Alcohol drinking and second primary cancer risk in patients with upper aerodigestive tract cancers: A systematic review and meta-analysis of observational studies

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Running title: Alcohol drinking and second primary cancers

Key words: alcohol drinking, second primary cancer prevention, systematic review, meta-analysis, upper aerodigestive tract cancer

Grant support
This work was supported by a grant (2010-144) of the French National Cancer Institute (P. Latino-Martel).

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Disclosure of potential conflict of interest

No potential conflicts of interest were disclosed.

Word counts: 2988 words

Total number of figures and tables: 3 figures, 1 table, 8 supplementary data files including 2 supplementary materials and 6 supplementary tables.
Abstract (249 words)

**Background** We conducted a systematic review and meta-analysis of existing data from observational studies to assess the strength of the association of alcohol drinking with second primary cancer risk in patients with upper aerodigestive tract (UADT: oral cavity, pharynx, larynx and oesophagus) cancer.

**Methods** PubMed and Embase were searched up to July 2012 and the reference lists of studies included in the analysis were examined. Random effects models were used to estimate summary relative risks (RRs) and 95% confidence interval (CIs).

**Results** Nineteen studies, eight cohort and eleven case-control studies, were included. In highest versus lowest meta-analyses, alcohol drinking was associated to significantly increased risk of UADT second primary cancers (RR = 2.97, 95% CI: 1.96-4.50). Significantly increased risks were also observed for UADT and lung combined (RR = 1.90, 95% CI: 1.16-3.11) and all sites (RR = 1.60, 95% CI: 1.22-2.10) second primary cancers. For an increase in alcohol intake of 10 g/day, dose-response meta-analyses resulted in significantly increased RR of 1.09 (95% CI: 1.04-1.14) for UADT second primary cancers.

**Conclusions** Alcohol drinking in patients with UADT cancer is associated with an increased risk of second primary cancers. Studies conducted in alcohol drinking UADT cancer patients and evaluating the effect of alcohol cessation on second primary cancer and other outcomes are needed.

**Impact** Our results emphasize the importance of prevention policies aiming to reduce alcohol drinking. Health care professionals should encourage alcohol drinking UADT cancer patients to reduce their consumption and reinforce the surveillance of this at-risk subpopulation.
Introduction

Cancers of the upper aerodigestive tract (UADT: oral cavity, pharynx, larynx and oesophagus) represent a major public health issue worldwide being the 4th most frequently occurring cancers in men and women with 1 116 405 new cases and the 2nd cancer mortality cause with 763 238 deaths estimated from population-based cancer registries in 2008. Their incidence has reached age standardised rates of 14.5 and 13.7 per 100 000 in 2008 in Europe and the United States of America (USA), respectively. UADT cancers have also an important impact in terms of overall mortality with age standardized rates per 100 000 of 5.0 in USA and 7.8 in Europe (1). One medical concern for UADT cancer survivors is the risk of developing new primary cancers, in particular for patients diagnosed with oral cavity, pharynx and larynx cancers for whom the 5-year relative survival rates are of approximately 60-65% (2). Patients with a primary UADT cancer have a variable increase in risk of developing a new malignancy ranging from 15% (oesophageal cancer) to 145% (oral cavity and pharynx cancers combined) (2-5). Subsequent cancers occur predominantly in the UADT and lung, with identified risk factors being younger age at initial diagnosis, human papillomavirus infection, tobacco smoking, and radiotherapy (2). Alcohol consumption, a modifiable risk factor of UADT cancers may also be involved (6-9).

Several studies have investigated the role of alcohol drinking in second primary cancer incidence. We performed a systematic review and meta-analysis of published observational studies to assess the strength of this association. Available data were analyzed according to second primary cancer site.
Materials and Methods

Literature search

We conducted a search in PubMed and Embase databases (up to July 2012), without publication date or language restrictions, by combining the medical subject headings or emtrees and corresponding entry terms for head and neck neoplasms, second or multiple primary neoplasms, alcohol drinking and observational studies (Supplementary Materials M1 and M2). The reference lists of all relevant articles that were included in the analysis were also examined.

