HHS Public Access

Author manuscript

Oral Dis. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Oral Dis. 2021 January ; 27(1): 73–93. doi:10.1111/odi.13502.

Lessons learned from the INHANCE consortium: an overview of recent results on head and neck cancer

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Abstract

Objective: To summarise the latest evidence on head and neck cancer epidemiology from the International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Subjects and Methods: INHANCE was established in 2004 to elucidate the etiology of head and neck cancer through pooled analyses of individual-level data on a large scale. We summarise results from recent INHANCE-based publications updating our 2015 overview.

Results: 17 papers were published between 2015 and May 2020. These studies further define the nature of risks associated with tobacco and alcohol, and occupational exposures on head and neck cancer. The beneficial effects on incidence of head and neck cancer were identified for good oral health, endogenous and exogenous hormonal factors, and selected aspects of diet related to fruit and vegetables. INHANCE has begun to develop risk prediction models and to pool follow-up data on their studies, finding that ~30% of cases had cancer recurrence and 9% second primary cancers, with overall- and disease--specific 5-year-survival of 51% and 57% respectively.

Conclusions: The number and importance of INHANCE scientific findings provides further evidence of the advantages of large-scale internationally collaborative projects and will support the development of prevention strategies.

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Authors' contributions: MH, YCAL, and PB are the pooled data coordinators of the INHANCE consortium; CLV, DIC, and MF provided advice on epidemiological issues and interpretation of results; FB and VE wrote the paper and had primary responsibility for final content; all the INHANCE investigators provided data from their original studies that were analysed together to derive the described results; all authors read and approved the final manuscript.

The authors have declared no conflicts of interest.

Keywords

oral cavity cancer; head and neck cancer; INHANCE; laryngeal cancer; pooled analysis; prognostic factors; risk factors

Head and neck cancer: descriptive epidemiology, risk factors, and status of research

Head and neck cancer (HNC), including cancers originating in the oral cavity, oropharynx, hypopharynx, and larynx, collectively accounted for over 700,000 new cases (3.9% of all cancer cases) and over 350,000 deaths (3.8% of all cancer cases) worldwide in 2018 (Bosetti et al., 2020; Ferlay et al., 2019; Miranda-Filho & Bray, 2020). Survival for patients with HNC remains unsatisfactory (Karim-Kos et al., 2008).

While tobacco smoking and alcohol drinking are well-established risk factors for HNC, the nature and extent of other factors, including dietary habits, hormonal factors, occupational exposures, viral factors, genetic variants and gene-environment interactions, are not fully established (Boffetta et al., 2016; Zhang et al., 2015). Heterogeneity in study designs and populations, limitations of observational studies, the limited sample sizes in some reports, as well as the overwhelming role of tobacco smoking and alcohol drinking, have limited the ability to have a clear picture on the relative contribution of other risk factors involved in HNC etiology.

Variations in the magnitude of the effects of risk factors across HNC sub-sites (Bagnardi et al., 2015; Turati et al., 2013) show the importance of having sufficient sample sizes to assess the role of risk factors in HNC sub-sites. This is especially true in countries where cases of these cancers are a few.

Meta-analyses of aggregated published data from epidemiological studies on the role of several risk factors for HNC or its sub-sites have been conducted (Bagnardi et al., 2015; Cirmi et al., 2018; Conway et al., 2008; Franceschi et al., 1992; Paget-Bailly et al., 2012; Pavia et al., 2006; Radoi & Luce, 2013; Zuo et al., 2017). However, pooled analyses or re-analyses of individual-participant or individual-level data from multiple epidemiological studies offer several advantages. Indeed, although the latter approach is always more time-consuming and not always possible as compared to the former one, it also has the potential to minimize confounding and reporting biases and to allow for detailed data checking and verification (Stewart et al., 2005). Advantages include the harmonization of definitions for risk factors as well as disease outcomes; consistent approaches to adjustment for confounding; determination of how exposure–risk relationships depend on age, sex and other potential effect modifiers; characterization of the shape of exposure–risk relationships, especially when there are suggestions of non-linearity; and a greater ability to correct for regression dilution bias (Stewart et al., 2012).

The International Head and Neck Cancer Epidemiology consortium: aims and design

The International Head and Neck Cancer Epidemiology (INHANCE) consortium was established in 2004 with the aim of setting up a collaboration among research groups involved in (ongoing or completed) epidemiological studies on HNC. The primary goal of the consortium is to carry out pooled analyses of individual-level data from studies on a large scale, in order to address etiological questions difficult to investigate within individual studies. These research questions included, among others, the independent and joint associations between tobacco smoking and/or alcohol drinking and HNC risk, the role of genes and their interactions with environmental factors, the etiology of HNC in rare subgroups, including young age at onset, non-smokers and/or non-drinkers, and the role of human papillomavirus.

To be included in the consortium, studies had to have a protocol for the recruitment of subjects and to use a structured questionnaire to collect data on socio-demographic and lifestyle factors, at least tobacco smoking and alcohol drinking habits, and tumor characteristics. In addition, informed consents and institutional review board approvals were obtained within the framework of the original studies. Data were gathered at the Study Coordinating Center and centrally checked for illogical or missing values; inconsistencies across studies were addressed methodologically. These efforts led to the creation of a comprehensive set of harmonized confounding and risk factors.

Cases were included in the INHANCE consortium if the original study reported that they had been diagnosed with an invasive cancer of oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or HNC unspecified according to the International Classification of Diseases for Oncology, version 2 (ICDO-2), or the International Classification of Diseases, 9th (ICD-9) or 10th Revision (ICD-10). For studies that applied ICD-10 or ICD-O-2 classification, cancers were classified according to one of the 6 following categories: (1) oral cavity (including lip, tongue, gum, floor of mouth, and hard palate); (2) oropharynx (including base of tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx); (3) hypopharynx (including pyriform sinus and hypopharynx); (4) oral cavity and pharynx unspecified or overlapping; (5) larynx (including glottis, supraglottis, and subglottis); and (6) HNC unspecified, also including overlapping lesions when more than one ICD topographic code was available for each case subject and the multiple sites were not within one of the categories listed above. For additional details on ICD codes and conversion of ICD-9 codes to ICD-O-2 code we refer the reader to the review of Winn and colleagues (Winn et al., 2015). Subjects with cancers of the major salivary glands (parotid, submandibular, or sublingual glands), of the nasal cavity/ear/paranasal sinuses, or of the thyroid were excluded (Dal Maso et al., 2009; Sun et al., 1999). When present in the original studies, corresponding controls were included in the analysis.

The INHANCE consortium has a dedicated protocol for the statistical analysis, in order to favor the reproducibility of statistical methods, in light of improving comparison of results within the INHANCE-based papers. The main analysis on HNC risk overall is based on a standard list of adjustment variables (i.e., age, sex, education, race/ethnicity, study center,

alcohol intensity, smoking status, cigarette duration, cigarette intensity, cigar duration and pipe duration), with pre-specified categories of interest; where appropriate and if numbers allow, detailed information is provided on the stratification variables to assess the presence of potential heterogeneity of the effects across strata, and on which HNC sub-sites to consider within the sub-site analysis. An influence analysis is also proposed to assure that the magnitude or statistical significance of the main effect measure is not dependent upon any one study.

The protocol suggests exploring a combination of one-stage and two-stage approaches to regression modelling for producing risk estimates for HNC overall or the sub-sites. In the one-stage approach, all individual participant data are entered into a single logistic regression model including the variable “study” and all the other relevant confounding and risk factors as independent variables. Following the two-stage approach to analysis, in the first stage individual participant data within a study are analyzed to generate study-specific summary estimates [e.g., odds ratios (ORs) or hazard ratios (HRs)]; in the second stage, results from each study are combined using conventional meta-analytical methods (Bowden et al., 2011).

In most INHANCE publications, the one-stage approach is followed as the first step: adjusted risk estimates are obtained from the logistic regression model including the full list of covariates under consideration. Then, the presence of heterogeneity between studies is tested through the likelihood ratio test, comparing models with and without the interaction term between the exposure of interest and study variable. When heterogeneity is detected (e.g., p-value from likelihood ratio test < 0.1), a random-effects model is suggested to derive the final risk estimates of overall HNC and its sub-sites. The two-stage approach is therefore implemented with the random-effects approach to meta-analysis. The two-stage approach is straightforward to use and produces easily interpretable and communicable results, including inspection of results from each study.

In some papers within the consortium [for example in (De Vito, Lee, et al., 2019; Edefonti et al., 2012)], generalized linear mixed-effects models with logit link function and binomial family are used that directly incorporated random-effects, instead of moving to the two-stage random-effects meta-analysis approach, in the presence of heterogeneity between studies. A few papers have compared (mixed-effects) one-stage and two-stage approaches in studies with a binary (Debray et al., 2013) or time-to-event (Bowden et al., 2011) outcomes. While both approaches have their own practical advantages (Debray et al., 2013), simulations indicate that, when the individual studies are large, two-stage methods produce nearly unbiased exposure estimates and standard errors of the exposure estimates of the one-stage methods via generalized linear mixed models (i.e., (Bowden et al., 2011)). However, it is unclear how well the two-stage method would perform if individual studies were smaller (Stukel et al., 2001). This is a critical issue, especially as far as evidence has been accumulating on the major research questions a consortium was created for, and time is mature for more specific analyses on subgroups of studies, including likely smaller studies.

Although originally organized among principal investigators of epidemiological studies of HNC, at present INHANCE also includes researchers with expertise across clinical and

scientific areas related to HNC. Annual meetings are expected to promote inter-disciplinary exchanges and new initiatives for the consortium, including proposals for grants supporting its activities. For additional details on the ways of working of the consortium see the INHANCE consortium website hosted by the University of Utah (https://www.inhance.utah.edu/, date last access May 28, 2020) and our earlier methods paper (Conway et al., 2009).

