Accepted Date : 19-Jan-2014

Article type : Review Article

Alcohol drinking and cutaneous melanoma risk – A systematic review and dose-risk meta-analysis

Running ahead: Alcohol and melanoma – A meta-analysis

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ACKNOWLEDGMENTS: This work was supported by the Italian Association of Cancer Research (AIRC), projects no. 10068 and 10258 (My First AIRC Grant). M.R. was supported by a fellowship of the Fondazione Umberto Veronesi. R.B. was partially supported by the Italian Ministry of University and Research (MIUR), project number: PRIN-2009, X8YCBN.

CONFLICT OF INTERESTS: None declared.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC ?

- Alcohol drinking increases sunburn severity, a major risk factors for cutaneous melanoma.
- Several epidemiological studies investigated the relation between alcohol consumption and CM, but evidence is inconsistent.

WHAT DOES THIS STUDY ADD ?

- We found a 20% increased risk of cutaneous melanoma with regular alcohol drinking.

ABSTRACT

It has been suggested that alcohol intake increases sunburn severity, a major risk factor for cutaneous melanoma (CM). Several epidemiological studies have investigated the relation between alcohol consumption and CM, but evidence is inconsistent.

Therefore, we aimed to better quantify this relation, using a meta-analytic approach. The dose-risk relationship was also modeled through a class of flexible non-linear meta-regression random-effects models.

The present meta-analysis included 16 studies (14 case-control and 2 cohort investigations) with a total of 6,251 CM cases. The pooled relative risk (RR) for any alcohol drinking compared with non/occasional drinking was 1.20 (95% confidence interval (CI), 1.06-1.37). The risk estimate was similar in case-control (RR=1.20, 95% CI, 1.01-1.44) and cohort studies (RR=1.26, 95% CI, 1.19-1.35). The pooled RR was 1.10 (95% CI, 0.96-1.26) for light alcohol drinking (≤1 drink/day) and 1.18 (95% CI, 1.01-1.40) for moderate to heavy drinking. The pooled RR from 10 studies adjusting for sun

exposure was 1.15 (95% CI, 0.94-1.41) while the RR from 6 unadjusted studies was 1.27 (95% CI, 1.20-1.35). No evidence of publication bias was detected.

This meta-analysis of published data revealed that alcohol consumption is positively associated to the risk of CM. Caution in interpreting these results is however required, as residual confounding by sun exposure cannot be ruled out.

KEYWORDS: alcohol drinking; cutaneous melanoma; dose-risk relation; meta-analysis.

ABBREVIATIONS: CM, cutaneous melanoma; UV, ultraviolet; RR, relative risk; CI, confidence interval.

INTRODUCTION

Cutaneous melanoma (CM) accounts for about 5% of all newly diagnosed cancer cases in the United States (US) in 2013, being slightly more frequent in males than in females [1]. Data from population-based cancer registries showed that CM accounted for 3% of all cancer cases in Europe in 2012 [2]. Stable trends in incidence rates and a decrease in mortality rates have been recently observed in Australia, New-Zealand, US, Canada and in Western European countries as a result of primary and secondary prevention campaigns, while incidence and mortality rates are still increasing in selected Eastern European countries [3].

Exposure to ultraviolet (UV) exposure from the sun is the main established cause of CM [4]. A meta-analysis of 57 published studies investigating the pattern of sun exposure found that intermittent sun exposure and sunburn history played a key role for melanoma, with relative risks (RRs) of 1.61 (95% confidence interval (CI), 1.31-1.99) and 2.03 (95% CI,

1.73-2.37), respectively [5]. Among host factors, phenotypic measures of sun sensitivity such as fair skin, number of naevi and freckling confer an about two-fold raised risk of CM [6].

Alcohol consumption is one of the most important, and potentially avoidable, risk factors of human cancers [7]. About 3.6% of all cancers (5.2% in men, 1.7% in women) are attributable to alcohol drinking worldwide [8]. In Western societies, consumption of alcoholic beverages during outdoor leisure activities such as barbecuing and sunbathing is common [9]. Alcohol intake may increase sunburn severity, that in turn increases the risk of CM [10]. The relationship between alcohol drinking and CM risk has been investigated in several, mainly case-control, studies [11-26], but results have been inconsistent. Only two cohort studies have investigated this association [19,25]. Freedman et al. found a positive, non-significant association in a large cohort of 68,588 white US radiologic technologists [19]. Similarly, the Million Women Study cohort showed a 4% increase (95% CI, -3% to 12%) in the risk of CM for an increment of 10 grams/day of alcohol intake [25].