Study selection

Abstracts or full-text manuscripts were identified and reviewed independently by two investigators. Studies were included if they met the following inclusion criteria: original research article, cohort or case-control study design conducted in adult with UADT cancer as first primary cancer site, assessment of alcohol consumption, with second primary cancer as outcome and report of the hazard ratio (HR), relative risk (RR) or odds ratio (OR) and 95% confidence interval (CI) for alcohol intake. In the case of duplicate information, we used the publication providing the most adjusted risk estimation, up to date and complete data concerning second primary cancer sites and defined alcohol consumption. Twenty potentially relevant full-text publications were identified (10-29). We excluded one duplicate publication, as confirmed by the authors (10).

Unpublished Data Collection

Based on full-text examination, 63 authors were contacted for additional information: possible unpublished risk estimate for alcohol drinking and second primary cancer risk (when alcohol and survival, or second/multiple cancers were mentioned in the full-text) or precisions
on the study characteristics or potential overlap between several publications. Collected data are cited as personal communications.

**Data extraction**

Using a standardized data collection form, two investigators extracted independently the following information for each study: first author’s last name, publication year, study characteristics (country and region or institution where the study was conducted, recruitment and mean follow-up period), participants characteristics (sample size, ethnic origin of participants, mean age, and percentages of men and current or ex-smokers), locations of the index tumor, index tumor characteristics (stage and treatment), second primary cancer diagnosis characteristics (diagnosis criteria, synchronous and/or metachronous, minimal time between the two diagnoses), second primary cancer site and number of cases, alcohol consumption assessment (period of consumption targeted, time and method of assessment and type of alcoholic beverages), alcohol comparison and corresponding HRs, RRs or ORs and 95% CIs by second cancer site, matching factors (for case-control studies only) and adjustment for covariates.

**Statistical analysis**

Random-effects models were used to calculate summary RRs and 95% CIs for highest versus lowest and dose-response analysis when at least two studies were available. If studies reported results separately for different UADT second primary cancer subsites, we combined the UADT subsite specific estimates using the method of Hamling to generate an estimate for all UADT second primary cancers (30). Dose-response meta-analyses were performed by second cancer site using the method described by Greenland and Longnecker to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs.
across alcohol consumption categories reported in the papers (31). The method requires the report of the distribution of cases and person-years or non-cases, the RRs with the variance estimates for at least three quantitative exposure categories. Using standard methods (32), we estimated the distribution of cases or person-years in studies that did not report these but reported the total number of cases and person-years. The median level of exposure in each category was assigned to the corresponding HR, RR or OR when reported. If not reported, the value assigned was the midpoint of the lower and upper bound in each category. For extreme open-ended categories, half the width of the adjacent exposure category was subtracted (for the lowest category) or added (for the uppermost category) to obtain the midpoint. Dose-responses slopes for an increment of 10 g of alcohol were estimated using the midpoint of each alcohol category.

Highest versus lowest meta-analyses were also conducted in subgroups defined according to study design, geographic location, adjustments, alcohol consumption assessment modalities (from interview, self-assessment questionnaire, questionnaire with a not specified method or medical record), alcohol consumption comparison (drinkers versus non-drinkers or by categories), index tumor location, or the minimal time between the two diagnoses, at least two months or none (exclusively metachronous second primary cancers (2,33), or not). Heterogeneity between the studies was assessed by the Q-test and \( I^2 \), which is the amount of total variation that is explained by the between-study variation. Heterogeneity was considered significant with \( P \leq .05 \). Publication bias was assessed with funnel plots, Egger’s test (34) and Begg’s test (35) and considered significant when \( P < .05 \)

All statistical analyses were performed with Stata version 10 (Stata Corp., College Station, Tex).
Results

