Alcohol drinking and head and neck cancer risk: the joint effect of intensity and duration

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Running title: Drinking intensity and duration in head and neck cancer

Manuscript word count: 2573 words

Abstract (200 words)

Background: Alcohol is a well-established risk factor for head and neck cancers (HNC). This study aims to explore the effect of alcohol intensity and duration, as joint continuous exposures, on HNC risk.

Methods: Data from 26 case-control studies in the INHANCE Consortium were used, including never and current drinkers who drunk ≤10 drinks/day for ≤54 years (24234 controls, 4085 oral cavity, 3359 oropharyngeal, 983 hypopharyngeal, and 3340 laryngeal cancers). The dose-response relationship between the risk and the joint exposure to drinking intensity and duration was investigated through bivariate regression spline models, adjusting for potential confounders, including tobacco smoking.

Results: For all sub-sites, cancer risk steeply increased with increasing drinks/day, with no appreciable threshold effect at lower intensities. For each intensity level, the risk of oral cavity, hypopharyngeal, and laryngeal cancers did not vary according to years of drinking, suggesting no effect of duration. For oropharyngeal cancer, the risk increased with durations up to 28 years, flattening thereafter. The risk peaked at the higher levels of intensity and duration for all sub-sites (odds ratio=7.95 for oral cavity, 12.86 for oropharynx, 24.96 for hypopharynx, and 6.60 for larynx).

Conclusions: Present results further encourage the reduction of alcohol intensity to mitigate HNC risk.

Keywords: bivariate spline models; alcohol drinking duration; alcohol drinking intensity; head and neck cancer; hypopharyngeal cancer; INHANCE; laryngeal cancer; oral cavity cancer; oropharyngeal cancer.

Introduction

Worldwide, harmful alcohol consumption causes 3 million deaths each year (5% of all deaths), and it is responsible for approximately 5% of the global burden of disease and injury.[1] In particular, alcohol consumption has been consistently associated with cancer risk at several sites.[2] Together with tobacco smoking, alcohol drinking is one the major risk factors for head and neck cancer (HNC), and it is responsible for approximately one third of the cases worldwide.[3-4]

Epidemiological studies firmly established a clear dose-response relationship between ethanol intake and HNC risk.[5-6] However, alcohol drinking has two related dimensions impacting on health outcomes: besides the quantity of alcohol consumed, time-related patterns of consumption, such as age at starting and duration, have a relevant role[1] and they may modify the reported association between drinking intensity and cancer risk. Notably, a joint effect of intensity and duration on cancer risk has already been reported for tobacco smoking in HNC[7-8] and in other tobacco-related cancers.[9-11]

In a previous analysis from the International Head and Neck Cancer Epidemiology (INHANCE) consortium including 15 studies,[7] the independent contribution of drinking intensity and duration was estimated through the calculation of drink-years. Similarly to pack-years for tobacco smoking, drink-years represent the lifetime cumulative exposure to alcohol, and it was obtained by multiplying intensity (in drinks/day) by duration (in years). Then, the effect of duration on HNC risk was estimated analysing the risk for drink-years within fixed categories of intensity; this analysis reported an independent effect of drinking duration for all HNC sub-sites.[7]

In the absence of a clear relationship between alcohol intensity and duration on the risk of HNC, we investigated their joint effect on the INHANCE database using an extension of the bivariate spline model presented in a previously published analysis on cigarette smoking.[8] Differently from the previous INHANCE paper,[7] this model allows risks to vary for different combinations of drinking intensity and duration, even when the cumulative drink-year exposure is the same. We will address the following research questions: 1. What are the relationships between intensity and duration of alcohol drinking and the risk of cancer at HNC sub-sites? 2. Do drinking intensity and duration have a similar impact on HNC risk? 3. Are there meaningful values of drinking intensity or duration where the risk pattern changes?

Materials and Methods

The INHANCE consortium was established in 2004 to elucidate the aetiology of HNC through pooled analyses of individual-level data from several studies on a large scale.[12-13] It included invasive cancer cases of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or unspecified HNC. Cases with cancers of the salivary glands or of the nasal cavity/ear/paranasal sinuses were excluded.[14]

At the time of this analysis, the INHANCE database (version 1.5) included 25 716 HNC cases and 37 111 controls (http://www.inhance.utah.edu, last access 25th May, 2020). The present analysis was restricted to 26 case-control studies (21 384 HNC cases; 30 651 controls) that collected information on alcohol drinking status (i.e., never, former, current), intensity (number of drinks/day), and duration (years) at individual level (Supplementary Table S1).[15-40] Cancer sites were grouped according to similar major aetiology: oral cavity (ICD10 codes: C02-C06; n=6 249), oropharynx (ICD10: C01, C09-C10; n=5 499), hypopharynx (ICD10: C13; n=1 798), and larynx (ICD10: C32; n=5 620). The following exclusion criteria were applied: a) cancers arising in sites other than those mentioned above, or mixed cancer sub-sites (2 218 subjects); b) missing information on drinking status, intensity, or duration (2 247 subjects); c) being former drinkers (i.e., having stopped drinking for at least one year before cancer diagnosis or interview for controls; 6 993 subjects), as these subjects are more likely to stop drinking for reasons related to medical conditions;[41] d) missing information on major covariates, namely sex, age, education, ethnicity (92 subjects), or on cigarette smoking status, intensity, or duration (392 subjects) (see the flow-chart in Supplementary Figure S1). In 15 studies[15-17,19,21,22,24,25,27,28,33,34,37,38,40] controls were selected among cancer-free patients admitted to hospital for non-oncologic reasons, whereas controls were from the general population in 9 studies;[18,20,23,29-32,36,39] two multicentre studies[26,35] enrolled a combination of hospital and population controls.

To prevent potential estimation distortion due to sparse data or misclassification at the highest levels of the exposure distributions, we further excluded subjects who reported the highest 5% of drinking intensity (i.e., >10 drinks/day) or duration (i.e., >54 years); consequently, 2 455 HNC cases (17.3%) and 1 637 controls (6.3%) were excluded. Finally, the current analysis included 4 085 individuals with cancers of the oral cavity, 3 359 oropharynx, 983 hypopharynx, 3 340 larynx, and 24 234 controls (Supplementary Table S2). For those studies reporting a case-control matching, separate sets of controls were matched for the three cancer sub-sites.

Informed consent was obtained from all study subjects (Supplementary Table S1). The investigations were approved by the relevant Boards of Ethics, according to the regulation in force at time the data were collected.