The International Head and Neck Cancer Epidemiology consortium in brief

Currently, 35 case-control studies contribute to the core database and had lifestyle and confounding factors harmonized and pooled together, giving a total of over 25,700 HNC cases and 37,100 controls. Fifteen studies come from North America, 13 from Europe, 3 from Asia, 3 from Latin America, and 1 study was conducted in multiple countries. Among them, 10 were population-based and 25 were hospital-based. In addition, 8 studies contributed genetic data only, with no lifestyle data being pooled in the core database. Basic information about the studies included in INHANCE (location, investigators, number of cases/controls) is available at https://www.inhance.utah.edu/membstud.php. Table 1 shows the key characteristics of the 43 studies currently available within the INHANCE consortium.

The INHANCE consortium has published 45 original papers, 1 editorial (Conway et al., 2009) and 1 review (Winn et al., 2015). In addition, periodic updates of the consortium's efforts and findings were presented in the Head and Neck Journal from 2011 to July 2017 thanks to Dr. Erich Sturgis (up to Update number 14) and Dr. José Zevallos (from Update number 15 to Update number 23). After the first few years, the number of published articles reached the peak of 5 or 6 papers per year in 2009, 2010, and 2011. The peak of 6 papers per year was then reached in 2015 again, with a range of 1 - 5 papers in the other years from 2011 to 2019. Two papers have already been published in 2020.

Figure 1 presents the distribution of INHANCE publications by topic considered. The role of dietary habits in HNC risk was the most investigated topic within INHANCE (24% of publications), followed by the "more than one risk factor" (i.e., 2 or more risk factors of different origin examined in the same paper with separate but parallel analyses or within an interaction model) category (11%) and tobacco alone (11%). The studies produced in the early years of the INHANCE consortium are summarized in our first *Oral Diseases* overview (Winn et al. 2015). Initially, the independent and joint effects of tobacco and alcohol consumption, including detailed analyses of patterns of consumption over time and cessation were explored. Family history and genetic factors were considered later on, whereas aspects of diet and anthropometric factors had been investigated and published first in 2010. Articles in 2015 assessed the effect of socioeconomic status and education on HNC risk; 2 papers on oral hygiene and mouthwash were published in 2016. More recent papers considered the role of occupational exposures. Papers on varied aspects of dietary habits, including single food groups, nutrients, and dietary patterns were regularly published from 2010 until today.

Forty-two of the 45 original papers examined HNC overall and/or 2 or more HNC sub-sites; 3 articles were specifically focused on HNC sub-sites, including oral cavity and pharynx combined (Galeone et al., 2015; Marks et al., 2014) or larynx (Hall et al., 2020).

Key findings published since 2015

The present overview paper provides a summary of major findings from the more recent INHANCE-based evidence, as published in international peer-reviewed journals from 2015 to present (May 2020). No *a priori* selection was made on the findings considered in the present overview. The term HNC used hereafter will include cancers of the oral cavity, pharynx, and larynx combined, unless otherwise specified. In addition, results shown below were obtained after controlling for major confounding factors, including age, race, and gender, together with major risk factors, such as tobacco use, alcohol intake, and education. In our summary of the evidence, we reported results obtained from the models including the maximum number of confounding factors considered in each paper. We commented on the results from models including a smaller set of confounding factors when adding the confounding factor provides evidence of a change in the sign or magnitude of the effect. Finally, articles were summarized with findings concerning similar risk factors grouped together.

In addition, we provided a graphical representation of the main findings, with separate figures for tobacco smoking and alcohol drinking, dietary habits, and the remaining exposures, including oral health and oral hygiene, exogenous and endogenous hormonal factors, and occupational exposures.

Tobacco smoking and alcohol drinking

Figure 2 summarizes the most important findings on tobacco smoking and alcohol drinking, as described in detail in the following.

Age at start of using tobacco products—To assess the relative contribution of time-related variables in tobacco, Chang and colleagues (Chang et al., 2019) analyzed INHANCE data on ever tobacco smokers derived from 27 case-control studies (17,146 HNC cases and 17,449 controls). One-stage random-intercept generalized linear mixed-effects model with logit link function and binomial family focused on age at start of using any tobacco products queried in the study-specific questionnaires. Without adjusting for pack-years of tobacco [e.g., 1 pack-year of cigarettes is equivalent to smoking 20 cigarettes (1 pack) per day for a year] (but including an adjustment for duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use), they found that a younger age of starting tobacco use was associated with an increased HNC risk for ever smokers (for <10 years vs. ≥30 years, OR =1.64, 95% confidence interval, CI: 1.35-1.97, p for trend <0.01). However, the observed association became null after adjusting for tobacco pack-years and the interaction between alcohol drinks per day and pack-years (OR=0.97, 95% CI: 0.80-1.19, p for trend=0.21). In the stratified analyses by tobacco status, tobacco packyears, or duration of using tobacco products, no heterogeneity was observed in the association between age at start and HNC risk across strata. In the analyses by HNC sub-sites, results were generally

similar to those for HNC overall, with nonsignificant associations in the final models including tobacco pack-years and the interaction between alcohol and tobacco.

Low frequency of cigarette smoking—The role of low frequency of cigarette smoking on HNC risk was investigated in a pooled analysis of 23 INHANCE studies including a total of 4093 HNC cases and 13,416 controls with information on cigarette, cigar and pipe smoking status, as well as frequency and duration of consumption (Berthiller et al., 2016). A combination of one-stage and two-stage approaches was adopted for estimating risk of HNC and sub-sites. Frequency of cigarette smoking was defined according to 4 categories (never smoker, >0 to ≤3 cigarettes/day, >3 to ≤5 cigarettes/day, >5 to ≤10 cigarettes/day), and analyzed in the overall sample. Additional analyses were carried out in strata of gender, in different categories of duration of cigarette smoking, and for HNC sub-sites. As compared to never smokers, all the considered categories of low frequency smokers showed an increased HNC risk: OR = 1.52 (95% CI: 1.21-1.90) for >0-3 cigarettes/day (from a two-stage random-effects model), OR = 2.14 (95% CI: 1.73-2.65) for >3-5 cigarettes/day (from a two-stage random-effects model), and OR = 2.60 (95% CI: 2.00-3.40), p for trend <0.01 (from a two-stage random-effects model). Considering HNC sub-sites, the dose-response relationship was stronger for hypopharynx and larynx. Considering men and women separately, the associations were similar. Combining frequency and duration of smoking in categories, a significant increased HNC risk was observed for combinations including the highest duration categories of cigarette smoking in one-stage fixed-effects generalized linear model with logit link function and binomial family: OR = 2.64 (95% CI: 1.92-3.63) for >0-3 cigarettes/day and duration >30 years, OR = 2.35 (95% CI: 1.52-3.65) for >3-5 cigarettes/day and duration >20-30 years, OR = 2.89 (95% CI: 2.13-3.91) for >3-5 cigarettes/day and duration >30 years, OR = 1.91 (95% CI: 1.49-2.43) for >5-10 cigarettes/day for >20-30 years, and OR = 4.17 (95% CI: 3.54-4.90) for >5-10 cigarettes/day and duration >30 years.

Interaction between cigarette smoking intensity and duration—Results from the previous analyses (Berthiller et al., 2016; Chang et al., 2019) highlighted how difficult is to model the effect of lifetime cumulative exposure to tobacco with standard logistic regression approaches to HNC risk. Indeed, the time-related variables age at start, duration, time since (potential) quitting, and age at interview or diagnosis are all relevant for HNC risk. In addition, the previous analyses confirmed the key role of tobacco intensity and duration across the lifespan, as jointly modeled with pack-years (Chang et al., 2019). A parallel analysis within INHANCE (Di Credico et al., 2019) considered data from a larger set of 33 case-control studies (18,260 HNC cases and 29,844 controls) to model the joint effect of intensity and duration of cigarette smoking on HNC risk using bivariate regression spline models. The aim of the paper was to address the following research questions: 1. Is there a nonlinear relationship between intensity and duration of cigarette smoking and HNC risk? 2. Is intensity more or less important than duration in determining HNC risk for a fixed cumulative exposure? 3. Are there critical values where the risk pattern changes? Within the Bayesian framework, the optimal knot locations and regression parameters were jointly estimated from a logistic regression model where exposures to cigarette smoking intensity and duration (compared with never smokers) were modeled as a linear piecewise function,

together with potential confounders. For cancers of the oral cavity and pharynx, an OR greater than 5 was reached after 30 years in current smokers of 20 or more cigarettes/day. The ORs of laryngeal cancer were over 20 in current smokers of ≥20 cigarettes/day for ≥30 years. In former smokers who quit ≥10 years ago, the ORs were approximately halved in cancers of the oral cavity and pharynx, and ~1/3 for laryngeal cancer, as compared to current smokers showing the same levels of intensity and duration.

Racial differences in the relationship between tobacco, alcohol and HNC in the US—Voltzke and colleagues (Voltzke et al., 2018) investigated ethnic disparities in the relationships of tobacco smoking and alcohol drinking with HNC risk. They considered a subset of INHANCE data including 13 US studies with a sufficient number of subjects belonging to non-Hispanic White and Black ethnic groups, for a total of 6599 cases and 8533 controls among Whites, and 975 cases and 953 controls among Blacks. The estimates for patterns of cigarette smoking and alcohol drinking were obtained from logistic regression models separately for Blacks and Whites, according to a one-stage fixed effect generalized linear model with logit link function and binomial family. The associations of tobacco and alcohol with HNC risk were consistently stronger for Blacks than for Whites.