Eight cohort studies and eleven case-control studies (19 publications) could be included in the meta-analysis of alcohol drinking and second primary cancer risk (Fig. 1) (11-29). Three cohort (11-13) and seven case-control (14-20) studies (ten publications) examined UADT second primary cancers. Seven studies, four cohort (12,13,21,22) and three case-control studies (23-25) investigated UADT and lung second primary cancers combined. Six cohort studies provided risk estimates for second primary cancers for all sites as defined by the authors (11-13,26-28). Most studies examined indistinctly synchronous or metachronous second primary cancers (11,15,18,23,26) or did not provide information on the delay between the two diagnoses (12,13,16,17,19-21,25,27,28). One study (14) examined only synchronous second primary cancers and three studies (22,24,29) only metachronous ones. Based on available data reported in studies, the cut points of the referent alcohol consumption categories across studies ranged from never/non-drinker status to 100 grams of ethanol per day. The highest category of alcohol intake in the studies ranged from drinker status to more than or equal to 170 grams per day. In most studies (11-16,19-29), alcohol consumption was assessed after primary cancer diagnosis: before treatment in three studies (14-16), after treatment in five studies (11,22,25-27), without information regarding treatment in nine studies (12,13,19-21,23,24,28,29). Two studies did not specify when alcohol intake was assessed (17,18). Only three studies investigated the effect of persistence of alcohol use after index tumor treatment or diagnosis (one cohort study (26) and one case-control study (29)) or cessation of drinking (24). In most studies, alcohol consumption was assessed retrospectively and drinking habits before index tumor diagnosis were reported (13,15-21,23-26,28,29), while no information was provided in five studies (11,12,14,22,27). Seven of the studies were from America, seven from Asia and five from Europe. Characteristics of the included studies are provided in Supplementary Tables S1-S4.
UADT second primary cancers

Ten studies (11-20), reporting 493 cases among 6385 participants, were included in highest versus lowest analyses of alcohol drinking and UADT second primary cancer. Figure 2 shows the summary RRs for highest versus lowest alcohol intake: 2.97 (95% CI: 1.96-4.50, $P = 0.0001$), with evidence of moderate heterogeneity ($P = 0.158$, $I^2 = 31.3\%$). Figure 3 shows no evidence of small-study bias as confirmed with Egger’s test ($P = 0.44$) and Begg’s test ($P = 0.53$). In the sensitivity analysis excluding the study cumulating a very high reference category compared to other studies and the absence of criteria to define second primary cancers (20), similar results were observed. Overall similar results were also obtained in subgroup meta-analyses conducted according to study design, geographic location (Europa or Asia), or second primary cancer site; with studies assessing alcohol consumption by interview or medical record; in studies comparing drinkers versus non-drinkers or different alcohol consumption levels; studies providing data adjusted on age, gender, smoking, occupation or index tumor site, or not. The summary RR was not statistically significant in cohort studies and in studies in which alcohol consumption was assessed by questionnaire (with an unspecified method) (Table 1). Two studies could be included in dose-response meta-analysis (12,14). One study could not be included because its number of cases was too small to calculate the slope (16). With a total of 157 cases among 3614 participants, the summary RR for an increase in alcohol consumption of 10 g per day was 1.09 (95% CI: 1.04-1.14, $P = 0.001$), with no heterogeneity ($P = 0.351$, $I^2 = 0.0\%$).

UADT and lung second primary cancers combined

Seven studies investigated the association between alcohol drinking and risk of second primary UADT and lung cancers combined and included 466 cases among 3720 participants
The summary RR for highest versus lowest alcohol intake was 1.91 (95% CI: 1.17-3.13, \( P = 0.010 \)), with evidence of heterogeneity (\( P = 0.025 \) and \( I^2 = 58.4\% \)). There was no evidence of publication bias with Egger’s test (\( P = 0.71 \)) or Begg’s test (\( P = 0.45 \)). In subgroup analyses, the summary RR was statistically significant for case-control but not for cohort studies, studies conducted in America, studies assessing alcohol consumption by interview or comparing drinkers versus non-drinkers, studies not examining exclusively metachronous second primary cancers. Studies adjusted on age, gender, and smoking tended to report on average weaker associations than not adjusted studies (Supplementary Table S5).

