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Authors

Di Credico, Gioia
Edefonti, Valeria
Polesel, Jerry
et al.

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Joint effects of intensity and duration of cigarette smoking on the risk of head and neck cancer: a bivariate spline model approach

A full list of authors and affiliations appears at the end of the article.

Abstract

Objectives—This study aimed at re-evaluating the strength and shape of the dose-response relationship between the combined (or joint) effect of intensity and duration of cigarette smoking and the risk of head and neck cancer (HNC). We explored this issue considering bivariate spline models, where smoking intensity and duration were treated as interacting continuous exposures.

Materials and Methods—We used individual-level pooled data from 33 case-control studies (18,260 HNC cases and 29,844 controls) participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. In bivariate regression spline models, exposures to cigarette smoking intensity and duration (compared with never smokers) were modeled as a linear piecewise function within a logistic regression also including potential confounders. We jointly estimated the optimal knot locations and regression parameters within the Bayesian framework.

Results—For oral-cavity/pharyngeal (OCP) cancers, an odds ratio (OR) >5 was reached after 30 years in current smokers of ~20 or more cigarettes/day. Patterns of OCP cancer risk in current smokers differed across strata of alcohol intensity. For laryngeal cancer, ORs>20 were found for current smokers of 20 cigarettes/day for 30 years. In former smokers who quit 10 years ago, the ORs were approximately halved for OCP cancers, and ~1/3 for laryngeal cancer, as compared to the same levels of intensity and duration in current smokers.

Conclusion—Referring to bivariate spline models, this study better quantified the joint effect of intensity and duration of cigarette smoking on HNC risk, further stressing the need of smoking cessation policies.

Introduction[a]

In recent years, tobacco smoking has confirmed its role as the worldwide leading cause of preventable diseases and death. It is responsible for at least 12% of all deaths and of 22% of all cancer deaths worldwide [1]. Tobacco has been strongly associated with head and neck

*Corresponding Author: Valeria Edefonti, PhD, Branch of Medical Statistics, Biometry and Epidemiology "G. A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, via Venezian 1, 20133 Milano, Italy; Tel: +39 02-50320853; fax: +39 02-50320866, valeria.edefonti@unimi.it.

cancer (HNC, i.e., cancers of the oral cavity, pharynx, and larynx), which is the sixth most common cancer type, accounting for nearly 900,000 new cases in 2018 [2].

A dose-response relationship with HNC risk has been reported for smoking intensity (cigarettes per day reported during the exposure period) and duration (years of exposure), as well as for a cumulative smoking exposure measured in pack-years [3,4]. Compared with intensity, smoking duration was shown to provide a greater risk of developing HNC [5,6], as well as, other tobacco-related cancers, such as lung [7,8] and bladder cancers [9,10].

So far, the association between tobacco smoking and HNC risk was evaluated by considering duration and intensity as either separate or interacting predictors. In the latter case, the combined exposure was modeled as either cross-product or pack-years [6,11,12]. Step-functions [4, page 369] were widely used to provide risk estimates for the cross-product of the categorized exposures. This approach assumed a constant rate within each combined category of exposure; however, this assumption may have been too rough and/or leading to some efficiency loss [13–15]. As an alternative, linear-exponential models estimated the excess odds ratio (OR) of HNC within models including pack-years and smoking intensity [6,9]. The pack-year approach was traditionally based on a strong assumption about the effects of smoking intensity and duration; for instance, the effect of smoking ½ pack per day (10 cigarettes) for 40 years was equivalent to smoking 2 packs (40 cigarettes) per day for 10 years. Indeed, both of them reflect a cumulative exposure of 20 pack-years [16]. However, the 2 exposures were measured on different metrics.

Bivariate spline models have the potential to provide a more realistic representation of the association between smoking intensity and duration and HNC risk [15]. First, they allow to model intensity and duration in their original scale of continuous exposures and, in this aspect, splines outperform step-function models. Second, the two exposures are allowed to determine disease risk in their separate or interacting role. Third, a non-linearity in the dose-response relationship may be modeled.

This study re-evaluated the joint effect of intensity and duration of tobacco smoking on HNC risk, by means of bivariate spline models, within the International Head and Neck Cancer Epidemiology (INHANCE) consortium [11].

Materials and methods

Data source

The INHANCE consortium was established in 2004 to elucidate the etiology of HNC through pooled analyses of individual-level data from several studies on a large scale [11]. Several aspects of tobacco smoking and HNC risk have been previously investigated within the consortium [5,6,11,17–19].

From the INHANCE consortium pooled dataset (version 1.5), we extracted all the available case-control studies (35 studies) that collected information on cigarette smoking status,

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[a]**Abbreviations**: CI: credible interval; HNC: head and neck cancer; INHANCE: International Head and Neck Cancer Epidemiology; NUTS: No-U-Turn Sampler; OCP: oral cavity and pharynx; OR: odds ratio; WAIC: Wanatabe-Akaike Information Criterion.

intensity, and duration at individual level (http://www.inhance.utah.edu, last accessed March 25th, 2019). Available data were harmonized at the study coordinating center [11]. In all the studies, information on smoking history was self-reported. While different studies had used different definitions of smoking status, the current study defined as never smokers those individuals who never smoked regularly, or smoked for a very short period, i.e., less than 12 months [11]; likewise, former smokers were defined as those who had abstained from any type of smoking since at least 12 months before cancer diagnosis (cases) or interview (controls).

Details on individual studies, data harmonization, and pooling methods are summarized in eTable 1. Informed consent was obtained from all study subjects. The investigations were approved by the relevant Boards of Ethics, according to the regulation in force at data collection time.

Selection of subjects

The INHANCE protocol allowed inclusion of 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 [11]. The original study sample included 25,865 HNC cases and 37,248 controls, giving a total of 63,113 subjects.

We conducted subjects' selection according to the following main steps (eAppendix, text and Figure 1), excluding: 1. cases with unspecified (95 subjects) or overlapping HNC (331 subjects); 2. subjects reporting smoking tobacco products other than cigarettes (i.e., cigar, pipe, and cigarillo), to avoid risk distortion due their use [5] (6,255 subjects); 3. subjects with missing information on duration and/or intensity of cigarette smoking (1,897 subjects); 4. all subjects from studies that included only never (i.e., Japan 1988–2000) (822 subjects) or current (i.e., France 1987–1992) smokers (457 subjects), after the previous selection steps.

