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Review

A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 2: Results by subsites

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SUMMARY

Oral and pharyngeal cancers are strongly related to alcohol drinking. We combined findings from all case-control and cohort studies published up to September 2009 and presented analyses by subsites, using a meta-analytic approach. Summary measures were obtained using random-effects models, and taking into account the correlation between estimates from the same study. We also performed a dose-risk analysis, using a random-effects meta-regression model. Compared to non- or occasional drinkers, the overall relative risks (RR) for light drinkers were 1.17 (95% confidence interval, CI, 1.01–1.35) for oral (nine studies) and 1.23 (95% CI, 0.87–1.73) for pharyngeal (five studies) cancer, with no significant heterogeneity between the two sites ($p = 0.793$). RRs for heavy drinkers were 4.64 (95% CI, 3.78–5.70) for oral (17 studies) and 6.62 (95% CI, 4.72–9.29) for pharyngeal (17 studies) cancer (p of heterogeneity between the two sites = 0.075). The summary RRs for heavy drinkers were 4.11 (95% CI, 2.46–6.87) for tongue (five studies), 7.76 (95% CI, 4.77–12.62) for oropharyngeal (four studies), and 9.03 (95% CI, 4.46–18.27) for hypopharyngeal (four studies) cancer. In conclusion, the alcohol-related RRs are higher for pharyngeal than for oral cancer, particularly at higher doses, while the association with cancer of the tongue was similar to that for oral cancer.

Introduction

Alcohol drinking increases the risk of oral and pharyngeal cancers. In a recent meta-analysis, including 45 studies for a total of 17,085 cases, we estimated relative risks (RR) of 1.29 for 10, 3.24 for 50, 8.61 for 100, and to 13.02 for 125 g of ethanol per day for oral cavity and pharynx combined.[1]

However, the anatomic sites most strongly associated with alcohol drinking have varied from study to study. Thus, in a case-control study from four areas of the United States[2] the association was less strong for tongue than for other oral sites or pharynx, particularly in men. In another case-control study, based on US Veterans,[3] patients with cancer at the floor of the mouth and oral tongue had higher RRs than those with cancer at other oral and pharyngeal sites. In a study from Italy and Switzerland,[4] the RRs were appreciably higher for oral than for pharyngeal cancer. In a study from Puerto Rico[5] there was no significant difference among tongue, other oral and pharynx in both sexes. However, no single study had adequate power to test the possible differences in alcohol-related risks across subsites, and the apparent differences may be due to chance alone. Human papillomavirus (HPV) is related to a subset of cancers of the oropharynx.[6,7] However, in a study comparing HPV-associated with HPV-independent cancers, no appreciable difference was observed for the alcohol-related RRs.[6]

In order to provide a detailed quantification of the association of alcohol consumption with oral and pharyngeal cancer separately, as

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well as with subsites of the oral cavity and of the pharynx, we conducted a meta-analysis of studies published up to September 2009.

Materials and methods

Identification of studies and collection of data

The methodology of identification of studies and collection of data has been previously described.[1] Briefly, using PubMed, we performed a literature search of all case-control and cohort studies published up to September 2009 and presenting data on the association between alcohol and risk of oral and/or pharyngeal cancer, following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[8] We did not consider cancer of the nasopharynx, as it shows an epidemiology and histopathology that is different from that of other cancers of the oral cavity and pharynx. In our previous meta-analysis, presenting the overall results and the dose-risk relation between alcohol drinking and oral and pharyngeal cancer combined, we included 45 studies fulfilling the inclusion criteria (case-control and cohort studies considering at least three levels of alcohol consumption and reporting the estimates of the odds ratio (OR) or RR and the corresponding confidence intervals (CI) – or information sufficient to calculate them – for each exposure level).[1] In the present analysis, we included only those articles reporting risk estimates for oral cavity and/or pharynx separately. As concern specific subsites within the oral cavity or pharynx, we considered those subsites for which at least four studies were available. These were the tongue, the oropharynx and the hypopharynx. Some articles excluded from the previous analysis, because an update of the study was available, were included in the present one, since the paper previously considered did not present data by subsite[4,9–11] (see Appendix 1). Appendix 2 shows the flowchart of the selection of articles.

For each study the following information was extracted: study design, country, number of subjects (cases, controls or cohort size), duration of follow-up (for cohort studies), sex of the study population, variables adjusted for in the analysis, RR estimates for categories of alcohol drinking and the corresponding 95% CI, and, when available, the number of cases and non-cases for each level of alcohol consumption.

