Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries

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Abstract

Low socioeconomic status has been reported to be associated with head and neck cancer risk. However, previous studies have been too small to examine the associations by cancer subsite, age, sex, global region, and calendar time, and to explain the association in terms of behavioural risk factors. Individual participant data of 23,964 cases with head and neck cancer and 31,954 controls from 31 studies in 27 countries pooled with random effects models. Overall, low education was associated with an increased risk of head and neck cancer (OR = 2·50; 95%CI 2·02– 3·09). Overall one-third of the increased risk was not explained by differences in the distribution of cigarette smoking and alcohol behaviours; and it remained elevated among never users of tobacco and non-drinkers (OR = 1·61; 95%CI 1·13 – 2·31). More of the estimated education effect was not explained by cigarette smoking and alcohol behaviours: in women than in men, in older than younger groups, in the oropharynx than in other sites, in South/Central America than in Europe/North America, and was strongest in countries with greater income inequality. Similar findings were observed for the estimated effect of low vs high household income. The lowest levels of income and educational attainment were associated with more than 2-fold increased risk of head and neck cancer, which is not entirely explained by differences in the distributions of behavioural risk factors for these cancers, and which varies across cancer sites, sexes, countries, and country income inequality levels.

Key words: head and neck cancer, socioeconomic inequalities, epidemiology,

Introduction

One hundred years ago, Charles Singer (1911), a London clinician, in a series of over 500 oral and pharyngeal cancer cases identified a preponderance of the disease among men and among low socioeconomic groups; in addition he hypothesised an association with alcohol and an infection (syphilis).[1]

Today, head and neck cancer – comprising tumours of the mucosal lining of the oral cavity, pharynx, and larynx – is amongst the most common in the world, with an estimated annual burden of over 550,000 new cases and 300,000 deaths,[2] and with wide variations in trends reported across the world by sex, age, and subsite.[3] Increasing incidence of oral and/or oropharyngeal subsites has been observed in Denmark[3], Netherlands[4], Sweden[5], the UK[6-8], USA,[9,10] parts of South/Central America[3], and Japan[3] – these increases being mainly among men[3], and sometimes among lower socioeconomic groups.[3,8] Moreover, head and neck cancer has generally poor survival and impacts heavily on quality of life – such as: eating, speech, and physical appearance.[11]

While smoking and alcohol behaviours have long been recognised as the major risk factors for head and neck cancer[15], and more recently the role of genetic variants[16] and human papillomavirus (HPV) infection[17] have been identified, the burden and aetiology of head and neck cancer associated with socioeconomic factors are yet to be fully understood. Head and neck cancer risk has been strongly associated with lower socioeconomic status (SES) especially among men.[18] The relative contributions of alcohol and tobacco consumption to the association of SES and head and neck cancer has varied considerably, with estimates of the unexplained or "direct" effect of low SES ranging from 10-50%.[9-21] These estimates have been from studies combining all head and neck sites, usually limited to men, and with small sample sizes leading to imprecise estimates of the true burden of exposure unable to explain the association in terms of behavioural risk factors. In addition, while country income inequality has consistently been associated with numerous negative health outcomes[22-25] to our knowledge no one has tested the hypothesis that the greater the country's income inequality the greater the head and neck cancer risks associated with low relative educational attainment.

We aim to assess the risk for head and neck cancer associated with low educational attainment and household income by age, sex, head and neck cancer subsite, and geographic location and to stratify the geographical location by the macroeconomic measure of income inequality.

Material and Methods

The INternational Head And Neck Cancer (INHANCE) consortium is a global data pooling initiative for epidemiology studies of head and neck cancer. Study inclusion and methodological details including individual study design, control sources, participation proportions, and case definition have been previously described[26,27] (Supplementary Table 1). All studies frequency matched controls to cases minimally on age and sex, and additional factors in some studies (Table 1).

At the time of this investigation, 35 studies (25,910 cases and 37,111 controls) were in the INHANCE pooled database (version 1.5). Data from 31 studies were included in the analysis because the France (1987–1992), Rome, Japan (1988–2000), and Japan (2001–2005) studies did not collect SES data. Case subjects had histologically confirmed diagnoses of cancers of the oral cavity, oropharynx, hypopharynx, oral cavity, oropharynx not otherwise specified, and larynx (ICD codes – see Supplementary Methods). We excluded lymphomas, sarcomas, and cancers of the nasopharynx and salivary glands.

Education data were standardised using the International Standard Classification of Education (ISCED 97)[28]; and grouped into 3 strata: (i) low education level, which included no education, or completed the first stage of basic education, or at most primary education (ISCED 0–1); (ii) intermediate education level, which included lower secondary or second stage of basic education or completed upper secondary education (ISCED 2–4); and (iii) high education level, which comprised further education including vocational education and higher education including university degree (ISCED 5–6). Household income data were standardised as far as possible (given the original study questionnaire categorization) by grouping comparable levels based on the strata used in the original study questionnaires (Supplementary Table 2), with category 1 being the lowest and category 5 the highest income levels.