In order to prevent potential estimation distortion at the highest levels of the exposure distributions (due to small numbers of subjects or information bias in heavy tobacco consumers), further excluded were those subjects reporting the highest 5% of cigarette smoking intensity (>40 cigarettes per day) or duration (>51 years) (14% HNC cases and 6% controls excluded).

After all the described selection steps (eAppendix, text and Figure 1), the analysis included 33 studies [20–53] with 48,104 subjects (18,260 HNC cases and 29,844 controls) (Table 1). When a study reported to have conducted a case-control matching, separate sets of controls were matched for oral cavity and pharynx (OCP) cancers combined and for laryngeal cancer cases. In detail, the analysis included: 5,423 cancers of the oral cavity; 6,261 pharyngeal cancer cases (4,648 oropharyngeal and 1,613 hypopharyngeal cancers cases); 1,633 unspecified oral cavity/pharynx cancers (giving a total of 13,317 OCP cancer cases combined), and 4,943 laryngeal cancers.

Statistical analysis

The bivariate regression spline models [54] used to investigate the dose–response relationship between HNC and the joint exposure to smoking intensity and duration was described extensively in eAppendix – Statistical Analysis and in Di Credico's PhD Thesis [55]. We assumed a generalized semi-parametric logistic regression model where 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 (i.e., age, sex, race, study, education, drinking status, drinking intensity, and drinking duration) [15]. Knots represented change points in the slope of the risk surface. The set of spline regression parameters described the shape of the risk surface. We further assumed that the knot locations for any of the two exposures were unknown parameters to be estimated, up to a maximum of 2 knots allowed for each exposure. At the maximum level of complexity, the risk surface was allowed to have 2 change-points in the slope for any exposure and 9 different areas with a possibly changing slope.

The optimal knot locations and regression parameters were jointly estimated within the Bayesian approach. Prior distributions expressed *a priori* knowledge (here vague) on plausible values of knot locations and regression parameters [56,57]. Their posterior distribution combined prior information and available data through the Bayes theorem. A joint posterior distribution was simulated for each cancer site, smoking-status stratum (current/former smokers), and combination of number of knots using the Markov Chain Monte Carlo-type NUTS (No-U-Turn Sampler) [58] algorithm. For each combination of site and stratum, the best model was selected among the convergent models with sensible knot locations (95th percentile of either exposures) as the one that minimized the Wanatabe-Akaike Information Criterion (WAIC) [59,60]. The optimal knot locations, the ORs, and their 95% credible intervals (CIs) were derived from the posterior distribution corresponding to the best model. The ORs were presented through three-dimensional mesh plots that displayed the surface of risk for any combination of cigarette smoking intensity and duration, and through two-dimensional contour plots that showed iso-risk curves identifying the combinations of the two exposures with the same OR. Also explored were trade-offs between intensity and duration in two-dimensional contour plots by comparison of ORs for a fixed cumulative exposure (i.e., pack-years).

To evaluate potential modifying effects of some covariates, analyses were carried out in strata of alcohol drinking intensity (i.e., <1, 1-<5, 5 drinks per day) for current smokers, and years since quitting (i.e., <10, 10 years) for former smokers. Separate results for the risk of laryngeal cancer across alcohol drinking intensity strata were presented, due to absence of heterogeneity of the risk surfaces across strata for current smokers. As a comparison, risk estimates were further estimated according to the Bayesian step-function regression model.

When possible, all the models were fitted with the full set of potential confounders shown in Table 1; moreover, "Never smokers" were assumed as the reference category. Calculations were carried out using the open-source Stan program [61] within the open-source R program [62,63].

Results

Table 1 shows selected characteristics of cases and controls, according to the variables included in the models as potential confounders. Approximately 70% of the subjects were white. Studies from Europe contributed with approximately 44% of subjects; 31% of subjects were from the United States, whereas the remaining ones were from Latin America (14%) and Asia (11%). Six studies provided only cases of OCP cancer.

Table 2 shows the distribution of cigarette smoking habits for OCP cancer, laryngeal cancer, and controls. Never smokers were 21% of OCP and 7% of laryngeal cancers, versus 45% of controls. Current smokers were 66% of laryngeal cancer cases, 57% of OCP cancer cases, and 26% of controls. The prevalence of former smokers was similar in cases and controls, but the percentage of subjects who quit cigarette smoking 10 years ago was ~52% among HNC cases and 72% among controls.

Figure 2 shows the mesh and contour plots for cancers of the OCP and larynx among current cigarette smokers. Knot locations were indicated by thicker black lines; the intersections of the lines defined the areas where the risk surface had different slopes. For both cancer sites, the best model was characterized by one knot for duration (at 33 years for OCP cancer and 30 years for laryngeal cancer) and one knot for intensity (at 16 and 25 cigarettes/day, respectively). Smoking duration modified OCP cancer risk at any levels of intensity (Figure 2A). In contrast, for any duration up to 10 years, the ORs were always <2, regardless of the intensity of cigarette smoking. In addition, at a fixed value of 20 pack-years, an intensity of 40 cigarettes/day and a duration of 10 years led to an OR of ~2, whereas the OR was equal to ~4 with a duration of 40 years in smokers of 10 cigarettes/day.

For laryngeal cancer, ORs>20 were found for intensities of >20 cigarettes/day and durations of >28 years (Figure 2B). Moreover, ORs>10 of laryngeal cancer were reached by current smokers of >20 cigarettes/day only when duration was >20 years; however, ORs>10 were not reached for any duration <15 years and any level of intensity. Finally, the OR was 6.2 for smokers of 40 cigarettes/day for 10 years, but it was higher (between 9 and 10) for 20 cigarettes/day smoked for 20 years, or for 10 cigarettes/day smoked for 40 years.

The shape of the risk surface and the values of the ORs were also very similar across major OCP cancer subsites (i.e., oral cavity and oropharyngeal cancers) (eFigure 2).

Figure 3 shows the joint effect of current smoking intensity and duration in strata of alcohol consumption. Among never drinkers (<1 drink/day), the shape of the risk surface was similar to the one presented for all alcohol intensities together (Figure 2A), but the ORs were generally lower; all the ORs were < 2 for durations 15 years and any intensity, whereas an OR>5 was observed only after ~25 years of duration or more (Figure 3A). However, the shape of the surface and/or the ORs of the joint effect of duration and intensity were different when light (Figure 3B) and heavy (Figure 3C) drinkers were considered.

