancestry.

Table 1. Main characteristics of the nested case–control and cohort studies on the association between alcohol consumption and liver cancer risk included in the meta-analysis

First author, year, name of the cohort	Country	No. of cases and sex	No. of controls/ non-cases/cohort size	Enrolment period and duration of follow-up	Adjustment/matching variables	Notes	Cirrhosis/HBV/HCV at baseline
Nested							
Chen et al. 1996 [14]	Taiwan	33 M and W (27 M – 6 W)	123 M and W	1991–1992 (2 years)	Age, sex, residence, date of blood collection	Nested case–control study based on a cohort of 6487 residents in the Penghu Islets (Taiwan) recruited in a community-based two-stage screening program	13% of the controls were HBsAg+, 9.8% were HCVAb+.
Murata et al. 1996 [15]	Japan	66 M	132 M	1984–1993 (9 years)	Age, residence	Nested case–control study based on a cohort of 17 200 men in a gastric mass screening by the Chiba Cancer Association in 1984. 95% CIs were calculated from the SEs of the crude ORs penalized by 1.5, using the distribution of cases and controls across exposure categories	
Yuan et al. 2006 [29]	China	213 M	1087 M	1986/1989–2001 (15 years)	Date of birth, date of blood collection, residence, serum level of retinol	Nested case–control study based on a cohort of 18 244 men followed up in the Shanghai Cohort Study	11.6% of the controls had history of hepatitis or liver cirrhosis; 9.6% were HBsAg+; 0.2% were HCVAb+
Ohishi et al. 2008 [30]	Japan	224 M and W (136 M–88 W)	644 M and W (387 M–257 W)	1970–2002 (baseline questionnaire in 1965 or 1978)	Age, sex, city, time of serum storage, method of serum storage, radiation exposure, smoking, coffee, BMI, diabetes, hepatitis virus infection	Nested case–control study based on the Adult Health Study longitudinal cohort of atomic bomb survivors in Hiroshima and Nagasaki	2.8% of the controls were HBSAg+; 6.4% were HCVAb+ and 0.3% were both HBSAg+ and HCVAb+.
Trichopoulos et al. 2011 [31]	Europe	115 M and W (80 M–35 W)	229 M and W (159 M–70 W)	1992–2006 (9 years)	Age/date/time of day at blood collection, study center, education, BMI, smoking, coffee, chronic HBV infection, chronic HCV infection, and, for women only, menopausal status and exogenous hormones. Stratified by sex	Nested case–control study based on the EPIC Cohort (4 409 809 PY). We included in the meta-analysis sex-specific RRs estimates since cut-off defining exposure categories of alcohol in the analysis on males and females combined were	2.6% of controls had chronic infection with HBV and 3.1% had chronic infection with HCV

Continued

Table 1. *Continued*

First author, year, name of the cohort	Country	No. of cases and sex	No. of controls/ non-cases/cohort size	Enrolment period and duration of follow-up	Adjustment/matching variables	Notes	Cirrhosis/HBV/HCV at baseline
						different according to the gender	
Cohort studies							
Kono et al. 1987 [37] Japanese Physicians' Study	Japan	51 M deaths	5130 M PR	1965–1983 (19 years)	Age, smoking	We defined occasional drinking as 1 go per week, corresponding approximately to 3.11 g of ethanol per day	
Kato et al. 1992 [34] American Men of Japanese Ancestry Study	USA (Hawaii)	53 M (29 cancers of the liver and 24 cancers of the biliary tract)	6701 M PR	1965–1990 (19 years)	Age, smoking	ml of ethanol were converted in g of ethanol by multiplying the dose in ml by 0.79	
Jee et al. 2004 [32] Korean Cancer Prevention Study	Korea	3807 M and W deaths. Only RRs for men were included[a] (n = 3341 HCC deaths)	1 283 112 M and W PR. Only RRs for men were included[a] (n = 823 158 PR) 10 years	1993–2002 (10 years)	Age, smoking, diabetes	Given the similar RRs estimates, HBsAg-not adjusted RRs based on all subjects were included, rather than HBsAg- adjusted RRs, which were based on the 47.2% of the study subjects only	At baseline, 9.4% of men and 6.5% of women were HBsAg+.
Joshi et al. 2008 [33] Cohort of civil servants	Korea	998 M deaths	548 530 M PR 3 268 427 M PY	1999–2004 (6 years)	Age, fasting serum glucose, BMI, smoking, HBsAg status		At baseline, 6.6% of participant were HBsAg +. Data on HCV exposure were not available
Allen et al. 2009 [19] Million Women Study	UK	337 W	1 280 296 W PR 9.2 million PY	1996/2001 – 2006[b] (7.2 years)	Age, region, socioeconomic status, BMI, smoking, physical activity, OC, HRT	RRs and 95% CIs for different categories of alcohol consumption compared with non-drinkers were derived from the 95% floated CIs provided by the authors	
Kim et al. 2010 [35] KNHIC HEC 2000	Korea	1680 M and W (1506 M–174 W)	1 341 393 M and W PR (919 199 M–422 194 W)	2001–2005 (5 years)	Age, residence, smoking, exercise, BMI, systolic and diastolic blood pressure, fasting blood sugar, total cholesterol (only women); stratified by sex		Subjects with liver diseases at baseline and those who died in the same year of the medical examination were excluded
Yi et al. 2010 [38] Kangwha Cohort Study	Korea	55 M and W deaths (36 M–19 W)	6291 M and W PR (2696 M–3595 W)	1985–2005 (20.8 years)	Age, education, BMI, smoking, history of chronic diseases,		Authors reported that results were largely unaffected when

