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History of Diabetes and risk of head and neck cancer: a pooled analysis from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium

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Abstract

Background—A history of diabetes is associated with an increased risk of several types of cancers. Whether diabetes is a risk factor for head and neck cancer (HNC) has received little attention.

Methods—We pooled data from 12 case-control studies including 6,448 cases and 13,747 controls, and estimated odds ratios (OR) and 95% confidence intervals (CI) for the associations between diabetes and HNC, adjusted for age, education level, sex, race/ethnicity, study center, cigarette smoking, alcohol use and body mass index (BMI).

Results—We observed a weak association between diabetes and the incidence of HNC overall (OR, 1.09; 95% CI, 0.95–1.24). However, we observed a modest association among never smokers (OR, 1.59; 95% CI, 1.22–2.07), and no association among ever smokers (OR, 0.96; 95% CI, 0.83–1.11); likelihood ratio test for interaction p=0.001.

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Conclusions—A history of diabetes was weakly associated with HNC overall, but we observed evidence of effect modification by smoking status, with a positive association among those who never smoked cigarettes.

Impact—This study suggests that glucose metabolism abnormalities may be a HNC risk factor in subgroups of the population. Prospective studies incorporating biomarkers are needed to improve our understanding of the relationship between diabetes and HNC risk, possibly providing new strategies in the prevention of HNC.

Keywords

head and neck cancer; head and neck squamous cell carcinoma; diabetes; INHANCE

Introduction

Diabetes and/or abnormal glucose metabolism are associated with an increased risk of various types of cancers, including colorectal (1), pancreatic (2), breast (3), liver (4) and endometrial cancer (5). There are several mechanisms through which diabetes may drive the carcinogenic process. Neoplasms have an inherently high need for glucose to fuel proliferation, raising the possibility that untreated hyperglycemia may contribute to tumor growth (6). Diabetics also exhibit increased generation of reactive oxygen species and greater oxidative damage to DNA (7,8). Exposure to high levels of insulin and insulin-like growth factors (IGFs), a hallmark of type II diabetes, results in increased cellular proliferation. The IGF receptor additionally activates the oncogenic epidermal growth factor receptor (EGFR) (9). In addition, IGFs also appear to exert anti-apoptotic effects (10–12).

Head and neck cancers (HNC) are among the most common worldwide, with an estimated nearly 400,000 new cases and approximately 200,000 deaths in 2008 worldwide (13). While tobacco, alcohol use and, infection with oncogenic HPV are established risk factors for HNC (14,15), emerging evidence suggests that abnormalities of glucose metabolism and diabetes may also play a role (16–19). Several studies have reported that diabetics have an increased prevalence of oral lesions such as erythroplakia and leukoplakia that predispose to oral cancer (17–19). A Danish population-based study comparing individuals hospitalized with a diagnosis of diabetes to the general population observed an increased risk of mouth/pharynx cancer associated with diabetes in subjects less than 50 years old but not in older persons (20); however, these results were based on only 30 cases. A hospital-based case-control study of 2,660 patients and 2,980 controls observed that elevated fasting glucose was strongly associated with oral cancer in females but not males (16).

We used pooled data from multiple studies from different countries to investigate whether a history of diabetes is associated with HNC overall, as well as within subgroups defined by known HNC risk factors.

Methods

Overview and Design

We conducted a pooled analysis of case-control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Data pooling methods for the INHANCE consortium have been previously described (21). The following 12 INHANCE studies collected data on diabetic status: Milan (22), Aviano (23), Italy Multicenter (24), Switzerland-Vaud (25), Germany-Saarland (26), Seattle (OralGen) (27), Seattle (LEO) (28), Tampa (29), Los Angeles (30), Rome (31), Japan (32), and North Carolina (33). The 12 studies comprised 6,448 cases and 13,747 controls for which data on diabetic status, as well as on HNC risk factors and other characteristics were available.

Study Population

Cases were patients with tumors classified by the original studies as invasive tumors of the (1) oral cavity, (2) oropharynx, (3) hypopharynx, (4) larynx, (5) oral cavity or pharynx not otherwise specified or (6) HNC unspecified, as defined previously (21). The pooled studies were all hospital-based, except for both Seattle studies, the North Carolina study and the Los Angeles study. For these four studies, cases were identified from population-based cancer registries. For all of the included studies, controls were frequency-matched on age and sex, with the exception of the Los Angeles study, for which controls were individually matched on age, sex and neighborhood. The Italy Multicenter study additionally matched on center, and the Tampa and North Carolina study additionally matched on race/ethnicity. The date of reference was defined as the date of diagnosis for cases and the date of selection for controls, except for the Seattle (OralGen) study (27)where the reference date for a particular control subject was assigned at random from among the possible case subject diagnosis dates (27). The North Carolina, Tampa and Rome studies restricted eligibility to case subjects with squamous cell carcinomas (SCC). For the other studies, SCC was identified by ICD-O-2 or ICD-0-1 histologic codes, with the exception of the Milan, Aviano and Italy Multicenter study, for which no data were available on histologic type. We excluded all known non-SCC cases (n=205).