As a comparison, the ORs and their corresponding 95% CIs were estimated for each cancer site in current smokers within the Bayesian logistic regression model that assumed the presence of step functions (Table 3, main ORs). These estimates were compared with the

range of OR estimates derived from the spline models for each joint category of duration and intensity (Table 3, bracketed ORs). For both cancer sites, all Min-Max ranges included the OR estimates obtained from the Bayesian logistic regression, and this replication reassured that the spline model was valid. In addition, within the examined categories, the step-function intervals widely overlapped with the Min-Max ranges of the ORs from the spline models, but failed to capture the ORs variability. For instance, for OCP cancer in current smokers of 26–40 cigarettes/day for 36–51 years, the categorical OR was 8.4 (95% CI: 8.0–8.9), whereas the OR varied from 7.1 to 10.6 under the spline model approach for the same combined category (Table 3). The same pattern emerged at any combination of duration and intensity for both cancer sites for former smokers who quit 10 years ago (eTable 2).

Among former smokers who quit 10 years ago, no ORs>4 were observed for OCP cancer (Figure 4A), and the ORs were approximately halved, as compared to the same levels of duration and intensity in current smokers (Figure 2A). A mean risk reduction of 2/3 was also found for laryngeal cancer in long-term former smokers, with ORs declines that varied from 1/3 to 4/5 depending on the different combinations of intensity and duration (Figure 4B). These estimates were derived from models that included one knot for intensity (27 cigarettes/day) for laryngeal cancer and no knots for OCP cancer. Results on the combined set of former smokers (regardless of time since quitting) were similarly presented in eFigure 3.

Discussion

Our large pooled analysis showed that cigarette smoking duration and intensity did not increase HNC risk to the same extent, but the effect was greater for longer durations. At the highest combined levels of cigarette intensity and duration, subjects may reach ORs>10 of OCP cancer and ORs>40 of laryngeal cancer, as compared to never smokers. Bivariate regression spline models have been proven successful in exploring the separate and joint effects of intensity and duration of cigarette smoking. Therefore, when possible, models that allow this differential impact of intensity and duration on the risk should be considered [8,12,16].

Results from the present study were consistent with previous findings showing no threshold effect on HNC risk of shorter durations or lower intensities of tobacco smoking [13,64]. Indeed, the literature supported the presence of a dose-response relationship between cigarette smoking and HNC risk over the entire range of consumption [5,13]. Our contribution additionally suggested that the dose-response relationship with OCP and laryngeal cancer risk was still far from being linear, with a steeper increase for intermediate consumptions and a possible plateaux indicating a 'saturation effect' in smokers with >20 years of duration and >30 cigarettes/day.

Our results also strengthen the evidence [18,65] on the impact of smoking cessation on HNC cancer risk, with the OR in former smokers who quit 10 years ago being more than halved for OCP cancer and ~1/3 lower for laryngeal cancer, in comparison with current smokers. These results convey to the general population and to public health professionals the valuable message that it is never too late to give up cigarette smoking, as quitting provides

far smaller risks of developing HNC cancer for OCP and, most of all, for laryngeal cancers. This is in accordance with another recently published meta-analysis of observational studies on laryngeal cancer based on 14,292 cases from 3 cohort and 15 case-control studies [65].

When the combined effect of smoking intensity and duration was modelled as a cross-product term, an interaction term between alcohol consumption and cigarette smoking was traditionally added to the models [3,4]. In our study this effect was explored by stratified regression spline models estimated within categories of alcohol consumption; we compared the shape of the risk surface and the ORs values from the iso-risk curves across the three stratified analyses. However, our results also showed that alcohol acts as a substantial modifier of the association between OCP cancer risk and the joint effect of cigarette intensity and duration [4,17].

Major strengths of our study included a large sample size, international representativeness, and valid information on potential confounding factors. In addition, we applied a novel Bayesian approach to jointly estimate the optimal knot locations and the ORs of HNC for the joint effect of intensity and duration in a bivariate context. After examining various frequentist solutions [66,67], we opted for the Bayesian approach that allowed to put the knots where the data suggested, once we had taken the entire set of confounding variables into consideration. Within the Bayesian framework, we were also able to choose the optimal number of knots (up to 2) and knot locations by model comparison based on information criteria, instead of just comparing models with fixed number and location of the knots. Finally, we could incorporate in the model selection process evidence from the literature on the maximum number of changes in the risk pattern, which is unlikely to be higher than 2. Indeed, cigarette smoking is supposed to have a protective or null effect on the risk at lower levels, a saturation effect at the highest intensity levels [68], as well as the expected increase previously described at the intermediate levels of consumption. The proposed Bayesian approach is applicable to other epidemiologic scenarios where continuous exposures in their potential interaction affect disease risk.

Among study limitations, the retrospective study design and the self-reported smoking history were the most relevant ones. Even if a large amount of literature has suggested acceptable correlations between self-reported smoking intensity and cotinine levels in blood or urine [69], inaccurate self-reporting may occur. Discrepancies between self-reported and objective information were more likely among long-term heavy smokers [70]; higher values of intensity and duration were therefore more prone to inaccurate reporting. Furthermore, smoking intensity may have varied over time and by age of exposure. However, its estimates were often based on the self-reported average number of cigarettes per day; these two aspects may have led to appreciable errors in measuring the true mean intensity of exposure over one's lifetime. These issues may well be serious here, given the continuous nature of the exposures considered in spline models. To reduce information bias and residual confounding at the extreme values of the exposure distributions, we excluded subjects reporting higher (>95th percentiles) cigarette intensity and/or duration from the present analysis [13,15,71]. In addition, to avoid bias due to the use of other tobacco products, we excluded subjects reporting use of tobacco products other than cigarettes. We were also obliged to combine different subsites of OCP cancer, although differences in aetiology (i.e.,

the causal role of human papillomavirus in oropharyngeal cancer) have been demonstrated [34]. However, results were similar for major subsites, although based on less stable models. Finally, our Bayesian approach was computationally time consuming, asking for several hours of server computing for each model fitted.

