RESEARCH ARTICLE

Different Levels in Alcohol and Tobacco Consumption in Head and Neck Cancer Patients from 1957 to 2013

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Abstract

Objective

To provide a precise quantification of the association between alcohol and tobacco consumption trends in head and neck cancer patients over the past 45 years.

Methods

We combined findings from all studies published until March 2014 and evaluated the association between different levels in alcohol and tobacco consumption and head and neck cancers through a meta-analytic approach.

Results

We included 28 studies involving 13830 patients with head and neck cancer. In patients with alcohol consumption, the pooled odds ratio (OR) and 95% confidence interval (CI) were 1.29(1.06-1.57), 2.67(2.05-3.48) and 6.63(5.02-8.74) for light drinkers, moderate drinkers and heavy drinkers, respectively. In patients with tobacco consumption, the pooled OR and 95% CI were 2.33(1.84-2.95), 4.97(3.67-6.71) and 6.77(4.81-9.53) for light smokers, moderate smokers and heavy smokers, respectively.

Conclusion

The increased alcohol and tobacco consumption trends increased the risk of head and neck cancer over the past 45 years. Tobacco consumption was found to be a stronger risk factor for head and neck cancer than alcohol consumption. Thus, the control should be considered to limit the intake of alcohol and tobacco.
Introduction

The broad ranges of alcohol and tobacco consumption patterns around the world create significant public health and safety problems. Convincing evidence demonstrated that alcohol and tobacco consumption increases the risk of cancer in the breast, colorectum, liver, esophagus and head and neck [1–3]. Cigarette contains amounts of chemicals, including many known carcinogens. The carcinogenic role of cigarette varies depending upon the cigarette product [4]. And the chemical products of alcohol metabolism are also explored to be toxic and hypothesized to cause DNA modifications that lead to cancers [5].

Head and neck cancers (HNC) including cancers in the oral cavity, pharynx and larynx, is one of the most common cancer in the world. There are approximately 300,000 oral cancers, 142,000 pharynx cancers and 157,000 larynx cancers been diagnosed each year [6]. The theory of multiple factors has been well-investigated. Ecological and individual-based studies have reported higher incidence of HNC in deprived populations [7]; lower education and nonprofessional occupations also exhibit a poorer prognosis of HNC [8]; in addition, dietary and nutritional habits have been reported to have a relevant role in the development of HNC [9]. Most of all, amounts of specific research have reported that alcohol and tobacco consumption are the major lifestyle-related risk factors [2,3,10–12]. However, a great amount of the studies with HNC cancers only focused on the intake of alcohol and tobacco, paying little attention on a precise evidence of an association between different levels of alcohol and tobacco consumption. So it is necessary to explore whether different levels of alcohol and tobacco consumption differ the HNC cancer risk. Therefore, we carried out a meta-analysis of epidemiological published studies to quantify the association between different levels of alcohol and tobacco consumption and patients with head and neck cancer.

Materials and Methods

Literature search and study inclusion

We carried out a systematic literature search in PubMed and ISI Web of Science for articles published before March 2014. We also reviewed references from reviews, meta-analyses and relevant studies for the sake of completeness. The key words used for the literature search was as follows: (alcohol OR alcoholic beverages) AND (smoke OR tobacco consumption) AND (lip cancer OR tongue cancer OR salivary gland cancer OR gingival cancer OR mouth cancer OR pharynx cancer OR larynx cancer). All titles and abstracts were reviewed by two of the authors.

The articles which met the following explicit criteria were included: 1. Case–control or cohort studies; 2. The exposure of interest were alcohol and tobacco consumption; 3. Risk estimates [odds ratio (OR) or risk ratio (RR)] and corresponding 95% confidence intervals (CIs) or sufficient data to calculate them were reported; 4. Never and/or occasional (non/occasional) drinking was taken as the reference category; 5. At least three levels of alcohol and tobacco consumption and reporting the OR or RR and 95% CIs or sufficient information to calculate them for each level.