Statistical analysis

Statistical methods have been previously described.[1] Briefly, our measure of interest was the RR for cohort or the OR for case-control studies. Whenever available, we considered multivariate risk estimates, adjusted for the largest number of potential confounding factors; otherwise we computed the crude OR (and the corresponding 95% CI) from the distribution of cases and controls in the exposure categories. When a study reported multivariate RRs but not the corresponding CIs, the standard error (SE) of the adjusted estimate was obtained by penalizing the standard error of the crude RR by a factor of 1.5.

We used grams of ethanol as measurement unit, assuming 1 drink = 12.5 g, 1 ml of ethanol = 0.8 g, 1 once = 28.35 g of ethanol. In a Chinese study, we converted spirit equivalent in grams of ethanol through the equation one spirit equivalent = 0.6 g of ethanol.[10]

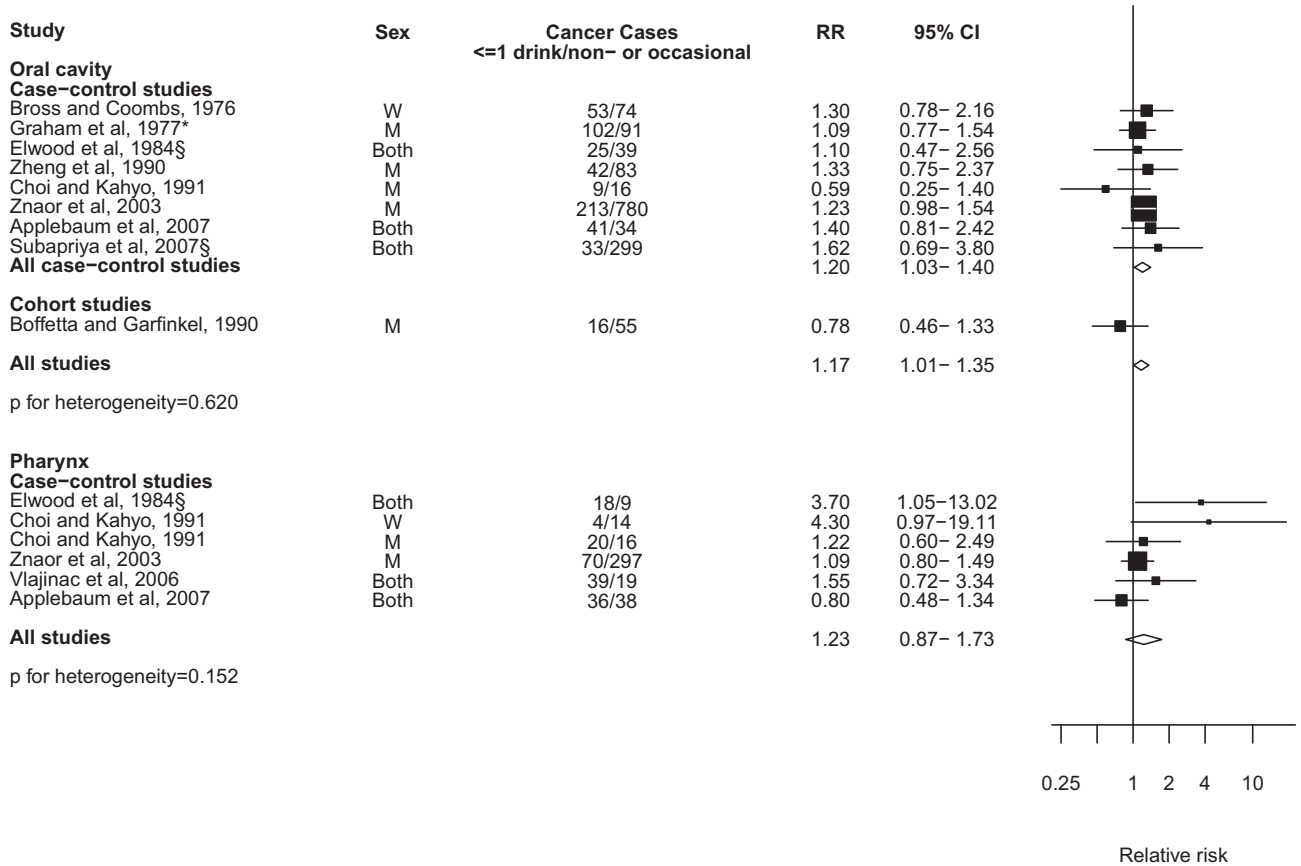

Figure 1 Summary RRs of cancer of oral cavity and pharynx separately[‡] for light alcohol drinkers (⩽1 drink per day) compared to non- or occasional drinkers. [*]The estimate was not adjusted for the main risk factors (i.e., sex, age and smoking). [§]The CI was computed by multiplying the SE of the crude estimate by 1.5. [‡]*p* of heterogeneity between the cancer-sites pooled estimates = 0.793.