					ginseng, pesticide use. Stratified by sex		excluding subjects who died in the first 2 years
Koh et al. 2011 [36] Singapore Chinese Health Study	Singapore	394 M and W	61 321 M and W PR	1993/1998–2007 (11.5 years)	Age, sex, year of recruitment, dialect group, education, BMI, diabetes, coffee	1 alcoholic drink was converted in 12.8 g of ethanol per day, based on the definition of one drink reported in the paper	A nested case–control study within the cohort revealed that 3% of control subjects were HBsAg+ and 1.0% HCVAb+.
Shimazu et al. 2011 [13] Pooled analysis of 4 cohort studies(1) JPHC I (2) JPHC II (3) JACC (4) MIYAGI	Japan	804 M and W(605 M–199 W) (1) 95 M–31 F (2) 263 M–85 F (3) 156 M–83F (4) 91 M–19 F	174 719 M and W PR(89 863 M–84 856 W) (1) 61 595 M and W PR (2) 78 825 M and W PR (3) 110 792 M and W PR (4) 47 605 M and W PR	11.2 year (1) 1990–2004 (2) 1993/ 1994–2004 (3) 1988/ 1990–2001 (4) 1990–2001	Age, area [in (1), (2), (3)], diabetes, smoking, coffee. Stratified by sex	Reference category was changed from occasional to non-drinkers	Authors reported that no information on HBV and HCV infection status was collected. In the cohort (2), 2.4% of non-cases were HBsAg+ and 5.1 were HCVAb+
Yang et al. 2012 [20]	China	1115 M deaths	218 189 M PR	1990/1991–2006 (15 years)	Age, area, education, smoking	RRs and 95% CIs for different categories of alcohol consumption compared with non-drinkers were derived from the 95% floated CIs provided by the authors	Authors reported a strong positive association between alcohol drinking and mortality from liver cirrhosis
Persson et al. 2013 [16] NIH-AARP Diet and Health Study	United States	435 M and W	494 743 M and W PR	1995/1996–2006 (6.3 years)	Age, sex, race, education, smoking, BMI, diabetes	Reference category was changed from drinkers of <1 drink per day to non-drinkers	Authors reported that the lack of biological samples precluded the determination of HBV and HCV status among the study participants

[a]Results for women were not included in the meta-analysis since the RR was for ever versus never alcohol drinking

[b]In the North Yorkshire and North West Merseyside regions, the last date of follow-up was 31 December 2005; in Scotland, it was 31 December 2002.

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HBsAg, hepatitis B virus surface antigen; HCVAb, hepatitis C virus antibody; HBV, hepatitis B virus; HC, hospital controls; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRT, hormone replacement therapy; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer; JPHC, Japan Public Health Center-based Prospective Study; KNHIC HEC 2000, Korea National Health Insurance Corporation's Health Examinee Cohort in 2000; M, men; NIH-AARP, National Institutes of Health-American Association of Retired Persons; OC, oral contraceptive; OR, odds ratio; PR, person at risk; PY, person-years; RR, relative risk; SE, standard error; W, women.