Results from the present study confirmed previous evidence on the main contribution of cigarette smoking duration in influencing HNC risk and on the important reduction in HNC risk observed in former smokers who quit 10 or 15 years ago. Both results strongly support an even wider diffusion of public interventions to encourage smokers to quit and help them succeed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Gioia Di Credico[1], Valeria Edefonti[2,*], Jerry Polesel[3], Francesco Pauli[4], Nicola Torelli[4], Diego Serraino[3], Eva Negri[5], Daniele Luce[6], Isabelle Stucker[7], Keitaro Matsuo[8], Paul Brennan[9], Marta Vilensky[10], Leticia Fernandez[11], Maria Paula Curado[12], Ana Menezes[13], Alexander W. Daudt[14], Rosalina Koifman[15], Victor Wunsch-Filho[16], Ivana Holcatova[17], Wolfgang Ahrens[18,19], Pagona Lagiou[20], Lorenzo Simonato[21], Lorenzo Richiardi[22], Claire Healy[23], Kristina Kjaerheim[24], David I. Conway[25], Tatiana Macfarlane[26], Peter Thomson[27], Antonio Agudo[28], Ariana Znaor[9], Leonardo F. Boaventura Rios[29], Tatiana N. Toporcov[16], Silvia Franceschi[3], Rolando Herrero[9], Joshua Muscat[30], Andrew F. Olshan[31], Jose P. Zevallos[32], Carlo La Vecchia[2], Deborah M. Winn[33], Erich M. Sturgis[34], Guojun Li[34], Eleonora Fabianova[35], Jolanda Lissowska[36], Dana Mates[37], Peter Rudnai[38], Oxana Shangina[39], Beata Swiatkowska[40], Kirsten Moysich[41], Zuo-Feng Zhang[42], Hal Morgenstern[43], Fabio Levi[44], Elaine Smith[45], Philip Lazarus[46], Cristina Bosetti[47], Werner Garavello[48], Karl Kelsey[49], Michael McClean[50], Heribert Ramroth[51], Chu Chen[52], Stephen M. Schwartz[52], Thomas L. Vaughan[52], Tongzhang Zheng[53], Gwenn Menvielle[54], Stefania Boccia[55,56], Gabriella Cadoni[57,58], Richard B. Hayes[59], Mark Purdue[33], Maura Gillison[60], Stimson Schantz[61], Guo-Pei Yu[62], Hermann Brenner[63,64,65], Gypsyamber D'Souza[66], Neil Gross[67], Shu-Chun Chuang[68], Paolo Boffetta[69], Mia Hashibe[70], Yuan-Chin Amy Lee[71], Luigino Dal Maso[3]

Affiliations

[1]Department of Statistics, Padua University, Padua, Italy [2]Branch of Medical Statistics, Biometry and Epidemiology "G. A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy [3]Cancer Epidemiology Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy [4]Department of Economics, Business, Mathematics and Statistics, University of Trieste, Trieste, Italy [5]Department of Biomedical and Clinical Sciences, Università degli Studi di Milano, Milano, Italy [6]Univiverité Rennes,

INSERM, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, Pointe-à-Pitre, France [7]Inserm, Center for Research in Epidemiology and Population Health (CESP), Cancer and Environment team, Université Paris-Sud, Université Paris-Saclay, Villejuif, France [8]Aichi Cancer Center Research Institute, Nagoya, Japan [9]International Agency for Research on Cancer, Lyon, France [10]Institute of Oncology Angel H. Roffo, University of Buenos Aires, Argentina [11]Institute of Oncology and Radiobiology, Havana, Cuba [12]Epidemiology - CIPE/ ACCAMARGO, Sao Paulo, Brazil [13]Universidade Federal de Pelotas, Pelotas, Brazil [14]Hospital Moinhos de Vento, Porto Alegre, Brazil [15]Escola Nacional de Saude Publica, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil [16]University of São Paulo School of Public Health, São Paulo, Brazil [17]Institute of Hygiene & Epidemiology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic [18]Leibniz Institute for Prevention Research and Epidemiology, BIPS, Bremen, Germany [19]University of Bremen, Faculty of Mathematics and Computer Science, Bremen, Germany [20]Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece [21]Department of Cardiovascular and Thoracic Sciences and Public Health, University of Padova, Padova, Italy [22]Department of Medical Sciences, University of Turin, Turin, Italy [23]Trinity College School of Dental Science, Dublin, Ireland [24]Cancer Registry of Norway, Oslo, Norway [25]School of Medicine, Dentistry, and Nursing, University of Glasgow, Glasgow, UK [26]University of Aberdeen Dental School, Aberdeen, UK [27]University of Hong Kong, Hong Kong, China [28]Institut Catala Oncologia, Barcelona, Spain [29]University of São Paulo School of Medicine, São Paulo, Brazil [30]Penn State College of Medicine, Hershey, PA, USA [31]University of North Carolina School of Public Health, Chapel Hill, NC, USA [32]Division of Head and Neck Surgical Oncology in the Department of Otolaryngology/Head and Neck Surgery at Washington University School of Medicine, USA [33]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA [34]UT- M.D. Anderson Cancer Center, Houston, Texas, USA [35]Regional Authority of Public Health in Banska Bystrica, Slovakia [36]The M. Skasodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Cancer Epidemiology and Prevention, Warsaw, Poland [37]National Institute of Public Health, Bucharest, Romania [38]National Institute of Environmental Health to National Public Health Institute, Budapest, Hungary [39]Cancer Research Centre, Moscow, Russia [40]Institute of Occupational Medicine, Lodz, Poland [41]Roswell Park Cancer Institute, Buffalo, NY, USA [42]UCLA School of Public Health, Los Angeles, CA, USA [43]Departments of Epidemiology and Environmental Health Sciences, School of Public Health and Department of Urology, Medical School, University of Michigan, Ann Arbor, MI, USA [44]Institut Universitaire de Medecine Sociale et Preventive (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland [45]College of Public Health, University of Iowa, Iowa City, IA, USA [46]Washington State University College of Pharmacy and Pharmaceutical Sciences, Spokane, WA, USA [47]Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy [48]Department of Otorhinolaryngology, School of Medicine and Surgery,

University of Milano - Bicocca, Monza, Italy [49]Brown University, Providence, RI, USA [50]Boston University School of Public Health, Boston, MA, USA [51]University of Heidelberg, Germany [52]Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA [53]Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA [54]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, Department of Social Epidemiology, F75012, Paris, France [55]Department of Woman and Child Health and Public Health - Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia [56]Sezione di Igiene, Istituto di Sanità Pubblica, Università Cattolica del Sacro Cuore, Roma, Italia [57]Dipartimento di Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia [58]Istituto di Clinica Otorinolaringoiatrica, Università Cattolica del Sacro Cuore, Roma, Italia [59]Division of Epidemiology, New York University School Of Medicine, NY, New York, USA [60]"Thoracic/Head and Neck Medical Oncology", The University of Texas MD Anderson Cancer Center, TX, USA [61]New York Eye and Ear Infirmary, New York, NY, USA [62]Medical Informatics Center, Peking University, China [63]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany [64]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany [65]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany [66]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [67]Department of Head and Neck Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA [68]Institute of Population Health Sciences, National Health Research Institutes, Taiwan [69]The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA [70]Division of Public Health, Department of Family & Preventive Medicine and Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah, USA [71]Division of Public Health, Department of Family & Preventive Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA.