The OR for ever cigarette smoking was 1.79 (95% CI: 1.65-1.95) among Whites and 2.52 (95% CI: 1.87-3.39) among Blacks (p for interaction between HNC and ethnicity <0.0001). Current smokers had a 3-fold risk among Whites (OR = 3.39, 95% CI: 3.07-3.75) and an almost 4-fold risk among Blacks (OR = 3.82, 95% CI: 2.77-5.27), p for interaction = 0.048. Both Whites and Blacks showed no significant association for former smokers. Smoking frequency was related to HNC risk, with stronger associations in Blacks than in Whites (e.g., for >30 cigarettes/day vs. never smokers, OR = 2.66, 95% CI: 2.37-2.99 in Whites and OR = 4.76, 95% CI: 2.94-7.70 in Blacks, p for interaction <0.0001). Smoking duration significantly increased HNC risk, the estimates being higher in Blacks than in Whites (e.g., for >30 years vs. never smokers OR = 4.53, 95% CI: 3.22-6.39, and OR = 3.01, 95% CI: 2.73-3.33, respectively, p for interaction <0.0001).

The OR for ever drinkers vs. never drinkers was 1.57 (95% CI: 1.42-1.73) among Whites and 2.85 (95% CI: 2.08-3.91) among Blacks, p for interaction = 0.0001. Among Whites, current drinkers had an OR of 1.74 (95% CI: 1.53-1.97), whereas corresponding estimate for Blacks was 2.39 (95% CI: 1.62-3.53), p for interaction <0.0001. The number of drinks per day was associated with lower HNC risks in Whites than in Blacks (e.g., for ≥5 drinks/day OR = 4.46, 95% CI: 3.80-5.25 and OR = 7.70, 95% CI: 4.92-12.06, respectively, p for interaction <0.0001). Increased duration of alcohol consumption was associated with higher HNC risk both among Whites (e.g., OR = 1.78, 95% CI: 1.58-2.01 for ≥40 years, compared to never drinkers) and Blacks (OR = 3.27, 95% CI: 2.20-4.87 for ≥40 years), with significant differences between Whites and Blacks (p for interaction <0.0001).

Diet: nutrients, foods, and dietary patterns

Most studies included in the INHANCE consortium collected information on dietary habits using a separate food-frequency questionnaire (FFQ). The study-specific FFQs queried subject's usual diet during a reference period preceding cancer diagnosis for cases or

interview for controls. The number of food items varied greatly across INHANCE studies, depending on the administration procedures adopted by each study and by the main aims of the study. The FFQs queried the frequency of consumption of single food items as absolute frequencies per unit of time or in pre-defined categories of consumption. Separate sections considered condiments and non-alcoholic beverages. Both interviewer- and self-administered FFQs were used in the studies belonging to the consortium. When relevant at the time of data collection within a population, the use of multi-vitamins and specific supplements was generally investigated in a separate section of the general questionnaire.

Whenever possible, intakes of total energy, several nutrients, and food components were calculated within the single studies and provided to the Data Coordinating Center by the PIs. Nutrients and food components were derived by combining information from the study-specific FFQs with that from country-specific food composition databases (i.e., (Gnagnarella et al., 2015; Resource Council Science and Technology Agency, 2000; US Department of Agriculture, 2013)). Reliable information on single nutrients and food components is currently available from 11 studies included in INHANCE. A core set of more than 20 nutrients was used for the identification of *a posteriori* dietary patterns and their association with HNC risk (De Vito, Lee, et al., 2019; Edefonti et al., 2012). Preliminary checks on the definitions of single food items and nutrients, reference periods of intake, and measurement units were conducted across studies by nutrition experts. In the analyses on nutrients, the daily intake from natural sources (i.e., no inclusion of intakes from fortified foods) was considered. To assess the comparability of nutrient intakes across studies, the study-specific kernel density estimation plots and summary statistics were inspected. The reports assessing the association between single nutrients and HNC risk (Edefonti, Hashibe, Parpinel, Ferraroni, et al., 2015; Edefonti, Hashibe, Parpinel, Turati, et al., 2015; Kawakita et al., 2017; Leoncini et al., 2016) considered non-alcohol energy-adjusted intakes as the exposure of interest, to compensate for systematic differences across studies in nutrient intakes. Non-alcohol energy-adjusted intakes were calculated within each study, on both cases and controls, referring to the residual method (Willett & Stampfer, 1986). The paper on the association between dietary patterns and HNC risk (De Vito, Lee, et al., 2019) considered a log-transformation (base e) of the study-specific nutrients to improve adherence to the assumption of normality of the shared and study-specific factors, as well as of the study-specific errors, as required by multi-study factor analysis.

The current INHANCE update includes results on single nutrients (intakes of vitamin E and fiber from foods) (Edefonti, Hashibe, Parpinel, Ferraroni, et al., 2015; Kawakita et al., 2017), glycemic index and load (Chang et al., 2020), foods (allium vegetables) and beverages (coffee and tea) (Galeone et al., 2010; Galeone et al., 2015), and *a posteriori* dietary patterns (De Vito, Lee, et al., 2019). Taken together, these results support a beneficial effect of a dietary pattern based on foods rich in antioxidant vitamins and fiber, like fruit and vegetables, and a detrimental effect of a pattern based on animal products and cereals or high-glycemic index foods on laryngeal cancer risk. Results on the role of fats suggest the need for further investigation. Details on results from single papers follow below, together with a graphical representation of the main findings on dietary habits, as presented in Figure 3.

Shared and study-specific dietary patterns—Dietary patterns allow the synthesis of information on multiple related dietary components (food items, food groups, or nutrients) in one or more combined variables representing overall diet or key aspects of the dietary habits of a population. Interest in this approach is motivated by the interactive effects of foods on bioavailability and circulating levels of nutrients, and potentially on disease risk. In addition, statistical issues including multiple comparisons and data dimensionality challenges affect the analysis of many single dietary variables.

A posteriori dietary patterns are identified by applying standard multivariate statistical methods (i.e., principal component analysis, factor analysis, cluster analysis) to the available data and represent actual eating behaviors in a population under consideration.

A few papers examined the reproducibility of *a posteriori* dietary patterns when multiple populations are available, as well as pattern association with HNC risk. Among them, a previous paper (Edefonti et al., 2012) within INHANCE derived *a posteriori* patterns with a standard principal component factor analysis, where 5 study-specific datasets (≈7500 subjects) providing information on 24 common nutrients were analyzed as a single dataset. In more recent versions of the Consortium dataset, another 2 studies (≈3200 additional subjects) provide comparable information on nutrient intakes. In addition, a partial sharing of patterns can be a good compromise between forcing the studies to express the same set of patterns, as in the previous paper (Edefonti et al., 2012), and allowing them to express separate sets of patterns to be somehow combined in a subsequent step. The recently proposed multi-study factor analysis (De Vito, Bellio, et al., 2019) generalizes standard factor analysis to handle information from multiple studies simultaneously. It identifies shared factors, which are common to all the studies, as well as additional study-specific factors for some of the studies. In addition, it allows to choose the best number of shared and study-specific patterns using a formal statistical approach.

In accordance with this “partial sharing” approach, a paper published by De Vito and coauthors (De Vito, Lee, et al., 2019) simultaneously derived shared and study-specific *a posteriori* patterns applying multi-study factor analysis on individual-level data from 7 case–control studies (3844 cases; 6824 controls) providing information on 23 nutrients. Three patterns were shared across all studies (75% variance explained). The *Antioxidant vitamins and fiber* (OR = 0.57, 95% CI: 0.41-0.78, highest vs. lowest score quintile, from a one-stage random-slope generalized linear mixed-effects model with logit link function and binomial family) and the *Fats* (OR = 0.80, 95% CI: 0.67-0.95, from the corresponding one-stage generalized linear fixed-effects model) patterns were inversely associated with oral cavity and pharyngeal cancer risk. The *Animal products and cereals* (OR = 1.51, 95% CI: 1.1-2.1, from a one-stage random-slope generalized linear mixed-effects model with logit link function and binomial family) and the *Fats* (OR = 1.8, 95%CI: 1.4-2.3, from the corresponding one-stage generalized linear fixed-effects model) patterns were positively associated with laryngeal cancer risk, whereas a linear inverse trend in laryngeal cancer risk was evident for the *Antioxidant vitamins and fiber* pattern. Four additional study-specific patterns were also identified (one for each of the 4 US studies examined) and consistently named as *Dairy products and breakfast cereals*. In 2 of these studies, the *Dairy products and breakfast cereals patterns* were associated with oral cavity and pharyngeal cancer risk, based

on corresponding one-stage generalized linear fixed-effects regression models with logit link function and binomial family.

Thus, multi-study factor analysis provides insight into cross-country reproducibility of dietary patterns and on their association with HNC risk.

Fiber intake—A complementary approach to the analysis of dietary patterns considers single nutrients or food groups in their association with HNC risk. Following previous papers on vitamin C (Edefonti, Hashibe, Parpinel, Turati, et al., 2015) and carotenoids (Leoncini et al., 2016) within INHANCE, the current update reports a brief summary of results on the association between risk at HNC sub-sites and estimated usual intakes of fiber or vitamin E in adulthood.