**All sites second primary cancers**

Six studies were included in highest versus lowest analyses of alcohol drinking and all sites second primary cancer, including 708 cases among 4267 participants (11-13,26-28). The summary RR for highest alcohol intake compared to lowest alcohol intake was 1.60 (95% CI: 1.22-2.10), with no heterogeneity (\( P = 0.388 \), \( I^2 = 4.4\% \)). There was no evidence of small-study bias with Egger’s test (\( P = 0.92 \)) or Begg’s test (\( P = 0.57 \)). No significant association was observed for studies conducted in America, in which index tumor was located in the oral cavity, or that compared drinkers versus non-drinkers. Studies that did not adjust for age tended to report stronger associations than those adjusted on age (Supplementary Table S6).

**Second primary cancers related to persistence of alcohol drinking after diagnosis**

Two studies investigated persistence of alcohol drinking after UADT tumor diagnosis and second primary cancer risk, including 457 cases among 1695 participants (26,29). In highest versus lowest analysis, the summary RR was 2.00 (95% CI: 0.82-4.88) for highest versus lowest alcohol intake after cancer diagnosis, with evidence of moderate heterogeneity (\( P = 0.160 \), \( I^2 = 49.4\% \)).
Discussion

To our knowledge, this meta-analysis, conducted with all the studies available, is the first one to assess the strength of the association of alcohol drinking at primary UADT cancer diagnosis with second primary cancer risk. Our results indicated that in UADT cancer survivors, alcohol drinking was associated to more than two-fold increased risk of second UADT cancers compared to not drinking alcohol. The dose-response meta-analysis showed that the risk of UADT second primary cancers increased in 9% for every increase in alcohol intake of 10 g/day. The risk increase associated to alcohol drinking was 91% for second UADT and lung cancers combined and 60% for any second primary cancers, compared to not drinking alcohol.

Persistence of alcohol use was associated to a two-fold increased risk of second primary cancer, although only two studies could be included in the meta-analysis and the association was not statistically significant. Although only three studies investigated the effect of persistence of alcohol use or cessation of drinking after index tumor treatment or diagnosis and second primary cancer risk, results were consistent across studies (24,26,29). These sparse results are in agreement with those of a pooled analysis indicating that cessation of alcohol is associated with a reduction of risks of first primary UADT cancers (36). Whether reducing alcohol intake after UADT cancer diagnosis modify the risk of second cancers deserves further investigation. The positive association observed between alcohol drinking and second primary cancer risk in our meta-analyses may result from a life-long exposure, rather than from a specific effect after the index cancer diagnosis: first, alcohol consumption increased the risk of second primary cancers at sites for which a relationship is well-established for first primary cancers (6), second, a long time-period is required to reduce the risk of former drinking following alcohol cessation (37). The mechanisms through which alcohol drinking confers an increased risk of first or second primary cancers are likely to be
quite similar. The positive association between alcohol drinking and risks of second primary cancers could be in large part explained by the genotoxicity of the metabolite of ethanol, acetaldehyde, and the action of ethanol as a solvent enhancing penetration of carcinogens into the mucosa of UADT organs (38,39).

Our analyses are subject to some limitations related to the quantity and the quality of the available data. First, in most studies alcohol consumption was estimated only after index UADT cancer diagnosis: these estimates may be affected by reporting bias and do not take into account any possible change after the index tumor diagnosis. Moreover, information on data collection concerning alcohol consumption assessment (period targeted, time and method) were mostly imprecise and only two studies provided data on type of alcoholic beverages (15,24). Referent categories of alcohol intake were heterogeneous across studies. However, results were consistent across highest versus lowest and dose-response meta-analyses. In the future, when a greater number of studies providing dose-responses will be available, the linearity or non-linearity of the relationship will deserve to be tested. Second, adjustments for potential confounding were not consistent across studies (Supplementary Tables S3 and S4). For example, in the case of UADT analyses, if most studies (seven/ten) provided data adjusted on smoking status, only half studies adjusted data on age at index tumor diagnosis and none on papilloma virus infection or treatment. Moreover none adjusted on other nutritional factors related to UADT cancer risk (fruits, vegetables, body weight). However, subgroup analyses performed according to adjustment on smoking status provided similar results. This observation is in agreement with the conclusion of the last IARC monograph indicating that alcohol drinking is also associated with an increased risk of UADT cancer in non smokers (39). Results were consistent across studies, meta-analyses, and subgroup meta-analyses for UADT and all sites second primary cancers, thus not supporting residual confounding. Nevertheless, additional studies are required to confirm our results with
better-adjusted data. Third, because our results suggest that the relationship of alcohol drinking and second primary cancers is stronger for second UADT cancers than for second cancers in other anatomical sites, future studies should aim to report the association of alcohol drinking with the risk of each cancer location separately. Fourth, although results of the Egger’s test, Begg’s test and funnel plot did not support the possibility of publication bias, the small number of included studies makes it difficult to distinguish a chance of finding from true asymmetry.