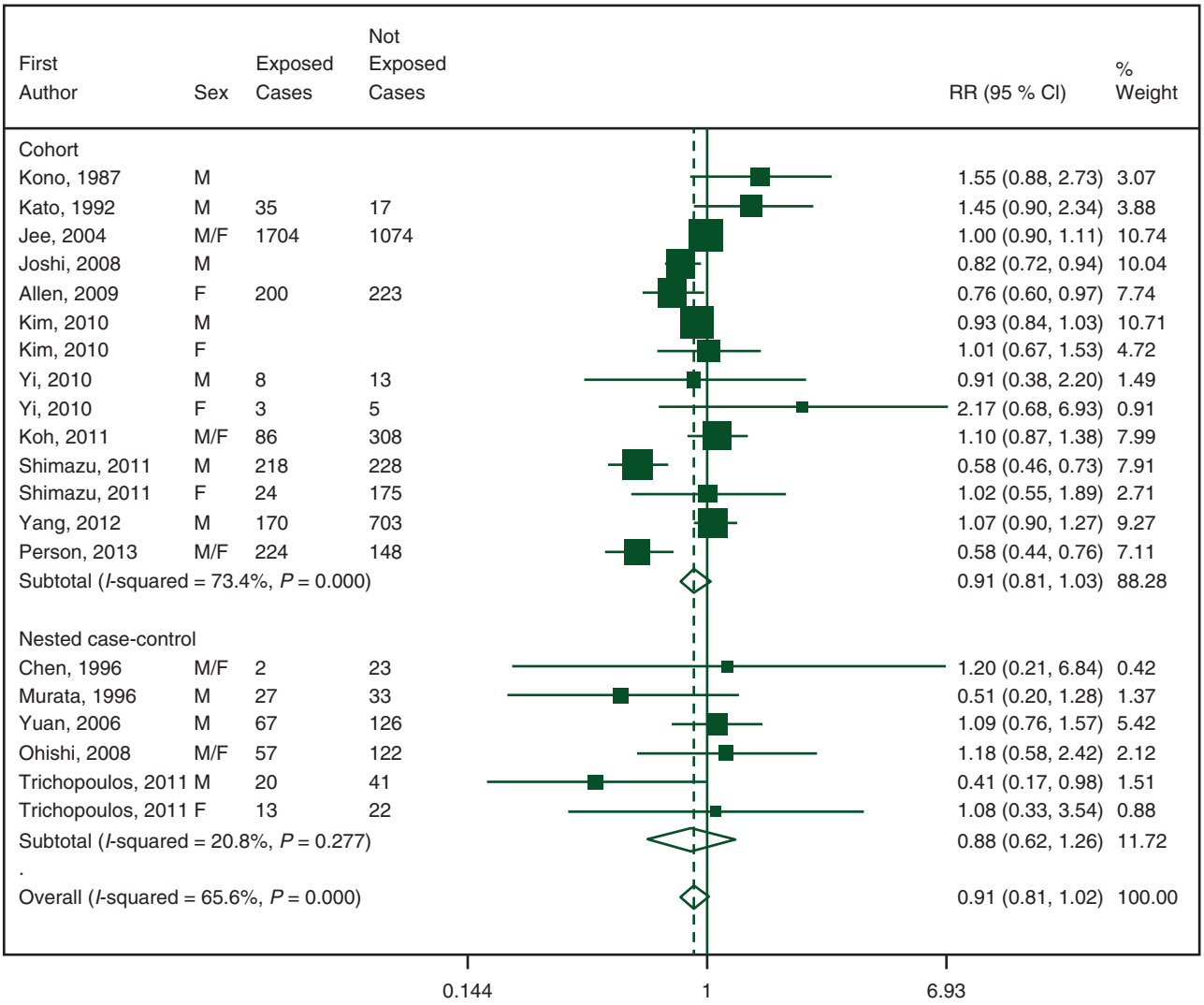

Figure 1. Forest plot for study-specific and pooled relative risk (RRs) and 95% confidence intervals (CI) of liver cancer for moderate alcohol drinking (<3 drinks per day) versus non-drinking.

There was no significant publication bias for both the moderate (P for Begg and Mazumdar's test = 0.496, P for Egger's test = 0.995) and the heavy drinking analyses (P for Begg and Mazumdar's test = 0.161, P for Egger's test = 0.101).

Figure 1 shows the study-specific and pooled RRs and 95% CIs of liver cancer for moderate drinking, i.e. <3 drinks per day, versus non-drinking. Based on 16 studies, the pooled RR was 0.91 (95% CI, 0.81–1.02), similar between cohort and nested case–control studies, with significant heterogeneity among studies ($P < 0.001$, $I^2 = 65.6\%$).

Figure 2 shows the study-specific and pooled RRs and 95% CIs of liver cancer for heavy drinking, i.e. ≥3 drinks per day, versus non-drinking. Ten RR estimates were above unity (significant in 6 studies) and three were below unity (non significant), resulting in a pooled RR of 1.16 (95% CI, 1.01–1.34), based on 13 studies. There was significant heterogeneity among studies ($P = 0.002$, $I^2 = 60.5\%$). The pooled RRs were 1.08 (95% CI, 0.98–1.19) for cohort (P for heterogeneity = 0.123, $I^2 = 38.4\%$) and 2.63 (95% CI, 1.62–4.28) for nested case–control studies (P for heterogeneity = 0.359, $I^2 = 8.3\%$). The exclusion of each study in turn did not materially change the pointwise estimate of the RR. However, statistical significance was lost after the exclusion, in turn, of 6 [14, 20, 29, 30, 35, 37] of the 13 studies from the meta-analysis. When heavy drinking was defined as ≥6 drinks per day, i.e. ≥75 g of ethanol per day, the pooled RR from six studies was 1.22 (95% CI, 1.10–1.35), with no significant heterogeneity ($P = 0.786$, $I^2 = 0\%$).