Several plausible mechanisms support a favorable effect of dietary fiber on HNC, including an improvement in insulin sensitivity [favorably influencing insulin-like growth factor 1 (IGF-1)], fiber's ability to bind carcinogens (limiting their contact with upper digestive tract epithelia), and the likely higher content of antioxidants in fiber-rich foods. In addition, a higher fiber intake may simply be an indicator of a diet rich in fruit, vegetables, whole gains, and poorer in refined cereals, meat, and animal fats, which have been positively associated with higher HNC risks. A pooled analysis by Kawakita and coauthors (Kawakita et al., 2017) considered the largest dataset (10 case-control studies, 5959 cases and 12,248 controls) on the association between fiber intake and HNC risk at that time. Fiber intake was inversely associated with oral cavity and pharyngeal cancers combined (for 5th vs. 1st quintile category, OR = 0.49, 95% CI: 0.40-0.59, p for trend <0.001, from a one-stage random intercept-random slope generalized linear mixed-effects model with logit link function and binomial family) and with laryngeal cancer (OR = 0.66, 95% CI: 0.54-0.82, p for trend <0.001, from the corresponding fixed-effects model). Inverse associations were observed for oral and pharyngeal cancer sub-sites and within most strata of the considered covariates, for both cancer sites. These results strengthen the evidence on the favorable effect of higher intakes of fiber-rich foods on HNC risk.

Vitamin E intake—Another single-nutrient analysis (Edefonti, Hashibe, Parpinel, Ferraroni, et al., 2015) explored the role of vitamin E from natural sources on HNC risk in the same subset of 10 case-control studies (5959 cases, 12,248 controls). Higher intakes of vitamin E were found to be inversely related to the risk of oral and pharyngeal cancers combined (for the 5th vs. 1st quintile category, OR=0.59, 95% CI: 0.49-0.71, p for trend < 0.001, from a one-stage random intercept-random slope generalized linear mixed-effects model with logit link function and binomial family) and to laryngeal cancer (OR =0.67, 95% CI: 0.54-0.83, p for trend < 0.001, from the corresponding fixed-effects model), although in the presence of heterogeneity of the estimated effect across studies for oral and pharyngeal cancers. Inverse associations were also observed for the anatomical sub-sites of oral cavity and pharyngeal cancer and within covariate strata for both cancer sub-sites. These findings suggest that a higher vitamin E intake, mainly derived from vegetables and oils of different origin (including olive oil), may lower HNC risk.

Glycemic index and load—In the absence of conclusive evidence on the association between glycemic index and/or load and HNC risk, the paper published by Chang and colleagues (Chang et al., 2020) reported on a pooled analysis of 8 case-control studies (4081 HNC cases and 7407 controls), which had sufficient power to explore risks in HNC sub-sites, including oropharyngeal cancer. The results supported the conclusion that glycemic index, but not load, had a weak positive association with HNC (for the 3rd vs. 1st quartile category, OR=1.16, 95% CI: 1.02-1.31, p for trend = 0.037, from a one-stage generalized linear fixed-effects model with logit link function and binomial family). In addition, in sub-sites, corresponding fixed-effects models showed a positive association between glycemic index and laryngeal cancer (OR=1.60, 95% CI: 1.30-1.96, p for trend < 0.001), whereas the association was inverse between glycemic load and oropharyngeal cancer (OR=0.78, 95% CI: 0.63-0.97, p for trend = 0.009). This indicated therefore a modest positive association between glycemic index and HNC risk, mainly driven by laryngeal cancer (excluding laryngeal cancer cases, the OR for glycemic index was 1.01, 95% CI: 0.88-1.16, p for trend =0.90, from a fixed-effects model).

Allium vegetables—To give an overall picture of diet effects on the risk of HNC and its sub-sites, 2 papers (Galeone et al., 2010; Galeone et al., 2015) integrated evidence from INHANCE consortium providing additional contributions at the food-and-beverage level, as derived from a combination of one-stage and two-stage approaches to risk assessment. The more recent of the 2 analyses (Galeone et al., 2015) assessed the separate role of the most common allium vegetables, garlic and onion, in 8 case-control studies (4590 HNC cases, 7082 controls). In consideration of their antioxidant properties, several epidemiological investigations have suggested a potential beneficial role of allium vegetables against cancer. Nonetheless, evidence dealing with HNC was still limited. The most comprehensive INHANCE publication on food groups (Chuang et al., 2012) reported significant results for allium vegetables overall (ORs for subsequent quartiles equal to 0.98, 0.86, and 0.66, p for trend <0.05). In the main results from the updated publication (Galeone et al., 2015), compared with no/low garlic use (i.e., corresponding to less than 0.2 servings per day of usual intake), the OR of HNC was 0.74 (95% CI: 0.55-0.99, p for trend= 0.02, from a two-stage random-effects approach) for high garlic use (i.e., more than 1 serving per day), based on 6 studies. The ORs of HNC for the highest category of consumption of usual onion intake (>3 portions vs. <1 portion per week) was 0.83 (95% CI: 0.60-1.13, p for trend= 0.02, from a two-stage random-effects approach), based on 7 studies. In HNC sub-sites, the paper reported inverse associations of similar magnitude between high garlic intake and oro/hypopharyngeal cancer risk (OR=0.62, 95% CI: 0.40-0.97, p for trend = 0.07, from a two-stage random-effects approach) and high onion intake and laryngeal cancer risk (OR=0.69, 95% CI: 0.54-0.88, p for trend = 0.04, from a one-stage fixed-effects approach), but no material associations for the other sub-sites (e.g., for garlic use: OR=0.77, 95% CI: 0.49-1.21 for oral and pharyngeal cancers combined and OR= 0.67, 95% CI: 0.42-1.07 for laryngeal cancer; for onion use: OR=0.88, 95% CI: 0.67-1.15, for oral and pharyngeal cancers combined). Results of this pooled analysis supported therefore previous evidence from INHANCE (Chuang et al., 2012) of a moderate protective effect of allium vegetables on HNC; it also allowed quantification of the separate effects of garlic and onion on the overall risk and in the available anatomical sub-sites.

Coffee and tea—Another paper (Galeone et al., 2010) took advantage of the INHANCE dataset to explore the association of the 2 most commonly consumed hot beverages in the world, coffee and tea, with HNC risk. As it was not mentioned in the previous update on INHANCE results, we provide a summary of its results in the current update. Nine case-control studies (5139 cases, 9028 controls) were included in this analysis, which was based on a combination of one-stage and two-stage approaches to risk assessment. Caffeinated coffee intake was inversely related with the risk of cancers of the oral cavity and pharynx combined: the ORs were equal to 0.96 (95% CI: 0.94-0.98) for an increment of 1 cup per day and to 0.61 (95% CI: 0.47-0.80, p for trend < 0.01, from a two-stage random-effects approach) in drinkers of >4 cups per day vs. non-drinkers. The latter risk estimates were similar across different anatomical sub-sites: the ORs were equal to 0.46 (95% CI: 0.30-0.71) for oral cavity, 0.58 (95% CI: 0.41-0.82) for oropharyngeal/hypopharyngeal cancer, and 0.61 (95% CI: 0.37-1.01) for oral cavity and pharynx not otherwise specified, from either one-stage fixed-effects or two-stage random-effects models; they were also similar across strata of selected covariates. No association was found between caffeinated coffee and laryngeal cancer risk (OR=0.96, 95% CI: 0.64-1.45, p for trend = 0.82, in drinkers of >4 cups per day vs. non-drinkers, based on a one-stage fixed-effects approach). Information on decaffeinated coffee was too sparse to reach a firm conclusion. Considering drinkers vs. non-drinkers, tea intake was not associated with the risk of oral and pharyngeal cancers combined (OR=0.99, 95% CI: 0.89-1.11), with single sub-sites, or with laryngeal cancer (OR=0.97, 95% CI: 0.80-1.18). No material associations were found when considering cups per day of tea (>2 vs. >=1), except for a higher risk of 1.48 (95% CI:1.03-2.14) for laryngeal cancer. In conclusion, this pooled analysis within INHANCE supports the hypothesis of an inverse association between caffeinated coffee drinking and oral and pharyngeal cancer risk. The observed inverse relation may have an appreciable public health relevance, given the widespread use of coffee, and the relatively high incidence and low survival of HNC.

Figure 4 shows the main findings from papers reporting on the remaining exposures, including oral health and oral hygiene, exogenous and endogenous hormonal factors, and occupational exposures.

Oral health and oral hygiene

The role of oral health and hygiene was investigated in a manuscript (Hashim et al., 2016), including 13 INHANCE studies for a total of 8925 HNC cases and 12,527 controls. Oral hygiene data was based on self-reported information in most studies. Significant inverse associations were found between HNC and gum disease (OR = 0.94, 95% CI: 0.89-0.99, yes vs. no disease, from one stage fixed-effects models), number of missing teeth (OR = 0.78, 95% CI: 0.74-0.82, for <5 vs. ≥5), toothbrushing (OR = 0.83, 95% CI: 0.79-0.88 for ≥once/day vs. <once/day), regular dentist visit (OR = 0.82, 95% CI: 0.78-0.87 for ≥once/year vs. <once/year). No association was found for wearing dentures. Estimates were similar across HNC sub-sites, except for gum disease, which was associated with cancer of the oral cavity only. The authors summed up the mentioned indicators of oral health and oral hygiene to obtain a score ranging from 0 (worst oral health) to 5 (best oral health). A lower score was associated with a significant increase in HNC risk (OR = 1.98, 95% CI: 1.68-2.35 for ≤1 vs.

≥4, p for trend < 0.0001). The association appeared stronger for oral cavity cancer (OR = 3.12, 95% CI: 2.08-4.68 for ≤1 vs. ≥4, p for trend<0.0001). The population attributable fraction for ≤2 out of 5 oral hygiene indicators was 8.9% (95% CI: 3.3-14%).

