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Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis

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Abstract

Objective: Meta-analysis was used to summarize the published evidence on the associations between alcohol and tobacco consumption and cancers of the oropharynx, pharynx, larynx, and esophagus. The objective was to produce summary risk estimates with uniform methods and on uniform exposure scales so that the magnitudes of the risks could be compared across tumor sites.
Methods: Epidemiologic studies that estimated the effects of alcohol and tobacco consumption on the risk of cancers of the upper aero-digestive tract were identified from the MEDLINE database, 1966–2001. Alcohol and tobacco data were converted into common units (grams/week). For all studies meeting eligibility criteria, effect parameters (slopes) were estimated for both exposures. The exposure-risk slopes for each study were combined, site by site, using random effects meta-regression methods.
Results: Fourteen studies met the final selection criteria. The carcinogenic effects of alcohol and tobacco were found to be multiplicative on the relative risk scale. Tobacco appeared to have a much stronger effect on the larynx than on any of the other aerodigestive sites, while alcohol's effect was strongest on the pharynx. The weakest association was that of alcohol and adenocarcinoma of the esophagus – an order of magnitude weaker than that for tobacco and laryngeal cancer.
Conclusions: Meta-analysis was used to combine the results from all available studies, providing a comprehensive summary of the combined effects of alcohol and tobacco on the upper aerodigestive cancers.

Introduction

Tobacco and alcohol use, separately and in combination, are the principal known causes of aerodigestive tract cancers [1–3]. Esophagus, larynx, pharynx, oral cancer, and to a lesser extent gastric cardia cancer, have all been linked to these two exposures. The strengths of these associations appear to vary from site to site, possibly due in part to the extent of physical contact between the agent and target tissue [4]. Further evidence of heterogeneity has been found in a few studies that have examined the associations for different cell types. There also appear to be different degrees of interaction between alcohol and tobacco from site to site, although this conclusion is hampered by the variety of methods that have been used in different studies.

In this investigation, meta-analysis was used to summarize the evidence from the published literature on the strengths of the associations between alcohol and tobacco exposures and the risks of aerodigestive cancers. The objective was to produce summary risk estimates with uniform methods and on uniform exposure scales so that the magnitudes of the risks could be compared across tumor sites. Where possible, the analysis was also performed for specific cancer cell types.

Meta-regression techniques are available for estimating the quantitative exposure–response relationships that can be extracted from published epidemiologic studies, when the exposure data are collected as

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quantitative or semi-quantitative measures [5, 6]. These methods, generally used with a single exposure variable, were adapted here to address the problem of the joint effects of alcohol and tobacco.

Materials and methods

Identification of studies

Epidemiologic studies that had examined the effects of alcohol and tobacco consumption on the risk of cancers of the upper aero-digestive tract (UADT – pharynx, larynx, and esophagus) were identified through the US National Library of Medicine's MEDLINE database for the years 1966–2001. Only those studies which collected individual data on drinking and smoking habits of participants were included. From this initial set, all studies meeting the following selection criteria were selected:

(1) Data presented on either the joint or independent effects of alcohol and tobacco on cancers of the upper aero-digestive tract (UADT), for these anatomical sites: pharynx (*oro-pharynx*, ICD-O code 10th revision: C10.0–C10.9; *hypopharynx*, ICD-O code: C13.0–C13.9), larynx (ICD-O code: C32.0–C32.9), esophagus (ICD-O code: C15.0–C15.9), and gastro-esophageal junction (ICD-O code: 16.0);
(2) Alcohol and tobacco exposure data expressed as intensity of exposure (and not, for example, only duration), and presented in units that could be converted into grams of alcohol and of tobacco consumed per day;
(3) The number of subjects for each joint smoking/drinking category presented, so that appropriate weighting could be performed;
(4) A true unexposed reference group (non-smokers and non-drinkers) used.

Initial meta-regression modeling using the natural logarithm of the odds ratio (ln[OR]) as the dependent variable included only those studies that provided effect estimates by joint categories of alcohol and tobacco, so that issues of interaction could be investigated. Only six such studies were identified (Table 1). Analysis of these studies found that the effects of alcohol and tobacco were substantially independent (results not shown). That is, on the log odds scale, there were no important departures from additivity of the main effects of alcohol and tobacco consumption on the UADT cancer risk; interaction terms did not improve model fits. Based on these results, the data set was expanded to include all studies which had investigated the *independent* effects of alcohol and/or tobacco, while controlling for the other. This increased the number of studies available for analysis (Table 1).