We estimated study-specific odds ratios (OR) and 95% confidence intervals (CI) for the association of education and income for head and neck cancer, using unconditional logistic regression. For details on covariate inclusion and modelling strategy see Supplementary Methods. We then estimated the summary effect estimates using a meta-analysis approach: by pooling study-specific risk estimates with random effects models.[29] For additional details on meta-analytic approaches and evaluation of heterogeneity see Supplementary Methods. We conducted a detailed series of subgroup analyses by smoking status; drinking status; cancer subsite; geographic region, age-group, country income inequality, control type and year of study conduct (Supplementary Methods). We also conducted a sensitivity analysis using a complete observation only dataset where no missing data existed across any variable in all studies in order to determine the potential biased effects of sample size reduction resulting from including additional covariates.

We estimated the proportion of the socioeconomic effect which remained after adjustment for behavioural risk factors by calculating the percentage change in OR as (OR1 – OR2) / (OR1 – 1), where OR1 is the minimally adjusted model and OR2 is the model adjusted for behavioural risk factors referred to as attributable fraction for covariates.[30] We then calculated the attributable fraction remaining/not explained by covariates by subtracting this from 100%. Statistical analyses were conducted using SAS v 9.2, and STATA v 10.

Results

The characteristics of included studies are presented in Table 1. There were 31 individual case-control studies that included 23,964 head and neck cancer subjects and 31,954 control subjects. The characteristics of the study subjects are detailed in Table 2. The distribution of selected behavioural factors by educational attainment in study subjects generally shows that smoking, alcohol consumption, and diets low in fruit and vegetables are greater in those with lower education (Supplementary Table 3).

Low relative to high educational attainment was associated with an increased risk of head and neck cancer (OR 2·50; 95%CI 2·02–3·09), with those in the intermediate level of educational attainment having an intermediate increased risk (OR 1·80; 95%CI 1·57–2·07) (Table 3). These associations were increasingly attenuated when models sequentially adjusted for lifestyle behaviours (Table 3); such that the proportion of the increased risk estimate associated with low educational attainment not explained by smoking alone was 58%; by smoking and alcohol combined was 31%; by smoking, alcohol, and diet was 29%, and by smoking, alcohol, diet, and other tobacco use was 23% (% computed from Table 3). The model adjusting for smoking and alcohol (Table 3 model 3) was adjusted further by including the cross-product terms involving alcohol and smoking to account for interaction on a multiplicative scale, however no further attenuation was observed (data not shown). Among those who never smoked, never used other tobacco, and never drank alcohol lower educational attainment remained associated with more than 50% increased risk (OR 1·61; 95%CI 1·13–2·31). Low relative to high household income was associated with a similar increased risk of head and neck cancer (OR 2·44; 95%CI 1·62–3·67), and 39% of this risk was not explained when adjusting for smoking and alcohol (Table 3).

Using our complete observation only dataset analysis, we observed very similar effects where low relative to high educational attainment was associated with an increased risk of head and neck cancer (OR 2·12; 95%CI 1·59–2·84), with those in the intermediate level of educational attainment conferring an intermediate increased risk (OR 1·69; 95%CI 1·35–2·11) (Supplementary Table 4)..

Figure 1 shows a forest plot of the study-specific risk estimates for low relative to high educational attainment (OR 1·86; 95%CI 1·54–2·25) and low relative to high household income (OR 1·82; 95%CI 1·57–2·11) in the models adjusting for age, sex, centre, smoking and alcohol behaviours. These results vary slightly from Table 3 due to using the data from the lowest and highest strata available (rather than limited to the absolute low and high categories used throughout). Studies that contributed to the heterogeneity of the overall pooled estimates were investigated using Galbraith radial plots (Supplementary Figures 1&2). Studies were removed in an iterative process until no further significant heterogeneity was observed. The examination of heterogeneity observed in the overall analysis of both education and income investigated no single factor was identified as the main cause of heterogeneity (results not shown).

After adjustment for smoking and alcohol behaviours the risk associated with low education was greatest among those from higher income inequality countries OR 1·65 (95%CI 1·27–2·15), although there was not a clear pattern across the other levels of country income inequality (Table 4). There was a tendency for more of the effect associated with low education to be left unexplained by smoking and alcohol in middle- and higher-income inequality countries.

Significant variation was observed in the risks associated with low relative to high education for the head and neck cancer subsites ($p<0·05$). The association was stronger for hypopharyngeal and laryngeal cancers than for oral cavity and oropharyngeal cancer. After adjustment for smoking and alcohol behaviours there were no significant differences, however, there was a tendency for more (around two thirds) of the risk associated with low education to remain unexplained by smoking and alcohol for oropharyngeal cancer compared to (around one-third for) all other head and neck cancer sites (Table 4).