Exogenous and endogenous hormonal factors

The role of exogenous and endogenous hormonal factors in female HNC was investigated by Hashim and colleagues (Hashim et al., 2017) in 11 INHANCE studies, including 1572 women with HNC and 4343 female controls. Inverse associations were observed between HNC and exogenous hormones use according to a combination of one-stage and two-stage approaches. In detail, a two-stage random-effects approach was used for the overall analysis on HNC, whereas a one-stage fixed-effects generalized linear model with binomial family and logit link function was used in stratified and sub-site analyses. In particular, the risk of HNC was almost halved by ever use of hormone replacement therapy (HRT, OR = 0.58, 95% CI: 0.34-0.77) and ever use of oral contraceptives (OC, OR = 0.59, 95% CI: 0.40-0.86). The inverse association was stronger for women who started OC use at ≥31 years old (OR = 0.37, 95% CI: 0.22-0.63, p value for trend <0.001). Among HRT users, HNC risk further decreased for each additional 10 years of age at starting use (OR = 0.59, 95% CI: 0.39-0.90); moreover, HNC risk further decreased for every additional 3 years of HRT use (OR = 0.87, 95% CI: 0.76-0.99). Considering endogenous hormones, inverse associations were observed for ever giving birth (OR = 0.70, 95% CI: 0.52-0.95, for ever vs. never), age at first pregnancy (OR = 0.61, 95% CI: 0.42-0.90 for <35 years, nonsignificant OR for ≥35 years old vs. never), age at first birth (OR = 0.59, 95% CI: 0.38-0.90 for <35 years, nonsignificant OR for ≥35 years old vs. never). Menopause at <52 years old was associated with an increased HNC risk (OR = 1.69, 95% CI: 1.06-2.71). When considering sub-sites, the associations of exogenous and endogenous hormones were similar to those observed for HNC overall. The authors also considered the role of hormonal factors by smoking or drinking status in HNC overall and its sub-sites. An interaction between smoking status and HRT use was observed for oropharyngeal cancer. Significant interactions were found between HRT use and alcohol drinking for HNC overall, and the oral cavity sub-site. A significant interaction between OC use and alcohol drinking emerged for overall HNC. The inverse association between OC use and oropharyngeal cancer risk was observed among ever tobacco smokers, but not in never smokers. The inverse association between ever giving birth and overall HNC was stronger among ever smokers.

Occupational exposures

Occupation and risk of head and neck cancer and sub-sites—Khetan and colleagues (Khetan et al., 2019) examined categories of occupations (according to the ISCO classification) in 12 case-control studies within the consortium (8839 HNC cases and 13,730 controls). The authors compared subjects who ever worked in each selected occupational category with those who never worked in all the occupations under investigation, to keep the occupational carcinogen exposure in the reference group to its minimum. Analyses were carried out in the overall sample and according to duration of employment (≤10 vs. >10 years), as well as considering duration as a continuous variable, according to one-stage fixed-effects approach.

Estimates for ever vs. never been occupied were significantly over the unity for most of the considered occupational categories, including many service workers, production and related workers, transport equipment operators, and laborers. In particular, the ORs were 1.45 (95% CI: 1.17-1.80) for waiters – bartenders and related workers (p-value for the effect of duration in continuum = 0.001), OR = 1.99 (95% CI: 1.36-2.91) for toolmakers – metal patternmakers and metal markers (p-value for duration in continuum = 0.02), OR = 1.52 (95% CI: 1.23-1.87) for carpenters – joiners and parquetry workers (p-value for duration in continuum = 0.01), and OR = 1.37 (95% CI: 1.18-1.60) for laborers not elsewhere classified (p-value for duration in continuum <0.0001). Most of the estimates for ever vs. never been occupied consistently remained across the two strata of duration and in HNC sub-sites.

Recognized occupational lung carcinogens and risk of laryngeal cancer—To investigate the role of recognized occupational lung carcinogens on laryngeal cancer risk, Hall and colleagues (Hall et al., 2020) analyzed data from 5 INHANCE case-control studies providing information on occupational histories coded according to the International Standard Classification of Occupations (ISCO)-68 of the International Labor Organization (International Labour Office, 1968). These studies included 2256 laryngeal cancer cases and 7857 controls (Hall et al., 2020). The authors linked the quantitative job exposure matrix (SYN-JEM) with the individual self-reported occupational history in order to estimate exposure levels for asbestos, respirable crystalline silica, chromium-VI, and chromium-VI & nickel combined. The association between laryngeal cancer risk and these agents was considered in terms of ever exposure, duration of exposure, and cumulative exposure, through a one-stage fixed-effects model adjusted for age, alcohol consumption, tobacco smoking, exposure to asbestos (when appropriate), in strata of gender. For all agents the ORs were higher for ever exposure vs. non exposure, both in men and women. Among men, significant associations were observed for asbestos at 90^{th} percentile of cumulative exposure (OR = 1.3, 95% CI: 1.0-1.6, p for trend=0.04), respirable crystalline silica for a duration of 30 years and more (OR = 1.4, 95% CI: 1.2-1.7, p for trend <0.0001) and at 75^{th}-90^{th} percentile of cumulative exposure (OR = 1.4, 95% CI: 1.1-1.8, p for trend=0.0002), for chromium-VI at more than 75^{th} percentile of cumulative exposure (OR = 1.9, 95% CI: 1.2-3.0, p for trend=0.0014), and for chromium-VI & nickel at a duration of 20-29 years (OR = 1.5, 95% CI: 1.1-2.2, p for trend=0.02). Thus, this work supported the existence of an association between selected lung carcinogens and laryngeal cancer risk.

Estimates and predictors of cancer recurrence and survival

Five studies within INHANCE had follow-up information on patients' overall and disease-free survival. Two papers investigated potential predictors of survival, recurrence and second primary cancer (SPC).

Recurrence and second primary cancer according to tumor stage and gender —Leoncini and colleagues (Leoncini et al., 2018) investigated demographic and lifestyle risk factors related to recurrence and SPC in the 5 follow-up studies. Cancer recurrence was defined as local, regional, or distant occurrence of cancer of the same histologic type, after a period in which cancer could not be detected. SPC was defined according to different criteria depending on the original study, with the common requirement of being pathologically

confirmed as a distinct malignancy. The survival rate was calculated according to the Kaplan-Meier method. A total of 4005 HNC cases were included in the analyses on recurrence and 3982 HNC cases were entered in the analysis on SPC. After a median follow-up time of 21 months (interquartile range, IQR: 9-55 months), 1161 patients (29%) had cancer recurrence. Considering cancer sub-sites, recurrence occurred in 117 (33%) of hypopharyngeal cancer patients, 423 (31%) of oral cancer patients, 244 (31%) of oropharyngeal cancer patients, 296 (24%) of laryngeal cancer patients, and 81 (32%) of HNC not otherwise specified. In the SPC analysis, after a median follow-up time of 26 months (IQR: 11-59 months), a SPC occurred in 343 patients (9%), with similar proportions across sub-sites. Recurrence-free 5-years survival was 5.90% for all HNC (standard deviation, SD = 0.24), 6.59% for oral cancer (SD = 0.25), 7.30% for oropharynx (SD = 0.26), 3.92% for hypopharynx (SD = 0.2), and 4.8% for larynx (SD = 0.21). SPC-free 5-year survival was 5.97% for all HNC (SD = 0.24), 8.56% for oral cancer (SD = 0.28), 5.92% for oropharynx (SD = 0.24), 4.92% for hypopharynx (SD = 0.22), and 4.25% for larynx (SD = 0.20).

Advanced tumor stage showed a higher risk of recurrence for HNC overall (HR = 1.76, 95% CI: 1.41-2.19), for oral cavity (HR = 1.85, 95% CI: 1.31-2.61), and oropharynx (HR = 2.56, 95% CI: 1.19-5.51). Women with laryngeal cancer had a lower recurrence risk as compared to men (HR = 0.39, 95% CI: 0.24-0.74). Among patients with hypopharyngeal cancer, current alcohol drinkers had a higher risk of recurrence, as compared to never drinkers (HR = 3.43, 95% CI: 1.05-11.26).

The risk of SPC was higher in women (HR = 1.68, 95% CI: 1.13-2.51) for HNC overall and for oropharyngeal cancer (HR = 1.74, 95% CI: 1.02-2.98). Among laryngeal cancer patients, SPC risk was increased by higher age at diagnosis (HR = 1.02, 95% CI: 1.00-1.04), and alcohol consumption (HR = 2.11, 95% CI: 1.13-3.94 for >1 drink per day).

Overall and head and neck cancer-specific mortality according to alcohol and cigarette consumption—Giraldi and colleagues (Giraldi et al., 2017) investigated potential predictors of overall and HNC-specific survival within the 5 INHANCE follow-up studies including 4759 HNC cases. The cumulative proportion surviving was estimated according to the Kaplan-Meier method. Cox's proportional hazard model was used to identify predictors of overall and HNC-specific survival, adjusting for major confounding.

A total of 1924 patients (45.8%) died during the follow-up period, of whom 1408 died from HNC. The 5-year overall survival was 51.4% for all HNC combined (50.3% for oral cavity, 41.1% for oropharynx, 35.0% for hypopharynx, and 63.9% for larynx). The 5-year HNC-specific survival was 57.4% for all HNC (54.6% for oral cavity, 45.4% for oropharynx, 37.1% for hypopharynx, and 72.3% for larynx).