To provide a quantitative assessment of the association in a larger numbers of CM cases and control groups, we performed a systematic review and meta-analysis of observational studies investigating the relation between alcohol drinking and CM.

MATERIALS AND METHODS

Identification of studies and data collection

We carried out a systematic literature search in Medline, using PubMed, for all epidemiological studies published as original articles in English up to 30 April 2012, investigating the association between alcohol drinking and CM. We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [27]. For the literature search, we used the following search string: ((ethanol OR alcohol drinking) AND (skin neoplasms OR melanoma)) OR (alcohol OR alcoholic beverages OR ethanol

OR alcohol drinking) AND melanoma), that comprises the following MeSH terms: 'Ethanol', 'Alcohol Drinking', 'Alcoholic Beverages' and 'Melanoma' or 'Skin Neoplams'. The process for article selection is showed in Figure 1. No studies were excluded a priori for design weakness or low quality data. Three investigators (M.R., E.P. and L.S.) independently screened each retrieved study for inclusion in the meta-analysis. In case of doubts or disagreement, a fourth investigator (V.B.) was consulted, and consensus was reached. We retrieved a total of 1,044 published papers, of which 997 were excluded since they were not relevant to the topic of our meta-analysis. From a detailed review of the reference lists of the remaining 47 potentially relevant articles, we identified 2 publications of interest. From a total of 49 articles, 33 were excluded because they did not satisfy the inclusion criteria; i.e. for the following reasons: i) studies investigating non-melanocytic skin cancer only, ii) studies neither reporting RRs nor odds ratios (ORs) and the corresponding 95% CIs, or sufficient information to calculate them, iii) studies conducted on special populations (i.e., alcoholics or cancer survivors), and iv) studies reporting only the result for specific alcoholic beverages (i.e., beer, wine and liquor/spirit). The latter studies were not included in the analyses, since nondrinkers of a specific alcoholic beverage may drink other beverages, leading to a likely under estimation of the association.

Finally, 16 studies were included in this meta-analysis: 14 case-control [11-18,20-24,26] and 2 prospective cohorts [19,25]. For each study, we extracted the following information: study design, location, number of subjects (cases, controls or cohort size), gender, type of controls (hospital or population based) and period of enrolment for case-control studies, duration of follow-up for cohort studies, RR estimates for categories of alcohol consumption along with the corresponding 95% CIs, and the variables which were adjusted/matched for in the analysis.

Statistical analyses

We used ORs, risk ratios and hazard ratios as comparable estimates of the RR [28]. We extracted multivariable-adjusted RR estimates whenever available. If RRs were not reported, we computed crude RRs using frequency distributions presented in the original reports.

As different units were used to express the amount of alcohol drinking, we turned all measures into grams of ethanol per day as a standard measurement unit, defining 1 drink as 12.5 grams of ethanol if not otherwise specified in the original report, 1 ml as 0.80 grams, and 1 ounce as 28.35 grams of ethanol. The dose associated to each RR estimate was computed as the midpoint of each exposure category, and for the open-ended upper category, as 1.2 times its lower bound [29]. When possible, we chose nondrinkers as the reference category, but in some studies occasional drinkers were also included. In the Million Women Study [25], we derived the floated variances - that describe the uncertainty in RRs without reference to a predefined category - from the 95% floated CI provided by the authors, in order to derive RRs and corresponding 95% CIs for different categories of alcohol consumption compared to nondrinkers [30].

We defined the daily amount of alcohol consumption as light (≤1 drink, or ≤12.5 grams of ethanol) and moderate to heavy (>1 drink, or >12.5 grams of ethanol per day). Since only two studies investigated high daily amounts of alcohol, we could not examine the effect of heavy drinking (>50 grams of ethanol per day) on the risk of CM. When more than one category of alcohol consumption fell in the same level, we combined the corresponding estimates using the method proposed by Hamling et al. [31], that takes into account the correlation between estimates. This method uses the dose-specific covariate-adjusted risk estimates and the numbers of cases and non-cases for each category of exposure to derive a set of pseudo-numbers of cases and non-cases consistent with both

the adjusted estimates. The pseudo-numbers of two or more categories of exposure can then be combined to provide adjusted risk estimates for light, or moderate to heavy alcohol drinking.

All the meta-analytic estimates were obtained using random-effects models [32]. Between-study heterogeneity was assessed using the χ^2 test, and inconsistency was measured by using the Higgins I^2 statistics [33], which is the proportion of total variation contributed by between-study variance.