We assigned to each consumption category the dose corresponding to the midpoint of the range and, for the open-ended upper category, the dose was calculated as 1.2 times the lower bound.[12]

The reference category was set to the one with the lowest alcohol consumption in each study (non-drinkers for most studies), and light and heavy drinkers were respectively defined drinkers of $\leqslant 1$ and $\geqslant 4$ drinks per day.

Summary measures were calculated using random-effects models, that consider both within- and between-study variations.[13] Statistical heterogeneity among studies was assessed using the χ^2 test[13] (results were defined heterogeneous for $p < 0.10$).

For the dose–response analysis, we used a random-effects meta-regression model in a non-linear dose–response relationship framework, providing the best-fitting two-term fractional–polynomial model.[14]

In addition, sensitivity analyses were performed by excluding from the analysis studies using a reference category different from non- or occasional drinkers, providing RRs not adjusted for the main oral and pharyngeal cancer risk factors (i.e., sex, age and smoking), and in which the SE was calculated by penalizing the crude SE by a factor of 1.5.

Results

The main characteristics of the studies have already been described.[1] Appendix 1 reports the characteristics of the five additional studies not included in the previous review.[1] The present analyses are based on 30[3,4,9–11,15–40] case-control and 1[17] cohort study. Some studies reported data for more than one anatomical site. Twenty-two reports[3,4,11,15–33] gave RRs for cancer of the oral cavity (7419 cases), and 22[3,4,11,16,19,20,23,25–31,33–40] for cancer of the pharynx (4664 cases). Six reports[3,9,10,22,29,32] provided risk estimates for cancer of the tongue (558 cases), four[3,11,20,33] for cancer of the oropharynx (1060 cases), and four[33,36,38,39] for cancer of the hypopharynx (910 cases). All studies were included in the dose–response analysis, but for a few studies the categories presented did not allow to include them in the light vs. non- or occasional drinkers and/or heavy vs. non- or occasional drinkers analysis.

Oral cavity and pharynx

Figure 1 shows the forest plot for light alcohol drinkers compared to non- or occasional drinkers, for cancers of the oral cavity and pharynx separately. The overall RR for oral cavity cancer was