Acknowledgements

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INHANCE:
original pooled dataset
25,865 Cases - 37,248 Controls

63,113 records

Excluded subjects with overlapping head and neck cancer or with missing information on cancer site

62,687 records

Excluded subjects who ever smoked cigar, pipe or cigarillo

56,432 records

Excluded subjects with missing or implausible information on age start smoking cigarettes and missing information on duration cigarettes and age stop smoking cigarettes

56,401 records

Excluded subjects having age stop smoking cigarettes greater than age and missing information on duration cigarettes and age start smoking cigarettes

56,398 records

Excluded subjects having duration of cigarette smoking greater than age or missing and missing information on other age smoking-related variables

55,990 records

Excluded subjects with missing information on cigarettes/day and packyear variables

54,468 records

Excluded subjects with missing information on smoking status and ever cigarette variables

54,466 records

Excluded subjects with missing or unrecoverable information on alcohol duration

54,459 records

Excluded subjects with missing information on ever alcohol variable

54,218 records

Excluded subjects with no coherent information between cigarette smoking and tobacco status variables

52,939 records

52,939 records

Excluded subjects with extreme (above the 95th percentile) values on both the exposures

48,212 records

Excluded subjects with missing information on sex, age, education, race

48,104 records

INHANCE:
final pooled dataset
18,260 Cases - 29,844 Controls

Oral cavity and Pharynx
13,317 Cases - 29,200 Controls

Larynx
4,943 Cases - 26,147 Controls

Figure 1 –.
Flow chart of subjects' selection

A. Oral and pharyngeal cancer
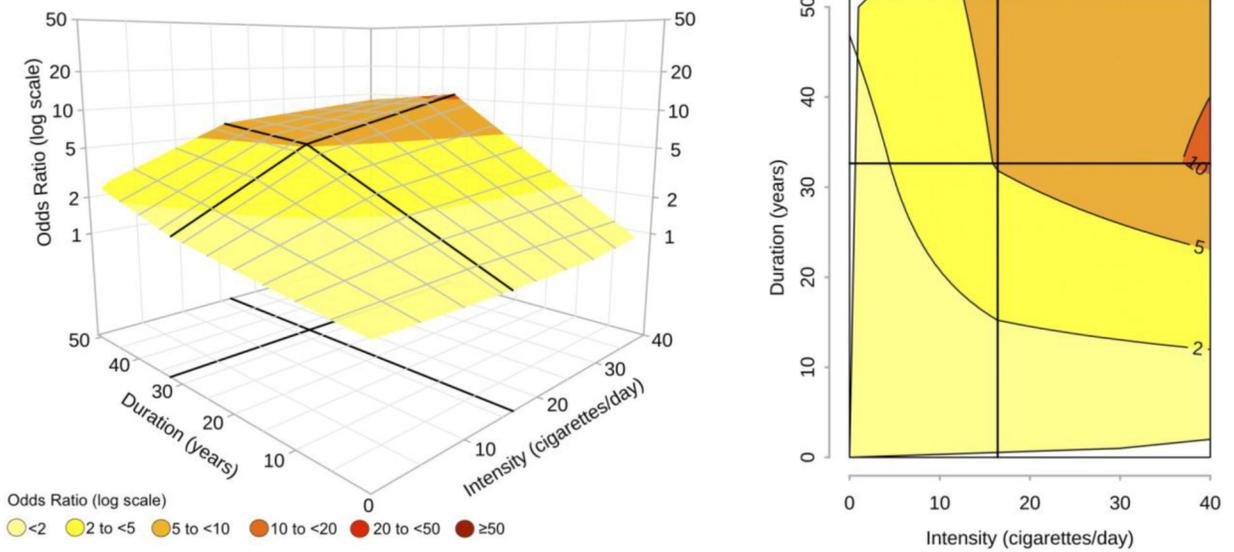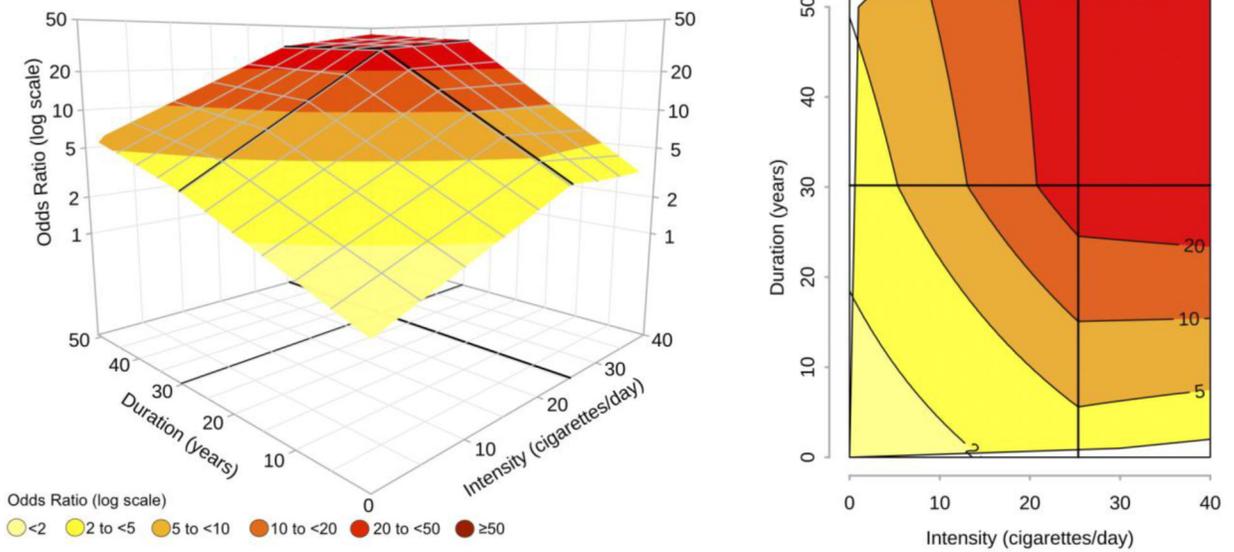
B. Laryngeal cancer

Figure 2 –. Odds ratios[a,b] of oral and pharyngeal cancer and laryngeal cancer in current smokers, for the joint effect of intensity (cigarettes/day) and duration (years) of cigarette smoking estimated through bivariate spline models. INHANCE consortium
[a] Fitted models included adjustment for age, sex, race, study, education, drinking status, drinking intensity, and drinking duration. The reference category was defined as "Never smokers". [b] On the grid, black thicker lines represent knot locations: 16 cigarettes/day and 33 years of duration for oral and pharyngeal cancer and 25 cigarettes/day and 30 years of duration for laryngeal cancer, respectively. Dark grey lines in contour plots indicate iso-risk curves at defined levels of risk.