We conducted sensitivity analyses by excluding each study at a time from the meta-analysis, in order to evaluate its impact on the final pooled estimate. In order to investigate possible sources of between-study heterogeneity, we conducted stratified analyses according to potentially relevant factors (i.e., study design, source of controls for case-control studies, geographic area, gender, adjustment for sun exposure).

We assessed the dose-response relationship between alcohol intake and CM using flexible non-linear meta-regression models [34]. In this analysis, we considered only studies reporting RRs estimates for at least three exposure categories, including the referent category.

Presence of publication bias was assessed by examination of the contour-enhanced funnel plot [35], and also by applying the Egger's test for funnel plot asymmetry [36].

Statistical analyses were performed using SAS (version 9.1.3; SAS Institute, Cary, NC) and Stata (version 11; Stata Corp, College Station, TX, USA).

RESULTS

The article selection process is showed in Figure 1. Summary characteristics of the 16 studies (14 case-control [11-18,20-24,26] and 2 cohorts [19,25]) included in the meta-analysis are summarized in Table 1. A total of 6,251 CM cases were included, of whom 2,459 (39%) were from the Million Women Study [25]. Six out of 16 studies were conducted in Europe

[13,17,21,22,24,25], 3 in Australia [11,12,15], 6 in North America [14,16,19,20,23,26] and 1 in South America [18].

Figure 2 shows the study-specific and pooled RRs along with 95% CIs of CM for any alcohol drinking versus none/occasional drinking. The overall pooled RR was 1.20 (95% CI, 1.06-1.37, P=0.006), similar between case-control (RR=1.20, 95% CI, 1.01-1.44, P=0.041) and cohort studies (RR=1.26, 95% CI, 1.19-1.35, P<0.001), with significant between-study heterogeneity (I^2=55.6%, P=0.003). The exclusion of each study in turn did not substantially change the magnitude of the pooled RR nor its statistical significance.

Table 2 shows results from analyses for any alcohol drinking and CM risk in strata of selected variables. Pooled RRs were higher in hospital-based (RR=1.42, 95% CI, 0.99-2.03) than in population-based case-controls studies (RR=1.13, 95% CI, 0.92-1.40). There was a significant heterogeneity across geographical areas (P=0.003): the pooled RR was 1.20 (95% CI, 0.87-1.66) in Australian studies (n=3), 1.04 (95% CI, 0.79-1.37) in European studies (n=6) and 1.41 (95% CI, 1.21-1.66) in studies conducted in America (n=7). Only 6 out of 16 studies reported gender specific estimates; men who consumed alcohol – as compared to those who did not - had higher risk of CM (RR=1.47, 95% CI, 0.94-2.29) than women (RR=1.26, 95% CI, 1.19-1.35), but there was no significant heterogeneity between these two groups (P=0.41). The pooled RR from 10 studies adjusting for sun exposure was 1.15 (95% CI, 0.94-1.41), while the RR from 6 unadjusted studies was 1.27 (95% CI, 1.20-1.35), in the absence of a significant heterogeneity (P=0.36).

The pooled RR estimates for the association between light (≤1 drink/day) alcohol drinking and CM (Figure 3) were 1.10 (95% CI, 0.96-1.26) overall, 1.06 (95% CI, 0.90-1.25) among case-control studies and 1.25 (95% CI, 1.15-1.35) among cohort studies.

Significant between-study heterogeneity was found (I^2=41.8%, P=0.045). The exclusion of each study in turn did not materially change the magnitude of the overall pooled RR or its significance.

Figure 4 shows the study-specific and pooled RRs of CM for moderate to heavy (>1 drink/day) alcohol drinking versus non-drinking. Based on a total of 12 studies, the pooled RRs were 1.18 (95% CI, 1.01-1.40) overall, 1.13 (95% CI, 0.90-1.41) among case-control studies and 1.29 (95% CI, 1.17-1.43) among cohort studies. The pooled RR estimate was no longer significant when considering the effect of moderate to heavy alcohol drinking in studies adjusting for sun exposure (RR=1.12, 95% CI, 0.86-1.45).

Among all the fitted two term random-effects fractional polynomials relations, the linear one represented the best fitting model. The pooled RRs estimates were 1.11 (95% CI, 1.01-1.23) for 12 grams, 1.25 (95% CI, 1.01-1.53) for 25 grams and 1.55 (95% CI, 1.02-2.35) for 50 grams of ethanol per day. The pointwise confidence bands revealed borderline statistical significance at all levels of intake (Supplementary Web-Only Figure 1).