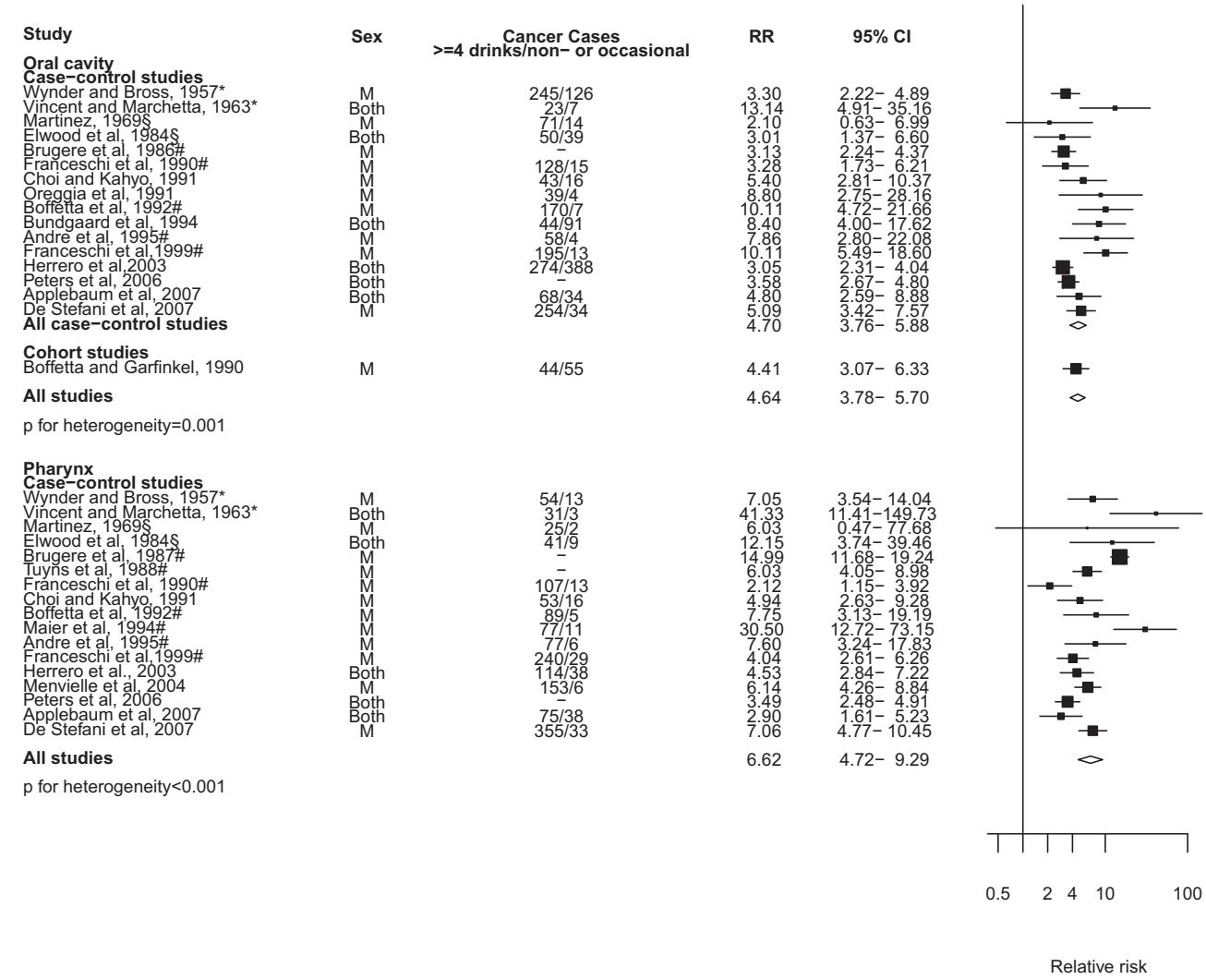

Figure 2 Summary RRs of cancer of oral cavity and pharynx separately[‡] for heavy alcohol drinkers ($\geqslant 4$ drinks per day) compared to non- or occasional drinkers. [*]The estimate was not adjusted for the main risk factors (i.e., sex, age and smoking). [§]The CI was computed by multiplying the SE of the crude estimate by 1.5. [#]In most of the studies the reference category was non- or occasional drinkers. In Boffetta et al.[3] was $\leqslant 1$ whisky equivalent/day (i.e., $\leqslant 10.24$ g of ethanol/day), in Tuyns et al.[38] was $\leqslant 1.5$ drinks/day, in Maier et al.[40] was <2 drinks/day, in Franceschi et al.[4] was <20 drinks/week, in Franceschi et al.[28] was <3 drinks/day, in Brugere et al.[33] and in Andre et al.[20] was $\leqslant 3$ drinks/day. [‡]p of heterogeneity between the cancer-sites pooled estimates = 0.075.

1.17 (95% CI, 1.01–1.35, p for heterogeneity = 0.620), from eight case-control and one cohort study. The pooled estimate for pharyngeal cancer was 1.23 (95% CI, 0.87–1.73, p for heterogeneity = 0.152), from five case-control studies. No heterogeneity between the two cancer sites was found (p = 0.793). When the analyses were limited to studies reporting RRs and CIs adjusted at least for sex, age and smoking (six studies on oral cancer and four on pharyngeal cancer), the RRs became 1.16 (95% CI 0.96–1.41) for oral, and 1.11 (95% CI 0.86–1.43) for pharyngeal cancer.

Figure 2 shows the risk for heavy drinkers as compared to non- or occasional drinkers. The pooled RR for oral cavity cancer was 4.64 (95% CI, 3.78–5.70, p for heterogeneity = 0.001), from 16 case-control and one cohort study, and the one for pharyngeal cancer was 6.62 (95% CI, 4.72–9.29, p for heterogeneity <0.001), from 17 case-control studies. These two estimates were significantly heterogeneous (p = 0.075). When we included in the meta-analysis only studies providing RRs for both oral cavity and pharynx, so that the two risk estimates for both cancer sites were based on the same 14 studies,[3,4,11,16,19,20,23,25,27–31,33] the pooled RR was 4.44 (95% CI, 3.54–5.57) for oral, and 6.08 (95% CI, 4.06–9.08) for pharyngeal cancer. The pooled RR for heavy drinking did not appreciably change when excluding studies not adjusting for age, sex and smoking (two for oral and two for pharyngeal cancer), or when studies with a reference category different from non- or occasional drinkers were excluded (five for oral and seven for pharyngeal cancer), or when removing from the analyses studies with the penalized SEs (two for oral and two for pharyngeal cancer).

Figure 3 gives the dose–risk curve and the 95% pointwise confidence bands for the relation between alcohol consumption and cancer of the oral cavity (Fig. 3a) and pharynx (Fig. 3b). For oral cavity cancer, among the two terms fractional–polynomial models, the best-fitting dose–response relationship was log(RR) = (beta1) * dose + (beta2) * dose^2, which leads to pooled RR estimates of 1.28 (95% CI, 1.23–1.32) for 10, 1.80 (95% CI, 1.66–1.95) for 25, 3.00 (95% CI, 2.75–3.49) for 50, 4.64 (95% CI, 3.72–5.75) for 75, and 6.65 (95% CI, 5.07–8.72) for 100 g of ethanol per day.