Additional selection criteria were applied, to reach the final data set (Table 1):

(1) Alcohol analyses controlled adequately for tobacco consumption, and tobacco analyses controlled adequately for alcohol consumption;
(2) Control for potential confounding by age, gender, and when appropriate race;
(3) Confidence intervals provided for the estimated effects (so that the adjusted variance could be estimated); and
(4) At least three strata for each exposure.

Only the results for males were analyzed, except in two studies in which both genders were pooled together [7, 8]. Unfortunately, separate analyses for females were not performed because there were so few data.

Conversion of exposures to common units

For those studies that had not presented their measure of alcohol and tobacco consumption in SI units, we converted their exposure estimates into 'grams per week' using the following conversion factors:

1 drink = 30 ml hard liquor = 150 ml wine = 330 ml beer = 11.87 g of pure ethanol [2];

1 cigarette = 0.2 cigars = 0.4 pipes of tobacco = 1 g tobacco [9].

Exposure levels for regression

All published data meeting the above criteria presented risk estimates for categories of exposure. For meta-regression analysis, it is necessary to assign an exposure level for each group or stratum, representing the 'typical' exposure level for those in the group [6]. The mean or median values are probably the most desirable measures, but the studies provided only the exposure cutpoints used to identify the groups, rather than a measure of central tendency. A common solution is to use the midpoint of the category. Two strategies were employed in the present investigation, and their results compared. First, category midpoints were used. Second, a Monte Carlo method was used to estimate what the mean might have been in each category, assuming a hypothetical, but plausible, exposure distribution.

The identification of category midpoints was straightforward, except for the highest exposure groups in each study, which were always open-ended ('greater than two packs per day', for example). For these categories, the midpoint is undefined. Midpoints for open-ended upper categories of tobacco and alcohol consumption were chosen by estimating maximum plausible consumption levels for tobacco and alcohol (see below), and then identifying the value halfway between the upper and lower bounds.

Table 1. Final data set: studies of aerodigestive cancer risk from alcohol and tobacco

Study	Site	ICD-O codes (9th revision)	Cell type	Country	No. of subjects[a]	Adjusted covariates[b]	Joint/independent data
Blot, 1988 [28]	Oropharynx	141, 143–146, 148–149	NS[c]	USA (1984–1985)	753/832	Age, race, study location, respondent status	Both
Brown, 1994 [37]	Esophagus, ECJ	150, 151.0	ADC[d]	USA (1986–1989)	174/750	Age, area of residence, income	Independent
Brownson, 1987 [27]	Larynx	161	NS	USA (1984–1985)	63/200	Age	Both
Castellague, 1999 [12]	Esophagus	NS	SCC[e]	South America (1986–1992)	655/1407	Age group, years of schooling	Both
Choi, 1991 [29]	Pharynx	146–149	NS	Korea (1986–1989)	133/399	–	Independent
	Larynx	161	NS		94/282		
De Stefani, 1987[f] [13]	Larynx	NS	SCC	Uruguay (1985–1986)	101/290	Age	Independent
De Stefani, 1990 [14]	Esophagus	NS	SCC	Uruguay (1985–1988)	261/522	Age, residence	Independent
Falk, 1989 [38]	Larynx	161, 231.0	SCC	USA (1980–1982)	151/235	Age, residence, occupation, dietary factors	Independent
Flanders, 1982 [9]	Larynx	NS	NS	USA (Wynder, 1976)	224/414	None-only crude data available	Joint
Franceschi, 1990[g] [39]	Pharynx	146–148	NS	Northern Italy (1986–1989)	134/1272	Age, residence, years of education, occupation	Independent
	Larynx	161.1, other 161	NS		162/1272		
	Esophagus	150	NS		288/1272		
Gao, 1994 [30]	Esophagus	NS	68.8% SCC 6.25% ADC	China (1990–1993)	624/1074	Age, education, birthplace, tea drinking, dietary factors	Both
Hayes, 1999 [31]	Oral cavity	141[h]	NS	Puerto Rico (1992–1995)	298/417	Age	Both
	Oropharynx	143–146, 148, 149[h]					
Negri, 1992[g] [40]	Esophagus	NS	NS	Northern Italy (1984–1990)	244/901	Age, education, b-carotene intake	Independent
Rolon, 1995 [8]	Esophagus	NS	NS	Paraguay (1988–1991)	131/381[i]	Age, gender, hospital group	Independent
Zhang, 1996 [7]	Esophagus	150.0–150.9	ADC	USA (1992–1994)	95/132[i]	Age, gender, race, education, BMI, total dietary intake of calories	Independent
	Gastric cardia/ECJ[j]	151.0					

(See text for selection criteria.)