The countour-enhanced funnel plot (Supplementary Web-Only Figure 2) of studies investigating the relationship between alcohol drinking and CM appears to be symmetrical (data not shown), suggesting the absence of significant publication bias, as also confirmed by the Egger's test (P=0.99).

DISCUSSION

In this systematic review and meta-analysis of published data, based on 16 studies and on a total of 6,251 CM cases, we found a 20% increased risk for alcohol drinking compared with non/occasional drinking. Moreover, there was a linear relationship with increasing alcohol intake in drinkers, with an estimated significant excess risk of 55% for 50 grams of ethanol per day. However, our meta-analysis could not shed light on the effect of high

levels of alcohol intake, since the available information on high alcohol doses and CM was scarse. The RR estimate was somewhat lower and no longer significant when we considered only the studies adjusted for sun exposure, the main recognized cause of CM. This was based on 10 out of 16 studies, i.e. on 2,840 out of 6,251 CM cases. The absence of statistical significance may therefore be due to reduced statistical power, also in consideration of the limited variation of the point estimate (1.15 vs. 1.20 overall). This is consistent with the results of a recent published study from the Women's Health Initiative cohort [37], but leaves open the issue on inadequate adjustment for the major risk factor of CM, requiring caution in the interpretation of the results. Moreover, significant heterogeneity in the results of the studies adjusted for sun exposure could also indicate that the sun exposure measurement may vary across the studies and across geographical area.

Skin carcinogenesis is a multistep process in which environmental carcinogens and lifestyle-related factors play a major role [38]. Exposure to (solar) UV radiation is the main recognized cause for cutaneous melanoma [4]. However, recent evidences also showed that (subcarcinogenic) solar UV radiation in combination with other behavioral, environmental and xenobiotic factors could increase episodes of skin-related health problems that could contribute to skin carcinogenesis [9].

In Western societies, consumption of alcoholic beverages during outdoor leisure activities such as barbecuing and sunbathing is common [9]. Warthan et al. showed that people who consumed alcohol during time spent at the beach had more severe sunburns compared to nondrinkers [10]. Moreover, a cross-sectional survey investigating the relation between alcohol drinking and sunburns prevalence found that about 18% of all sunburn cases among American adults were imputable to alcohol drinking [39]. In accordance with these

results, our analyses also showed a significant effect of alcohol drinking in American studies (RR=1.41, 95% CI, 1.21-1.66), showing a North-South gradient [3].

The mechanisms for the carcinogenic effect of alcohol drinking on melanocytes cancer are not clear. However, in the presence of UV radiation, alcohol intake lead to altered immunocompetence, and can substantially enhance cellular damage and subsequently lead to formation of skin cancers [9]. Ethanol is converted to acetaldehyde (AA) soon after its ingestion; the metabolite may act as a photosensitizer, generating reactive oxygen species (ROS) and related intermediates (ROI). ROS generated by AA-UV further induces oxidative DNA damage, enhances the binding of AA to DNA (genetic effect), and activates signal-transduction cascades and prostaglandin synthesis (epigenetic effect). Thus, the combination of alcohol and UV sun exposure potentiates both initiating and promoting activities, thereby leading to synergistic carcinogenicity [9].

This is the first systematic review and meta-analysis that investigates the dose-risk relationship between alcohol drinking and CM risk. Major strengths were the collection of a large number of cases which enabled us to explore the association among selected subgroups, including separate calculations of pooled risks among studies that controlled/did not control for sun exposure. Moreover, the contour enhanced funnel plot and the Egger's test for funnel plot asymmetry did not support the presence of major publication bias, providing further indication of the robustness of our findings.

With reference to possible limitations, our meta-analysis is largely based on results from case-control studies, which are more subject to bias, particularly recall and selection bias. However, findings from case-control studies were consistent with those from prospective cohort studies. It is also possible that alcohol consumption is systematically underreported, leading to the underestimation of the real risk. However, studies

investigating reproducibility and validity of self-reported alcohol drinking in various populations found satisfactory correlation coefficients [40-42].

In conclusion, this meta-analysis found evidence of a modest detrimental role of alcohol drinking at moderate to high doses. Caution in interpreting these results is however required, as residual confounding by sun UV exposure cannot be ruled out.

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Table 1. Main characteristics of studies included in the meta-analysis on alcohol drinking and cutaneous melanoma risk.