Table 2 gives the pooled RRs and 95% CIs of liver cancer at different levels of alcohol drinking in strata of selected factors. Results for moderate and heavy drinking were not materially different in strata of sex, geographic area, and outcome. Considering adjustment for hepatitis, very similar RRs were found for moderate drinking, while, for heavy drinking, an RR of 1.25 (95% CI, 1.01–1.55) was estimated from studies not adjusting for hepatitis and an RR of 1.08 (95% CI, 0.88–1.33) from those adjusting for hepatitis.

Figure 3 gives the dose–risk curve and the 95% pointwise confidence bands for the relation between alcohol consumption and cancer of the liver. Among the two terms fractional–polynomial models, the linear regression represented the best-fitting

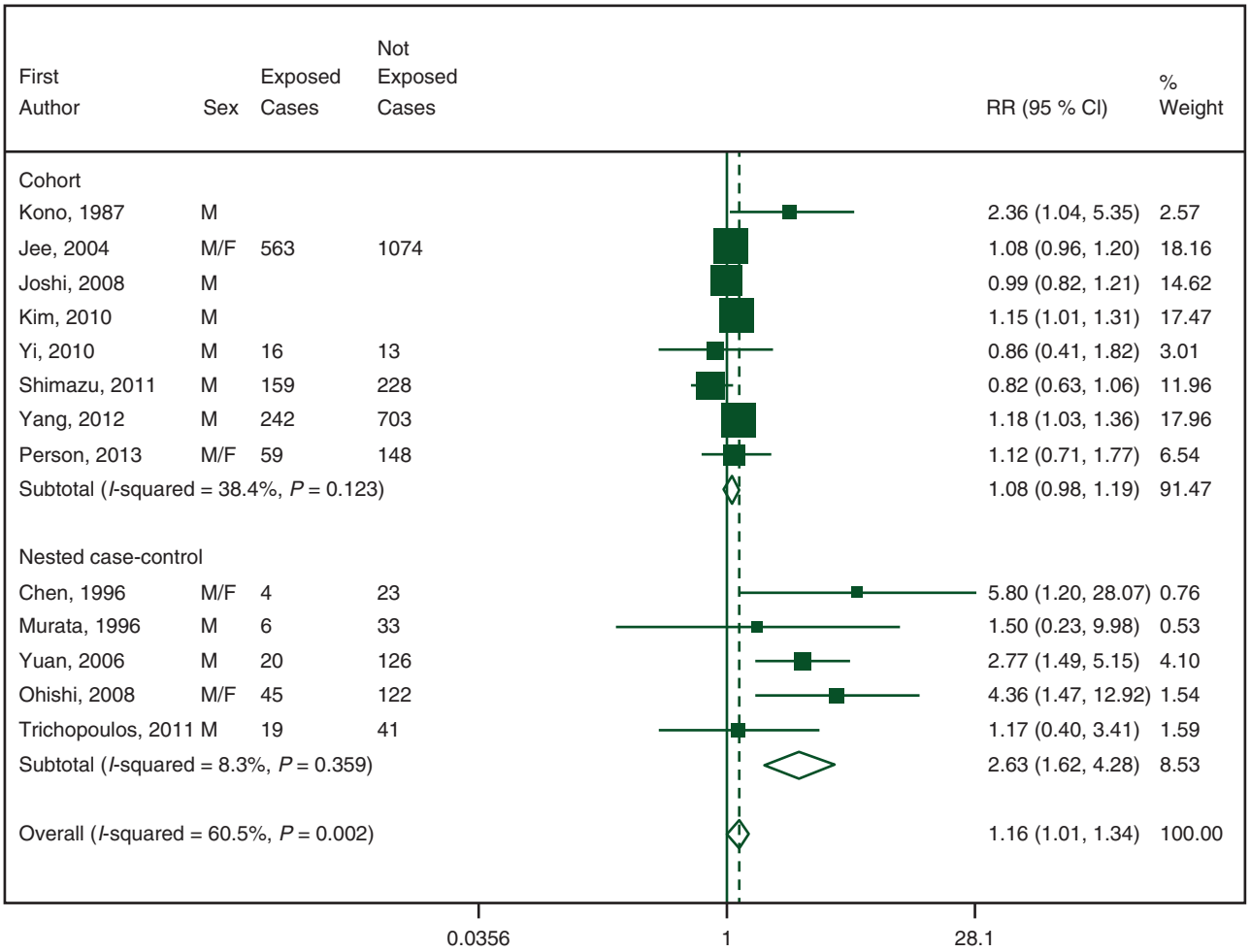

Figure 2. Forest plot for study-specific and pooled RRs and 95% CIs of liver cancer for heavy alcohol drinking (≥3 drinks per day) versus non-drinking.