A. Never drinkers (<1 drink/day), 3,899 cases, 12,802 controls
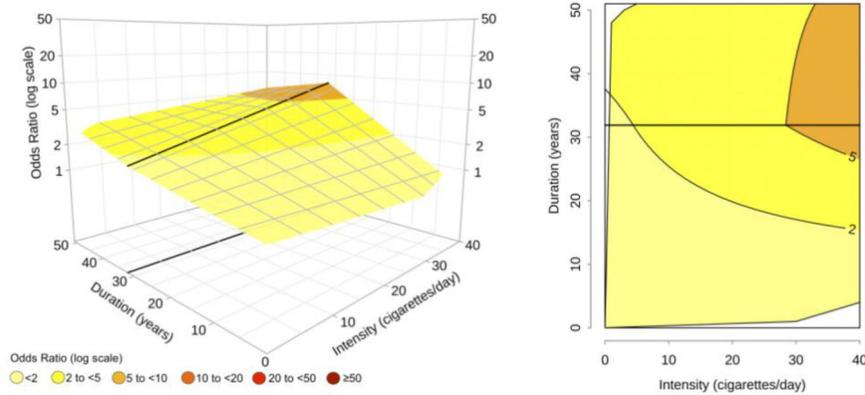
B. Light drinkers (1- <5 drinks/day), 3,050 cases, 5,477 controls
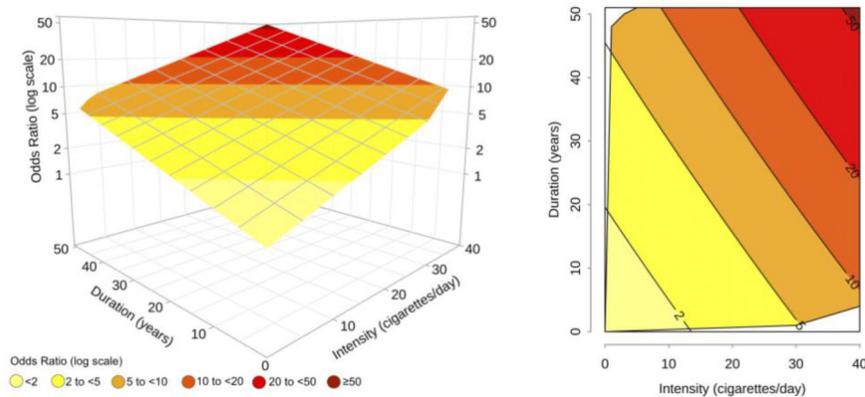
C. Heavy drinkers (≥5 drinks/day), 3,035 cases, 1,883 controls

Figure 3 –. Odds ratios[a,b] of oral and pharyngeal cancer in current smokers by alcohol drinking intensity, for the joint effect of intensity (cigarettes/day) and duration (years) of cigarette smoking, estimated through bivariate spline models. INHANCE consortium
[a] Fitted models included adjustment for age, sex, race, study, education, and alcohol drinking status. The reference category was defined as "Never smokers", in each strata of alcohol drinking intensity. [b] On the grid, black thicker lines represent knot locations: 32 years of duration for never drinkers, and 12 cigarettes/day and 25 years of duration for heavy drinkers, respectively. Dark grey lines in contour plots indicate iso-risk curves at defined levels of risk.