Available data were harmonized at the Study Coordinating Center.[14] While different studies had used different definitions of alcohol drinking status, the current paper defined as never drinkers those individuals who have never had any alcohol (0 ml of ethanol or 0 drinks over lifetime), or were defined as never drinkers by the individual studie. A similar definition was adopted for smoking habits.[8] Study subjects were asked to report their drinking habits (drinking status, intensity and duration). Drinking intensity was then expressed in drinks/day of alcoholic beverages. To account for variation of ethanol content across alcoholic beverages and across countries, intensity was harmonized on a standard drink, corresponding to 15.6 ml (i.e., 12 g) of ethanol, weighting intensity by study-specific beverages volume and ethanol intake.[14] Average lifetime alcohol intake was calculated as the total intake of wine, beer, and hard liquor, taking into account possible intensity modification or quitting periods occurring in subjects' life. Duration of alcohol drinking was calculated as the period of time between the subject's age at the start of drinking any alcoholic beverages and the age at cancer diagnosis (or interview, for controls), discarding periods when the subject abstained from any alcoholic beverages.

The dose-response relationship between cancer risk and the joint exposure to alcohol drinking intensity and duration in current drinkers was investigated through bivariate regression spline models,[42] as described elsewhere.[8,43] In contrast to drink-years, this method allows risks to vary for different combinations of the two continuous exposures intensity and duration, even when the cumulative drink-year exposure is the same (i.e., people drinking 1 drink/day for 10 years are allowed to have a different risk than those drinking 10 drinks/day for one year). Briefly, within a generalized semi-parametric logistic regression model, the two exposures were entered as a joined piecewise polynomial of a linear degree with constraints for continuity at each join point (called knot), together with potential confounders. Knots represented change points, where the slope of the risk surface changes to account for potential departures from linearity. The set of spline regression parameters described the shape of the risk surface. For each cancer sub-site, the optimal number of knots, their location, the regression and spline coefficients were jointly estimated within the Bayesian approach[43]. Vague prior distributions were assumed on the regression and spline coefficients, with spike-and-slab priors on the spline coefficients managing the choice of the optimal number of knots within a modified Stochastic Search Variable

Selection approach.[44] The Markov Chain Monte Carlo (MCMC)-type NUTS (No-U-Turn Sampler) algorithm[8,45-46] allowed to implement the Stochastic Search Variable Selection approach for identifying the optimal number of knots and then to derive the final joint posterior distribution of all the parameters, with the optimal combination of number of knots previously identified. Convergence was tested by algorithm-specific and generic MCMC diagnostics, reporting low number of divergences, a R-hat statistic<1.05 for each parameter, and a generally high effective sample size, suggesting the chains efficiently explored the posterior distribution. For each sub-site, the ORs and their 95% credible intervals (CIs) were derived from the corresponding (final) posterior distribution. The ORs were presented through three-dimensional plots that displayed the surface of risk for any combination of alcohol drinking intensity and duration. In addition, we presented two-dimensional plots that displayed patterns of risks corresponding to one variable exposure for fixed levels of the other exposure. All the models were fitted with the full set of potential confounders, i.e., sex, age, study, race, education, cigarette smoking status, cigarette smoking intensity, cigarette smoking duration, and pipe and cigar status (Supplementary Table S2); ''Never drinkers'' were assumed as the reference category. Calculations were carried out using the open-source Stan program[47] within the open-source R program.[48]

Results

Study subjects were predominantly males (70.7%); the median age was 58 years for controls and for all cases together. Current smoking was reported in the majority of cancer patients (51.5% of oral cavity, 52.4% of oropharyngeal cancers, 63% of hypopharyngeal, and 61.2% of laryngeal cancers), but not in the controls (24.2%; Supplementary Table S2).

In the study population (Table 1), patients with cancer of the oral cavity who were current drinkers drank at higher intensities (but not for a longer time period) than controls. The proportion of never drinkers was much lower among patients with oropharyngeal (17.4%), hypopharyngeal (8.9%), and laryngeal (17.8%) cancers; drinking habits in these cancers showed a higher intensity and a longer duration.

The surfaces of HNC cancer risk for the joint exposure to drinking intensity and duration were displayed in Figure 1. For all sub-sites, the risk steeply increased with increasing number of drinks/day, with no appreciable threshold effect at lower intensities. The risk peaked at the higher levels of duration and intensity

(i.e., for people drinking 10 drinks/day for 54 years) for all sub-sites, reaching ORs of 8.0 (95% CI: 4.6-13) for oral cavity, 12.9 (95% CI: 7.2-23.7) for oropharynx, 25.0 (95% CI: 11.6-51.5) for hypopharynx, and 6.6 (95% CI: 4.9-9) for larynx. For oral cavity (Figure 1.a) and hypopharynx (Figure 1.c), the risk flattened after 5 and 4 drinks/day, respectively. Moreover, the risk surfaces for cancers of the oral cavity, hypopharynx, and larynx (Figure 1.a, 1.c, and 1.d) suggested no effect of drinking duration in addition to intensity: the risk remained stable when duration increased, for fixed levels of intensity. For oropharyngeal cancer (Figure 1.b), the risk increased with increasing years of duration up to 28 years, flattening thereafter; this effect was more marked at higher intensities. A sensitivity analysis conducted excluding only extremely high values (i.e., intensity >28 drink/day or >61 years, 1% of study subjects) showed similar results. The same analyses were further conducted in strata of gender (Supplementary Figure S2): risk surfaces were similar in shape to those in the main analysis, even if cancer risk was slightly higher for women than for men. The subgroup analysis was not performed for the hypopharynx sub-site, due to low number of cases.

The same effects between alcohol intensity and duration across HNC sub-sites are also shown in Figure 2, which presents the risk for increasing intensities at defined duration levels (upper panels), and the risk for increasing durations at defined levels of intensity (lower panels). For cancers of the oral cavity, hypopharynx, ~~(Figure 2.a)~~ and larynx (Figures 2.a, 2.c, and 2.d), the curves for intensity at different durations were largely overlapping and showed an upward trend. This indicated that duration did not substantially modify cancer risk, which was mainly driven by drinking intensity. Figures 2.e, 2.g, and 2.h confirmed this conclusion, showing generally flat curves for the three levels of intensities up to 5 drinks/day, as also suggested by the CIs (Supplementary Table S3); a modest upward trend was present at the highest intensity level (i.e., 10 drinks/day). Differently, a joint effect of intensity and duration was found for oropharyngeal cancer risk: the risk increased with increasing intensities, but higher levels of duration raised up the curves to the highest risk (Figure 2.b); duration increased oropharyngeal cancer risk up to approximately 28 years (Figure 2.f), although the contribution of duration to the risk was particularly evident at the highest level of intensity (i.e., 10 drinks/day).

Discussion

The present analyses show that, consistently between genders, drinking intensity was the predominant measure of alcohol affecting the risk of oral cavity, hypopharyngeal, and laryngeal cancers, whereas the contribution of duration, for fixed alcohol intensities, was modest. Notably, this suggests that drinking alcohol beverages, even for a short period, increases the risk at these cancer sub-sites and that duration of alcohol use has little or no consistent effect on the risk of these cancers. Differently, there was a joint effect of drinking intensity and duration in determining oropharyngeal cancer risk.