The best-fitting dose–response curve describing the relation between alcohol drinking and pharyngeal cancer risk was log(RR) =

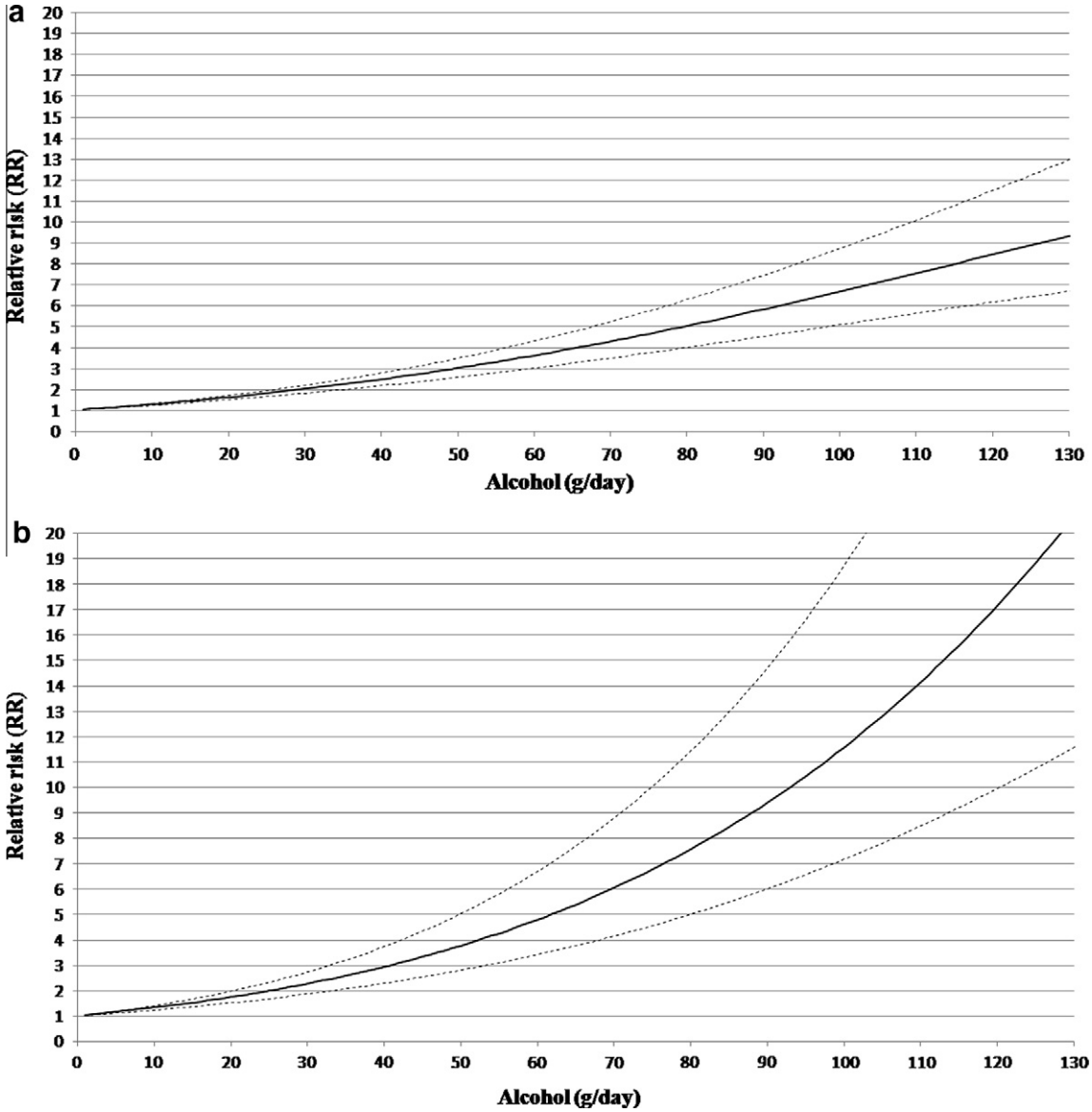

Figure 3 (a) Relative risk function and the corresponding 95% CI describing the best-fitting dose–response relationship between alcohol consumption and the risk of oral cavity cancer. (b) Relative risk function and the corresponding 95% CI describing the best-fitting dose–response relationship between alcohol consumption and the risk of pharyngeal cancer.

(beta1) * dose + (beta2) * dose^2, which, compared to non-drinkers, gives RRs of 1.32 (95% CI, 1.23–1.42) for 10, 1.99 (95% CI, 1.69–2.34) for 25, 3.76 (95% CI, 2.80–5.04) for 50, 6.76 (95% CI, 4.55–10.05) for 75, and 11.58 (95% CI, 7.16–18.72) for 100 g of ethanol per day.