[a] Cases/controls.

[b] Analyses for alcohol adjusted for tobacco, and *vice versa*, as well as for the shown covariates.

[c] Not specified.

[d] Adenocarcinoma.

[e] Squamous cell carcinoma.

[f] Only alcohol data were used because of a non-zero reference group for tobacco.

[g] Only tobacco data were used because of a non-zero reference group for alcohol.

[h] Excluded morphology codes 8082 (lymphoepithelial carcinoma), 8140 (adenoma), 8200 (adenoid cystic carcinoma), and 8430 (mucoepidermoid carcinoma), regardless of the anatomic definition.

[i] Both genders used in the analysis.

[j] Esophageal cardia junction.

Tobacco

National Health Interview Survey data [10] for a stratified random sample of US adults were used to obtain information on the distribution of smoking habits. To approximate the maximum level of smoking likely to have occurred in a study population, the 99th percentile of weekly tobacco consumption was determined. This level was found to be approximately 560 g or 28 packs of cigarettes per week (four pack per day). The midpoint for the highest tobacco category in each study was calculated using this level and the lower cutpoint of the highest category, which varied from study to study.

Alcohol

The same procedure was used for alcohol [11], and the 99th percentile for the empirical distribution of pure alcohol consumption was found to be 1000 g per week (84 drinks per week). This upper bound was found to be too low for several non-US studies. Those of Castellague [12] and De Stefani [13, 14], reported *lower* bounds of the highest alcohol category that were approximately 1050 g/week – above the 99th percentile of the US distribution. For these studies, upper bounds were set based on the blood alcohol levels slightly below that which would cause narcosis/deep sleep in an adult male of average weight, and assuming a pattern of regular daily consumption [15]. This quantity was estimated based on Gullberg's method [16] to be approximately 1250 g ethanol/week.

Exposure category *means* were also estimated for comparison with the results using midpoints. Empirical cumulative distribution functions for smoking or drinking habits were estimated based on the NHIS data [10, 11]. Based on the cut-off points for each exposure category for a specific study, probability density function intervals were estimated after fitting a logit function to the cumulative distribution functions of tobacco and alcohol consumption. Random samples of size equal to the number of controls in each exposure category in each study were then drawn, and the mean consumption of the sample calculated. Mean values were generated in this way from one thousand trials for each exposure category. Random values were selected from the distributions of the means for each of the categories of both alcohol and tobacco for each study, and these were used as the exposure levels in a meta-regression (see below). The distributions of parameter estimates (slopes) were derived from these simulations and compared to the parameters estimated from the meta-regressions using exposure category midpoints.

Meta-regression methods

Study-specific slopes

Effect parameters (slopes) were estimated separately in each study for cancer of one or more sites and alcohol and tobacco consumption using the published odds ratios (all studies used case control sampling). Weights for each category-specific odds ratio were estimated as the inverse of the variance of the ln(OR) [17]. When confidence limits (upper: UCL, lower: LCL) were presented for the category-specific odds ratios, then the standard error for ln[OR] was estimated based on the formula: SE = (ln(UCL)−ln(LCL))/(2*1.96) for 95% limits [17]. It was necessary to correct for the non-independence of the stratum-specific odds ratios that are the data points for these meta-regression models [5]. This non-independence derives from the fact that each stratum-specific odds ratio contains within it the information on the non-exposed reference category. The method of Greenland and Longnecker and the SAS IML procedure were used to produce study-specific slopes and associated adjusted variance estimates. As noted above, the effects of alcohol and tobacco could be estimated separately, because the two factors were not found to interact when their effects were evaluated on the ln[OR] scale.