Measures and Data Collection

Data collection procedures regarding the data pooling and harmonization have been described in detail (21). All interviews for the studies used in this pooled analysis were face-to-face interviews, with the exception of the Germany-Saarland study, for which a self-administered questionnaire was used. Blank questionnaires were collected from the studies to assess comparability and wording of interview questions. Data from each study were received at the INHANCE Data Coordination Center with personal identifiers removed. Each data item was checked for illogical or missing values and queries were sent to the investigators to resolve inconsistencies.

We classified diabetic status as a binary variable (yes/no). Studies from Tampa, Los Angeles, Rome, North Carolina, Seattle (OralGen) (27), Seattle (LEO) (28), Germany, and Japan had a specific question in the interview that asked whether the subject had ever been diagnosed with diabetes (yes/no). The interview from the Milan, Aviano, Italy, and Switzerland-Vaud studies asked for the age at diabetes, coded as zero for no history of diabetes. Nine out of 12 studies had data on age or date at diagnosis, and this variable was used to estimate duration of diabetes (continuous). Only the Rome study collected information on whether subjects with a history of diabetes were diagnosed with type I or type II diabetes, or had used insulin or oral hypoglycemic agents.

Other relevant subject characteristics, including ethnicity, education, tumor site and histology, cigarette smoking, other tobacco habits, alcohol consumption, height, and weight were harmonized across studies, as described previously (21). Pack-years of cigarette smoking was calculated by multiplying packs (defined as 20 cigarettes) of cigarettes per day and number of years smoking. Alcohol consumption was standardized across studies by first converting beverage-specific number of drinks to ethanol volume in milliliters. The average daily number of ethanol-standardized drinks was then calculated as frequency of consumption of each alcoholic beverage type weighted by the corresponding duration, with the exception of the Tampa, Rome and Germany-Saarland studies in which the average of the frequency of all alcoholic beverage type was used (due to missing data for duration) (34).

Body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters). Height and weight at the reference date were self-reported. One study also collected data on height and weight 2–5 years prior to diagnosis, and three studies collected data on height and weight between ages 20–30 years. In a previous INHANCE study on the relationship between BMI and HNC, results were similar for analyses using BMI at these differing time periods (35). We thus used BMI at reference date in the analyses for simplicity and completeness.

A number of subjects were missing data on education level (13% of cases and 26% of controls) and BMI (10% of cases and 5% of controls). There were also a small amount of missing data for smoking (1.8% of cases and 1.6% of controls) and alcohol use (3.5% of cases and 2.0% of controls). We thus imputed data on these characteristics conditional upon covariates by using a 'MICE' procedure (multiple imputation by chained equations), developed for use in STATA as 'ICE' (36). This algorithm uses a sequence of regression equations to impute missing data conditional on other predictors, cycling through the equations until all variables have complete data. We used age, sex, race/ethnicity, study, case/control status, education level, BMI, smoking status, pack years of smoking, alcohol drinking status, and alcohol drinks per day (excluding the variable to be imputed) to impute the missing data.

Statistical Analyses

We estimated adjusted odds ratios (OR) and 95% CI using unconditional logistic regression models. We performed three levels of covariate adjustment: (1) a minimally adjusted model that controlled for age (categorical), sex, education level (categorical), race/ethnicity (categorical), and study center; (2) a model that adjusted for age, sex, education level, race/ethnicity, study center, pack-years of cigarette smoking (continuous), and alcohol drinks per day (continuous); and (3) a model controlling for all the previously listed covariates as well as BMI (continuous). We did not adjust for pipe or cigar smoking because of a substantial amount of missing data for these covariates. Based on previous research that suggested an association between diabetic status and oral cancer risk among women, but not among men (16), we calculated adjusted odds ratios for men and women separately in all primary analyses.

To determine whether a history of diabetes is a risk factor for HNC for those cases not associated with excess tobacco/alcohol, we stratified by cigarette smoking and alcohol drinking status. To statistically assess departures from multiplicative effects on the odds scale we included product terms in these stratified analyses, and used a log-likelihood ratio test to compare logistic models with and without the product terms.

To attempt to disentangle the effects of obesity and diabetes on HNC risk and to explore possible interactions, we also stratified by BMI using categories recommended by the World Health Organization (obese ≥ 30; overweight ≥ 25 and < 30; normal, ≥ 18.5 and < 25; and underweight, < 18.5). The previous INHANCE study on the relationship between BMI and HNC reported effect modification by tobacco alone and by tobacco/alcohol (35). We therefore stratified by BMI in analyses that additionally dichotomized subjects according to tobacco use (ever/never).