The direct association between alcohol intensity and HNC risk has been extensively described[2,6,49] and potential mechanisms have been proposed.[5,50] Ethanol is oxidized to alcohol acetaldehyde (AA), which is a recognized carcinogen.[2] Alcohol may also have a local effect, acting as a solvent of cell membranes to enhance the penetration of carcinogens, notably those from tobacco smoking, into the mucosa.[50] Further, nutritional deficiencies may occur in alcoholics.[50]

The relationship between drinking duration and HNC risk was more complex, with a clear association with oropharyngeal cancer risk up to approximately 28 years of drinking. These results are in agreement with previous findings derived from a standard approach on a smaller set of INHANCE studies (15 studies) including never smokers only, which showed no association with alcohol duration in all HNC sub-sites but hypo-/oropharynx.[14] Furthermore, the application of a different statistical approach[7] on the 15 INHANCE studies supported the presence of a stronger association with intensity than with duration for HNC risk. Although the lack of association with duration may seem counterintuitive, it has been reported in oesophageal adenocarcinomas, another alcohol-related cancer, in a large pooled analysis on 12 case-control studies.[51] Although these results did not allow to draw biological interpretations, they suggest that alcohol intake acts as a late-stage carcinogen.[52]

A major limitation of the present study was information bias, which may have occurred as a consequence of the complexity of lifetime drinking patterns. Changes in the intensity, in type of alcohol beverages, and temporary quitting are more frequent for alcohol drinking than for other lifestyle habits,[53] such as tobacco smoking; lifetime patterns may have an impact on the risk of cancer.[54] Therefore, misclassification may have occurred for both intensity and duration. The calculation of lifetime average alcohol intake may have protected against this source of bias, thus not allowing the investigation of specific drinking patterns (e.g., infrequent

heavy binge drinking). In addition, the use of linear bi-dimensional spline models may have contributed too, as they are quite robust with respect to small variations in the predictors, as compared to bi-dimensional splines of higher degrees. To test for model robustness, we adopted different solutions of truncation or approximation of drinking intensity and duration, and the resulting surface estimates were similar. Further, self-reporting of drinking habits may have led to additional information bias, since higher values of intensity and duration are more prone to inaccurate reporting.[55-56] To reduce information bias and residual confounding at the extreme values of the exposure distributions, we excluded subjects reporting higher (>95th percentiles) drinking intensity and/or duration from the present analysis; however, this could have led to a reduced study power and differential exclusion of cases and controls. Finally, our Bayesian approach was computationally time consuming, requiring dedicated server devices.

Although risk estimates were adjusted for tobacco smoking (considering cigarettes, cigars, and pipes), some residual confounding may remain. An analysis among never smokers would rule out possible residual confounding due to tobacco smoking. However, considering that the present logistic models includes several covariates, they require large sample sizes to produce precise estimates; thus, we were unable to conduct this subgroup analysis with sufficient precision. Nonetheless, the previously cited INHANCE analysis on never smokers[14] reported results similar to the current ones, with HNC risk generally increasing with alcohol intensity and no dose-response relation with drinking duration. Further, the lack of information on infection with human papilloma virus (HPV) has to be accounted among study limitations, considering the recognized role of HPV in oropharyngeal cancer.[57] Unfortunately, HPV status was not collected in the majority of studies, since they were conducted before the awareness of the HPV role in oropharyngeal cancer. International representativeness is guaranteed by the large dataset including studies from different geographical areas. On the other hand, the inclusion of heterogeneous populations, in particular that of genetic origin, may have led to estimation bias. Compared to other populations, East Asians have a much higher frequency of A allele of ALDH2 rs671,[58] which slows acetaldehyde metabolism, thus increasing alcohol-related risk. However, the exclusion of East Asian studies[16,33] did not substantially modify the risk estimates.

Results of the present study are strengthened the availability of information on several potential confounding factors. In addition, we applied a Bayesian approach to jointly estimate the optimal knot locations and the ORs of HNC for the joint effect of our continuous predictors.[8] As compared to the companion paper

on cigarette-smoking intensity and duration, in the current application the optimal number of knots was estimated within a two-step procedure including the Stochastic Search Variable Selection approach[43]. To our knowledge, this is the first time that a similar approach is applied within the context of spline models in epidemiology.

In conclusion, findings of the present study indicate that the risk of cancer of the oral cavity, hypopharynx, and larynx increases with drinking intensity, whereas the role of duration is complex. The trend is linear for larynx, but it showed a plateaux at the highest intensity for cancer of the oral cavity and hypopharynx. The joint effect of intensity and duration increases the risk of oropharyngeal cancer. In addition, no threshold effect is evident at the lowest doses. Although abstinence from alcohol drinking would be the ultimate goal to reduce HNC incidence, these findings suggest that any reduction in alcohol intake[59] would be an effective strategy to mitigate HNC risk, as well as the risk of few other neoplasms.[60]

Additional information

Acknowledgements: The authors would like to thank Xavier Castellsague, who collected data in the IARC International Multicenter study and passed away in 2016. We thank Mrs Luigina Mei for editorial assistance.

Authors' contributions: LDM, JP, NT, FP, GDC, DS, and VE designed research; DL, LR, KM, DS, Paul Brennan, IH, WA, PL, CC, LR, JP, CH, KK, DIC, GJM, PT, AA, AZ, SF, RH, TNT, RAM, JM, EN, VE, MV, LF, MPC, AM, AWD, RK, VWF, AFO, JPZ, EMS, GL, FL, ZFZ, HM, ES, PL, CLV, WG, CC, SMS, TZ, TLV, KK, MMC, SB, RBH, MP, MG, SS, GPY, Paolo Boffetta, LDM conducted research and provided single-study databases; SCC and YAL prepared the pooled dataset for the analysis; MH and Paolo Boffetta are the scientific coordinators of the INHANCE consortium and pooled data coordinators; GDC and VE performed all statistical analyses; FP and NT provided advice on statistical issues; CLV provided advice on epidemiological issues and interpretation of results; JP, LDM, GDC, and VE wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript. The authors have declared no conflicts of interest.

Ethics approval and consent to participate: The Informed consent and institutional review board approval were obtained within the framework of the original studies, according to the laws in force at the time of data

collection. In addition, a central Institutional Review Board approval was obtained from the University of Utah, #42912.

Consent for publication: Not applicable

Data availability: Data are available for scientific purposes upon reasonable request to the corresponding authors.

Conflict of interest: The authors declare no competing interests.