Combining slopes and testing for homogeneity

Once the estimates of the exposure-risk slopes and standard errors for each study were obtained as described above, these were combined by site, using a random effects meta-regression method described by Berlin and colleagues [6]. A weighted average slope over multiple studies is

$$\bar{b}_{\mathrm{w}} = \frac{\sum_{i=1}^{k} w_i b_i}{\sum_{i=1}^{k} w_i}, \tag{1}$$

where $\bar{b}_{\mathrm{w}}$ is the weighted average slope defined over k number of studies, and b_i is the estimated adjusted slope for each study based on the method of Greenland and Longnecker [5]. Weights for the fixed-effects adjusted slopes are defined as follows:

$$w_i = \frac{1}{v_i}, \tag{2}$$

where v_i is the variance for the adjusted slope. This weighted mean slope was used to calculate Q, a statistic testing the homogeneity of the slopes over studies [18]:

$$Q = \sum_{i=1}^{k} w_i (b_i - \bar{b}_{\mathrm{w}})^2. \tag{3}$$

Assuming that the adjusted variances are unbiased estimates of the true variances, Q has a χ^2 distribution with $k-1$ degrees of freedom. If the null hypothesis of homogeneity of the slopes is rejected, then the effect should be considered random, and the between study component of variance, τ^2, should be estimated:

$$\tau^2 = \max\left[0, \frac{Q-(k-1)}{\sum_{i=1}^{k} w_i - \frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}}\right]. \quad (4)$$

If one does not reject homogeneity of the slopes, then the weighted average slope, $\bar{b}_w$, is an estimate of the common slope. Alternatively, heterogeneity implies that there is not a common slope, but instead a grand mean slope – the mean of the distribution of study-specific slopes [6]. The latter can be calculated, using new weights that include both the within and between study components of variance:

$$w_i^* = (w_i^{-1} + \tau^2)^{-1} = (v_i + \tau^2)^{-1}. \quad (5)$$

The grand mean slope is

$$\hat{\mu}_w = \sum_{i=1}^{k} w_i^* \frac{b_i}{\sum_{i=1}^{k} w_i^*} \quad (6)$$

and the standard error of the grand mean slope is

$$\left(\sum_{i=1}^{k} w_i^*\right)^{-1/2}. \quad (7)$$

Results

Thirty studies were identified in the initial selection. Of these, six presented results on the joint effects of alcohol and tobacco: two each for laryngeal, esophageal, and oro-pharyngeal cancer. As noted, these six studies were used in a preliminary analysis that suggested the adequacy of a simple additive model for the log of the odds ratio. Fourteen studies met the final selection criteria (Table 1). Only for the esophagus were there studies that enabled analyses by cell type; there were two studies of squamous cell carcinomas, two of adenocarcinomas, and four that did not distinguish cell type.

Individual slope estimates were calculated for each study, for both alcohol and tobacco, using the mid-points of the exposure categories (Table 2). Expressed in the same units, increments in ln[OR] per 100 g/week, the slopes for alcohol and tobacco were of the same order of magnitude across all tumor sites. The oropharynx and pharynx appeared to have quite similar slopes for tobacco and alcohol, while for larynx and esophagus, the effect of tobacco was somewhat stronger than that of alcohol. The studies of oropharynx and pharynx also appeared to have more homogeneous results than for the other two sites, although there were only two studies for oropharynx, and two for pharynx (only one could be used for estimating the alcohol effect on pharynx because the other used a non-zero reference group).

The individual study slopes in Table 2 were then combined to yield pooled estimates of the slopes for each tumor site, and for the two main cell types of esophageal cancer (Table 3).

The test for study homogeneity failed to reject the null hypothesis of common slopes for both alcohol and tobacco for the oropharynx and the pharynx (unsurprising, given that the two available studies yielded almost identical slope estimates, Table 2). Homogeneity of slopes was rejected for cancers of the larynx and esophagus. The evidence for heterogeneity was particularly strong for the effects of alcohol on the larynx and esophagus ($p < 0.01$), while the tobacco slopes were less variable from study to study ($p < 0.05$). This heterogeneity among studies indicates that the mean slopes shown in Table 3 for larynx and esophagus should be considered the means of the distributions of study slopes, rather than as common slopes across all studies. There may be sources of variability from study to study that have an important effect on the magnitude of these exposure–response slopes.

The effect of alcohol on the esophagus appeared to depend strongly on cell type; squamous carcinoma had a slope nearly four times that for adenocarcinoma. In contrast, the effects of tobacco were quite similar on the two different cell types. Tobacco appeared to have a much stronger effect on the larynx than on any of the other aerodigestive sites, while alcohol's effect was strongest on the pharynx. The weakest association was that of alcohol and adenocarcinoma of the esophagus – an order of magnitude weaker than that for tobacco and laryngeal cancer.