Study	Country	Gender	No. of Cases	No. of Controls/Size of Cohort	Type of controls	Enrolment period/ Duration of Study Follow-up	Variables adjusted/ matched for in the analyses
Case-control studies							
Green et al, 1986	Australia	M&W	236	236	PB	1979-1980	Age, gender, county, pigment cell phenotype, lifetime sun exposure
Holman et al, 1986	Australia	M&W	511	511	PB	1980-1981	Age, sex, county (matching factors)
Osterlind et al, 1988	Denmark	M&W	474	926	PB	1982-1985	Age, gender, sunbathing, socio-economic group
Stryker et al, 1990	USA	M&W	204	248	HB	1982-1985	Age, gender, hair color, ability to tan
Bain et al, 1993	Australia	W	41	297	PB	1983-1985	Age, hair color, painful sunburns, energy intake, education, BMI
Kirkpatrick et al, 1994	USA	M&W	234	248	PB	1984-1987	Age, gender, county, education, energy

							intake
Westerdahl et al, 1996	Sweden	M&W	306	523	PB	1988-1990	Age, gender, county, sunburns history, hair color, raised naevi
Rolón et al, 1997	Paraguay	M	41	168	HB	1988-1993	Age, period, hospital
Millen et al, 2004	USA	M&W	497	561	HB	1991-1992	Age, sex, study site, confirmed dysplastic naevi status, education, skin response after repeated/prolonged sun exposure
Naldi et al, 2004	Italy	M&W	542	537	HB	1992-1994	Age, sex, education, BMI, sunburns history, sunburns propensity, number of naevi and freckles, color of hair, eyes and skin, smoking
Vinceti et al, 2005	Italy	M&W	59	59	PB	NA	Age, gender, energy intake
Le Marchand et al, 2006	USA	M, W	278	278	PB	1986-1992	Age, gender, height, education, hair color, number of

							blistering sunburns, ability to tan
Gogas et al, 2008	Greece	M&W	55	165	PB	2002-2003	Age, gender, sun sensitivity score, education, physical exercise, smoking, diabetes, serum leptin levels, BMI, food patterns
Benedetti et al, 2009	Canada	M	107	507	PB	Early 1980s	Age, smoking, respondent status, ethnicity, census tract income, education
Cohort studies							
Freedman et al, 2003	USA	M,W, M&W	207	68,588 (PR) 698,028 (PY)	-	1983/1989-1998	Age, gender, smoking, skin pigmentation, hair color, non-melanoma skin cancer history, decade began work as a technologist, education, proxy measures for residential

							childhood and adult sunlight exposure
Allen et al, 2009	UK	W	2459	1,280,296 (PR) 9,160,000 (PY)	-	1996/2001-2006 (average: 7.2 years)	Age, residence, socioeconomic status, BMI, smoking, physical activity, oral contraceptive use, hormone replacement therapy

Abbreviations: PB, population-based; HB, hospital-based; M, men; W, women; M&W, men and women; BMI, body mass index; NA, not available; PR, person at risk; PY, person-year.

Table 2. Pooled RRs and 95% CIs for alcohol drinking and CM risk in strata of selected covariates.

	Number of studies	**RR (95% CI)**	**I^2 (%)**	**P-value for heterogeneity**
Study design				
Case-control	14	1.20 (1.01-1.44)	57.7%	0.003
Cohort	2	1.26 (1.19-1.35)	0%	0.657
Source of controls[a]				
Population based	10	1.13 (0.92-1.40)	55.7%	0.012
Hospital based	4	1.42 (0.99-2.03)	63.5%	0.042
Geographic area				
Australia	3	1.20 (0.87-1.66)	36.5%	0.207
Europe	6	1.04 (0.79-1.37)	79.5%	<0.001
America	7	1.41 (1.21-1.66)	0%	0.687
Gender[b]				
Men	3	1.47 (0.94-2.29)	45.7%	0.159
Women	3	1.26 (1.19-1.35)	0%	0.665

Sun exposure adjustment				
No	6	1.27 (1.20-1.35)	0%	0.442
Yes	10	1.15 (0.94-1.41)	60.5%	0.005

[a] Among case-control studies only
[b] Studies reporting estimates separately for men and women were selected.

FIGURE LEGENDS

Figure 1. Flow-chart of study selection.

Figure 2. Forest plot for study-specific and pooled relative risk (RR) along with 95% confidence interval (CI) of CM risk for any alcohol drinking versus none/occasional drinking.

Figure 3. Forest plot for study-specific and pooled relative risk (RR) along with 95% confidence interval (CI) of CM risk for light alcohol drinking (≤1 drink/day) versus none/occasional drinking.