Tongue, oropharynx and hypopharynx

Figure 4 shows the forest plots for heavy as compared to non- or occasional alcohol drinkers for cancer of the tongue, oropharynx and hypopharynx. The summary estimate was 4.11 (95% CI, 2.46–6.87, *p* for heterogeneity = 0.154) from five case-control studies on tongue cancer, 7.76 (95% CI, 4.77–12.62, *p* for heterogeneity = 0.008) from four case-control studies on oropharyngeal cancer, and 9.03 (95% CI, 4.46–18.27, *p* for heterogeneity <0.001) from four case-control studies on hypopharyngeal cancer. Removing from the analysis on tongue cancer one study[10] with heavy alcohol drinking defined as >50 spirit equivalent per day (approximately 30 g of ethanol per day), the pooled RR increased to 4.71 (95% CI, 3.21–6.90). When we excluded from the analysis on hypopharyngeal cancer one study,[36] in which heavy alcohol category was defined as drinkers of ⩾40.5 ml per day (approximately 32.2 g of ethanol per day), we found a summary RR of 9.60 (95% CI 4.15–22.20).

Figure 5 shows the resulting pooled dose–risk functions for cancer of the tongue, oropharynx and hypopharynx. From the RR functions describing the best-fitting dose–response relation between alcohol consumption and the risk of cancer of the tongue (log (RR) = (beta1) * dose^2 + (beta2) * dose^2 * log(dose)), we obtained pooled RR estimates of 1.05 (95% CI, 1.03–1.06) for 10, 1.22 (95% CI, 1.17–1.28) for 25, 1.79 (95% CI, 1.57–2.04) for 50, 2.75 (95% CI, 2.21–3.42) for 75, and 4.15 (95% CI, 3.09–5.57) for 100 g of ethanol per day. As regard oropharyngeal cancer, the best-fitting dose–response curve log(RR) = (beta1) * dose + (beta2) * dose$^{0.5}$ gives risk estimates of 1.20 (95% CI, 0.74–1.95) for 10, 1.57 (95% CI, 0.91–2.71) for 25, 2.46 (95% CI, 1.56–3.87) for 50, 3.83 (95% CI, 2.59–5.65) for 75, and 5.96 (95% CI, 3.51–10.13) for 100 g of ethanol per day. The best dose–risk relation between alcohol consumption and hypopharyngeal cancer risk was log(RR) = (beta1) * dose^2 + (beta2) * dose^2 * log(dose), with pooled estimates of 1.08