Recently, it has been shown that survivors of a cancer related to excessive body weight are at higher risk of second primary cancers at various sites also related to excessive body weight (40). Similarly, we show that survivors of a cancer related to alcohol drinking are at higher risk of second primary cancers at sites also related to alcohol drinking. These observations illustrate the capacity of these risk factors to favour the development of cancers simultaneously or successively at various sites, and justify to reinforce prevention on such major nutritional risk factors. Alcohol consumption at index diagnosis of UADT cancer has been associated with significantly increased mortality and recurrence (41-46). Moreover, quitting drinking after UADT cancer diagnosis has been shown to be associated with a better prognosis (44,47). Our results also provide further evidence that alcohol drinking may influence outcomes in UADT cancer survivors.

In conclusion, results from the present meta-analyses show that alcohol drinking in patients with UADT cancer is associated with an increased risk of second primary cancers. Studies conducted in alcohol drinking patients with UADT cancer and evaluating the effect of alcohol cessation on second primary cancer incidence and other outcomes are needed. Our results clearly underline the importance of prevention policies aiming to reduce alcohol drinking. At least, health care professionals should encourage UADT cancer patients that
consume alcohol to reduce their consumption and reinforce the surveillance of this at-risk subpopulation.
Grant Support

This work was supported by a grant (2010-144) of the French National Cancer Institute (P. Latino-Martel). T. Norat and D.S.M. Chan are supported by the World Cancer Research Fund (Continuous Update Project grant number 2007/SP01). The funding organizations played no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The views expressed in this publication do not necessarily represent the position of the French National Cancer Institute or World Cancer Research Fund. The authors have declared no conflicts of interest.
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Table 1. Subgroup analyses of alcohol drinking and UADT second primary cancer risk

<table>
<thead>
<tr>
<th>Alcohol drinking (highest versus lowest)</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>Overall Effect (P)</th>
<th>Q (P)</th>
<th>I² (%)</th>
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<td>All studies</td>
<td>10</td>
<td>2.97 (1.96-4.50)</td>
<td>0.0001</td>
<td>0.158</td>
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<td>Excluding study&lt;sup&gt;20&lt;/sup&gt;</td>
<td>9</td>
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<td>Cohort</td>
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<td>Europe</td>
<td>3</td>
<td>3.06 (1.51-6.17)</td>
<td>0.002</td>
<td>0.759</td>
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<td>Asia</td>
<td>6</td>
<td>3.47 (1.90-6.31)</td>
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<td>By interview</td>
<td>6</td>
<td>2.76 (1.44-5.31)</td>
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<td>By questionnaire&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2</td>
<td>5.45 (0.69-42.98)</td>
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<td>Drinkers vs. non-drinkers</td>
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<td>2.70 (1.28-5.70)</td>
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<td>By categories</td>
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<td>Second primary cancer site&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>UADT&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Age</td>
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<td>0.513</td>
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<tr>
<td></td>
<td>No</td>
<td>3.58 (1.65-7.78)</td>
<td>0.001</td>
<td>0.044</td>
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<td>Gender&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>3.22 (1.72-6.03)</td>
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<td>No</td>
<td>2.80 (1.97-3.97)</td>
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<sup>N</sup> denotes the number of risk estimates.
<sup>CI</sup>, confidence interval; <sup>RR</sup>, relative risk; <sup>UADT</sup>, upper aerodigestive tract.
<sup>1</sup>Questionnaire (method not specified).
<sup>2</sup>Data from the study of Hori et al 2011 could be included in both oral cavity, pharynx and larynx and oesophagus analyses.
<sup>3</sup>UADT including oesophagus.
<sup>4</sup>Data from the studies of Dikshit et al, Hsairi et al and Morita et al, although not adjusted on gender were included in the adjusted group since all the participants were men.
<sup>5</sup>Data from the studies of Morita et al and Katada et al, although not adjusted on index tumor site were included in the adjusted group since all index tumors were oesophageal.
Figure Legends