Table 2. Summary relative risk (RR) and 95% confidence intervals (CI) for heavy (≥3 drinks per day) and moderate (<3 drinks per day) drinking, compared with non-drinking, overall and by strata of selected covariates

	Moderate drinking (<3 drinks per day)				Heavy drinking (≥3 drinks per day)			
	n studies	RR (95% CI)	I^2 (%)	*P* heterogeneity	*n* studies	RR (95% CI)	I^2 (%)	*P* heterogeneity
All	16	0.91 (0.81–1.02)	65.6	<0.001	13	1.16 (1.01–1.34)	60.5	0.002
Sex								
Males	10	0.90 (0.76–1.07)	72.9	<0.001	9	1.14 (0.96–1.34)	59.5	0.011
Females	5	0.89 (0.71–1.12)	10.9	0.344	—	—	—	—
Area								
Asia[a]	13	0.97 (0.86–1.08)	59.8	0.001	11	1.17 (1.00–1.37)	67.1	0.001
Other	3	0.66 (0.52–0.84)	26.1	0.225	2	1.13 (0.75–1.71)	0.0	0.945
Hepatitis adjustment								
No	11	0.91 (0.78–1.07)	72.6	<0.001	8	1.25 (1.01–1.55)	67.4	0.003
Yes[b]	5	0.92 (0.77–1.10)	46.0	0.085	5	1.08 (0.88–1.33)	45.3	0.120
Outcome								
Incidence	10	0.84 (0.67–1.05)	68.3	<0.001	7	1.70 (0.89–2.93)	75.0	0.001
Mortality	6	0.97 (0.88–1.07)	42.8	0.093	6	1.11 (1.03–1.21)	20.9	0.276

[a]Including one study carried out in Hawaii on men of Japanese ancestry [34].
[b]Including one study adjusting for chronic conditions [38].

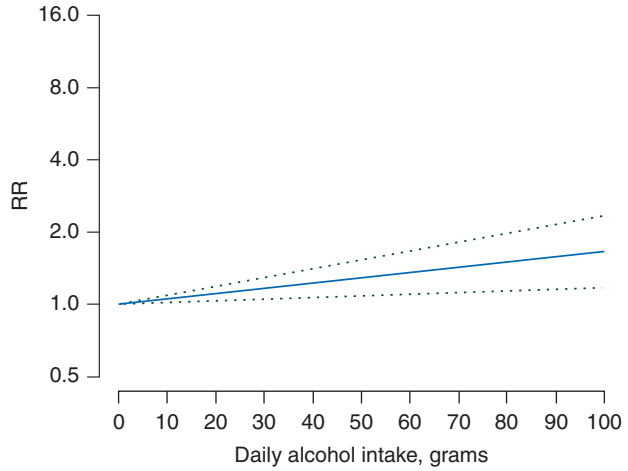

Figure 3. RR function and the corresponding 95% CI describing the best-fitting dose–response relationship between alcohol consumption and the risk of liver cancer.

dose–response relationship, leading to pooled RR estimates of 1.06 (95% CI, 1.02–1.11) for 12 g, 1.13 (95% CI, 1.04–1.24) for 25 g, 1.29 (95% CI, 1.08–1.53) for 50 g, 1.46 (95% CI, 1.13–1.89) for 75 g, and 1.66 (95% CI, 1.17–2.34) for 100 g of ethanol per day.

discussion

This meta-analysis of 19 cohorts, including a total of 4445 incident cases and 5550 deaths from liver cancer, found a significant 16% increased risk of liver cancer among alcohol drinkers of 3 or more drinks per day, compared with non-drinkers. Evidence of a positive association between heavy alcohol drinking and liver cancer derived mainly from nested case–control studies. The increased risk for those drinking 6 or more drinks per day, compared with non-drinkers, was 22%. Moderate drinkers (i.e. drinkers of <3 drinks per day) were not at increased risk of liver cancer. The dose–risk curve suggested a linear relationship with increasing alcohol intake in drinkers, with estimated excess risk of 46% for 50 g of ethanol per day and 66% for 100 g per day, and points to a possible strong detrimental effect of even higher doses of alcohol. However, quantitative data provided from original studies included in this meta-analysis did not allow us to provide reliable meta-analytic RR estimates for such elevated alcohol doses. A detrimental role of extremely high alcohol doses has been suggested by studies on alcoholics and cirrhotic subjects, which globally showed evidence of a strong association between alcoholism, cirrhosis, and liver cancer [39–43]. Indeed, in alcoholics, prolonged, excessive alcohol consumption results in alcoholic cirrhosis, which is a pathogenic step in liver carcinogenesis [3].

In addition to the carcinogenicity of acetaldehyde, which is the first metabolite of alcohol [6], several potential biologic mechanisms have been proposed to explain the effect of alcohol on hepatocarcinogenesis. These include chronic inflammation, resulting in increased oxidative stress, induction of cytochrome P-450 2E1, leading to increased reactive oxygen species production, lipid peroxidation and DNA damage, a decrease in antioxidant defense and DNA repair, disturbed methyltransfer associated with DNA hypomethylation, decreased hepatic retinoic acid, iron overload, and impairment of the immune system [4].