Older age at diagnosis was unfavorably related to overall and HNC-specific survival, the estimates being slightly above 1 for overall HNC and most sub-sites. A lower educational level was associated with a significantly lower overall survival among laryngeal cancer patients only (HR = 2.54 for less than high school compared to college graduate), and with HNC-specific survival in HNC cases overall (HR = 1.45). Tumour stage (IV vs. I) was

associated with a significantly lower overall survival for HNC and its sub-sites (except hypopharynx), with HRs ranging between 2.5 and 3.8. A similar pattern of risk was observed for HNC-specific survival with overall HNC and most sub-sites. Cigarette smoking was unfavorably associated with overall survival of oropharyngeal cancer (HR = 1.83 for current vs. never smokers, HR = 2.33 for duration of smoking ≤20 years vs. never smokers, HR = 1.87 for ≤ 20 cigarettes/day vs. never smokers). Among oral cavity cancer patients, smokers of >20 cigarettes/day had a lower overall survival, as compared to never smokers (HR = 1.41). Alcohol drinking was associated with a reduced overall survival in HNC patients (HR = 1.31, for current, HR = 1.30, for ≤1 drink/day, and HR = 1.27, for >1 drink/day vs. never drinkers), and HNC-specific survival in overall HNC cases (HR=1.31 for current drinkers, and HR = 1.32 for ≤1 drink/day vs. never drinkers). The unfavorable role of alcohol drinking on overall and HNC-specific survival appeared stronger among patients with laryngeal cancer.

Probability of developing head and neck cancer according to risk factor profiles in the US population: a risk prediction model

Risk prediction models may be used in a clinical setting for identifying high-risk individuals, or in a public health perspective for promoting healthier behaviors, or at the individual level for aiding subjects with family history of cancer to evaluate their cancer risk. However, to date, only one risk calculator is available for HNC and it is based on a combination of a few demographic characteristics (i.e., age and gender) and clinical symptoms, likely present during cancer development. In addition, it would be important to have separate estimates for HNC sub-sites. The paper by Lee and coauthors (Lee et al., 2019) considered 14 INHANCE studies from the US (7299 HNC cases and 10,301 controls) to build (70% of the data) and internally validate (30% of the data) the first sex-specific HNC predictive model which provided absolute risk estimates of HNC (i.e., probability of HNC development) and the single sub-sites starting from different risk factor profiles. Well-established risk factors, such as age, sex, race, education, cigarette smoking duration and intensity, and/or alcohol drinking intensity, were included in the model, additionally considering family history of HNC in a second set of models. The risk factors were entered into the Freedman model (Freedman et al., 2009), which accounted for the competing risk of death other than the cancer of interest and considered tumor sub-sites separately.

To provide an example of results, the 20-year absolute HNC risk was 7.61% for a 60-year-old woman who smoked >20 cigarettes/day for >20 years, drank 3 or more alcoholic drinks/day, was a high school graduate, had a family history of HNC and was non-Hispanic White; men with a similar profile had a 20-year risk of 6.85%. Absolute risks of oropharyngeal and hypopharyngeal cancers were generally lower than those of cancers of the oral cavity and larynx. The identified risk prediction model showed good to fair validity when tested in the validation set.

In addition to having overcome most of the limitations of the existing HNC risk calculator, the INHANCE-based risk prediction model developed was based on the largest sample size ever available in the US.

Conclusions

The INHANCE consortium has been successful thus far in helping to clarify important questions on the causes and mechanisms involved in HNC etiology. This overview demonstrates ongoing progress, providing important updates on HNC risk – particularly in relation to: understanding specific aspects of the dominant risk factors of tobacco and alcohol; providing in-depth exploration of dietary factors; and providing important new contributions in the areas of the role of race, occupational exposures, endogenous and exogenous hormonal factors, and oral health and hygiene. The INHANCE consortium has further adapted to explore issues associated with survival from HNC.

The aim of cancer epidemiology is to limit cancer burden as far as possible, and the development of a HNC risk prediction model is an important contribution to future efforts of applying this knowledge into practical cancer prevention efforts.

The studies currently included within the INHANCE consortium examined populations largely in North and Latin America, Europe, and Asia. However, very few patients were included from areas with very high HNC rates, such as those from South and South-East Asia or Africa; a few studies on risk factors have been conducted so far for this set of cancers within these regions of the world. Nowadays, high-incidence areas include both developing and developed countries. During recent decades, the rapid socioeconomic development experienced by countries like Thailand has led to major changes in lifestyle habits (including alcohol, tobacco, and sexual behaviours) that have been already reflected in changes in temporal trends for HNC incidence resembling the United States (Argirion et al., 2019).

Supporting the design of new studies from developing and developed countries in high-risk areas and including them within the consortium could lead to a much more comprehensive picture of HNC etiology.

At the same time, investigators already included in the consortium should continue to exchange ideas, promote new research, and share resources in an equitable manner. There is room for exploring the role of other etiological factors in HNC development, following both standard and innovative statistical approaches. In the former case, the association of relevant macronutrients (especially fats) and vitamins (for example, vitamin D) with HNC and its sub-sites could be of interest. An example of the latter case includes the development of a more refined bivariate spline model approach tailored at assessing the joint effect of intensity and duration of alcohol drinking, while avoiding to fix the maximum number of change-points in the risk surface. In addition, our uniquely large set of studies offers the opportunity to explore the role of selected anthropometric characteristics, as well as behavioural and environmental factors on survival from HNC.

In conclusion, results from the INHANCE consortium confirm that international collaborative efforts and pooling of data and resources can contribute to advance knowledge on the causes of common cancers such as HNC.

Further information can be obtained from the consortium's website (https://www.inhance.utah.edu, date last access May 28, 2020). If an investigator would like to have more information on becoming a member, she/he can contact one of the authors of the paper, Yuan-Chin Amy Lee, whose contact information is available on the INHANCE website (https://www.inhance.utah.edu/contact.php, date last access May 28, 2020).

Acknowledgements:

The authors would like to thank Xavier Castellsagué who collected data in the IARC International Multicenter study and passed away in 2016.

The INHANCE consortium and the single studies included were supported by grants from the: National Institutes of Health (NIH) [no grant number provided for the INHANCE Pooled Data Project and Intramural Research Program for the Puerto Rico study, 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**]; 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 Research Program supporting the **Puerto Rico study** and the **US Multicenter study**, grant number R01-CA90731 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 Research 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**, and for the **Rome 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 **Aviano** and **Italy Multicenter studies**]; 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, INCO-COPERNICUS Program Contract number IC15- CT98-0332 for the **Central Europe** 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**, grant number P30ES010126 for 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 (1988-2000) study** and **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 (1988-2000) study** and **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**]; 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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**]; World Cancer Research Fund [no grant number provided for the **Central Europe study**]; Ministry of Science, Research and Arts Baden-Wurttemberg [no grant number provided for the **Germany-Saarland** study]; German Ministry of Education and Research [grant number 01GB9702/3 for the **Germany-Heidelberg study**]; Johns Hopkins Richard Gelb Cancer Prevention Award [no grant number for the **HOTSPOT study**]; no grants provided for the **France (1989 - 1991), Houston, and Buffalo studies**; VE was supported by Università degli Studi di Milano 'Young Investigator Grant Program 2017'.

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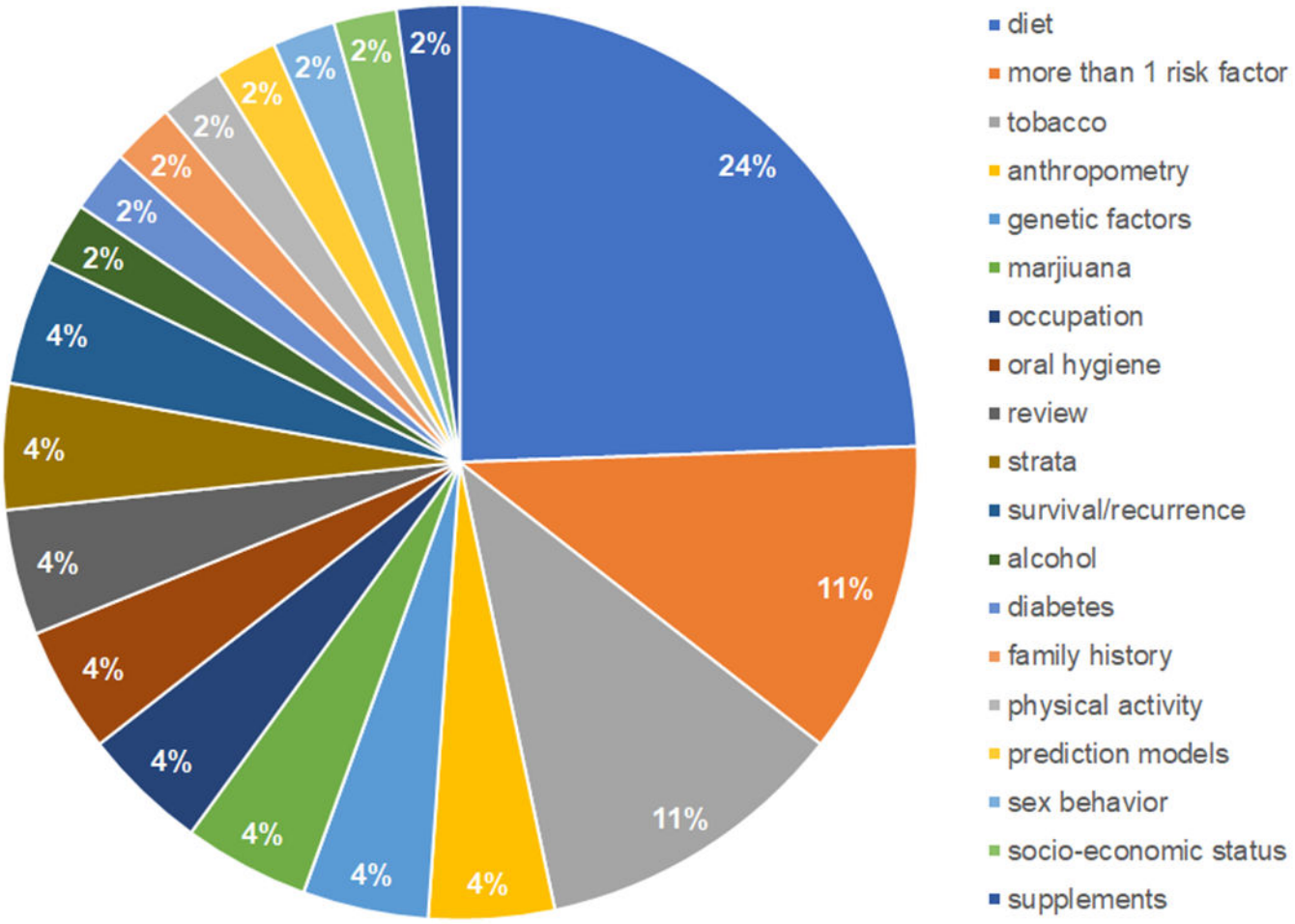