To determine whether duration of diabetes is associated with HNC risk, we estimated adjusted ORs for the following exposure categories: (1) no history of diabetes; (2) duration of diabetes less than 10 years; and (3) duration of diabetes greater than 10 years. Based on a previous study showing differential results according to age at diabetes diagnosis (20), we estimated adjusted ORs for the categories: (1) no history of diabetes; (2) diabetes diagnosis

before age 50; and (3) diabetes diagnosis after age 50. We additionally examined diabetes diagnosis before or after age 50 stratified by duration of diabetes.

To address possible selection bias due to control participants being systematically healthier than non-participants, we repeated the main analyses after dichotomizing the pooled studies according to participation proportions (<90% (five studies) vs, *≥90% (five studies)). These participation rate percentages were available for all studies, with the exception of the Germany-Saarland study.

We categorized cases by tumor site and performed polytomous logistic regression to assess how the association with diabetes varied across tumor sites. We derived study-specific and summary estimates and evaluated the extent of between-study heterogeneity using the Stata "Metan" command for random effects meta-analyses (37). Finally, we used the "Metainf" module (38) for "leave-one-out" influence analyses to determine whether the associations were dependent on any one study. We used Stata statistical software (version 10.0, Stata Corp.) for all analyses.

Results

Cases were more likely to be male, non-Hispanic White, cigarette smokers, alcohol drinkers, and to have lower BMI compared to controls (Table 1). Of the cases, 18.9% had cancer of the oral cavity, 26.3% had oropharyngeal cancer, and 33.1% had cancer of the larynx. The majority of cases (64.4%) were known to be squamous cell carcinomas, with a sizeable proportion of cases having unknown histologic type (32.5%).

Diabetes was not associated with HNC overall in models adjusted for age, race, sex, study center, education level, pack-years of cigarette smoking, and alcohol drinks per day (OR, 0.95; 95% CI, 0.83–1.08; Table 2) and was weakly associated in models that additionally adjusted for BMI (OR, 1.09; 95% CI, 0.95–1.24). Results for minimally adjusted models were similar to results obtained with adjustment for age, race, sex, study center, education level, pack-years of cigarette smoking, and alcohol drinks per day. ORs were slightly higher for women than for men (Table 2), but a comparison of models with and without a product term for sex and diabetes yielded p=0.09. Adjustment for BMI reported at age 20 to 30, versus BMI reported at the reference date, did not materially affect the estimates (results not shown).

The adjusted association between diabetes and HNC was stronger among never smokers (fully adjusted OR, 1.59; 95% CI, 1.22–2.07) than among ever smokers (fully adjusted OR, 0.96; 95% CI, 0.83–1.11; p=0.001 for homogeneity of the OR; Table 3). The pattern of results among never smokers and never alcohol drinkers versus ever smokers and drinkers was similar to those obtained by stratification on smoking status alone, but ORs were not as high in the never smoking-drinking category as those obtained in the never smoking category. There was an interaction by smoking status in comparisons of models that did and did not include a product interaction term for smoking and diabetes (likelihood ratio p=0.001), but not in models with and without an interaction term for alcohol and diabetes (p=0.36). In analyses that classified smoking status as never, former or current, the OR's were highest for never smokers (fully adjusted OR, 1.61; 95% CI, 1.24–2.10; Supplemental Table 1), lower for former smokers (fully adjusted OR, 1.14; 95% CI, 0.94–1.39) and lowest for current smokers (fully adjusted OR, 0.91; 95% CI, 0.73–1.12).

We observed little departure from multiplicativity of effects for diabetes and BMI (likelihood ratio p=0.25), and there was no discernable pattern in the results of analyses stratified by BMI, either overall or dichotomized by sex (results not shown). Among never smokers, there was a slight indication of an elevated risk of HNC associated with diabetes

among normal weight and overweight subjects (fully adjusted OR, 1.64; 95% CI, 0.92–2.93 and fully adjusted OR, 1.42, 95% CI, 0.86–2.33 respectively), but not underweight or obese subjects (fully adjusted OR, 1.13; 95% CI, 0.37–3.49 and fully adjusted OR, 1.12, 95% CI, 0.66–1.92 respectively).