A. Oral and pharyngeal cancer
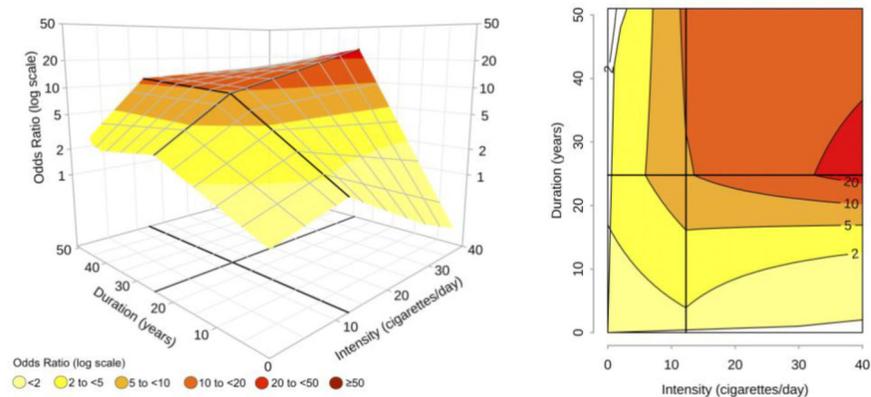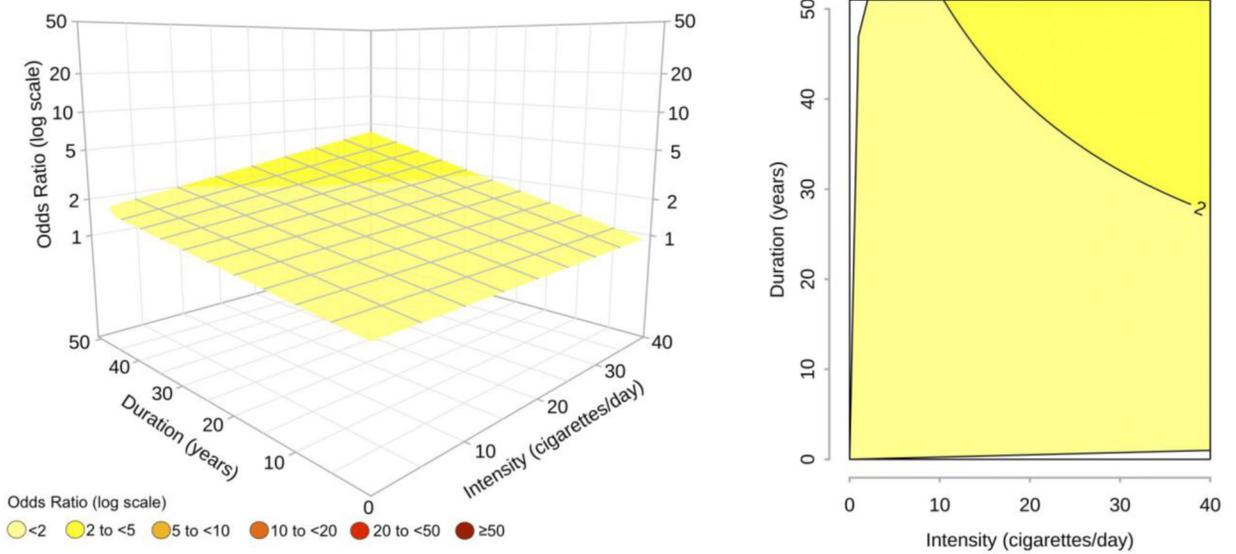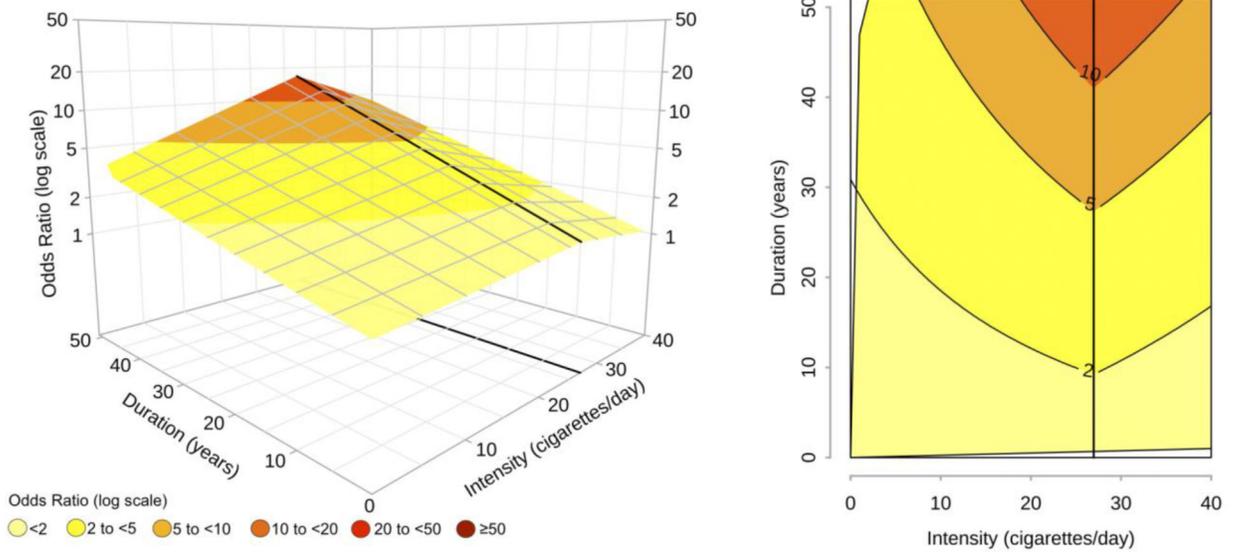

B. Laryngeal cancer

Figure 4 –. Odds ratio[a,b] of oral and pharyngeal cancer and laryngeal cancer in former smokers who quit   10 years ago, for the joint effect of intensity (cigarettes/day) and duration (years) of cigarette smoking estimated through bivariate spline models. INHANCE consortium

[a] Fitted models included adjustment for age, sex, race, study, education, drinking status, drinking intensity, and drinking duration. The reference category was defined as "Never smokers". [b] On the grid, the black thicker line represents the knot location: 27 cigarettes/day for laryngeal cancer. Dark grey lines in contour plots indicate iso-risk curves at defined levels of risk.

Table 1 –

Distribution of cases of oral and pharyngeal cancer, laryngeal cancer, and controls according to selected variables. INHANCE consortium

	Controls	(%)	Oral and pharyngeal cancer cases	(%)	Laryngeal cancer cases	(%)
	29,844		**13,317**		**4,943**	
Sex[a]						
Female	9,599	(32)	3,786	(28)	730	(15)
Male	20,245	(68)	9,531	(72)	4,213	(85)
Age (years)[a]						
<40	2,063	(7)	708	(5)	94	(2)
40 to 44	2,045	(7)	823	(6)	207	(4)
45 to 49	3,018	(10)	1,692	(13)	471	(10)
50 to 54	4,231	(14)	2,321	(17)	787	(16)
55 to 59	5,044	(17)	2,627	(20)	1,025	(21)
60 to 64	4,726	(16)	2,185	(16)	1,011	(20)
65 to 69	4,181	(14)	1,489	(11)	754	(15)
70 to 74	3,044	(10)	922	(7)	413	(8)
75	1,492	(5)	550	(4)	181	(4)
Race[a]						
White	21,462	(72)	9,076	(68)	3,627	(73)
Black	976	(3)	683	(5)	169	(3)
Hispanic	421	(1)	149	(1)	41	(1)
Asian and Pacific Islanders	3,849	(13)	1,293	(10)	77	(2)
Others and Brazilians	3,136	(11)	2,116	(16)	1,029	(21)
Study						
Aviano	802	(3)	288	(2)	128	(3)
Baltimore	163	(1)	123	(1)	29	(1)
Beijing	377	(1)	322	(2)	0	(0)
Boston	473	(2)	339	(3)	75	(2)
Buffalo	863	(3)	282	(2)	113	(2)
Central Europe	730	(2)	238	(2)	295	(6)
France Multicen. (1989–1991)	255	(1)	163	(1)	247	(5)
France Multicen. (2001–2007)	2,964	(10)	1,343	(10)	366	(7)
Germany-Heidelberg	644	(2)	0	(0)	172	(3)
Germany-Saarland	83	(0)	53	(0)	22	(0)
HOTSPOT	59	(0)	63	(0)	0	(0)
Houston	738	(2)	561	(4)	119	(2)
International Multicenter	1,450	(5)	1,053	(8)	0	(0)
Iowa	600	(2)	344	(3)	58	(1)
Italy Multicenter	2,506	(8)	685	(5)	421	(9)
Japan (2001–2005)	2,817	(9)	392	(3)	71	(1)