Data extraction

For each included study, we extracted details on publication year, country, study name, cancer site, study design, variables adjusted or matched, risk estimates and 95% CIs. Two reviewers assessed the quality of included articles, and resolved doubts or disagreements. When same studies were published in more than one paper, only the most recent article was included in the analysis. Since different studies used different units to measure alcohol consumption, we converted it into a uniform measurement (grams per day (g/day)) and the equivalencies was formulate as...
0.8 g/ml = 28 g/ounce = 12.5 g/drink. The risk estimates of alcohol consumption were separated into light, moderate, and heavy drinkers, which were ≤12.5 g/day, 12.6–49.9 g/day, and ≥50 g/day of alcohol consumption, respectively [13]. Due to the same units of tobacco measurement found in all included studies, we separated tobacco consumption into light, moderate, and heavy smokers, which were ≤19 cigarettes/day, 20–39 cigarettes/day, and ≥40 cigarettes/day of tobacco consumption, respectively. We combined them into a single estimate using the method for pooling non-independent estimates, if more than one value fell into one of these three levels in the study [14].

Statistical analysis

Because all included publications were case-control studies, we used ORs to measure the interest. When available, we used adjusted risk estimates; otherwise the unadjusted risk estimates were used. Chi-square statistics was calculated to evaluate the heterogeneity across the studies. When \( P < 0.10 \), the random effect model was selected, otherwise, the fixed effect model was performed [15]. The Egger regression test and Begg-Mazumdar test were used to measure the potential publication bias [16]. We carried out meta-regression models to explored potential sources of between-study heterogeneity [17]. All statistical analyses were carried out in STATA version 12.0. \( P < 0.05 \) was considered statistically significant. All \( P \) values were two-sided.

Results

Characteristics of studies

The process of selection of articles for inclusion was summarized in Fig 1. A total of 2199 relevant articles were identified in initial search, and 28 published studies from 1957 and 2013 were included for this meta-analysis finally. Table 1 showed the main characteristics of the 28 studies [18–45]. A total of 13830 patients with head and neck cancer were included in the meta-analysis. There were 11 studies conducted in America (6 in the USA), 6 in Asia and 11 in Europe.

Meta-analysis

Table 2 showed the major results between different levels of alcohol consumption and HNC cancer risk, including the pooled ORs, 95% CIs and heterogeneity. Moreover, in order to obtain a more precise quantification of the association, stratified analyses by cancer type, regional distribution, and gender were performed. Compared with non/occasional drinkers, the pooled ORs and 95% CIs were 1.29(1.06–1.57), 2.67(2.05–3.48) and 6.63(5.02–8.74) for light drinkers, moderate drinkers and heavy drinkers, respectively in Fig 2, with significant heterogeneity between study designs \( (I^2 > 50\%) \). The dose-response analysis was carried out in Fig 3, and the plot also showed the risk of HNC increased with increasing alcohol consumption. As the gender subgroup analysis showed, there were not significant differences in gender in three different levels. However, patients with pharynx cancers seem more susceptible when alcohol consumption increased. At the same time, no susceptibility of cancer risk was found in larynx cancer patients who drink a little. By Geographic area in classification analysis, the association between alcohol drinking and cancer risk was stronger among people from America and Europe than those from Asia.

Table 3 showed the characteristics of results between different levels of tobacco consumption and HNC cancer risk. Compared with non/occasional smokers, the pooled ORs and 95% CIs were 2.33(1.84–2.95), 4.97(3.67–6.71) and 6.77(4.81–9.53) for light smokers, moderate smokers and heavy smokers in Fig 4, respectively, with significant heterogeneity between study
2199 relevant articles identified from database searches

1866 articles excluded (title or abstract were not relevant to the point)

333 articles have possible association

279 articles excluded (provided insufficient data of at least three levels of alcohol or tobacco consumption)

54 articles considered for the inclusion

26 articles excluded (24 for meta-analysis or reviews or systematic reviews; 2 for unavailable data)

28 case-control studies included in this meta-analysis

Fig 1. Flowchart of selection of studies for inclusion in meta-analysis.
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designs ($I^2 > 50$%). We also carried out a dose-response analysis in Fig 5. The result of the plot showed a significantly increased risk of HNC with increasing tobacco consumption. In female patients, no differences were found in light and moderate levels of tobacco intake, but a higher cancer risk was found with heavy tobacco consumption. By cancer type, larynx cancers seem
more susceptible when tobacco intake increased. Moreover, patients of HNC in Europe countries were more susceptible in all three different levels. Tobacco consumption was found to be a stronger risk factor for head and neck cancer than alcohol consumption.