The combined risk estimates can be expressed as odds ratios characterizing the risk for various combinations of alcohol and tobacco consumption, compared to non-drinkers and non-smokers (Table 4), using the following equation:

$$\ln(\mathrm{OR}) = \beta_{\mathrm{alcohol}} * (\text{grams of ethanol/week}) + \beta_{\mathrm{tobacco}} * (\text{grams of tobacco/week}),$$

where β_{alcohol} and β_{tobacco} are the pooled estimates presented on Table 3. Risks rose very steeply with increasing quantities of alcohol and tobacco; a trend

Table 2. Individual study results[a]

Site	Study	Alcohol slope[b] (SE)[c]	Cases/controls	Tobacco slope[b] (SE)[c]	Cases/controls
Oropharynx	Blot, 1988 [28]	0.25 (0.02)	753/832	0.24 (0.05)	704/776
	Hayes, 1999 [31]	0.25 (0.03)	269/384	0.35 (0.07)	274/408
Pharynx	Choi, 1991 [29]	0.32 (0.06)	133/399	0.30 (0.11)	133/399
	Franceschi, 1990 [39]	–[d]		0.24 (0.09)	134/1256
Larynx	Brownson, 1987 [27]	0.17 (0.03)	63/200	0.45 (0.16)	63/200
	Choi, 1991 [28]	0.34 (0.06)	94/282	0.74 (0.13)	94/282
	De Stefani, 1987 [13]	0.21 (0.04)	107/290	–[d]	
	Franceschi, 1990 [39]	–[d]		0.35 (0.07)	160/1256
	Falk, 1987 [38]	0.07 (0.04)	151/235	0.65 (0.15)	117/143
Esophagus					
SCC[e]	Castellague, 1999 [12]	0.19 (0.03)	647/1386	0.23 (0.04)	643/1389
	De Stefani, 1990 [14]	0.16 (0.03)	199/370	0.22 (0.07)	199/398
ADC[f]	Brown, 1994 [37]	0.06 (0.03)	173/750	0.23 (0.07)	162/675
	Zhang, 1996 [7]	0.02 (0.05)	95/132	0.33 (0.18)	95/128
Mixed[g]	Franceschi, 1990 [39]	–[d]		0.21 (0.06)	281/1256
	Gao, 1999 [30]	0.11 (0.02)	486/702	0.47 (0.07)	486/702
	Negri, 1992 [40]	–[d]		0.24 (0.05)	244/901
	Rolon, 1995 [8]	0.29 (0.05)	131/378	0.50 (0.13)	131/381

Slopes of tobacco and alcohol risk relations, adjusted for non-independence of category specific odds ratios.
[a] Alcohol and tobacco category midpoints were used in the analyses.
[b] Ln(OR) per 100 g/week.
[c] Standard errors adjusted by method of Greenland and Longnecker (1992).
[d] Could not be calculated due to non-zero reference group.
[e] Squamous cell carcinoma.
[f] Adenocarcinoma.
[g] Cell type not specified.

Table 3. Pooled estimates of alcohol and tobacco effects on aerodigestive cancers[a]

Site	Alcohol					Tobacco				
	N[b]	Slope[c]	SE	*Q* statistic[d]	*p*-value[e]	N[b]	Slope[c]	SE	*Q* statistic[d]	*p*-value[e]
Oropharynx	2	0.25	0.02	0.001	0.98	2	0.28	0.10	1.3	0.25
Pharynx	1	0.32	0.05	–	–	2	0.27	0.04	0.2	0.68
Larynx	4	0.19	0.04	13.9	0.003	4	0.53	0.05	9.0	0.03
Esophagus	8	0.14	0.03	30.0	<0.0001	8	0.28	0.07	14.0	0.05
ADC	2	0.05	0.03	0.4	0.51	2	0.24	0.07	0.3	0.62
SCC	2	0.18	0.01	0.9	0.35	2	0.22	0.04	0.01	0.91
Mixed[f]	2	0.19	0.09	12.2	<0.001	4	0.33	0.07	11.5	0.01

[a] Alcohol and tobacco category midpoint consumption values used in analyses.
[b] Number of studies.
[c] Per 100 g/week of consumption. Weighted mean slope is estimated.
[d] *Q*-statistic for heterogeneity. Ho: Between study variance = 0.
[e] *p*-value for *Q* statistic.
[f] Cell type not specified.

seen in nearly all of the included studies. Laryngeal and pharyngeal cancer risks were increased about 35-fold for the highest joint category of alcohol and tobacco consumption (Table 4). Esophageal cancer, the least affected among the UADT cancers, had about a 13-fold increase in risk from the highest combined category of consumption compared to the non-exposed. The multiplicative nature of the joint exposure of alcohol and tobacco is illustrated in Figure 1, which presents the results of the pooled estimates for esophageal cancer (1a) and laryngeal cancer (1b) – the sites with the most numerous studies available.