There was no strong evidence of heterogeneity by tumor site in the association between diabetes and HNC (Supplemental Table 2). In sex-specific strata, results for women were close to unity for all sites except the hypopharynx; however, wide confidence intervals limit interpretation. There was some indication of heterogeneity by tumor site when analyses were stratified by smoking status (Supplemental Table 3). Among never smokers, ORs appeared to be greatest for oral cavity and larynx cancers, with null results for oropharyngeal cancers. However, small sample sizes within strata limited our ability to draw meaningful conclusions. In a fully-adjusted polytomous logistic regression model, we did not observe associations between history of diabetes and HNC risk across tumor sites.

Compared to subjects with no history of diabetes, those with diabetes for less than 10 years had a small elevated OR (fully adjusted OR, 1.15; 95% CI, 0.95–1.39; Supplemental Table 4), with similar results obtained for those with diabetes greater than 10 years (fully adjusted OR, 1.16; 95% CI, 0.90–1.49). Compared to non-diabetics, we observed an elevated association between HNC and diabetes diagnosed before age 50 (fully adjusted OR, 1.37; 95% CI, 1.07–1.74), and no association for those diagnosed after age 50 (fully adjusted OR, 1.00; 95% CI, 0.83–1.20). We observed the same pattern for men, but ORs for women diagnosed before and after age 50 were both similarly elevated. An analysis of diabetes diagnosis before or after age 50 stratified by duration of diabetes did not provide meaningful results due to small stratum specific numbers, and did not yield evidence of a particularly unique subgroup (results not shown).

Among the eleven studies with information on control participation proportions, the fully adjusted OR was 1.09 (95% CI, 0.96–1.24). The estimate from five studies with control participation rates below 90% (OR=1.11; 95% CI, 0.89–1.38) was similar to the estimate from six studies with control participation rates above 90% (OR=1.09; 95% CI, 0.92–1.29).

There was evidence of heterogeneity in a meta-analyses of the study-specific ORs (chi-squared p=0.002; Figure 1). “Leave-one-out” influence analyses indicated that the North Carolina study had a large impact on results, due to its unique inverse relationship between diabetes and HNC (Figure 2). The association between history of diabetes and HNC in fully adjusted models was greater when the North Carolina study was excluded (OR=1.19; 95% CI, 1.02–1.38). Similarly, the association among never smokers was appreciably increased after exclusion of the North Carolina study (OR=1.91; 95% CI, 1.39–2.62); with the association among ever smokers increasing slightly after exclusion, but remaining close to unity (OR=1.07; 95% CI, 0.90–1.26).

Discussion

In this large pooled analysis of 12 international studies, we observed a weak association between history of diabetes and risk of HNC overall. However, we observed a stronger association between history of diabetes and HNC in never smokers. In addition, we observed a positive association between diabetes diagnosed before age 50 and HNC.

An association between history of diabetes and HNC only in never smokers may exist if the diabetic condition affects an, as yet, unknown causal pathway for HNC among never smokers. Alternatively, a substantial proportion of people who are both heavy smokers and diabetic and who would have developed HNC in the future, may be at particular risk for early death or illness, and may have died before developing HNC. A third possibility is that

adjustment for pack years of smoking is not sufficient to remove all confounding among smokers, and that examining the association between a history of diabetes and HNC among never smokers circumvents this source of residual confounding. This possibility is supported by results from studies on the association between HNC and BMI, which is strongly associated with diabetes (39,40). A recent INHANCE pooled analysis observed an etiologically improbable reduced risk of HNC associated with overweight and obesity even after adjustment for duration and intensity of smoking (35). However, when analyses were confined to never smokers, the reduced risk associated with overweight and obesity was attenuated to the null.

We observed a positive association between HNC and diabetes diagnosed before age 50, and no association for those diagnosed after age 50. Only 5 cases and 9 controls were diagnosed with diabetes before age 20, making it unlikely that these results were due to the inclusion of type I diabetics. Cases diagnosed as diabetic before age 50 had a mean age of 55 at HNC diagnosis and a mean duration of diabetes of 15 years, while cases with a diabetes diagnosis over age 50 had a mean age of 64 at HNC diagnosis and a mean diabetes duration of 6 years. These data suggest that a younger age of type II diabetes onset may confer particular risk for subsequent development of HNC, and that these cancers may develop at a relatively young age. The difference according to age may partly be explained by the observation that younger HNC patients are less likely to have extensive histories of tobacco and alcohol use (41,42). The longer duration of exposure to the diabetic condition could also explain the increased risk for younger patients. In addition, it has been suggested that adults diagnosed with diabetes at a younger age may represent a more aggressive phenotype than people diagnosed late in life (43), and thus the diabetic condition in older people may not predispose to HNC to the same degree as in younger diabetics. The exclusion of several studies due to lack of diabetes diagnosis age data and the small numbers in each of the strata limit interpretation of these results.