For the head and neck cancer is a chronic process, the duration of alcohol and tobacco consumption should be considered for a risk factor. So we showed results of pooled and subgroup analysis for head and neck cancers by years of cigarette smoking. As shown in Table 4, the pooled ORs and 95%CIs were 1.93(1.37–2.73), 3.39(2.47–4.66) and 3.39(2.47–4.66) for patients who smoke for 1–19 years, 20–40 years and >40 years, respectively. Unfortunately, we could not get enough data of the duration of alcohol consumption.

| Study | Country | Cases | Sex | Cancer site | Ethnicity | Source of controls | Design |
|-------|---------|-------|-----|-------------|-----------|--------------------|--------|
| Wynder and Bross [18], 1957 | USA | 297 | MF<sup>a</sup> | Oral, larynx | Mixed | Population based | Case-control |
| Keller and Terris [19], 1965 | USA | 544 | MF | Oral, larynx | Caucasian | Hospital based | Case-control |
| Blot et al. [20], 1988 | USA | 1105 | MF | Oral, pharynx | Mixed | Population based | Case-control |
| Merletti et al. [21], 1989 | Italy | 122 | MF | Oral, pharynx | Caucasian | Population based | Case-control |
| Zheng et al. [22], 1990 | China | 165 | M<sup>b</sup> | Oral | Asian | Hospital based | Case-control |
| Franceschi et al. [23], 1990 | Italy | 453 | MF | Oral, larynx, pharynx | Caucasian | Hospital based | Case-control |
| Choi and Kahyo [24], 1991 | Korea | 364 | MF | Oral, larynx, pharynx | Asian | Hospital based | Case-control |
| Orejias et al. [25], 1991 | Uruguay | 57 | MF | Oral | Caucasian | Hospital based | Case-control |
| Maier et al. [26], 1994 | Germany | 106 | M | pharynx | Caucasian | Population based | Case-control |
| Hayes et al. [27], 1999 | Puerto Rico | 321 | MF | Oral | Caucasian | Population based | Case-control |
| Bouchardy et al. [28], 2000 | France | 257 | MF | Oral, larynx, pharynx | Caucasian | Hospital based | Case-control |
| Garrote et al. [29], 2001 | Cuba | 160 | MF | Oral, pharynx | Mixed | Hospital based | Case-control |
| Schwartz et al. [30], 2001 | USA | 326 | MF | Oral | Mixed | Population based | Case-control |
| Zavras et al. [31], 2001 | Greece | 95 | MF | Oral | Caucasian | Hospital based | Case-control |
| Znaor et al. [32], 2003 | India | 2192 | M | Oral, pharynx | Asian | Hospital based | Case-control |
| Castellsague et al. [33], 2004 | Spain | 375 | MF | Oral, pharynx | Caucasian | Hospital based | Case-control |
| Menvielle et al. [34], 2004 | France | 526 | MF | Larynx, pharynx | Caucasian | Hospital based | Case-control |
| Rosenquist et al. [35], 2006 | Sweden | 128 | MF | Oral, pharynx | Caucasian | Population based | Case-control |
| Vlajinac et al. [36], 2006 | Yugoslavia | 100 | MF | Pharynx | Caucasian | Population based | Case-control |
| Peters et al. [37], 2006 | USA | 692 | MF | Oral, larynx, pharynx | Mixed | Population based | Case-control |
| De Stefani et al. [38], 2007 | Uruguay | 776 | MF | Oral, pharynx | Caucasian | Hospital based | Case-control |
| Applebaum et al. [39], 2007 | USA | 483 | MF | Oral, larynx, pharynx | Mixed | Hospital based | Case-control |
| Subapriya et al. [40], 2007 | India | 388 | MF | Oral | Asian | Hospital based | Case-control |
| Oze et al. [41], 2010 | Japan | 255 | MF | Oral, larynx, pharynx | Asian | Hospital based | Case-control |
| Boing et al. [42], 2011 | Brazil | 1017 | MF | Oral, larynx, pharynx | Caucasian | Hospital based | Case-control |
| Matsuo et al. [43], 2012 | Japan | 1099 | MF | Oral, larynx, pharynx | Asian | Hospital based | Case-control |
| Rador et al. [44], 2012 | France | 749 | MF | Oral | Caucasian | Hospital based | Case-control |
| Bravi et al. [45], 2013 | Italy | 768 | MF | Oral, pharynx | Caucasian | Hospital based | Case-control |