The above analyses were repeated for the larynx and esophagus (the two sites with the most studies) using

Table 4. Estimated effects of alcohol and tobacco[a] on aerodigestive cancer risks

Tobacco consumption (cig/day)	Cancer types	Alcohol consumption (drinks/day)		
		0	>0–4	4+[b]
0	Oropharynx	1[d]	1.5	7.2
	Pharynx	1	1.7	12.6
	Larynx	1	1.4	4.5
	Esophagus[c]	1	1.4	4.2
>0–30	Oropharynx	1.3	2.0	9.7
	Pharynx	1.3	2.3	16.7
	Larynx	1.8	2.4	7.9
	Esophagus	1.4	1.8	5.6
30+[b]	Oropharynx	2.9	4.5	21.2
	Pharynx	2.8	4.8	35.6
	Larynx	7.7	10.6	34.6
	Esophagus	3.1	4.1	12.7

[a] Category midpoints were used for the estimation of OR.
[b] Midpoints for the upper categories: 55 cigarettes per day and 9.5 drinks per day.
[c] SCC and mixed cell type.
[d] Reference category.

estimated mean tobacco and alcohol consumption instead of the category midpoints (Table 5). The pooled slope estimates were about 10–100% larger than when midpoints were used. Berlin has previously reported similar sensitivity of meta-regression results to the choice of exposure category measure of central tendency [6]. Despite this, comparisons of the relative magnitudes of slopes between tumor types and the two exposures, yielded consistent patterns. The choice of midpoint or simulated mean consumption did not change the trends in the effects among cancer sites (however, this could be evaluated only for larynx and esophagus, since the analysis with the mean consumption was performed only on these two sites). The effects of both alcohol and tobacco were greater for the larynx then for the esophagus (risk per 100 g/week of either agent), and tobacco had a stronger effect than alcohol for both cancer sites.

Discussion

The links between alcohol, tobacco, and aerodigestive cancers have been studied epidemiologically for nearly fifty years [19–26]. The substantial body of literature that has resulted has generally been consistent in its findings, but differences in methods and presentation make it difficult to draw more than the most basic conclusions without careful study. Differences in measures of drinking and smoking habits, in the definition of reference groups, and simply in the varying sizes of the studies are a challenge to anyone wishing to pull the literature together into a coherent picture.

Meta-analysis methods were used to combine the results from as many published studies as possible, while maintaining standards of study quality and consistency. Despite the large literature on UADT cancers, alcohol and tobacco, quality criteria reduced the available