Results from the majority of studies in these pooled analyses indicated a positive relationship between history of diabetes and HNC, with the notable exception of the North Carolina study, for which an inverse relationship was observed. Subjects from the North Carolina study made up 14% of the total pooled sample, resulting in a relatively heavy influence of this study on the overall results. A notable difference in the North Carolina study is the high prevalence of diabetes among controls (17%) (44) compared with controls from other US studies and other countries (mean prevalence of 6% in controls for all other studies). The North Carolina study population had a larger proportion of African Americans than other studies; however race is unlikely to play a role because cases and controls were frequency matched on race and estimates were adjusted for race.

Our results support previous research suggesting involvement of abnormal glucose metabolism in HNC. Suba et al. conducted a hospital-based case-control study in Hungary in 2,660 in-patients with confirmed OSCC and 2,980 “complaint-free” controls who volunteered to participate in oral cancer screenings during the same period, and observed that repeatedly elevated (>5.5 mmol/l) fasting glucose over a period of 4 days was strongly associated with oral cancer in females (OR, 1.61; no 95% CI reported; $p<0.05$), but that no such association existed in males (OR, 0.97; $p>0.05$) (16). Cases and controls were matched on age, but no adjustment was made for, or effect modification examined with, known OSCC risk factors. In a study on the risk of multiple cancers in a nationwide cohort of diabetics in Denmark, Wideroff et al. reported increased risk of mouth/pharynx cancer associated with diabetes (20). However, there were only 30 cases in those analyses. Additionally, the association was only observed in subjects less than 50 years old at diabetes diagnosis (standardized incidence ratios (SIR) based on age, sex and calendar year, 1.8; 95% CI, 1.2–2.6). The estimates were similar for males and females.

In a previous pooled INHANCE study, it was observed that HNC risk is elevated among lean people and reduced among overweight or obese people (35). If overweight and obesity are negatively associated with HNC, it could be argued that this makes a positive association between diabetes and HNC less likely since obesity is strongly associated with conditions such as metabolic syndrome, and an increased risk of developing insulin resistance, followed by glucose intolerance and type II diabetes (45,46). However, glucose intolerance can also occur independently of insulin resistance (46–48).

Diabetes is emerging as more of a heterogeneous disease than initially thought, with subtypes of people who are classified as type II diabetics, but who exhibit defects in insulin secretion with no evidence of insulin resistance. Examples include maturity-onset diabetes of the young (MODY) (49) and mitochondrial diabetes (50). There are also populations that have type II diabetes, especially in Asia, who are not overweight or obese by Western criteria. For example, in a study of type II diabetics in Taiwan, only 43% of women and 48% of men had a BMI greater than 25 kg/m^2 (51). These observations suggest that, although there is an association of overweight with diabetes, the diabetic condition is a distinct disease state that frequently also develops in people who are not overweight.

Hyperglycemia and associated biochemical consequences, independent of obesity-linked characteristics of diabetes, may be a mechanism by which diabetes increases the risk of cancer. Interestingly, several prospective cohort studies indicate that cancer risk starts to increase at blood glucose levels even below the diabetic range. Studies in Korea (52), Austria (53) and Sweden (54)found a linear increase in risk for multiple cancers across the entire spectrum of glucose values, regardless of weight.

A limitation of this study is that we were only able to examine self-reported diabetic status, which may have resulted in exposure misclassification. In the United States, it is estimated that one third of type II diabetics are undiagnosed (55). However, we have no reason to believe that this misclassification would differ between cases and controls; thus any error from this source is most likely to bias results toward the null. The heterogeneity of HNC may also hinder the ability to adequately examine whether diabetes is a risk factor. Weak or inconsistent associations with all HNC may result if the subtypes of HNC are etiologically distinct. Although we performed analyses for separate sites (larynx, hypopharynx, oropharynx, oral cavity, and non-specific pharynx), small sample sizes prevented meaningful interpretation of the results. The inability to control for HPV infection is a further limitation. However, cancers occurring in the oropharynx, as opposed to other HNC sites, are most strongly associated with HPV infection (27,56,57), and we are not aware of any studies that suggest that diabetics are more likely to be infected with HPV.

We did not have sufficient data to adjust for factors such as diabetic medication use or extent of glycemic control in this study. Many diabetics are able to maintain good glycemic control and/or lowered insulin levels by oral hypoglycemic agents, diet, appropriate use of exogenous insulin, etc. In addition, recent evidence suggests that some oral hypoglycemic agents used to treat diabetes, such as metformin, may reduce incidence of a wide variety of cancers (58). Researchers have observed an association of use of exogenous insulin with increased risk of cancer of the breast, colon, pancreas, prostate, or any solid tumor (59), and increased risk of death from any type of cancer (60). Among 710 subjects who reported a history of diabetes and who had data on insulin use in the present study, 33% were insulin users. Between the years 1997 to 2008 in the United States, the proportion of diabetics aged 65–74 using any diabetes medication (pills, insulin or both) ranged from 83.2% to 90.0% (61). Even if rates of medication use are not this high in our international pooled data, it is nonetheless likely that a large percentage of diabetics were taking oral hypoglycemic agents.