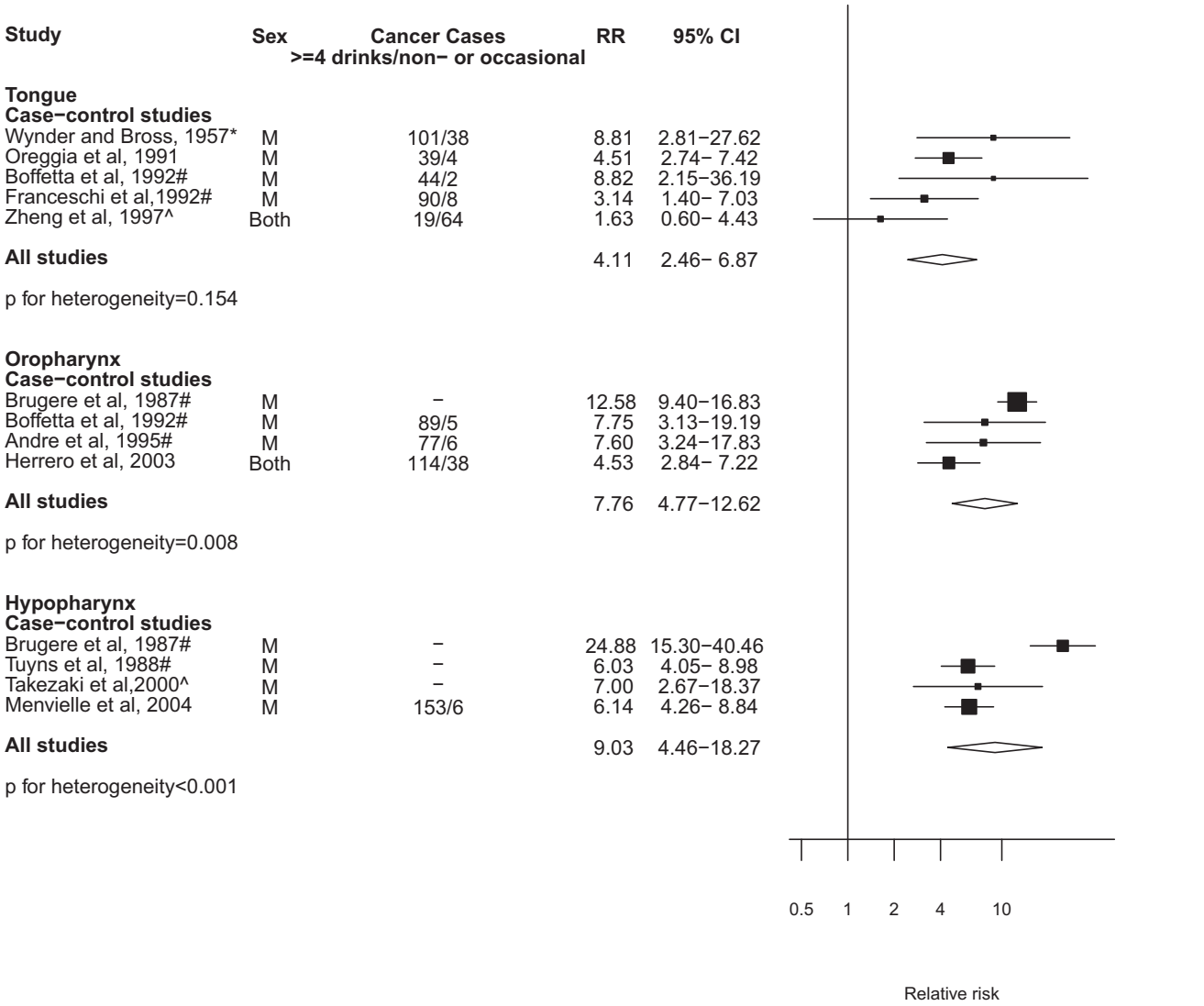

Figure 4 Summary RRs of cancer of the tongue, the oropharynx and the hypopharynx[‡] for heavy alcohol drinkers (⩾4 drinks per day) compared to non- or occasional drinkers.[*] The estimate was not adjusted for the main risk factors (i.e., sex, age and smoking). [#]In most of the studies the reference category was non- or occasional drinkers. In Boffetta et al.[3] was ⩽1 whisky equivalent/day (i.e., ⩽10.24 g of ethanol/day), in Tuyns et al.[38] was ⩽1.5 drinks/day, in Brugere et al.[33], in Andre et al.[20] was ⩽3 drinks/day, in Franceschi et al.[9] was ⩽19 drinks/week. [^]In most of the studies heavy drinking category was ⩾4 drinks/day, in Zheng et al.[10] was ⩾30 g/day (approximately 2.4 drinks/day) and in Takezaki et al.[36] was ⩾1.5 drinks/day. [‡]*p* of heterogeneity between the cancer-sites pooled estimates = 0.113.

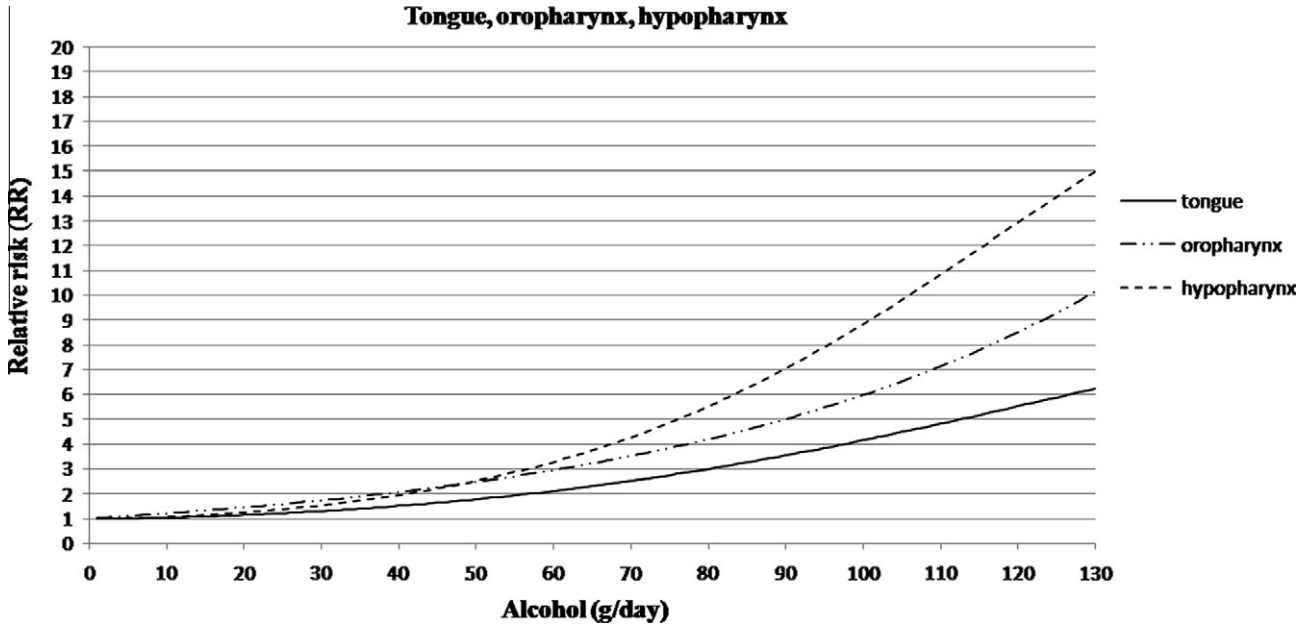

Figure 5 Relative risk functions describing the best-fitting dose–response relationships between alcohol consumption and the risk of cancer of the tongue, the oropharynx and the hypopharynx.