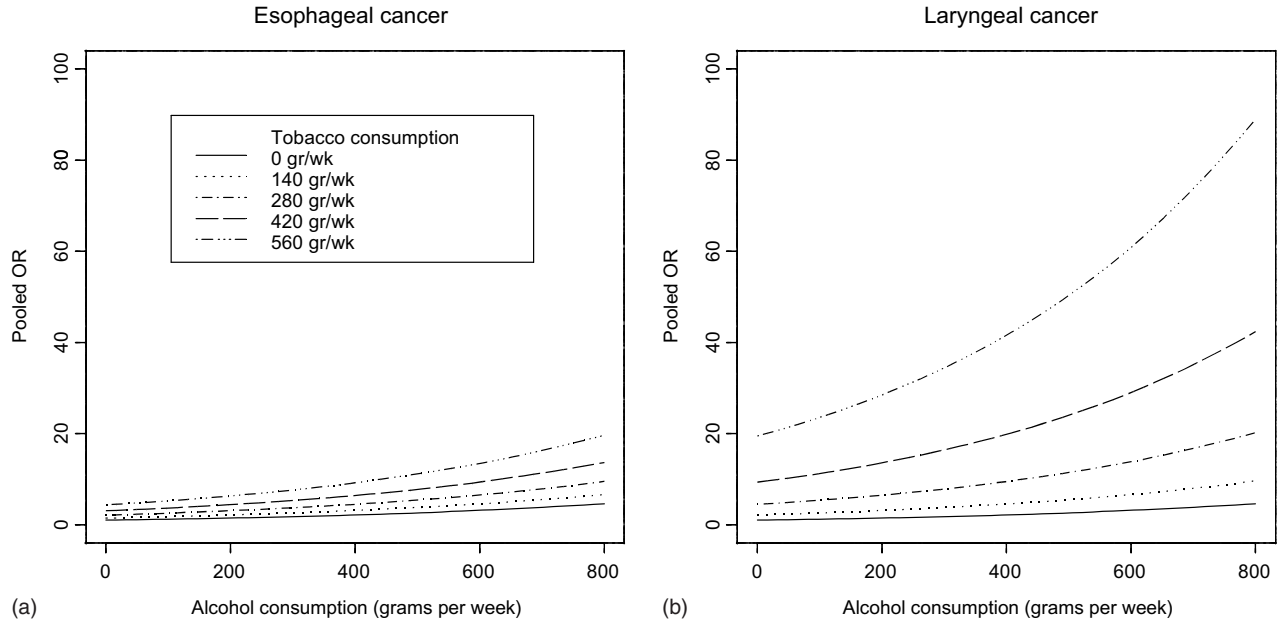

Fig. 1. Combined effects of tobacco and alcohol on esophageal and laryngeal cancer risk. Results of pooled meta-regression models.

Table 5. Alternative pooled estimates of alcohol and tobacco effects on cancers of the larynx and esophagus, using estimated category mean consumption values[a]

Site	Alcohol				Tobacco			
	N[b]	Slope[c]	SE	*p*-value[d]	N[b]	Slope[c]	SE	*p*-value[d]
Larynx	4	0.27	0.004	0.02–0.04	4	0.82	0.016	0.24–0.70
Esophagus[e]	4	0.21	0.002	0.001–0.007	6	0.61	0.008	0.17–0.49

[a] Alcohol and tobacco category consumption values used in analyses.
[b] Number of studies.
[c] Per 100 g/week of consumption. Weighted mean slope is estimated. See text for explanations.
[d] *p*-value for *Q* statistic.
[e] SCC and mixed cell type.

studies considerably; for several sites, our results were based on only two studies (Table 3).

Methods are now available for estimating pooled or combined exposure–response trends from studies presenting categorical results [5, 6]. Meta-analysis provides guidance in the estimation of common effect estimators; which removes many of the potentially arbitrary decisions that a reviewer previously had to make when seeking to combine results. Nevertheless, the results are potentially sensitive to the choice of specific models and methods of data handling, some of which are noted below.

Numerous authors have discussed the extent of interaction or synergy between alcohol and tobacco in the causation of aerodigestive cancers [2, 9, 12, 25, 27–31]. Most studies have reported that the combined effects appeared to be more than additive, and often a simple multiplicative model adequately described the data. In this analysis, an additive model on the loglinear scale appeared to fit the data. This means that the effects of the two exposures are predicted to behave in a multiplicative fashion on the relative risk scale. Is the additive model for ln[OR] correct? There were few studies that provided information with which to evaluate this hypothesis, and those studies provided raw cell counts of cases and controls in the various joint exposure strata. Using these data meant that it was not possible to control for confounding by age, or other covariates. Thus the adequacy of the additive model must be considered a tentative conclusion. Using this conclusion, however, permitted us to use more data sets, and to use odds ratios that were conditional on covariates – always age, and often other risk factors as well.

It should be stressed that the independence of the effects of alcohol and tobacco on the loglinear scale does *not* imply that, biologically, alcohol and tobacco act as independent or complete carcinogens. There is ample experimental evidence for the carcinogenicity of tobacco smoke [1, 3], but alcohol more likely functions as a cancer promoter [2], or facilitates the entry of tobacco carcinogens into cells [9]. One can find consistency, if not confirmation, of these different roles of tobacco and alcohol in carcinogenesis by looking at the present results. Tobacco has its strongest effect on the larynx – a large surface area of target cells exposed to high concentrations of carcinogenic aerosols [1, 3]. The other sites, with less heavily exposed cells, show lower tobacco slopes. Alcohol shows quite a different pattern; the large, directly exposed surface area belongs to the esophagus, which shows the *lowest* risk per unit of alcohol exposure. All this evidence suggests that alcohol's effects maybe indirect; with one possible mechanism being the interaction between this factor and other agents, tobacco included.