Figure 4. Forest plot for study-specific and pooled relative risk (RR) along with 95% confidence interval (CI) of CM risk for moderate to heavy alcohol drinking (>1 drink/day) versus none/occasional drinking.

Figure 1

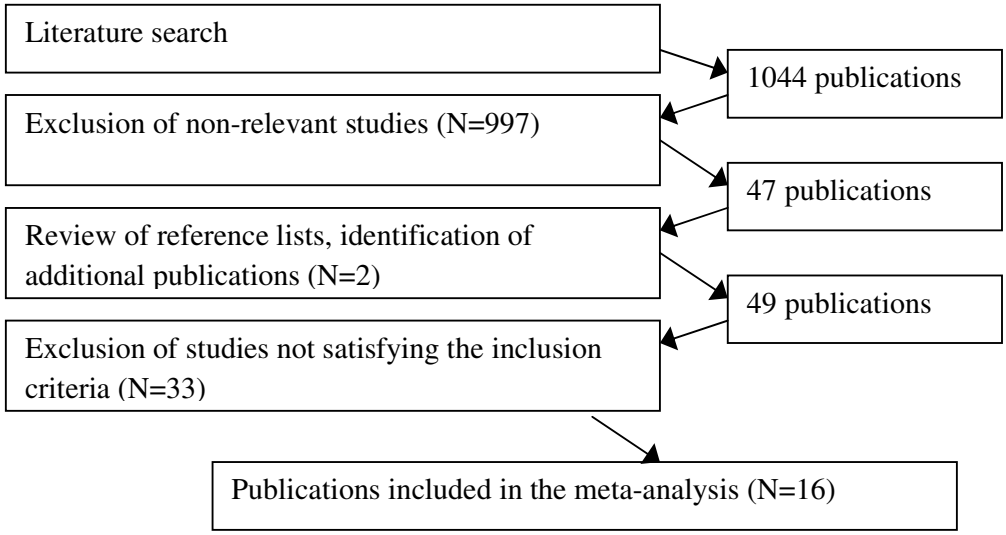


Figure 2

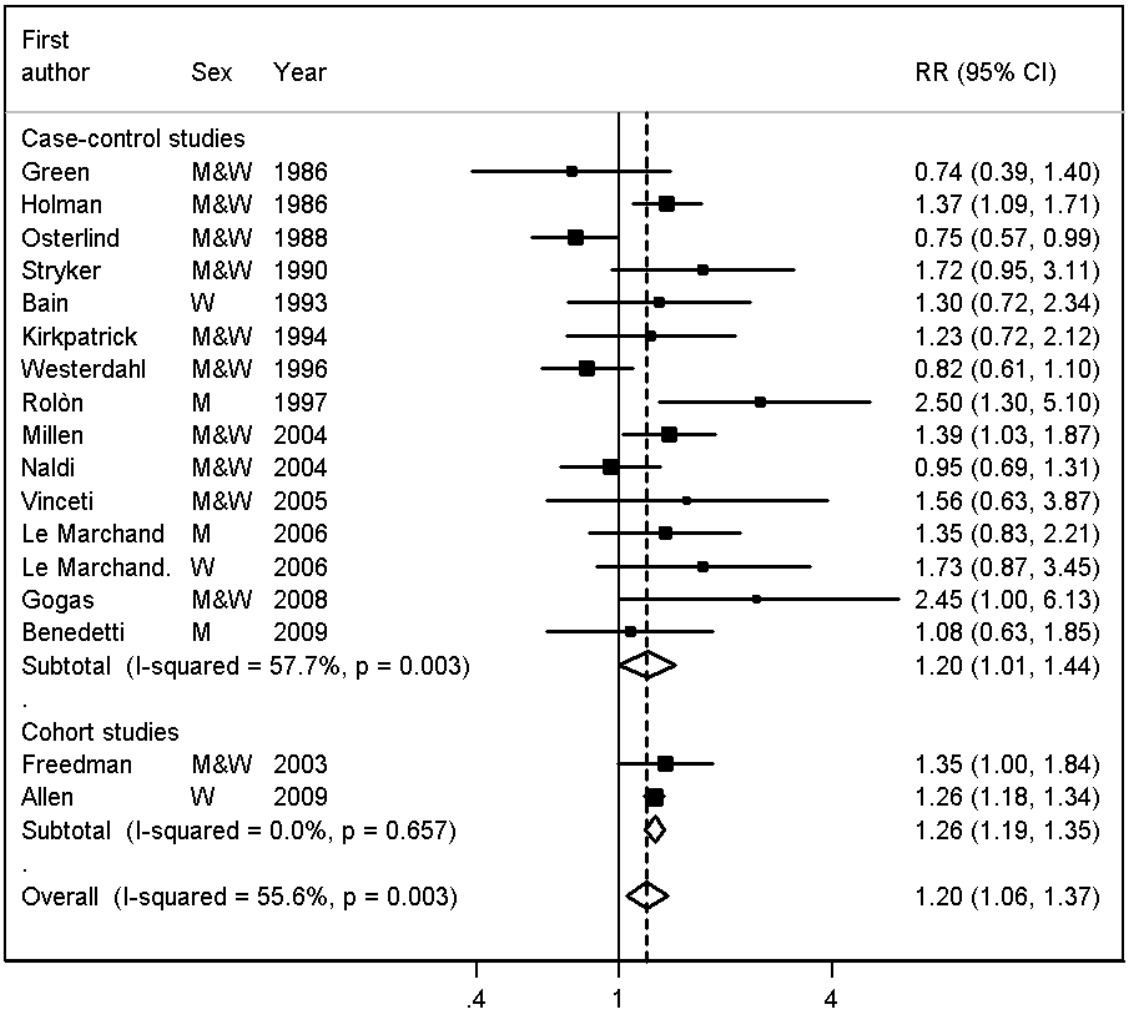