<sup>a</sup> Male and female  
<sup>b</sup> Male

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Sensitivity analysis and publication bias

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we repeated the meta-analysis with one study excluded at each time. The results did not have significant change of the pooled OR even if the most influential study was omitted. We also excluded...
studies by different subgroup (cancer site, geographic area, sample size and study time), and we did not find any significant change of the pooled OR (data not shown). These indicated the robustness of our findings. Funnel plot and Egger’s test were performed to assess the publication bias. The shape of the funnel plot (S1–S6 Figs) did not show any obvious evidence of asymmetry for $P = 0.070$, $P = 0.154$, $P = 0.960$, $P = 0.899$, $P = 0.274$, and $P = 0.139$, respectively.

**Discussion**

The results of the present meta-analysis, based on 13,830 HNC cases, provide quantitative testimony for a positive association between alcohol and tobacco consumption and HNC risks. Compared with non/occasional drinkers, we found that alcohol consumption was associated with a significantly increased risk at moderate and heavy levels for HNC patients, while our results showed much higher ORs of pharynx cancer compared with those presented among patients with oral and larynx cancers. Moreover, our results were rather similar to those shown in previous studies [46, 47]. The association between alcohol consumption and cancer risk was

| Light vs. non/occasional | Moderate vs. non/occasional | Heavy vs. non/occasional |
|--------------------------|----------------------------|-------------------------|
| **OR (95% CI)**          | **P-value**                | **I²**                  |
| All studies              | **OR (95% CI)**            | **P-value**             | **I²**       |
| 1.29(1.06–1.57)          | 0.010                      | 83%                     |              |
| 2.67(2.05–3.48)          | <0.001                     | 92%                     |              |
| 6.63(5.02–8.74)          | <0.001                     | 91%                     |              |
| **Cancer site**          |                            |                         |              |
| Oral                     | 1.30(1.14–1.49)            | <0.001                  | 0%           |
| Oral                     | 2.28(1.68–3.10)            | <0.001                  | 87%          |
| Oral                     | 3.93(2.78–5.57)            | <0.001                  | 93%          |
| Pharynx                  | 1.39(1.02–1.89)            | 0.035                   | 54%          |
| Pharynx                  | 2.87(1.91–4.30)            | <0.001                  | 73%          |
| Pharynx                  | 5.70(3.61–9.02)            | <0.001                  | 78%          |
| Larynx                   | 0.98(0.75–1.29)            | 0.880                   | 0%           |
| Larynx                   | 2.06(1.53–2.79)            | <0.001                  | 16%          |
| Larynx                   | 3.00(1.76–5.11)            | <0.001                  | 64%          |
| **Gender**               |                            |                         |              |
| Male                     | 1.72(1.22–2.44)            | 0.002                   | 90%          |
| Male                     | 3.00(2.29–3.91)            | <0.001                  | 0%           |
| Male                     | 7.46(5.32–10.46)           | <0.001                  | 0%           |
| Female                   | 1.60(1.04–2.46)            | <0.001                  | 0%           |
| Female                   | 5.37(2.22–13.00)           | <0.001                  | 0%           |
| Female                   | 7.84(2.32–26.52)           | <0.001                  | 0%           |
| **Geographic area**      |                            |                         |              |
| America                  | 1.38(1.06–1.78)            | 0.020                   | 76%          |
| America                  | 2.98(2.19–4.06)            | <0.001                  | 86%          |
| America                  | 7.65(5.60–10.45)           | <0.001                  | 81%          |
| Europe                   | 1.19(0.72–1.98)            | 0.500                   | 89%          |
| Europe                   | 2.64(1.35–5.14)            | 0.004                   | 94%          |
| Europe                   | 7.36(3.34–13.24)           | <0.001                  | 95%          |
| Asia                     | 1.28(0.91–1.82)            | 0.160                   | 82%          |
| Asia                     | 2.22(1.27–3.89)            | 0.005                   | 95%          |
| Asia                     | 4.83(3.15–7.43)            | <0.001                  | 89%          |

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Table 3. Odds ratio (95% confidence interval) of pooled and subgroup analysis for head and neck cancers by tobacco intake.