**Figure 1.** Flow-chart of study selection

**Figure 2.** Risk Estimate for alcohol drinking and UADT second primary cancer in observational studies

Error bars indicate 95% confidence intervals. Size of the squares indicates the weight of each study in the meta-analysis. CI=confidence interval.

**Figure 3.** Funnel plot for assessing publication bias for alcohol drinking and UADT second primary cancer.

Each diamond represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line: summary estimate of ln(RR) from the meta-analysis; dashed line: 95% confidence limits around ln(RR).
2591 reports identified with Medline and Embase

2362 reports excluded by review of the abstract

229 full-text articles assessed for eligibility

209 full-text articles excluded for irrelevant design, outcome, exposure or incomplete data

20 publications meeting inclusion criteria for further examination

1 publication excluded for duplicate publication

19 studies with usable information included in the meta-analysis
8 cohort studies
11 case-control studies
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<th>author</th>
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<th>participants</th>
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<td>2738</td>
<td>3.72 (1.14, 12.15)</td>
<td>9.08</td>
</tr>
<tr>
<td>Morita</td>
<td>1994</td>
<td>30</td>
<td>143</td>
<td>16.50 (3.27, 83.20)</td>
<td>5.52</td>
</tr>
<tr>
<td>Barbone</td>
<td>1996</td>
<td>39</td>
<td>380</td>
<td>2.00 (0.53, 7.54)</td>
<td>7.63</td>
</tr>
<tr>
<td>Tanabe</td>
<td>2001</td>
<td>17</td>
<td>134</td>
<td>17.70 (1.92, 163.54)</td>
<td>3.16</td>
</tr>
<tr>
<td>Muto</td>
<td>2002</td>
<td>54</td>
<td>389</td>
<td>3.30 (1.19, 9.14)</td>
<td>11.25</td>
</tr>
<tr>
<td>Dikshit</td>
<td>2005</td>
<td>37</td>
<td>876</td>
<td>3.50 (1.10, 11.17)</td>
<td>9.36</td>
</tr>
<tr>
<td>Gal</td>
<td>2005</td>
<td>34</td>
<td>279</td>
<td>0.86 (0.18, 4.05)</td>
<td>5.93</td>
</tr>
<tr>
<td>Hori</td>
<td>2011</td>
<td>59</td>
<td>1060</td>
<td>2.54 (1.67, 3.86)</td>
<td>25.91</td>
</tr>
<tr>
<td>Wang</td>
<td>2011</td>
<td>69</td>
<td>315</td>
<td>3.79 (1.55, 9.27)</td>
<td>13.35</td>
</tr>
<tr>
<td>Katada</td>
<td>2012</td>
<td>34</td>
<td>71</td>
<td>1.11 (0.33, 3.72)</td>
<td>8.81</td>
</tr>
<tr>
<td>Overall (I-squared = 31.3%, p = 0.158)</td>
<td></td>
<td></td>
<td></td>
<td>2.97 (1.96, 4.50)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Funnel plot with pseudo 95% confidence limits

Standard error of ln(RR) vs. ln(RR)
Alcohol drinking and second primary cancer risk in patients with upper aerodigestive tract cancers: A systematic review and meta-analysis of observational studies

Nathalie druesne-pecollo, Youssouf Keita, Mathilde Touvier, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst December 4, 2013.

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doi:10.1158/1055-9965.EPI-13-0779

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