An earlier meta-analysis of epidemiological studies on the association between alcohol drinking and the risk of cancer at several sites included data from 17 case–control and 3 cohort studies on liver cancer, for a total of 2294 cases [5]. The RR estimates were 1.17 (95% CI, 1.11–1.23), 1.36 (95% CI, 1.23–1.51), and 1.86 (95% CI, 1.53–2.27) for 25, 50, and 100 g of ethanol per day, respectively. A more recent meta-analysis, assessing the risk for light drinking only and including 7 cohort and 13 case–control studies, gave a RR of 1.03 (95% CI, 0.90–1.17) [44]. A review of the Chinese literature investigating the role of alcohol on several cancers pooled results from 18 case–control studies on HCC and found a summary odds ratio of 1.56 (95% CI, 1.16–2.09) for any drinking versus non-drinking [45]. No information on the dose–risk relationship was provided. A systematic review on alcohol drinking and liver cancer risk among the Japanese population identified 22 cohort and 24 case–control studies [46]. On the basis of those studies, authors concluded that there is convincing evidence that alcohol drinking increases the risk of primary liver cancer. However, the association was not quantified.

A possible explanation for the relatively modest effect of alcohol on liver cancer occurrence is that at least part of the cohorts might have included subjects with chronic liver diseases at baseline. Those subjects are at increased liver cancer risk due to their liver condition, and are likely to have stopped drinking or to have reduced alcohol consumption due to symptoms of the disease or advice from a physician. This would lead to underestimation of the association between alcohol and liver cancer. This may be particularly relevant since most of the studies were conducted in Asia, where the prevalence of HBV is high [47]. However, the association was, if anything, smaller when the analyses were restricted to non-Asian countries. Careful allowance for hepatitis, in addition, did not explain the association between alcohol and liver cancer risk in a case–control study with third-generation enzyme immunoassay [48].

Cohort studies may also underestimate the real association if a considerable proportion of the cohort stops exposure during follow-up. This is a major issue in the analysis of smoking and myocardial infarction whenever part of the cohort stops smoking [49]. However, after stopping exposure, the risk of cancer declines over considerably longer time than the risk of infarction, and in particular the time–risk relation after stopping alcohol drinking gives clear evidence of falls in risk of cancer only after 20 years [50–53].

Among the limitations, significant heterogeneity was detected across studies. Therefore, even if we used random-effects models to take heterogeneity into account, our pooled estimates should be interpreted with caution. A limitation of the dose–risk analysis is that it assumes a dose–response effect with no threshold. Since the slope of the function depends on the level of misclassification in the different categories of alcohol consumption, if heavy drinking is more frequently misclassified than drinking at lower doses, the slope of the dose–risk function at low doses will be over-estimated [25].

It is possible that alcohol consumption is systematically underreported in several studies. This would lead to systematic underestimation of any real association. However, studies

investigating reproducibility and validity of self-reported alcohol drinking in various populations found satisfactory correlation coefficients [54–57].

Another problem regarding misclassification is the inclusion of former drinkers in the non-drinkers reference category, thus leading to possible underestimation of the risk of current drinkers. Indeed, among the 16 studies included, only two [14, 29] investigated lifetime alcohol consumption, separating never from former drinkers. However, we included only studies with a prospective design, which should be less affected by this problem than those with a retrospective design, since in prospective studies, information is collected among (apparently) healthy participants before the onset of symptoms.

An increased liver cancer risk has been consistently associated with tobacco smoking [31, 58], which usually correlates positively with alcohol drinking. Moreover, liver cancer risk was found to be increased among overweight and obese subjects [59, 60]. The relation between alcohol drinking and body mass index is complex [61–64], but heavy drinkers tend to have lower body mass index, if anything, due to their frequent poor nutrition. Therefore, whenever available, we included multivariate RRs adjusted for tobacco and overweight/obesity. However, some role of residual confounding cannot be excluded.

We could not investigate the role of different drinking patterns as well as of smoking in modifying the effect of the total amount of alcohol consumed, since only a limited number of studies provided details on these issues.

The major strengths of our meta-analysis were the collection of a uniquely large number of liver cancer cases or deaths, which enabled us to explore in detail the association of interest among selected subgroups, and the use of a systematic meta-analytic approach to summarize our results. Moreover, the funnel plot and the Begg and Mazumdar's and Egger's tests for funnel plot asymmetry did not support the presence of major publication bias, providing further indication of the robustness of our findings.