|                          | Light vs. non/occasional | Moderate vs. non/occasional | Heavy vs. non/occasional |
|--------------------------|--------------------------|-----------------------------|--------------------------|
|                          | OR (95% CI)              | P-value        | $I^2$       | OR (95% CI)              | P-value        | $I^2$       | OR (95% CI)              | P-value        | $I^2$       |
| All studies              | 2.33(1.84–2.95)          | <0.001         | 88%         | 4.97(3.67–6.71)          | <0.001         | 94%         | 6.77(4.81–9.53)          | <0.001         | 94%         |
| Cancer site              |                          |                |            |                          |                |            |                          |                |            |
| Oral                    | 1.51(1.19–1.93)          | 0.001          | 84%         | 2.79(1.93–4.04)          | <0.001         | 91%         | 4.00(2.57–6.22)          | <0.001         | 92%         |
| pharynx                 | 2.07(1.28–3.34)          | 0.003          | 74%         | 3.52(2.03–6.11)          | <0.001         | 78%         | 5.72(3.34–9.80)          | <0.001         | 73%         |
| larynx                  | 2.89(1.81–4.61)          | <0.001         | 0%          | 5.37(3.33–8.67)          | <0.001         | 0%          | 11.30(6.26–20.39)        | <0.001         | 0%          |
| Gender                  |                          |                |            |                          |                |            |                          |                |            |
| Male                    | 1.68(1.19–2.38)          | <0.001         | 32%         | 3.25(1.94–5.44)          | <0.001         | 88%         | 4.03(2.45–6.62)          | <0.001         | 41%         |
| Female                  | 1.62(0.69–3.78)          | 0.267          | 62%         | 3.66(2.45–5.48)          | <0.001         | 0%          | 7.80(3.04–19.96)         | <0.001         | 17%         |
| Geographic area         |                          |                |            |                          |                |            |                          |                |            |
| America                 | 2.44(1.66–3.58)          | <0.001         | 85%         | 5.78(3.50–9.53)          | <0.001         | 92%         | 6.99(4.72–10.33)         | <0.001         | 86%         |
| Europe                  | 2.74(1.53–4.92)          | <0.001         | 91%         | 7.20(3.37–15.37)         | <0.001         | 94%         | 10.48(4.89–22.49)        | <0.001         | 94%         |
| Asia                    | 1.78(1.27–2.50)          | <0.001         | 87%         | 2.67(2.03–3.52)          | <0.001         | 80%         | 3.29(2.64–4.10)          | <0.001         | 58%         |

Fig 3. Relative risk function and 95% confidence intervals for the association between alcohol consumption per day and HNC.

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stronger among people from America and Europe than those from Asia. One possible theory was that the proportion of moderate and heavy drinkers was higher in America and Europe population. Another possible theory was that people from America and Europe carried a higher prevalence of the polymorphisms of alcohol metabolism related genes, such as aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH), having a lower risk of some alcohol-related cancer consequently [48,49].

A significantly increased risk at all three different levels was found from the results of the tobacco consumption meta-analysis. It showed a significantly higher increased risk for larynx cancers than oral and pharynx cancer. One of the possible theory was that fibers of tobacco could be released and then penetrated into the laryngeal tissue, thus becoming a further risk factor initiating tumorigenesis [50]. Another possible reason was that the number of studies from larynx is limited. Meanwhile, patients with tobacco smoking habit in Europe countries seemed more susceptive with HNC risks.

In some epidemiologic studies, ethanol had been described as a risk enhancer in smokers, but not as an independent risk factor [51]. However, most of the studies provided strong evidence that alcohol consumption, independently from exposure to tobacco consumption, increased the risk of head and neck cancer [20,46,52,53]. Unfortunately, we did not get enough data between alcohol and tobacco consumption in patients with HNC, the analysis of the alcohol and tobacco interaction was not explored.

Limitations of our meta-analysis include some possible residual confounding, such as diet, physical activity and human papillomavirus (HPV) infection. But we could not ignore and exclude these residual confounding. Some studies demonstrated that HPV infection is a risk factor for HNC cancer, especially for cancers of the tongue [54,55]. However, from the result of
Fig 5. Relative risk function and the 95% confidence intervals for the association between tobacco consumption per day and HNC.