Figure 3

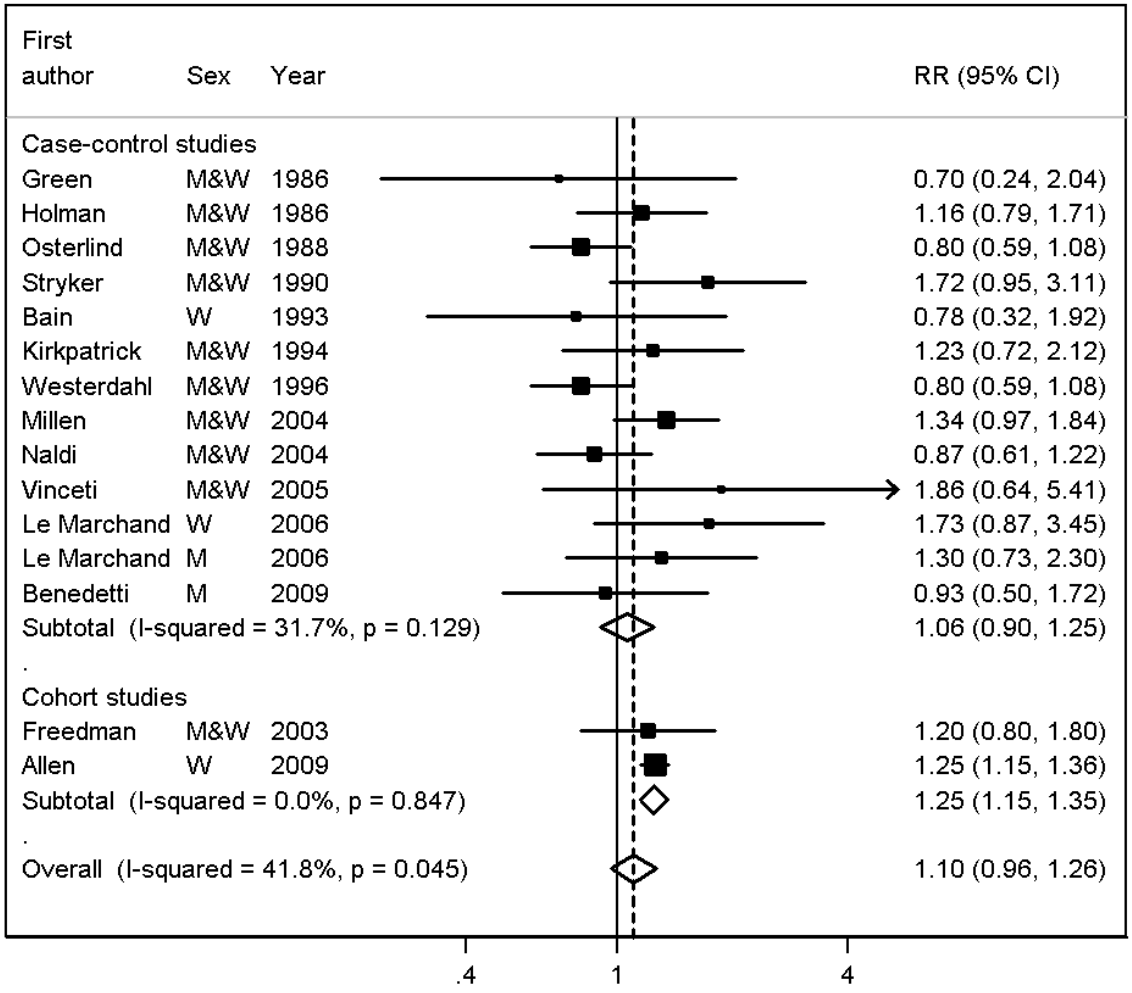
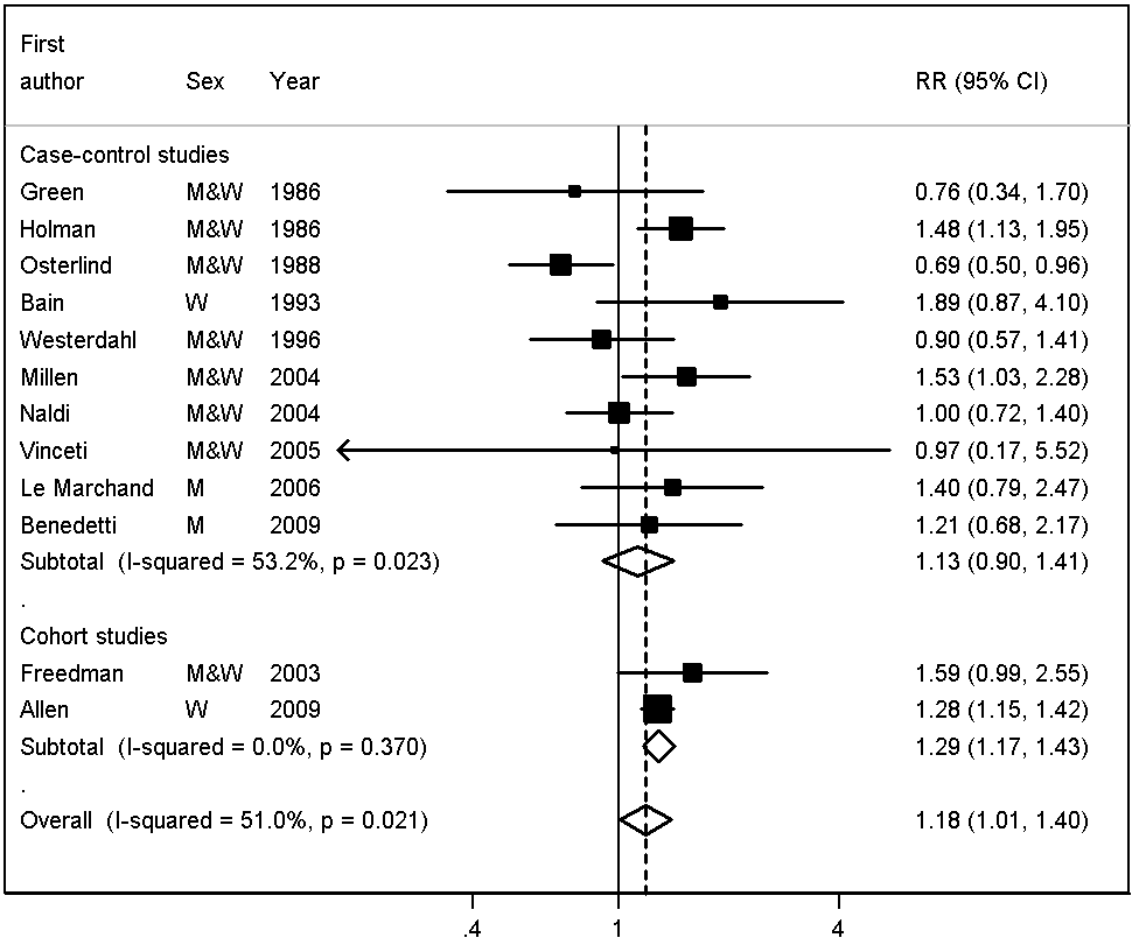


Figure 4



LEGENDS TO THE SUPPLEMENTARY FIGURES

Supplementary Web-Only Figure 1. Relative risk (RR) function and the corresponding 95% confidence bands describing the best fitting dose-risk relationship between alcohol drinking and cutaneous malignant melanoma.

Supplementary Web-Only Figure 2. Contour-enhanced funnel-plot to visually assess presence of publication bias for studies investigating the relationship between alcohol drinking and cutaneous malignant melanoma risk.