Thus, the diabetes effect in the absence of treatment might be stronger than the association observed in our study.

Selection bias may have influenced results in a positive or negative direction. Diabetics are more likely to have multiple hospitalizations than non-diabetics (62,63), creating a selection bias when controls are recruited in hospital-based studies. The possible influence of bias due to controls in hospital-based studies was difficult to evaluate because exclusion of the hospital-based studies increased the proportional influence of the North Carolina study on the results, attenuating the odds ratio toward the null. An alternative source of selection bias may occur if control participants are systematically healthier than control non-participants, thus spuriously raising the OR. However, this source of bias is unlikely because the pooled OR for studies with control participation rates less than 90% was almost identical to the OR for studies with control participation above 90%.

Conclusion

In this large pooled analysis of 12 case-control studies, we observed a weak association between diabetes and HNC in all subjects, adjusting for several potential confounders; however, we did find a modest association among never smokers. Prospective studies, with data that more accurately captures potential confounding relationships, may provide insight into a possible relationship between glucose metabolism abnormalities and HNC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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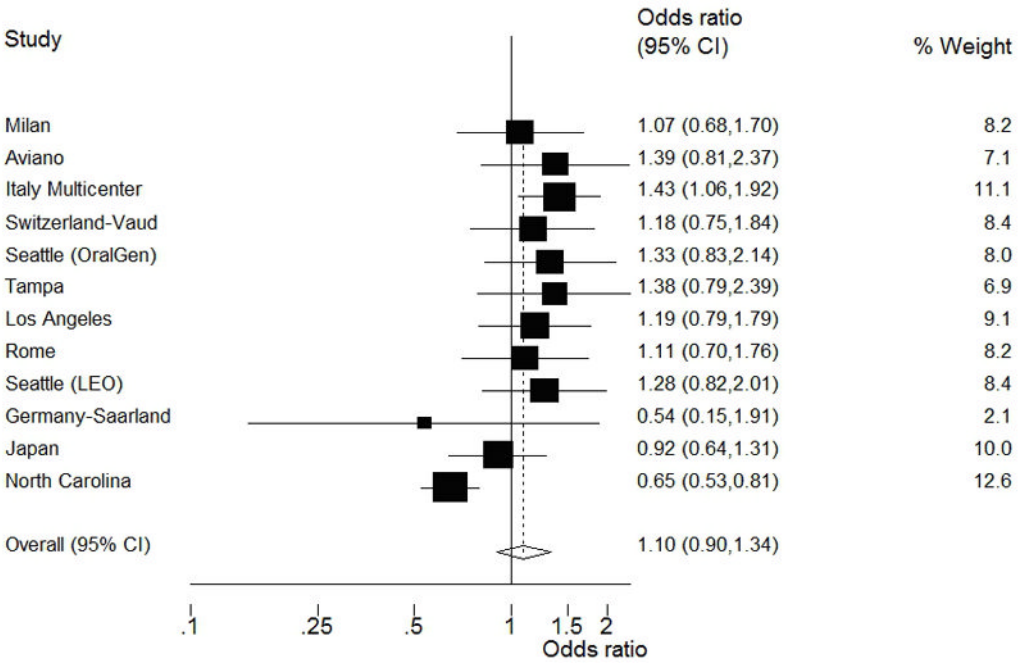

Figure 1. Forest plot of study-specific ORs and 95% CIs for the association between history of diabetes and HNC risk, INHANCE Pooled Case-Control Study of Head and Neck Cancer

The squares represent the OR estimates and the horizontal lines represent the 95% CIs for each study. The area of the square reflects the weight that the study contributes. This random-effects model incorporates an estimate of between-study heterogeneity in the weighting. The diamond at the center indicates the random-effects estimate and the width of the diamond indicates the 95% CI.