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Table 4. Odds ratio (95% confidence interval) of pooled and subgroup analysis for head and neck cancers by years of cigarette smoking.

| Cancer site | 1–19 years | 20–39 years | >40 years |
|-------------|------------|-------------|-----------|
| OR (95% CI) | P-value    | \( \hat{f} \) | OR (95% CI) | P-value | \( \hat{f} \) | OR (95% CI) | P-value | \( \hat{f} \) |
| All studies | 1.93(1.37–2.73) | <0.001 | 82% | 3.39(2.47–4.66) | <0.001 | 78% | 5.17(3.93–6.80) | <0.001 | 70% |
| Oral | 1.77(1.21–2.61) | 0.004 | 46% | 3.33(2.07–5.37) | <0.001 | 68% | 4.73(1.70–8.29) | <0.001 | 76% |
| pharynx | 2.09(1.08–4.05) | 0.029 | 69% | 3.29(1.18–9.13) | 0.022 | 86% | 6.03(2.34–15.54) | <0.001 | 83% |
| larynx | 3.18(1.70–5.97) | <0.001 | 0% | 4.13(2.25–7.58) | <0.001 | 0% | 9.32(4.06–21.42) | <0.001 | 50% |
| Gender | | | | | | | | |
| Male | 1.57(0.86–2.56) | 0.138 | 75% | 3.34(1.73–6.43) | <0.001 | 77% | 4.94(2.84–8.61) | <0.001 | 69% |
| Female | 1.79(0.99–3.27) | 0.056 | 46% | 3.26(2.21–4.80) | <0.001 | 0% | 4.35(2.88–6.59) | <0.001 | 0% |
| Geographic area | | | | | | | | |
| America | 1.75(0.99–3.11) | 0.055 | 91% | 3.35(2.10–5.34) | <0.001 | 86% | 5.54(3.96–7.74) | <0.001 | 73% |
| Europe | 2.86(1.81–4.52) | <0.001 | 27% | 4.91(2.56–9.41) | <0.001 | 64% | 7.46(4.18–13.29) | <0.001 | 52% |
| Asia | 1.52(1.12–2.06) | 0.008 | 0% | 2.14(1.53–3.01) | <0.001 | 0% | 2.80(2.00–3.92) | <0.001 | 0% |

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other different studies, whether the associations between alcohol and tobacco consumption and HNC cancer risk differ according to HPV status was not clear [39,56,57]. Nevertheless, significant heterogeneity among 28 included studies was observed, which possibly due to the study design and quality. However, random-effects model was allowed to be used into compute the heterogeneity [17]. Additionally, the lifetime of patients’ exposure to alcohol or tobacco and the different type of alcoholic and smoking beverage were not studied in this meta-analysis. Recall bias was another possible limitation of our study, we paid attention to collect the value of alcohol and tobacco consumption in a standardized manner, but differential reporting between articles could not be excluded.

In conclusion, tobacco consumption was found to be a stronger risk factor for head and neck cancer than alcohol consumption. The pharynx was the most affected by the harmful effects of alcohol, while larynx was the most affected by the harmful effects of tobacco. Europeans should pay more attention to harmful effects of tobacco. Tobacco consumption increased the risk of head and neck cancer even for smaller quantities whereas alcohol drinking increased this risk significantly at moderate and heavy levels. Precancerous lesions or cancer at an early stage should be detected by regular check-ups. Prevention efforts should be focused on smoking and drinking cessation [58].

Supporting Information
S1 Fig. Funnel plot of publication bias in light drinkers vs. non/occasional. (TIF)
S2 Fig. Funnel plot of publication bias in moderate drinkers vs. non/occasional. (TIF)
S3 Fig. Funnel plot of publication bias in heavy drinkers vs. non/occasional. (TIF)
S4 Fig. Funnel plot of publication bias in light smokers vs. non/occasional. (TIF)
S5 Fig. Funnel plot of publication bias in moderate smokers vs. non/occasional. (TIF)
S6 Fig. Funnel plot of publication bias in heavy smokers vs. non/occasional. (TIF)
S1 Table. Summary statistics for the association between tobacco intake and HNC risk in strata of selected covariates. (DOCX)
S2 Table. Summary statistics for the association between alcohol intake and HNC risk in strata of selected covariates. (DOCX)

Author Contributions
Conceived and designed the experiments: HY RW. Performed the experiments: YZ RW. Analyzed the data: YZ LM LZ. Contributed reagents/materials/analysis tools: HJ. Wrote the paper: YZ RW HY.
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