(95% CI, 1.06–1.09) for 10, 1.39 (95% CI, 1.30–1.48) for 25, 2.52 (95% CI, 2.09–3.06) for 50, 4.86 (95% CI, 3.42–6.91) for 75, and 8.83 (95% CI, 5.08–15.35) for 100 g of ethanol per day.

Discussion

In this meta-analysis, we found higher risk estimates for alcohol intake for pharyngeal (oro- and hypopharynx) as compared to oral (including tongue) cancer. There was, however, significant heterogeneity among studies.

We conducted several sensitivity analyses, which confirmed the stronger association of alcohol with pharyngeal rather than oral cancer. In particular, we found that the different effect of alcohol on oral and pharyngeal carcinogenesis persists even when only studies reporting risk estimates for both oral and pharyngeal cancer separately[4,11,16,19,20,23,25,27–31,33] were considered.

Our results are consistent with those from a US case-control study, considering the effects of alcohol and smoking on the risk of cancer of selected subsites of oral cavity and oropharynx.[3] In that paper, the authors suggested that the stronger effect of alcohol on distal tract may be due to a longer contact time with the pharyngeal mucosa, than with the oral one. To be in agreement with this hypothesis, alcohol should have a stronger effect on structures belonging to the "food channel" and "reservoir system" by acting as solvents and reducing the defense mechanisms of the mucosa and consequently enhancing the effect of tobacco or other carcinogens.[23] However, a few individual studies[4,25,41] suggested a greater effect of alcohol on oral than pharyngeal cancer. The role of chance is a possible explanation for those findings, particularly in smaller studies.

For both the oral cavity and the pharynx there was substantial heterogeneity among studies. This heterogeneity concerns the strength of the association rather than its direction, at least for heavy drinkers, since in all studies the risk was above two. As concerns light doses, the vast majority of studies found a RR above one for both oral and pharyngeal cancer. The only cohort study,[17] however, presented data for oral cavity only and did not find an increased risk in light drinkers (RR = 0.78). The estimate for heavy drinkers in that study, however, was very similar to the overall pooled estimate.

Our dose–response analysis on subsites of the oral cavity and pharynx showed that the dose-risk relation between alcohol intake and cancer of the tongue was similar to that with oral cancer as a whole and less steep than for the pharyngeal subsites. As concern oro- and hypopharynx, although the best-fitting models were mathematically different, they led to fairly similar dose-risk relations.

HPV is another major recognized risk factor for cancers of the oropharynx and the base of the tongue, but evidence is less clear for cancers of other oral subsites.[7,11,42] Only one study in this meta-analysis accounted for HPV.[25] It is possible that the greater risk for oropharyngeal cancers is due to residual confounding by HPV (i.e., more frequent HPV positives among heavy drinkers) and/or interaction between HPV and alcohol.[6] The role of alcohol on oropharyngeal cancer risk, however, seems greater among (or restricted to) HPV-negative subjects.[25,43]

Possible limitations of the present meta-analysis are inherent to the available data, and include the role of under-reporting of alcohol consumption, the problem of bias and confounding in observational studies, the limitation of data derived from retrospective exposure assessment in case-control studies, the lack of availability of data from all cohort studies except one, and the possible residual confounding by tobacco or other risk factors of oral and pharyngeal cancer.[1] A limitation of the dose–response analysis is that it assumes a dose–response with no threshold. Furthermore, the slope depends on the level of misclassification in the different categories of alcohol consumption, and if heavy drinking is more frequently misclassified than drinking at lower doses, the slope of the dose-risk function will be over-estimated. In addition, when we investigated subsites of the oral cavity and pharynx, only for a few sites (tongue, oro- and hypopharynx) a meaningful number of studies were available, and for these three sites, estimates were also based on a limited number of cases.

In conclusion, the present comprehensive meta-analysis indicates that alcohol drinking is strongly related to all oral subsites.

If anything, the association is stronger for oropharyngeal cancers. Focusing towards early diagnosis of oral cancers among heavy drinkers should therefore not be restricted to the oral cavity, but include all the oral and pharyngeal sites.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.oraloncology.2010.07.010.

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