In conclusion, this meta-analysis suggests a moderate detrimental role of consumption of 3 or more alcoholic drinks per day, compared with no alcohol consumption, on liver cancer risk. Caution is however required in interpreting the present results because of the possible limitations of the original studies included in the meta-analysis, despite the restriction of our analyses to studies with a prospective design. These limitations include mainly underestimation of drinking, reverse causation (i.e. inclusion of subjects with liver diseases at baseline), and changes in drinking habits over time.

acknowledgements

Authors thank Ms I. Garimoldi for editorial assistance.

funding

This work was supported by the Italian Association of Cancer Research (AIRC) [grants numbers 10068, 10258 (My First AIRC Grant)]. FT was supported by Environmental Cancer Risk, Nutrition and Individual Susceptibility 2 [ECNIS2—European Union, Sixth Framework Program (FP6) Network of Excellence]. CG and MR were supported by Fondazione Umberto Veronesi.

disclosure

The authors have declared no conflicts of interest.

references

1. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006; 118: 3030–3044.
2. Stuver S, Trichopoulos D. Cancer of the liver and biliary tract. In Adami H-O, Hunter D, Trichpoulos D (eds), Cancer Epidemiology, 2nd edition. New York: Oxford University Press 2008; 308–332.
3. La Vecchia C, Negri E, Cavalieri d'Oro L et al. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998; 7: 315–320.
4. Seitz HK, Stickel F. Risk factors and mechanisms of hepatocarcinogenesis with special emphasis on alcohol and oxidative stress. Biol Chem 2006; 387: 349–360.
5. Bagnardi V, Blangiardo M, La Vecchia C et al. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001; 85: 1700–1705.
6. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 96. Alcohol Consumption and Ethyl Carbamate. Lyon: International Agency for Research on Cancer, 2010.
7. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
8. Songserm N, Promthet S, Sithithaworn P et al. Risk factors for cholangiocarcinoma in high-risk area of Thailand: role of lifestyle, diet and methylenetetrahydrofolate reductase polymorphisms. Cancer Epidemiol 2012; 36: e89–e94.
9. Mori M, Hara M, Wada I et al. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan. Am J Epidemiol 2000; 151: 131–139.
10. Shibata A, Fukuda K, Toshima H et al. The role of cigarette smoking and drinking in the development of liver cancer: 28 years of observations on male cohort members in a farming and fishing area. Cancer Detect Prev 1990; 14: 617–623.
11. Shibata A, Hirohata T, Toshima H et al. The role of drinking and cigarette smoking in the excess deaths from liver cancer. Jpn J Cancer Res 1986; 77: 287–295.
12. Sakoda LC, Graubard BI, Evans AA et al. Toenail selenium and risk of hepatocellular carcinoma mortality in Haimen City, China. Int J Cancer 2005; 115: 618–624.
13. Shimazu T, Sasazuki S, Wakai K et al. Alcohol drinking and primary liver cancer: a pooled analysis of four Japanese cohort studies. Int J Cancer 2012; 130: 2645–2653.
14. Chen CJ, Wang LY, Lu SN et al. Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. Hepatology 1996; 24: 38–42.
15. Murata M, Takayama K, Choi BC et al. A nested case–control study on alcohol drinking, tobacco smoking, and cancer. Cancer Detect Prev 1996; 20: 557–565.
16. Persson EC, Schwartz LM, Park Y et al. Alcohol consumption, folate intake, hepatocellular carcinoma, and liver disease mortality. Cancer Epidemiol Biomarkers Prev 2013; 22: 415–421.
17. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose–response data. Epidemiology 1993; 4: 218–228.
18. Jung EJ, Shin A, Park SK et al. Alcohol consumption and mortality in the Korean Multi-Center Cancer Cohort Study. J Prev Med Public Health 2012; 45: 301–308.
19. Allen NE, Beral V, Casabonne D et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009; 101: 296–305.
20. Yang L, Zhou M, Sherliker P et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. Int J Epidemiol 2012; 41: 1101–1113.
21. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case–control analysis avoiding an arbitrary reference group. Stat Med 1991; 10: 1025–1035.
22. Hamling J, Lee P, Weitkunat R et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27: 954–970.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558.
25. Rota M, Bellocco R, Scotti L et al. Random-effects meta-regression models for studying nonlinear dose–response relationship, with an application to alcohol and esophageal squamous cell carcinoma. Stat Med 2010; 29: 2679–2687.
26. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001; 54: 1046–1055.
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–1101.
28. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–634.
29. Yuan JM, Gao YT, Ong CN et al. Prediagnostic level of serum retinol in relation to reduced risk of hepatocellular carcinoma. J Natl Cancer Inst 2006; 98: 482–490.
30. Ohishi W, Fujiwara S, Cologne JB et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case–control study. Cancer Epidemiol Biomarkers Prev 2008; 17: 846–854.