Funding This work was supported by grants from the: National Institutes of Health (NIH) [no grant number provided for the INHANCE Pooled Data Project, grant numbers P01CA068384, K07CA104231 for the New York Multicenter study, grant numbers R01CA048996, R01DE012609 for the Seattle (1985-1995) study, grant number TW001500 for the Fogarty International Research Collaboration Award (FIRCA) supporting the Iowa study, grant number R01CA061188 for the North Carolina (1994-1997) study, grant numbers P01CA068384, K07CA104231, R01DE013158 for the Tampa study, grant numbers P50CA090388, R01DA011386, R03CA077954, T32CA009142, U01CA096134, R21ES011667 for the Los Angeles study, grant numbers R01CA078609, R01CA100679 for the Boston study, grant number R01CA051845 for the MSKCC study, grant number R01CA030022 for the Seattle-Leo study, grant number DE016631 for the Baltimore study, no grant number provided for the Puerto Rico study]; National Cancer Institute (NCI) at the National Institutes of Health (NIH) [grant number R03CA113157 for the INHANCE Pooled Data Project, no grant number provided for the Intramural Program supporting the Puerto Rico study, grant number R01CA90731-01 for the North Carolina (2002-2006) study]; National Institute of Dental and Craniofacial Research (NIDCR) at the National Institutes of Health (NIH) [grant number R03DE016611 for the INHANCE Pooled Data Project, grant numbers R01DE011979, R01DE013110 for the Iowa study, no grant number provided for the Intramural Program supporting the Puerto Rico study]; Italian Association for Research on Cancer (AIRC) [no grant number provided for the Milan (1984-1989) study, for the Aviano study, for the Italy Multicenter study, grant number 10068 for the Milan (2006-2009) study]; Italian League against Cancer [no grant number provided for the Aviano and Italy Multicenter studies]; Italian Ministry of Research [no grant number provided for the Italy Multicenter study]; Ministero della Salute Ricerca Corrente [no grant number provided for the Aviano study]; the Swiss Research against cancer/Oncosuisse [grant numbers KFS-700, OCS-1633 for the Switzerland study, grant number KFS1096-09-2000 for the France (1987-1992) study]; European Commission [grant number

IC18-CT97-0222 (INCO-DC Program) for the Latin America study]; Veterans Affairs Merit Review Funds [no grant number provided for the Iowa study]; National Institute of Environmental Health Sciences (NIEHS) [grant number P30ES010126 for the North Carolina (1994-1997) study, National Cancer Institute (NCI) [grant number R01-CA90731for the North Carolina (2002-2006) study]; Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center [no grant number provided for the Los Angeles study]; Fondo para la Investigacion Cientifica y Tecnologica Argentina (FONCYT) [no grant number provided for the Latin America study]; Institut Hospital del Mar d'Investigacions Mediquès (IMIM) [no grant number provided for the Latin America study]; Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP) [grant number 01/01768-2 for the Latin America study, grant numbers GENCAPO 04/12054-9, 10/51168-0 for the Sao Paulo study]; Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government [grant number FIS 97/0024, FIS 97/0662, BAE 01/5013 for the International Multicenter study]; International Union Against Cancer (UICC) [no grant number provided for the International Multicenter study]; Yamagiwa-Yoshida Memorial International Cancer Study Grant [no grant number provided for the International Multicenter study]; European Community (5th Framework Programme) [grant number QLK1-CT-2001-00182 for the Western Europe study]; Scientific Research grant from the Ministry of Education, Science, Sports, Culture and Technology of Japan [grant number 17015052 for the Japan (2001-2005) study]; Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan [grant number H20-002 for the Japan (2001-2005) study]; Italian Foundation for Cancer Research (FIRC) [no grant number provided for the Milan (2006-2009) study]; Italian Ministry of Education - PRIN 2009 Program [grant number X8YCBN for the Milan study (2006-2009) study]; Fribourg League against Cancer [grant number FOR381.88 for the France (1987-1992) study]; Swiss Cancer Research [grant number AKT 617 for the France (1987-1992) study]; Gustave-Roussy Institute [grant number 88D28 for the France (1987-1992) study]; French National Research Agency (ANR) [no grant number provided for the France Multicenter (2001-2007) study]; French National Cancer Institute (INCA) [no grant number provided for the France Multicenter (2001-2007) study]; French Agency for Food, Environmental and Occupational Health and Safety (ANSES) [no grant number provided for the France Multicenter (2001-2007) study]; French Institute for Public Health Surveillance (InVS) [no grant number provided for the France Multicenter (2001-2007) study]; Fondation pour la Recherche Médicale (FRM) [no grant number provided for the France Multicenter (2001-2007) study];

Fondation de France [no grant number provided for the France Multicenter (2001-2007) study]; Fondation ARC pour la Recherche sur le Cancer [no grant number provided for the France Multicenter (2001-2007) study]; French Ministry of Labour (Direction Générale du Travail) [no grant number provided for the France Multicenter (2001-2007) study]; French Ministry of Health (Direction Générale de la Santé) [no grant number provided for the France Multicenter (2001-2007) study]; VE was supported by Università degli Studi di Milano 'Young Investigator Grant Program 2017'.

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Figure legends

Figure 1. Bivariate spline models estimates of odds ratios of oral cavity (a), oropharyngeal (b), hypopharyngeal (c), and laryngeal (d) cancers in current drinkers for the joint effect of intensity and duration of alcohol consumption. On the grid, black thicker lines represent knot locations, at 5 drinks/day for oral cavity, at 4 drinks/day for hypopharyngeal cancer, and at 28 years for oropharyngeal cancer. INHANCE consortium.

Figure 2. Bivariate spline models estimates of odds ratios of oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers in current drinkers for alcohol intensity and fixed levels of alcohol duration (a. to d.) and for duration and fixed levels of intensity (e. to h.). INHANCE consortium.

Table 1 - Distribution of cases of oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers, and controls according to intensity and duration of alcohol drinking in current drinkers. INHANCE consortium

	Controls		**Oral cavity**		**Oropharynx**		**Hypopharynx**		**Larynx**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**
Total	24 234		4 085		3 359		983		3 340	
Never drinkers	7 873	(32.5)	1,353	(33.1)	583	(17.4)	87	(8.9)	593	(17.8)
Drinking intensity (drinks/day)										
≤1	6 921	(28.6)	757	(18.5)	801	(23.8)	105	(10.7)	583	(17.5)
>1-≤3	5 470	(22.6)	805	(19.7)	787	(23.4)	242	(24.6)	771	(23.1)
>3-≤10	3 970	(16.4)	1 170	(28.6)	1 188	(35.4)	549	(55.8)	1 393	(41.7)
Drinking duration (years)										
1-30	6 218	(25.7)	975	(23.9)	889	(26.5)	217	(22.1)	647	(19.4)
31-40	5 061	(20.9)	920	(22.5)	1 049	(31.2)	337	(34.3)	986	(29.5)
41-54	5 082	(21.0)	837	(20.5)	838	(24.9)	342	(34.8)	1 114	(33.4)
Age at start drinking (years)										
≤18	5 482	(22.6)	1,047	(25.6)	1 172	(34.9)	324	(33.0)	1 050	(31.4)
19-25	7 016	(29.0)	1,110	(27.2)	1 126	(33.5)	423	(43.0)	1 209	(36.2)
26-35	2 435	(10.0)	332	(8.1)	328	(9.8)	106	(10.8)	331	(9.9)
>35	1 428	(5.9)	243	(5.9)	150	(4.5)	43	(4.4)	157	(4.7)

Figure 1.