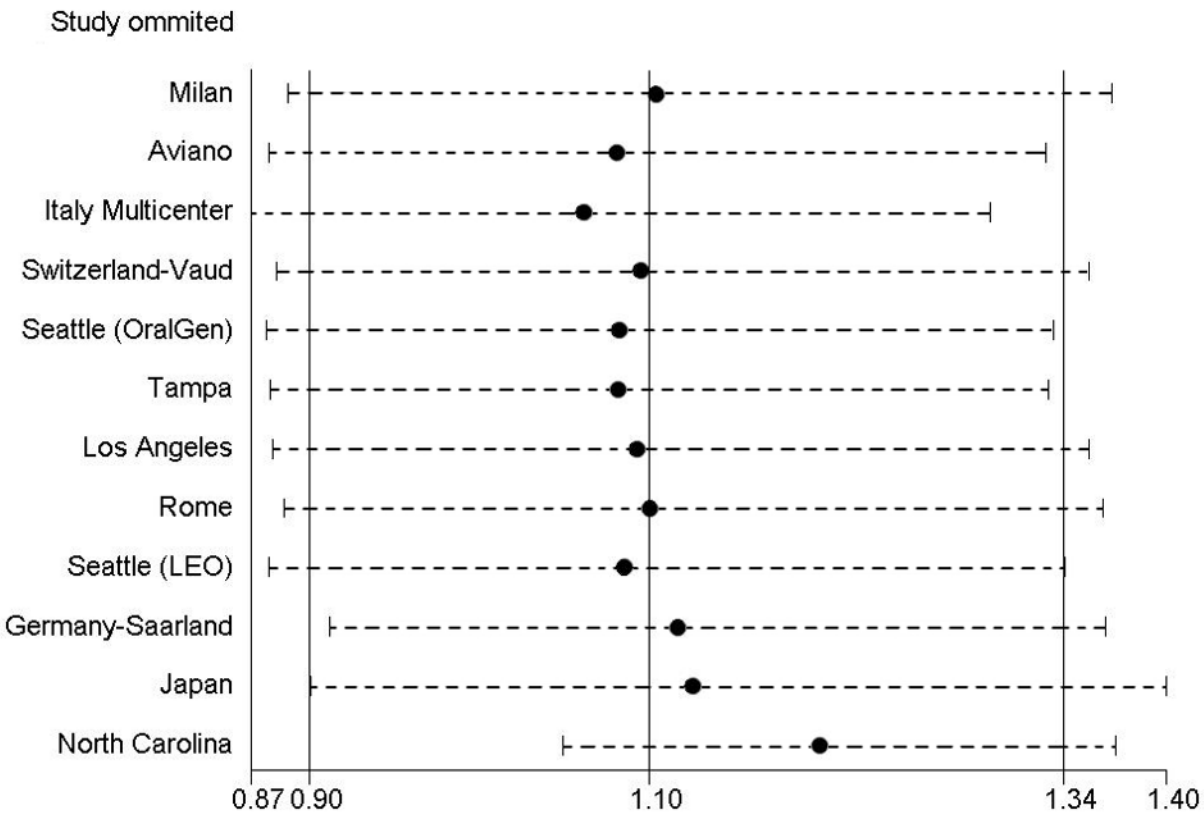

Figure 2. Influence analyses of single studies on the overall estimate for the association between history of diabetes and HNC risk, INHANCE Pooled Case-Control Study of Head and Neck Cancer

The circle for each study represents the OR estimate and the horizontal line represents the 95% CI from the pooled data after excluding that study. The three vertical lines represent the random-effects pooled point estimate and associated 95% CI.

Table 1

Characteristics of cases and controls with data on history of diabetes, INHANCE Pooled Case-Control Study of Head and Neck Cancer.[a]

Characteristic	Cases (n=6,448)		Controls (n=13,747)	
	N	%	n	%
Age (years)				
17–39	237	3.7	920	6.7
40–44	300	4.7	787	5.7
45–49	641	9.9	1235	9.0
50–54	1024	15.9	2089	15.2
55–59	1253	19.4	2408	17.5
60–64	1222	19.0	2314	16.8
65–69	953	14.8	1946	14.2
70–74	596	9.2	1464	10.7
75–93	222	3.4	584	4.3
Sex				
Men	5152	79.9	9810	71.4
Women	1296	20.1	3937	28.6
Race				
Non-Hispanic White	5417	84.0	9805	71.3
Black	445	6.9	479	3.5
Hispanic	82	1.3	255	1.9
Asian	471	7.3	3179	23.1
Other	33	0.5	29	0.2
Study center				
Milan	416	6.5	1531	11.1
Aviano	470	7.3	821	6.0
Italy Multicenter	1208	18.7	2545	18.5
Switzerland-Vaud	560	8.7	820	6.0
Seattle (OralGen)	381	5.9	607	4.4
Tampa	203	3.2	893	6.5
Los Angeles	414	6.4	1005	7.3
Rome	321	5.0	389	2.8