31. Trichopoulos D, Bamia C, Lagiou P et al. Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case–control study. J Natl Cancer Inst 2011; 103: 1686–1695.
32. Jee SH, Ohrr H, Sull JW et al. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 2004; 96: 1851–1856.
33. Joshi S, Song YM, Kim TH et al. Socio-economic status and the risk of liver cancer mortality: a prospective study in Korean men. Public Health 2008; 122: 1144–1151.
34. Kato I, Nomura AM, Stemmermann GN et al. Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. Cancer Causes Control 1992; 3: 145–151.
35. Kim MK, Ko MJ, Han JT. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health insurance corporation's health examinee cohort in 2000. Cancer Causes Control 2010; 21: 2295–2302.
36. Koh WP, Robien K, Wang R et al. Smoking as an independent risk factor for hepatocellular carcinoma: the Singapore Chinese Health Study. Br J Cancer 2011; 105: 1430–1435.
37. Kono S, Ikeda M, Tokudome S et al. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. Jpn J Cancer Res 1987; 78: 1323–1328.
38. Yi SW, Sull JW, Linton JA et al. Alcohol consumption and digestive cancer mortality in Koreans: the Kangwha Cohort Study. J Epidemiol 2010; 20: 204–211.
39. Sigvardsson S, Hardell L, Przybeck TR et al. Increased cancer risk among Swedish female alcoholics. Epidemiology 1996; 7: 140–143.
40. Saieva C, Bardazzi G, Masala G et al. General and cancer mortality in a large cohort of Italian alcoholics. Alcohol Clin Exp Res 2012; 36: 342–350.
41. Adami HO, McLaughlin JK, Hsing AW et al. Alcoholism and cancer risk: a population-based cohort study. Cancer Causes Control 1992; 3: 419–425.
42. Adami HO, Hsing AW, McLaughlin JK et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992; 51: 898–902.
43. Sorensen HT, Friis S, Olsen JH et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998; 28: 921–925.
44. Bagnardi V, Rota M, Botteri E et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol 2013; 24: 301–308.
45. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population—a systematic review and meta-analysis. PLoS One 2011; 6: e18776.
46. Tanaka K, Tsuji I, Wakai K et al. Alcohol drinking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2008; 38: 816–838.
47. Custer B, Sullivan SD, Hazlet TK et al. Global epidemiology of hepatitis B virus. J Clin Gastroenterol 2004; 38: S158–S168.
48. Franceschi S, Montella M, Polesel J et al. Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. Cancer Epidemiol Biomarkers Prev 2006; 15: 683–689.
49. Negri E, La Vecchia C, D'Avanzo B et al. Acute myocardial infarction: association with time since stopping smoking in Italy. GISSI-EFRIM Investigators. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto. Epidemiologia dei Fattori di Rischio dell'Infarto Miocardico. J Epidemiol Community Health 1994; 48: 129–133.
50. Marron M, Boffetta P, Zhang ZF et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol 2010; 39: 182–196.
51. Altieri A, Bosetti C, Talamini R et al. Cessation of smoking and drinking and the risk of laryngeal cancer. Br J Cancer 2002; 87: 1227–1229.
52. Bosetti C, Franceschi S, Levi F et al. Smoking and drinking cessation and the risk of oesophageal cancer. Br J Cancer 2000; 83: 689–691.
53. Franceschi S, Levi F, Dal Maso L et al. Cessation of alcohol drinking and risk of cancer of the oral cavity and pharynx. Int J Cancer 2000; 85: 787–790.
54. Giovannucci E, Colditz G, Stampfer MJ et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991; 133: 810–817.
55. Ferraroni M, Decarli A, Franceschi S et al. Validity and reproducibility of alcohol consumption in Italy. Int J Epidemiol 1996; 25: 775–782.
56. Flagg EW, Coates RJ, Calle EE et al. Validation of the American Cancer Society Cancer Prevention Study II Nutrition Survey Cohort Food Frequency Questionnaire. Epidemiology 2000; 11: 462–468.
57. Horn-Ross PL, Lee VS, Collins CN et al. Dietary assessment in the California Teachers Study: reproducibility and validity. Cancer Causes Control 2008; 19: 595–603.
58. Lee YC, Cohet C, Yang YC et al. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. Int J Epidemiol 2009; 38: 1497–1511.
59. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer 2007; 97: 1005–1008.
60. Wang Y, Wang B, Shen F et al. Body mass index and risk of primary liver cancer: a meta-analysis of prospective studies. Oncologist 2012; 17: 1461–1468.
61. Tavani A, Negri E, La Vecchia C. Determinants of body mass index: a study from northern Italy. Int J Obes Relat Metab Disord 1994; 18: 497–502.
62. Colditz GA, Giovannucci E, Rimm EB et al. Alcohol intake in relation to diet and obesity in women and men. Am J Clin Nutr 1991; 54: 49–55.
63. Thomson CA, Wertheim BC, Hingle M et al. Alcohol consumption and body weight change in postmenopausal women: results from the Women's Health Initiative. Int J Obes (Lond) 2012; 36: 1158–1164.
64. Lourenco S, Oliveira A, Lopes C. The effect of current and lifetime alcohol consumption on overall and central obesity. Eur J Clin Nutr 2012; 66: 813–818.