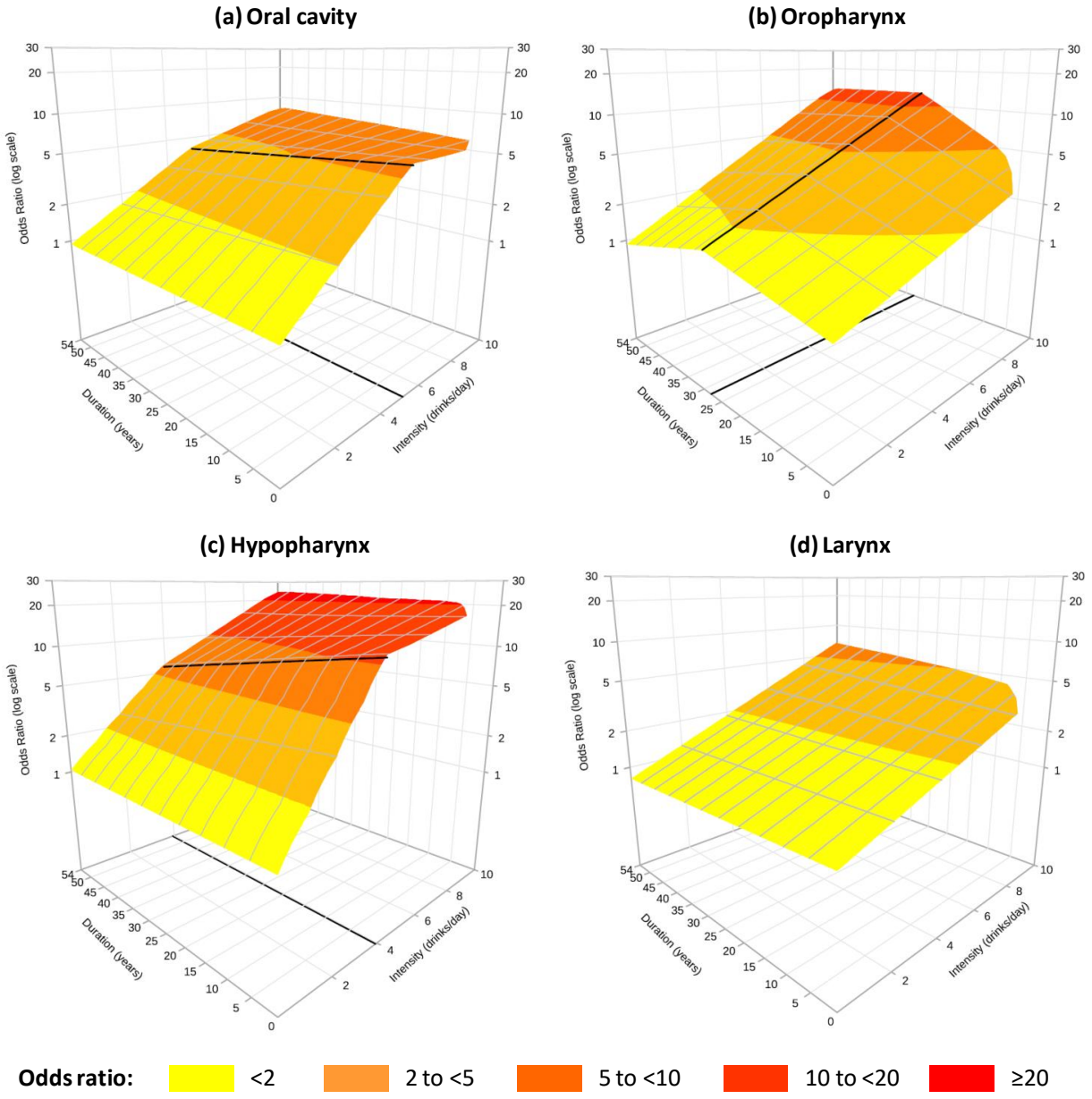
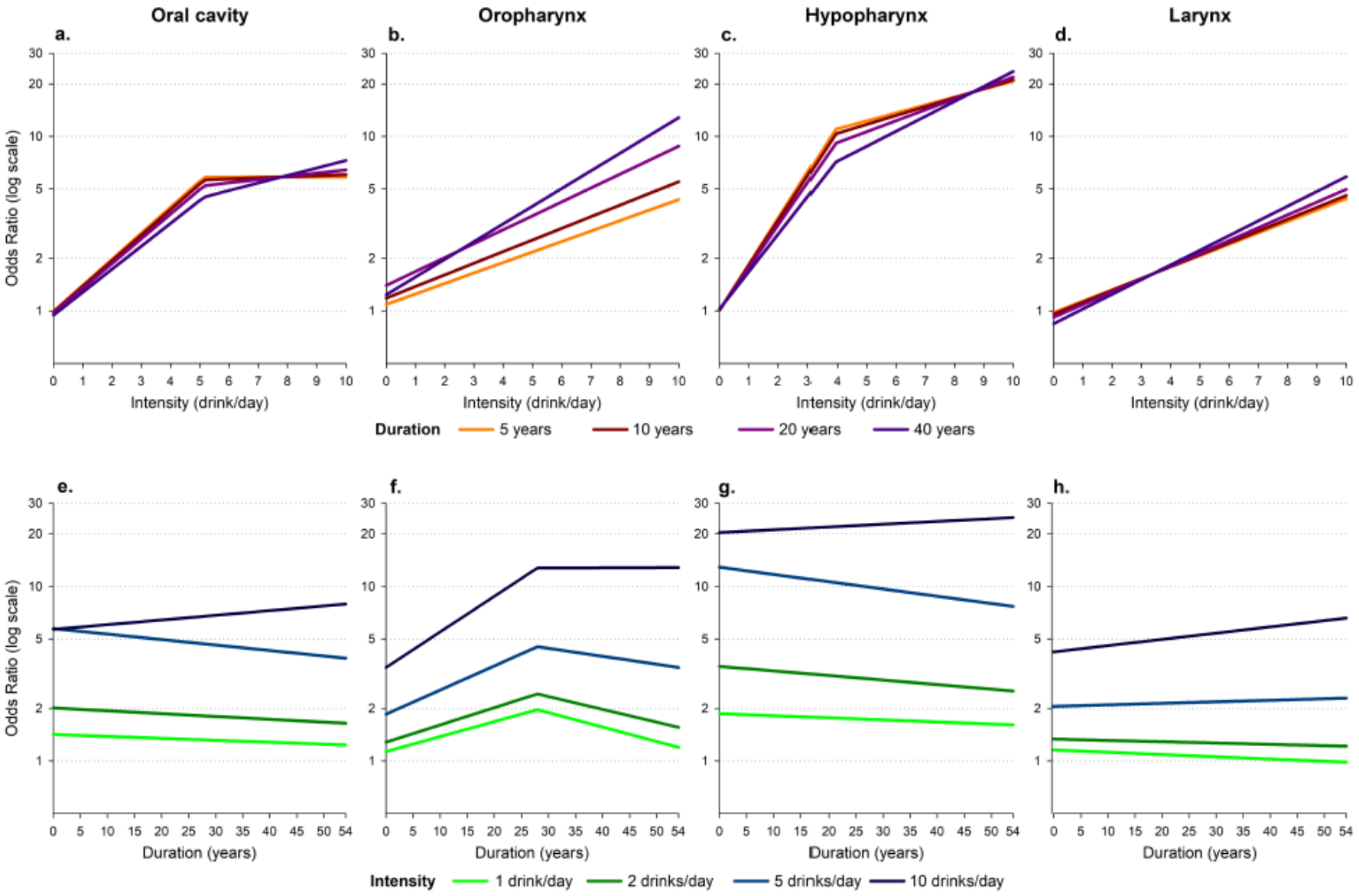