Most published studies provided data on tobacco and alcohol consumption in the form of average daily or weekly intensity of exposure, rather than as duration or cumulative exposure. There were a few exceptions, however [32–34]. It is not clear that these intensity measures are 'the best' in either a statistical or biologic sense, but in any case, there were insufficient data to investigate this question [35]. Olsen [36] reported that intensity measures of alcohol and tobacco consumption showed stronger evidence of synergy (departure from additivity) in laryngeal cancer risk than when lifetime cumulative exposure measures were used.

There were several large, potentially useful studies that were eliminated from analysis because they did not use truly unexposed reference groups. When 'low exposure' is the reference, all odds ratios will be biased downwards by the exposure-related risk in the reference group. Researchers probably decided to use low exposure reference groups because they lacked adequate numbers of truly unexposed participants. In the future, researchers might consider presenting a secondary analysis with a truly unexposed group, even if these results are unstable, to facilitate eventual comparisons to other studies.

Defining midpoints for open-ended alcohol categories required estimation of the maximum exposure levels. These probably varied among studies, and especially

across cultures, which may have introduced additional error into the midpoint estimates. The estimation of category means also required some assumptions. The means were estimated in a Monte Carlo method which used the study and category-specific cutpoints and an estimate of the cumulative distribution functions based on empirical distributions for tobacco and alcohol habits, derived from US National Health Interview Survey data [10, 11]. It is doubtful that the US tobacco and alcohol consumption distributions are correct for several of the countries studied (Spain, Paraguay, Poland for example), however this source of error is probably not too serious because it was only the *shape* of the distribution that was drawn from the US data; the category cutpoints, which strongly influence the location of the mean, were specified by the authors of each study, based on their data.

Quite different results were found, when the means or the midpoints were used for the exposure levels in the categories. This problem has been noted previously [6, 17]. Berlin compared the midpoint, mean and median in a meta-regression analysis of alcohol and breast cancer risk, and found that the slope using the means was considerably *lower* than when using the midpoint, the opposite trend from that found here. This probably occurred because Berlin's midpoint for the upper, unbounded category was arbitrarily set at 1.2 times the lower bound of the highest category. In the present analyses, the upper bounds were chosen based on the 99th percentiles of empirical drinking and smoking distributions of the US population in 1988 NHIS survey [10, 11] (1250 g per week for alcohol and 560 g per week for tobacco consumption). The midpoints that resulted were approximately 1.5–2 times higher than the lower bound for the highest exposure category (these proportions varied from study to study). When Berlin's [6] 'midpoint' rule of 1.2 times the lower bound was used for the highest exposure categories for laryngeal cancer studies, the results were very close to the means estimated from the Monte Carlo simulations (data not shown). It is not likely that the meta-regression uncertainty from open-ended upper exposure categories can be reduced, without more data from the original studies. If authors would present the mean or median exposures in their categories, then these values could be used directly. Alternatively, quantitative exposure–response trends could be published alongside the categorical results; eliminating entirely the need to estimate the trends from published categorical data.

There was strong evidence of heterogeneity among the studies reporting on laryngeal and esophageal cancers. This is perhaps not surprising, given that the studies come from many different countries (Table 1), where smoking and drinking habits may vary in ways not captured simply by the estimated grams of tobacco or alcohol consumed. Also, recall bias is likely to have been a problem in these studies, and one that may have varied from country to country, depending on many factors, including the degree of social stigma attached to these habits in a particular time and place. Thus it may be unreasonable to expect that case control studies of alcohol and tobacco and cancer risks in different countries would all converge on a single common risk estimate. Rather, the random effects model used here allows explicit estimation of the mean of the *distribution* of exposure–response slopes; which may be a more plausible way to think about a common risk estimate in this context. There were only two studies available with which to evaluate risks for oropharyngeal and pharyngeal cancers, and so the fact that the homogeneity test statistics failed to reject homogeneity of the slopes for either alcohol or tobacco cannot be given much weight. One wonders whether additional studies would result in the kind of heterogeneity seen for laryngeal and esophageal cancers.

In summary, we present estimates of the combined risks of tobacco and alcohol for cancers of the oropharynx, pharynx, larynx, and esophagus based on consistent meta-regression techniques and all available published studies (Table 4). These findings allow comparisons among tumor sites and between the two exposures. Future meta-analyses would be facilitated if investigators would follow these recommendations:

(1) A truly unexposed group should be used whenever possible as the reference category.

(2) When categorical exposure data are used, the mean exposure level in each category should be published.

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