Figure 1 -

Distribution of publications produced within the International Head and Neck Cancer Epidemiology (INHANCE) consortium from its beginning in 2004 to present (May 2020), by topic considered

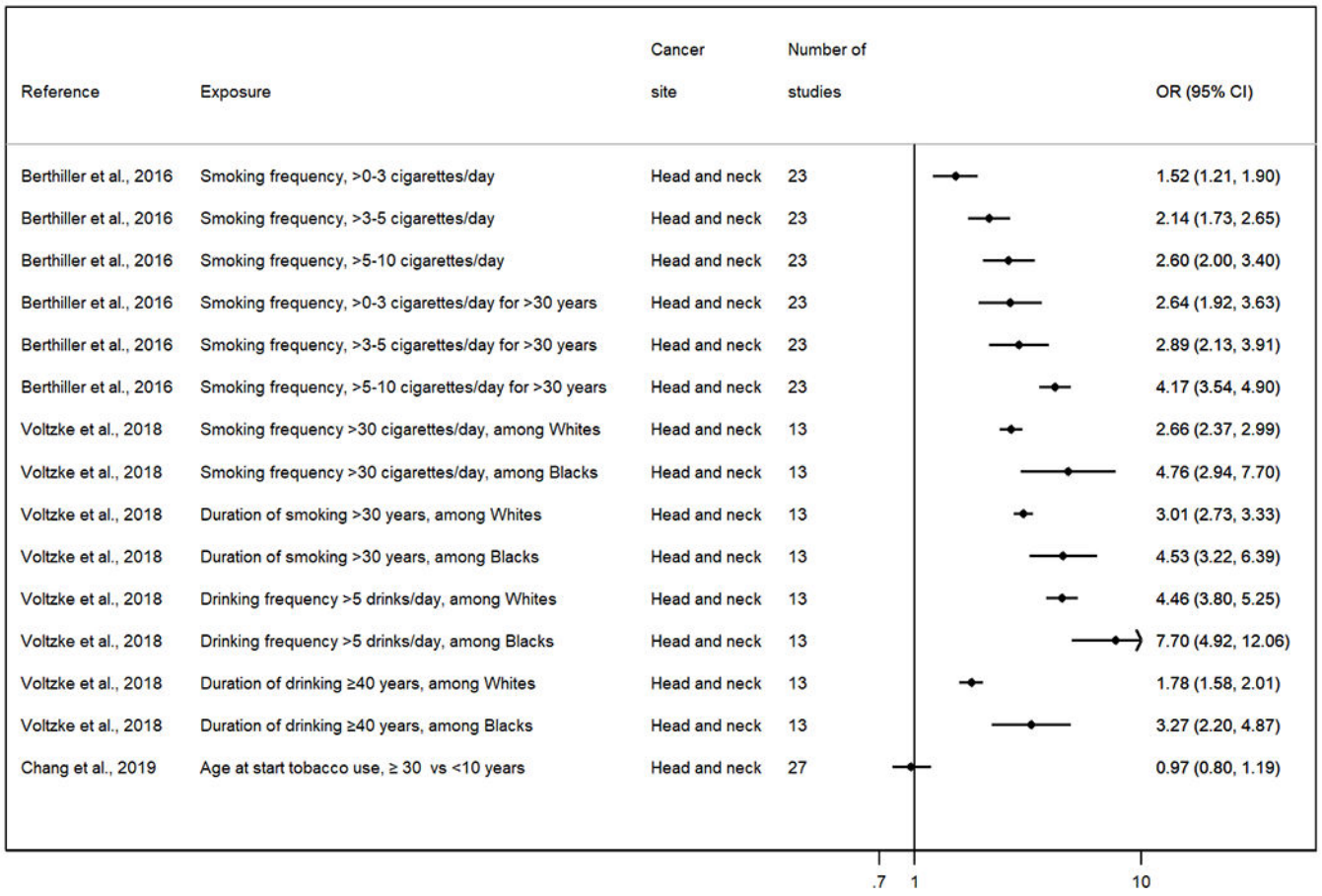

Figure 2 -

Relevant associations between tobacco smoking or alcohol drinking and head and neck cancer (or its subsites), as described in the current overview. International Head and Neck Cancer Epidemiology (INHANCE) consortium

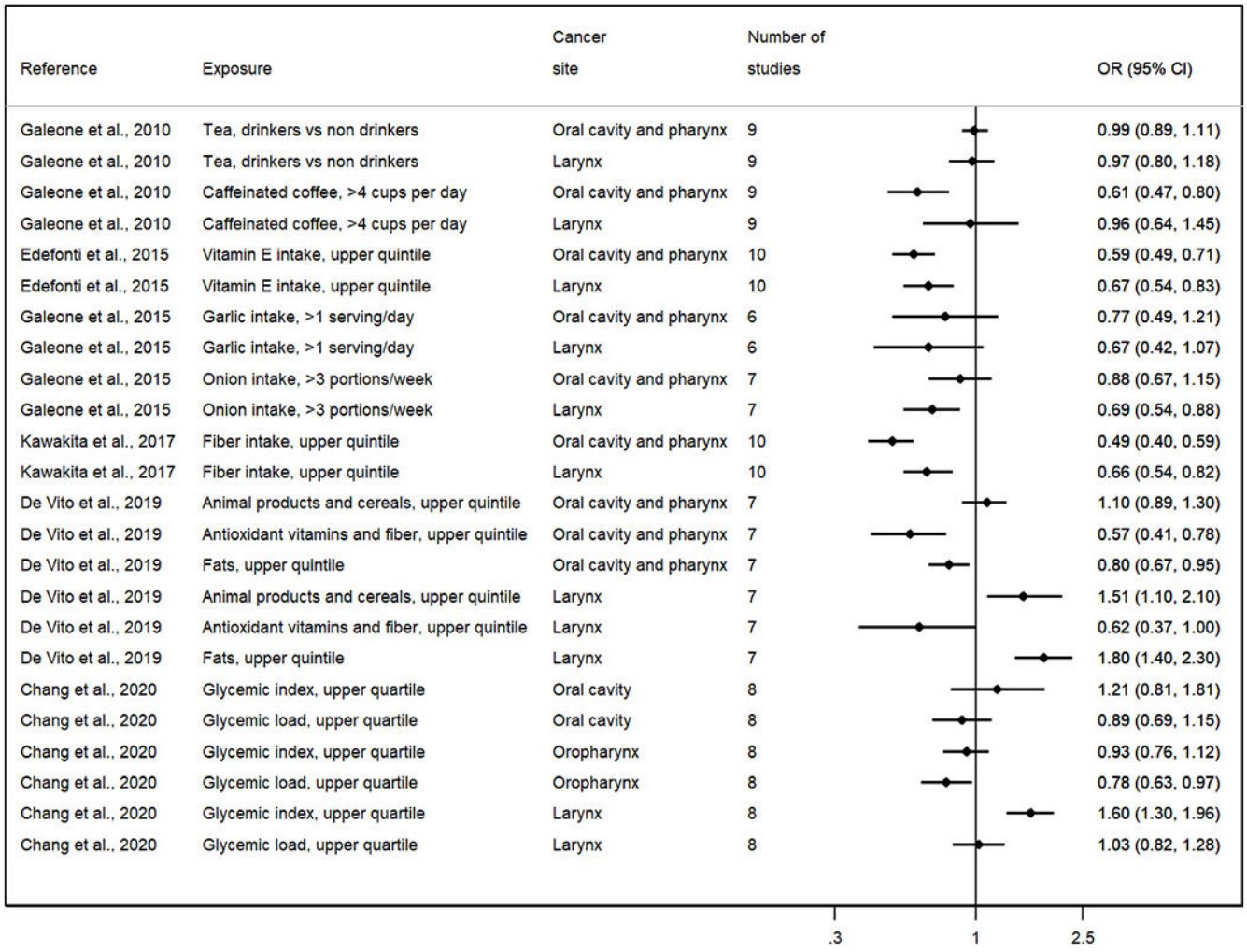

Figure 3 -

Relevant associations between dietary habits and head and neck cancer (or its subsites), as described in the current overview. International Head and Neck Cancer Epidemiology (INHANCE) consortium