(a) Oral cavity
(b) Oropharynx
(c) Hypopharynx
(d) Larynx
Odds Ratio (log scale)
Duration (years)
Intensity (drinks/day)
Odds ratio:
<2
2 to <5
5 to <10
10 to <20
≥20

Figure 2.


Oral cavity
Oropharynx
Hypopharynx
Larynx
a.
b.
c.
d.
Odds Ratio (log scale)
Intensity (drink/day)
Duration
5 years
10 years
20 years
40 years
e.
f.
g.
h.
Duration (years)
Intensity
1 drink/day
2 drinks/day
5 drinks/day
10 drinks/day

Supplementary Table S1. Characteristics of the individual studies from the International Head and Neck Cancer Epidemiology (INHANCE) consortium used in the current analysis. INHANCE consortium.

Study name, location	Case source	Age eligibility	Case participation rate, %	Control source	Control participation rate, %	Matched factors	Recruitment period
Milan (1984-1989), Italy	Hospital	<80	95[1]	Hospital - unhealthy	95[1]	--	1984-1989
Aviano, Italy	Hospital	>18	>95[1]	Hospital - unhealthy	95[1]	--	1987-1992
France (1987-1992), France	Hospital	NA	95[1]	Hospital - unhealthy	95[1]	Age, sex, hospital	1987-1992
Italy Multicenter	Hospital	18-80	>95	Hospital - unhealthy	>95	--	1990-1999
Switzerland	Hospital	<80	>95	Hospital - unhealthy	>95	--	1991-1997
New York, NY, USA (multicenter)	Hospital	21-80	91	Hospital- unhealthy	97	Age, sex, hospital, year of interview	1981-1990
Seattle (1985-1995), WA, USA	Cancer registry	18-65	54.4,63.3[2]	Random digit dialing	63.0,60.9[2]	Age, sex	1985-1995
Iowa, IA, USA	Hospital	>18	87	Hospital - unhealthy	92	Age, sex	1993-2006
North Carolina (1994-1997), NC, USA	Hospital	>17	88	Hospital - unhealthy	86	Age, sex	1996-1997
Tampa, FL, USA	Hospital	≥18	98	Hospital - noncancer	90	Age, sex, ethnicity	1994-2003
Los Angeles, CA, USA	Cancer registry	18-65	49	Neighborhood	68	Age, sex, neighborhood	1999-2004
Houston, TX, USA	Hospital	≥18	95	Hospital visitors	>80	Age, sex, ethnicity	2001-2006
Puerto Rico	Cancer registry	21-79	71	Residential records (healthy population)	83	Age, sex	1992-1995
Latin America	Hospital	15-79	95	Hospital - unhealthy	86	Age, sex, ethnicity, city	2000-2003
International Multicenter, IARC	Hospital	NA	88,7	Hospital/Community	87,3	Age, sex, center	1992-1997
Boston, MA, USA	Hospital	≥18	88,7	Residential records	48,7	Age, sex, neighborhood	1999-2003
Sao Paulo, Brazil	Hospital	NA		Hospital-unhealthy		age, sex, city of residence, hospital	2002-2007
New York (MSKCC), NY, USA	Hospital	NA	--	Blood donors	--	Age, sex	1992-1994
Seattle-Leo, WA, USA	Cancer registry	20-74	81	Random digit dialing	75	Age, sex	1983-1987
Western Europe (ARCAGE)	Hospital	NA	82	Hospital-unhealthy (population-based for UK centers)	68	Age, sex, ethnicity, city	2000-2005

Japan (2001-2005)	Cancer Hospital	20-79	97,00	Hospital - unhealthy	97,00	Age, sex	2001-2005
North Carolina (2002-2006), NC, USA	Cancer registry	20-80	82	DMV files	61	Age, sex, ethnicity	2002-2006
France Multicenter (2001-2007)	Cancer registry	<=75	82,5	Random digit dialing	80,6	Age, sex, region	2001-2007
Baltimore, MD, USA	Hospital	NA	100	Hospital - benign conditions	70	age, sex, HPV status	2000-2005
Beijing, China	Hospital	18-80	100	Hospital	100	Age, sex	1988-1989
Milan (2006-2009), Italy	Hospital	18-80	>95	Hospital	>95	----	2006-2009

ABBREVIATIONS: ARCAGE: Alcohol-Related Cancers And Genetic susceptibility in Europe; DMV: Department of Motor Vehicles; HPV: Human Papilloma Virus; IARC: International Agency for Research on Cancer; MSKCC: Memorial Sloan Kettering Cancer Center; NA: Not Available.

[a] Participation rate was not formally assessed, estimated response rate reported.
[b] Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

Supplementary Table S2. Distribution of cases of oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers, and controls according to selected variables. INHANCE consortium