	Controls	(%)	Oral and pharyngeal cancer cases	(%)	Laryngeal cancer cases	(%)
Latin America	1,446	(5)	981	(7)	612	(12)
Los Angeles	905	(3)	273	(2)	70	(1)
Milan (1984–1989)	1,413	(5)	161	(1)	215	(4)
Milan (2006–2009)	669	(2)	118	(1)	162	(3)
MSKCC	115	(0)	61	(0)	20	(0)
New York Multicenter	1,246	(4)	818	(6)	202	(4)
North Carolina (1994–1997)	154	(1)	91	(1)	31	(1)
North Carolina (2002–2006)	982	(3)	594	(4)	283	(6)
Puerto Rico	410	(1)	182	(1)	0	(0)
Rome	350	(1)	98	(1)	173	(3)
Sao Paulo	1,519	(5)	1,042	(8)	406	(8)
Seattle (1985–1995)	465	(2)	317	(2)	0	(0)
Seattle-Leo	371	(1)	264	(2)	123	(2)
Switzerland	824	(3)	311	(2)	104	(2)
Tampa	789	(3)	115	(1)	48	(1)
US Multicenter	936	(3)	710	(5)	0	(0)
Western Europe	1,726	(6)	932	(7)	378	(8)
Education[a]						
No education	1,078	(4)	726	(5)	118	(2)
Junior high school	10,456	(35)	4,674	(35)	2,371	(48)
Some high school	5,330	(18)	2,751	(21)	922	(19)
High school graduate	3,883	(13)	1,883	(14)	717	(14)
Technical school, some college	4,825	(16)	1,989	(15)	496	(10)
College graduate	4,272	(14)	1,294	(10)	319	(6)
Drinking status						
Never user	8,068	(27)	2,279	(17)	578	(12)
Former user	3,072	(10)	2,521	(19)	833	(17)
Current user	14,210	(48)	6,943	(52)	2,442	(49)
Missing	4,494	(15)	1,574	(12)	1,091	(22)
Alcohol drinking intensity (number of drinks/day)						
0-<1	17,207	58)	4,899	37)	1,433	(29)
1-<5	8,913	30)	4,099	31)	1,757	(35)
5	2,925	10)	3,814	29)	1,626	(33)
Missing	799	3)	505	4)	127	(3)
Alcohol duration (years)						
Never drinkers	8,068	(27)	2,279	(17)	578	(12)
0-<20	2,984	(10)	1,182	(9)	297	(6)
20-<40	9,427	(32)	5,422	(41)	1,848	(37)
40-<60	6,013	(20)	2,920	(22)	1,435	(29)
60	412	(1)	176	(1)	123	(2)
Missing	2,940	(10)	1,338	(10)	662	(13)

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

[a]We excluded subjects with missing information on age, sex, and race (see Figure 1). Missing values for education were imputed according to the INHANCE protocol.[11]

Table 2 –

Distribution of cases of oral and pharyngeal cancer, laryngeal cancer, and controls according to selected aspects of cigarette smoking habits. INHANCE consortium

	Controls	(%)	Oral and pharyngeal cancer cases	(%)	Laryngeal cancer cases	(%)
Cigarette smoking status						
Never user	13,347	(45)	2,791	(21)	330	(7)
Former user	8,792	(29)	2,909	(22)	1,353	(27)
Current user	7,705	(26)	7,617	(57)	3,260	(66)
Cigarette smoking intensity (number of cigarettes/day)						
Never user	13,347	(45)	2,791	(21)	330	(7)
1–15	7,199	(24)	2,814	(21)	1,054	(21)
>15–25	6,166	(21)	4,483	(34)	2,083	(42)
>26–40	3,132	(10)	3,229	(24)	1,476	(30)
Cigarette smoking duration (years)						
Never user	13,347	(45)	2,791	(21)	330	(7)
1–25	7,214	(24)	2,019	(15)	604	(12)
>25–35	4,360	(15)	3,370	(25)	1,330	(27)
>35–51	4,923	(16)	5,137	(39)	2,679	(54)
Time since quitting cigarette smoking (years) (for formers only)[a]						
1-<10	2,300	(26)	1,310	(45)	626	(46)
10	3,655	(72)	1,522	(52)	711	(53)
Missing	137	(2)	77	(3)	16	(1)

[a]Proportions were calculated among former smokers only.

Table 3 –

Odds ratios (ORs)[a] and 95% credible intervals (CIs) of oral and pharyngeal cancer and laryngeal cancer in current smokers, for the joint effect of intensity (cigarettes/day) and duration (years) of cigarette smoking estimated through step-function as compared with results from bivariate spline models. INHANCE consortium

| Cancer type | Intensity (cigarettes/day) | | | | | |
| | 1–15 | | 16–25 | | 26–40 | |
	Ca:Co	OR (95%CI) [Min-Max][b]	Ca:Co	OR (95%CI) [Min-Max][b]	Ca:Co	OR (95%CI) [Min-Max][b]
Oral cavity and pharynx						
Duration (years)						
1–25	322:1,046	1.5 (1.4–1.7) [0.9–3.1]	371:663	2.7 (2.4–2.9) [0.9–4.2]	191:270	3.3 (2.8–3.9) [0.8–5.9]
26–35	583:911	2.9 (2.7–3.1) [1.4–4.8]	1,138:954	5.1 (4.9–5.4) [3.5–6.9]	849:466	7.2 (6.7–7.8) [4.6–11.0]
36–51	912:1,175	3.7 (3.5–3.9) [1.6–5.8]	1,838:1,409	6.0 (5.8–6.2) [5.2–7.1]	1,413:694	8.4 (8.0–8.9) [7.1–10.6]
Larynx						
Duration (years)						
1–25	75:908	3.8 (3.3–4.4) [1.1–8.8]	112:576	9.4 (8.3–10.5) [2.3–20.1]	70:247	14.8 (12.2–17.8) [2.8–23.1]
26–35	183:812	7.3 (6.9–7.9) [2.9–12.6]	423:845	17.2 (16.8–17.6) [10.1–29.6]	319:415	28.5 (27–30.2) [22.4–37.7]
36–51	394:1,064	8.9 (8.8–9.1) [3.9–15.3]	966:1,274	19.5 (19.3–19.8) [13.9–31.0]	718:616	33.9 (33.5–34.3) [30.9–43.2]

[a] Fitted models included adjustment for age, sex, race, study, education, drinking status, drinking intensity, and drinking duration. The reference category was defined as "Never smokers". The reference category included 2,791 cases and 13,139 controls for the analysis on oral and pharyngeal cancer and 330 cases and 11,433 controls for that on laryngeal cancer.

[b] Min and Max represent the lowest and the highest OR values estimated for any combinations of intensity and duration by bivariate spline models.