Characteristic	Cases (n=6,448)		Controls (n=13,747)	
	N	%	n	%
Seattle (LEO)	587	9.1	546	4.0
Germany-Saarland	92	1.4	92	0.7
Japan	433	6.7	3102	22.6
North Carolina	1363	21.1	1396	10.2
Study design				
Hospital-based	3611	56.0	10101	73.5
Population-based	2837	44.0	3646	26.5
Pack-years of cigarette smoking[b]				
Never	779	12.1	5429	39.5
1–10	351	5.4	1830	13.3
11–20	579	9.0	1560	11.4
21–30	888	13.8	1420	10.3
31–40	975	15.1	1212	8.8
41–50	873	13.5	835	6.1
>50	2003	31.1	1461	10.6
Number of alcohol drinks per day[b]				
Never	710	11.0	3352	24.4
>0 to <1	1077	16.7	3752	27.3
1 to <3	1260	19.5	3244	23.6
3 to <5	896	13.9	1645	12.0
≥5	2505	38.9	1754	12.8
Body mass index (in kg/m^2)				
<18.5	299	4.6	287	2.1
18.5 to <25	3233	50.1	6396	46.5
25 to <30	2109	32.7	5208	37.9
≥30	807	12.5	1856	13.5
Tumor site				
Oral cavity	1218	18.9		
Oropharynx	1693	26.3		
Hypopharynx	558	8.7		

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Characteristic	Cases (n=6,448)		Controls (n=13,747)	
	N	%	n	%
Oral cavity/pharynx NOS	838	13.0		
Larynx	2135	33.1		
Overlapping head and neck sites	6	0.1		
Tumor histology				
Squamous cell	4287	64.4		
Unknown	2161	32.5		

[a] Percentages have been rounded and may not total 100.

[b] Data from first imputed dataset (out of 4 imputations) used for missing data.

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Table 2

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between head and neck cancer and diabetes (yes/no), INHANCE Pooled Case-Control Study of Head and Neck Cancer

Diabetes (yes/no)	Cases exposed/unexposed	Controls exposed/unexposed	Covariate Set 1[a]		Covariate Set 2[b,c]	
	N	N	OR	(95% CI)	OR	(95% CI)
All	533/5915	1024/12723	0.95	(0.83–1.08)	1.09	(0.95–1.24)
Women	118/1178	249/3688	1.06	(0.82–1.38)	1.33	(1.02–1.73)
Men	415/4737	775/9035	0.91	(0.79–1.06)	1.03	(0.89–1.19)

[a] Adjusted for age, race, sex, study center, education level, pack-years of cigarette smoking, and alcohol drinks per day.

[b] Adjusted for age, race, sex, study center, education level, pack-years of cigarette smoking, alcohol drinks per day, and BMI.

[c] Likelihood ratio test for interaction by sex: p=0.09.

Table 3

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between head and neck cancer and diabetes (yes/no) by cigarette smoking and alcohol drinking status,[a] INHANCE Pooled Case-Control Study of Head and Neck Cancer

Diabetes (yes/no)	Cases exposed/unexposed	Controls exposed/unexposed	Covariate Set 1[b]		Covariate Set 2[c,d]	
	N	N	OR	(95% CI)	OR	(95% CI)
Never cigarette smokers						
All	82/694	366/5047	1.38	(1.06–1.79)	1.59	(1.22–2.07)
Women	39/309	164/2370	1.39	(1.02–1.89)	1.70	(1.25–2.32)
Men	43/385	202/2677	1.36	(1.00–1.84)	1.49	(1.10–2.03)
Ever cigarette smokers						
All	451/5221	658/7676	0.85	(0.73–0.98)	0.96	(0.83–1.11)
Women	79/869	85/1318	0.86	(0.64–1.16)	1.07	(0.79–1.45)
Men	372/4352	573/6358	0.84	(0.73–0.98)	0.94	(0.81–1.10)
Never cigarette smokers and never alcohol drinkers						
All	33/242	172/1827	1.04	(0.69–1.56)	1.26	(0.83–1.91)
Women	22/162	103/1157	1.00	(0.65–1.54)	1.26	(0.81–1.96)
Men	11/80	69/670	1.12	(0.68–1.83)	1.26	(0.76–2.06)
Ever cigarette smokers and ever alcohol drinkers						
All	398/4866	534/6516	0.84	(0.72–0.98)	0.98	(0.84–1.14)
Women	57/732	54/933	0.76	(0.52–1.12)	0.98	(0.66–1.45)
Men	341/4134	480/5583	0.85	(0.73–1.00)	0.98	(0.83–1.15)

[a] Numbers of never smokers/drinkers do not match numbers for zero pack years/drinks per day because missing data for these variables were simultaneously imputed.

[b] Adjusted for age, race, sex, study centers, education level, pack-years of cigarette smoking (if ever smoker), and alcohol drinks per day (if ever drinker).

[c] Adjusted for age, race, sex, study centers, education level, pack-years of cigarette smoking (if ever smoker), alcohol drinks per day (if ever drinker), and BMI.

[d] Likelihood ratio test for interaction by smoking status: p=0.001; and by alcohol drinking status: p=0.36.