	Controls		Oral cavity		Oropharynx		Hypopharynx		Larynx	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
TOTAL	24,234	(100)	4,085	(100)	3,359	(100)	983	(100)	3,340	(100)
Sex[a]										
Female	7,533	(31.1)	1,552	(38.0)	780	(23.2)	138	(14.0)	533	(16.0)
Male	16,701	(68.9)	2,533	(62.0)	2,579	(76.8)	845	(86.0)	2,807	(84.0)
Age (years)[a]										
<40	1,720	(7.1)	284	(7.0)	124	(3.7)	7	(0.7)	68	(2.0)
40 to 44	1,711	(7.1)	234	(5.7)	211	(6.3)	38	(3.9)	116	(3.5)
45 to 49	2,479	(10.2)	442	(10.8)	449	(13.4)	104	(10.6)	294	(8.8)
50 to 54	3,547	(14.6)	645	(15.8)	617	(18.4)	184	(18.7)	493	(14.8)
55 to 59	4,217	(17.4)	743	(18.2)	727	(21.6)	211	(21.5)	682	(20.4)
60 to 64	3,944	(16.3)	670	(16.4)	542	(16.1)	182	(18.5)	671	(20.1)
65 to 69	3,431	(14.2)	492	(12.0)	409	(12.2)	144	(14.6)	603	(18.1)
70 to 74	2,304	(9.5)	336	(8.2)	206	(6.1)	92	(9.4)	310	(9.3)
≥75	881	(3.6)	239	(5.9)	74	(2.2)	21	(2.1)	103	(3.1)
Study name										
Aviano	652	(2.7)	52	(1.3)	71	(2.1)	38	(3.9)	91	(2.7)
Baltimore	162	(0.7)	36	(0.9)	83	(2.5)	4	(0.4)	31	(0.9)
Beijing	380	(1.6)	377	(9.2)						
Boston	400	(1.7)	90	(2.2)	145	(4.3)	22	(2.2)	68	(2.0)
France (1987-1992)	194	(0.8)	41	(1.0)	50	(1.5)	27	(2.7)	127	(3.8)
France Multicenter (2001-2007)	3,149	(13.0)	343	(8.4)	489	(14.6)	275	(28.0)	368	(11.0)
Houston	712	(2.9)	182	(4.5)	306	(9.1)	30	(3.1)	108	(3.2)
International Multicenter	1,297	(5.4)	640	(15.7)	224	(6.7)			2	(0.1)
Iowa	550	(2.3)	173	(4.2)	97	(2.9)	7	(0.7)	60	(1.8)
Italy Multicenter	2,246	(9.3)	126	(3.1)	193	(5.7)	77	(7.8)	324	(9.7)
Japan (2001-2005)	2,796	(11.5)	100	(2.4)	63	(1.9)	63	(6.4)	80	(2.4)
Latin America	993	(4.1)	199	(4.9)	154	(4.6)	66	(6.7)	367	(11.0)
Los Angeles	815	(3.4)	34	(0.8)	93	(2.8)	8	(0.8)	51	(1.5)
Milan (1984-1989)	1,450	(6.0)	40	(1.0)	32	(1.0)	25	(2.5)	229	(6.9)
Milan (2006-2009)	568	(2.3)	64	(1.6)	10	(0.3)	9	(0.9)	145	(4.3)
MSKCC	89	(0.4)	34	(0.8)	5	(0.1)	5	(0.5)	24	(0.7)
New York Multicenter	1,098	(4.5)	303	(7.4)	286	(8.5)	17	(1.7)	123	(3.7)
North Carolina (1994-1997)	157	(0.6)	28	(0.7)	24	(0.7)	10	(1.0)	25	(0.7)
North Carolina (2002-2006)	962	(4.0)	99	(2.4)	218	(6.5)	33	(3.4)	239	(7.2)
Puerto Rico	278	(1.1)	25	(0.6)	35	(1.0)	10	(1.0)		
Sao Paulo	1,145	(4.7)	347	(8.5)	111	(3.3)	52	(3.4)	224	(6.7)
Seattle (1985-1995)	502	(2.1)	160	(3.9)	113	(3.4)				
Seattle-Leo	431	(1.8)	113	(2.8)	85	(2.5)	29	(3.0)	116	(3.5)
Switzerland	823	(3.4)	109	(2.7)	110	(3.3)	72	(7.3)	111	(3.3)
Tampa	738	(3.0)	16	(0.4)	37	(1.1)	1	(0.1)	38	(1.1)
Western Europe	1,647	(6.8)	354	(8.7)	325	(9.7)	103	(10.5)	389	(11.6)

Continues

Supplementary Table S2. Continued

Race[a]										
Asian and Pacific Islanders	3,779	(15.6)	833	(20.4)	132	(3.9)	64	(6.5)	87	(2.6)
Black	631	(2.6)	149	(3.6)	108	(3.2)	30	(3.1)	109	(3.3)
Hispanic	304	(1.3)	29	(0.7)	37	(1.1)	2	(0.2)	7	(1.0)
Others and Brazilians	2,267	(9.3)	564	(13.8)	301	(9.0)	121	(12.3)	598	(17.9)
White	17,253	(71.2)	2,510	(61.4)	2,781	(82.8)	766	(77.9)	2,514	(75.3)
Education[a]										
No education	980	(4.0)	472	(11.6)	55	(1.6)	32	(3.3)	94	(2.8)
≤Junior high school	8,408	(34.7)	1,341	(32.8)	969	(28.8)	409	(41.6)	1,495	(44.8)
Some high school	4,340	(17.9)	787	(19.3)	715	(21.3)	257	(26.1)	632	(18.9)
High school graduate	3,097	(12.8)	567	(13.9)	510	(15.2)	121	(12.3)	458	(13.7)
Technical sch., some college	3,680	(15.2)	513	(12.6)	559	(16.6)	90	(9.2)	408	(12.2)
≥College graduate	3,729	(15.4)	405	(9.9)	551	(16.4)	74	(7.5)	253	(7.6)
Cigarette smoking status										
Never user	10,570	(43.6)	1,263	(30.9)	660	(19.6)	72	(7.3)	223	(6.7)
Former user	7,804	(32.2)	717	(17.6)	939	(28.0)	292	(29.7)	1,072	(32.1)
Current user	5,860	(24.2)	2,105	(51.5)	1,760	(52.4)	619	(63.0)	2,045	(61.2)
Cigarette smoking intensity (cigarettes/day)										
≥1-10	4,046	(16.7)	475	(11.6)	452	(13.5)	138	(14.0)	352	(10.5)
>10-20	5,837	(24.1)	1,254	(30.7)	1,157	(34.4)	391	(39.8)	1,366	(40.9)
>20-30	1,826	(7.5)	567	(13.9)	503	(15.0)	186	(18.9)	657	(19.7)
>30-40	1,301	(5.4)	373	(9.1)	412	(12.3)	149	(15.2)	503	(15.1)
>40	654	(2.7)	153	(3.7)	175	(5.2)	47	(4.8)	239	(7.2)
Cigarette smoking duration (years)										
1-10	1,801	(7.4)	132	(3.2)	166	(4.9)	20	(2.0)	72	(2.2)
11-20	2,696	(11.1)	228	(5.6)	220	(6.5)	56	(5.7)	169	(5.1)
21-30	3,426	(14.1)	572	(14.0)	562	(16.7)	172	(17.5)	523	(15.7)
31-40	3,327	(13.7)	1,004	(24.6)	968	(28.8)	347	(35.3)	1,084	(32.5)
>40	2,414	(10.0)	886	(21.7)	783	(23.3)	316	(32.1)	1,269	(38.0)
Cigar smoking status										
Never user	19,438	(80.2)	3,347	(81.9)	2,991	(89.0)	853	(86.8)	3,023	(90.5)
Current user	1,004	(4.1)	186	(4.6)	248	(7.4)	57	(5.8)	197	(5.9)
Unknown	3,792	(15.6)	552	(13.5)	120	(3.6)	73	(7.4)	120	(3.6)
Pipe smoking status										
Never user	20,269	(83.6)	3,719	(91.0)	3,073	(91.5)	862	(87.7)	3,074	(92.0)
Current user	1,125	(4.6)	242	(5.9)	205	(6.1)	52	(5.3)	164	(4.9)
Unknown	2,840	(11.7)	124	(3.0)	81	(2.4)	69	(7.0)	102	(3.1)

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

[a] We excluded subjects with missing information on age, sex, race and cigarette smoking habits. Missing values for education were imputed according to the INHANCE protocol.