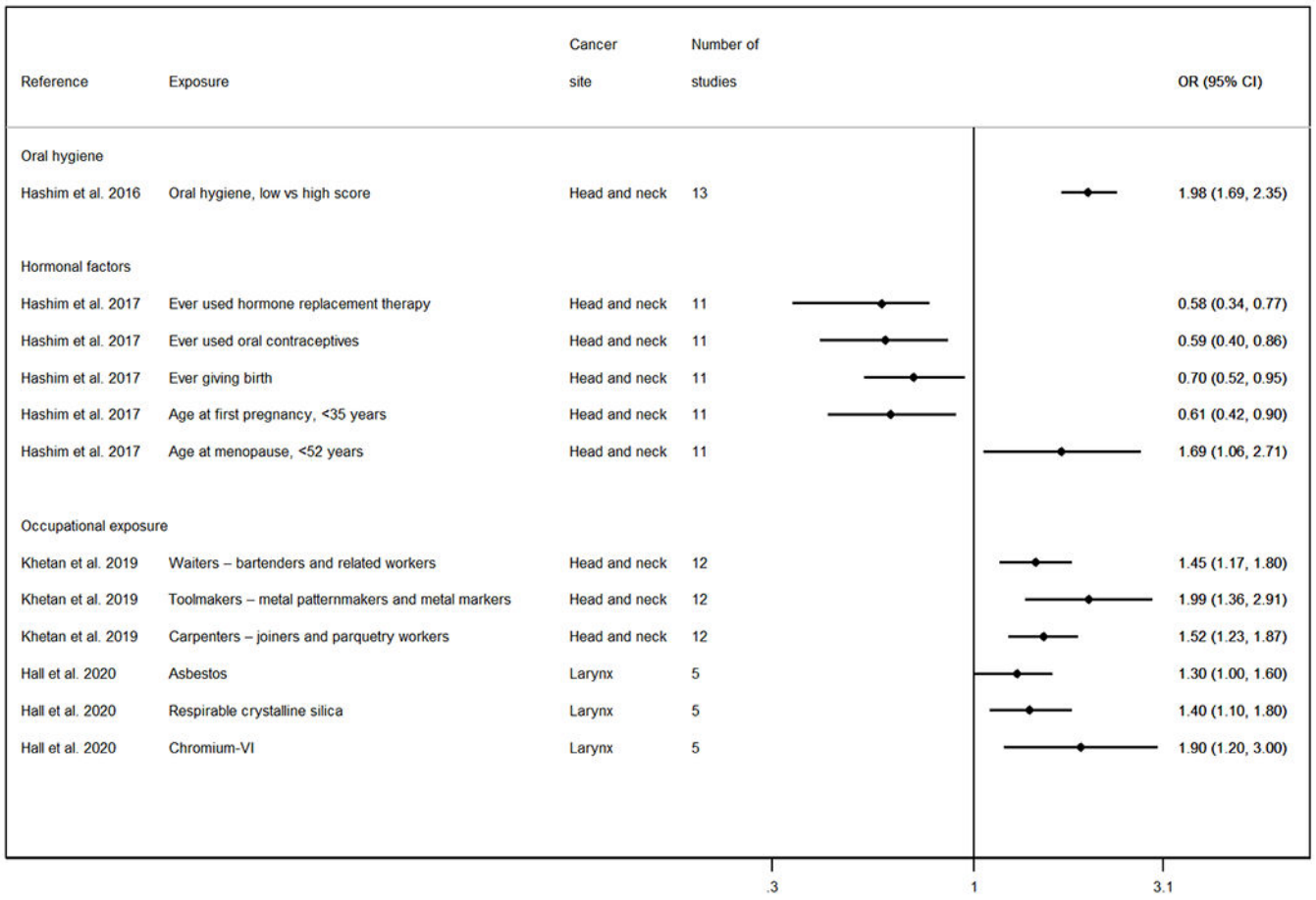

Figure 4 -

Relevant associations between oral health and oral hygiene, exogenous and endogenous hormonal factors, and occupational exposures, and head and neck cancer (or its subsites), as described in the current overview. International Head and Neck Cancer Epidemiology (INHANCE) consortium

Table 1 –

Characteristics of the individual studies currently included in the International Head and Neck Cancer Epidemiology consortium (2004 - May 2020).

Study location	Case source	Age eligibility	Case participation proportion, %	Control source	Control participation proportion, %	Matched factors	Recruitment period	Lifestyle data pooling
Milan, Italy	Hospital	<80	95[1]	Hospital - unhealthy	95[1]	--	1984-1989	yes
Aviano, Italy	Hospital	>18	>95[1]	Hospital - unhealthy	95[1]	--	1987-1992	yes
France	Hospital	NA	95[1]	Hospital - unhealthy	95[1]	Age, sex, hospital	1987-1992	yes
Italy Multicenter	Hospital	18-80	>95	Hospital - unhealthy	>95	--	1990-1999	yes
Switzerland	Hospital	<80	>95	Hospital - unhealthy	>95	--	1991-1997	yes
Central Europe	Hospital	≥15	96	Hospital - unhealthy	97	Age, sex, ethnicity, city	1998-2003	yes
New York, USA (multicenter)	Hospital	21-80	91	Hospital - unhealthy	97	Age, sex, hospital, year of interview	1981-1990	yes
Seattle, WA, USA (Schwartz)	Cancer registry	18-65	54.4,63.3[2]	Random digit dialing	63.0,60.9[2]	Age, sex	1985-1995	yes
Iowa, USA	Hospital	>18	87	Hospital - unhealthy	92	Age, sex	1993-2006	yes
North Carolina, USA	Hospital	>17	88	Hospital - unhealthy	86	Age, sex	1996-1997	yes
Tampa, FL, USA	Hospital	≥18	98	Hospital - noncancer	90	Age, sex, ethnicity	1994-2003	yes
Los Angeles, CA, USA	Cancer registry	18-65	49	Neighborhood	68	Age, sex, neighborhood	1999-2004	yes
Houston, TX, USA	Hospital	≥18	95	Hospital visitors	>80	Age, sex, ethnicity	2001-2006	yes
Puerto Rico	Cancer registry	21-79	71	Residential records (healthy population)	83	Age, sex	1992-1995	yes
South America	Hospital	15-79	95	Hospital - unhealthy	86	Age, sex, ethnicity, city	2000-2003	yes
Intl Multicenter	Hospital	NA	88.7	Hospital- community	87.3	Age, sex, center	1992-1997	yes
Boston, MA, USA	Hospital	≥18	88.7	Residential records	48.7	Age, sex, neighborhood	1999-2003	yes
Rome, Italy	Hospital	>18	98	Hospital - unhealthy	94	no matching	2002-2007	yes
US Multicenter	Cancer registry	18-79	75	Random digit dialing and health care rosters	76	Age, sex, ethnicity	1983-1984	yes
Sao Paulo, Brazil	Hospital	NA		Hospital - unhealthy		age, sex, city of residence, hospital	2002-2007	yes
New York, USA (Memorial Sloan	Hospital	NA	--	Blood donors	--	Age, sex	1992-1994	yes

Study location	Case source	Age eligibility	Case participation proportion, %	Control source	Control participation proportion, %	Matched factors	Recruitment period	Lifestyle data pooling
Kettering Cancer Center)								
Seattle, WA, USA (Vaughan)	Cancer registry	20-74	81	Random digit dialing	75	Age, sex	1983-1987	yes
Western Europe	Hospital	NA	82	Hospital - unhealthy (population based for UK centers)	68	Age, sex, ethnicity, city	2000-2005	yes
Germany-Saarland	Hospital	50-75	94	Health examination	--	Age, sex	2001-2003	yes
Germany-Heidelberg	Hospital	<80	96	Population registries	62.4	Age, sex, residence	1998-2000	yes
Japan	Cancer Hospital	20-79	97.00	Hospital - unhealthy	97.00	Age, sex	2001-2005	yes
North Carolina, USA	Cancer registry	20-80	82	Department of Motor Vehicles files	61	Age, sex, ethnicity	2002-2006	yes
Paris (1989-1991), France	Hospital	NA	80	Hospital	86	Age, men only	1989-1991	yes
HOTSPOT	Hospital	≥18	>85	Hospital - benign conditions	>80	Age, sex, race	2009-2013	yes
Japan 2	Hospital	18-79	97.00	Hospital	97.00	Age, sex, year of visit	1988-2000	yes
Buffalo	Hospital	NA	~50	Hospital	~50	Age, sex	1982-1998	yes
Paris (2001-2007), France	Cancer registry	<=75	82.5	Random digit dialing	80.6	Age, sex, region	2001-2007	yes
Baltimore	Hospital	NA	100	Hospital - benign conditions	70	age, sex, human papillomavirus status	2000-2005	yes
Beijing	Hospital	18-80	100	Hospital	100	Age, sex	1988-1989	yes
Milan (2006-2009), Italy	Hospital	18-80	>95	Hospital	>95	----	2006-2009	yes
Mumbai, India	Hospital	minors excluded	--	Hospital - unhealthy	--	Age, sex, tobacco and alcohol habits	2001-2004	no
Northeast US	Hospital			Hospital - unhealthy		Age, sex		no
Pittsburgh, PA, USA	Medical Center	18-84		Hospital - unhealthy		Age, sex, ethinicy	2000-2009	no
Netherlands	Medical Center	23-93		Blood Bank - healthy		Age, sex, race, smoking behavior	1995-present	no
Tissue Array Initiative Study	National Institutes of Health			Case Only		--	2000-2009	no

Study location	Case source	Age eligibility	Case participation proportion, %	Control source	Control participation proportion, %	Matched factors	Recruitment period	Lifestyle data pooling
Seattle, WA, USA	Hospital			Case Only		--	2003-2007	no
Ann Arbor, MI, USA	Hospital	≥18		Case Only		--	2008-present	no
Toronto, Canada	Hospital	≥18		Hospital		Age, sex	2007-present	yes

ABBREVIATIONS: NA: not available.

[1]Participation proportion was not formally assessed, estimated response proportion reported.

[2]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.

Oral Dis. Author manuscript; available in PMC 2022 January 01.