Supplementary Table S3. Odds Ratio (OR) and 95% Credible Intervals (CI) of cases of oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers, for selected levels of alcohol intensity and duration. INHANCE consortium

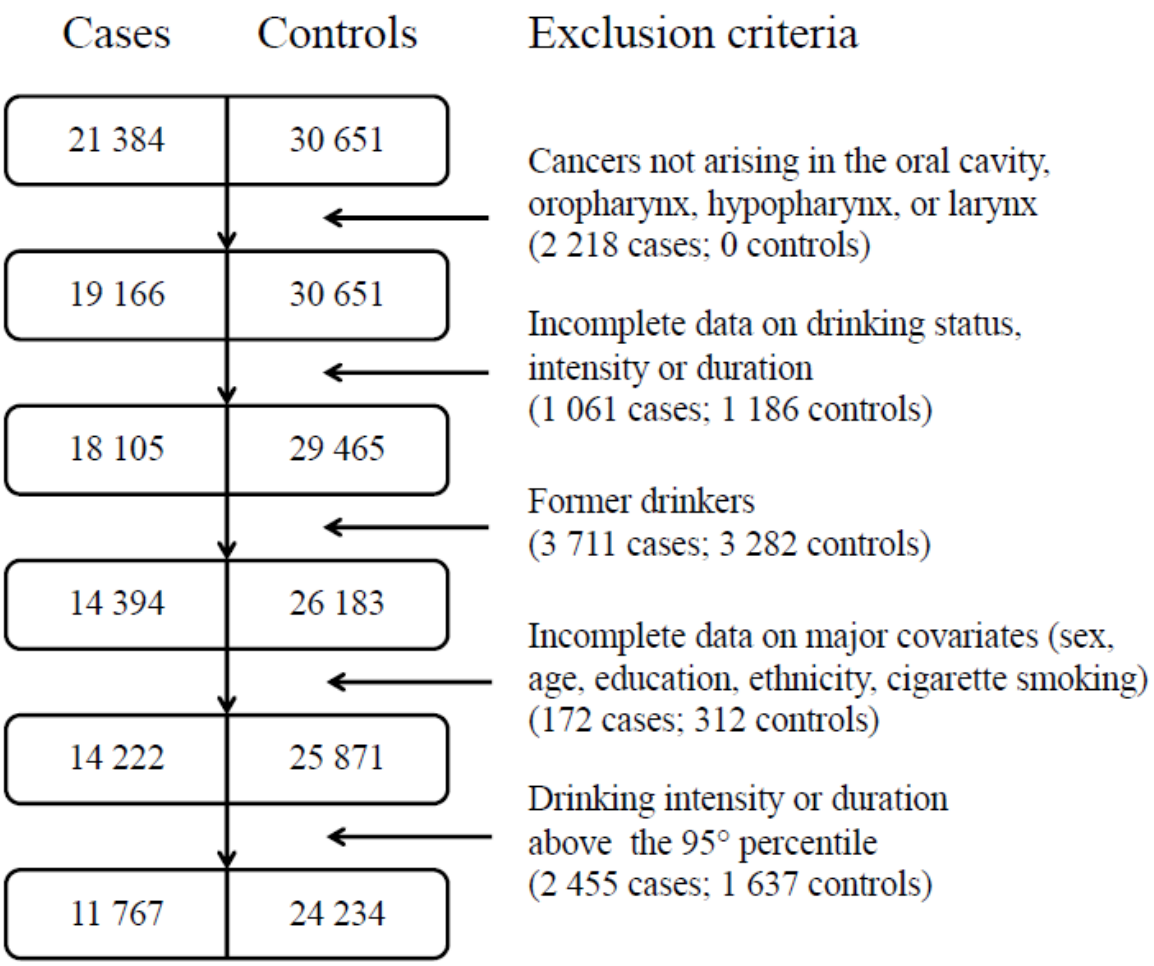
		Oral cavity		Oropharynx		Hypopharynx		Larynx	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Intensity (drinks/day)	**Duration (Years)**								
1	**5**	1.40	1.30-1.51	1.25	1.14-1.36	1.84	1.58-2.20	1.14	1.08-1.20
	10	1.38	1.29-1.48	1.38	1.26-1.52	1.81	1.55-2.17	1.12	1.06-1.19
	20	1.35	1.25-1.45	1.67	1.46-1.99	1.76	1.48-2.13	1.09	1.01-1.17
	40	1.28	1.14-1.44	1.56	1.16-2.73	1.67	1.28-2.21	1.03	0.90-1.16
2	**5**	1.97	1.72-2.29	1.44	1.19-1.70	3.35	2.52-4.83	1.32	1.20-1.46
	10	1.94	1.71-2.21	1.61	1.39-1.86	3.25	2.49-4.55	1.31	1.20-1.44
	20	1.86	1.68-2.08	2.01	1.74-2.40	3.07	2.42-4.14	1.29	1.18-1.41
	40	1.73	1.54-1.94	1.97	1.45-2.73	2.73	2.10-3.64	1.25	1.10-1.40
5	**5**	5.52	3.92-7.97	2.19	1.35-3.32	11.95	6.94-25.47	2.07	1.63-2.65
	10	5.32	3.96-7.32	2.56	1.81-3.53	11.41	6.93-23.31	2.09	1.70-2.60
	20	4.95	3.95-6.27	3.49	2.88-4.38	10.38	6.85-19.58	2.14	1.83-2.52
	40	4.29	3.59-5.16	3.93	2.92-6.03	8.58	6.06-15.20	2.23	1.96-2.52
10	**5**	6.07	1.99-13.49	4.43	1.64-10.13	21.62	4.45-82.86	4.37	2.71-7.15
	10	6.23	2.32-12.67	5.55	2.74-10.53	21.65	5.31-75.35	4.56	3.01-6.98
	20	6.54	3.19-11.13	8.79	6.16-12.65	21.91	7.43-65.55	4.95	3.66-6.77
	40	7.32	4.75-10.31	12.48	8.89-22.72	23.29	11.85-51.70	5.88	4.83-7.16

Legends to supplementary figures

Supplementary Figure S1. Flow-chart of subjects' selection process. INHANCE consortium.

Supplementary Figure S2. Bivariate spline models estimates of odds ratios of oral cavity, oropharyngeal, and laryngeal cancers in current drinkers for the joint effect of intensity and duration of alcohol consumption, in strata of gender. On the grid, black thicker lines represent knot locations, at 5 drinks/day for oral cavity in men, and at 30 years for oropharyngeal cancer in men. INHANCE consortium.

Supplementary Figure S1.



Supplementary Figure S2.