The risk of head and neck cancer tended to be more strongly associated with lower educational attainment in North American studies and South / Central American studies with European studies. There was full attenuation of this risk association by adjustment for smoking and alcohol behaviours in European studies. By contrast, in the North American and South / Central American studies adjustment for smoking and alcohol left substantial socioeconomic risk unexplained by smoking and alcohol (Table 4).

The risk associated with low relative to high educational attainment was lower for oral cavity in studies from Europe compared with those in North America and South / Central America, but stronger for larynx cancer in North America compared to other regions (Supplementary Table 5). The proportion of the risk left unexplained by smoking and alcohol behaviours by subsite and region was highly variable.

The risk associated with lower educational attainment varied across global regions by sex and age subgroups (SupplementaryTable 6). We observed that it was only in the European studies where the elevated risk associated with lower educational attainment was found only among men and not in women. However, after adjustment for smoking and alcohol behaviours these differences do not remain significant as the elevated risk associations among women in both North and South/Central America were attenuated.

Discussion

Our results from this large pooled analysis indicate that low socioeconomic status is a strong risk factor for head and neck cancer. We found that variation in the influence of socioeconomic status on the risk of head and neck cancer exists across the world, and that there is increased risk associated with both lower income levels and lower educational attainment with the strongest effect remaining among those from higher income inequality countries. We also showed that these findings are not confined to men, nor to older people, and they are not entirely explained by the traditional recognised lifestyle behavioural risk factors of smoking and alcohol, nor by diet or other tobacco use, although residual confounding could not be ruled out.

The lowest levels of income and educational attainment are associated with a more than 2-fold increased risk of head and neck cancer, which remain elevated, although strongly attenuated after adjusting for smoking, other tobacco, alcohol, and diet risk factors. Adjustment for these behaviours reduced the increased risk associated with low educational attainment by around two-thirds, leaving a potentially unexplained risk, suggesting that low socioeconomic status confers risk that operates through pathways other than through these risk behaviours. This finding was further supported by the strong association with low educational attainment remaining in the analysis restricted to those who were never smokers, never tobacco users, and never drank alcohol, and by no studies showing the converse significant association of increased risk associated with higher educational attainment.

Differences in the smoking epidemic by region, sex, and socioeconomic status may help explain the global differences we observed. North[34] and South[35] American smoking prevalence declined in the late 20th Century, but those with lower educational attainment, regardless of gender or ethnicity, had a higher prevalence of smoking over time and smoked longer.[36,37] Prevalence among men remains greater than among women, but there has also been a more rapid and greater decline in smoking prevalence for men than women irrespective of educational attainment.[34,38] Our findings of a sustained effect associated with low education after adjusting for smoking and alcohol in North and South/Central America compared with Europe is consistent with earlier INHANCE analyses, which found the risk of head and neck cancer associated with smoking and alcohol was lower in North America.[26,39] These differences were considered to be potentially due to variation in the tobacco carcinogen content of cigarettes (which have also changed over time)[40] or could be due to other aspects of smoking behaviour such as the depth of inhalation, or interaction with alcohol. Alcohol consumption on its own has been shown to exert a weak risk association for head and neck cancer, however, in combination with smoking the risk is synergistically elevated[39,41], although we did not observe magnified attenuation when we included adjustment for the interaction between cigarette smoking and alcohol. Hashibe et al (2009) reported a significant lower population attributable risk associated with tobacco and alcohol in North America relative to Europe or South / Central America, which was perhaps due to the lower proportion of cases who both smoked and drank alcohol in North America.[39] These geographical differences suggest that other risk factors varying across populations may be more important in relation to explaining the socioeconomic associations with head and neck cancer risk. The role of sexual history and HPV are beginning to emerge as a potentially more important risk factor in North America[17] compared to Europe[42-44] or South America[43] – particularly for oropharyngeal cancer. However, this is unlikely to explain these differences as sexual history and HPV do not seem be associated with low educational attainment.[17]

Our findings that the risk associated with lower educational attainment was stronger for hypopharyngeal and laryngeal cancers than for oral cavity and oropharyngeal cancers and that adjustment by smoking *and* alcohol attenuated substantially less for oropharyngeal cancer is consistent with the evidence related to the risk associated with smoking which shows a similar pattern.[45] Here, oropharyngeal cancer is the site least associated with socioeconomic differences, and the site for which socioeconomic differences are least explained by smoking and alcohol behaviours, which is also consistent with earlier findings that oropharyngeal cancer is strongly associated with HPV and risk factors for HPV-positive oropharyngeal cancers seem to differ from those of other head and neck cancers.[17]

The causal mechanisms between low educational attainment or income and disease are via behavioural lifestyle factors[46] and / or through psychosocial, material and life-course pathways.[47] We have observed both an attenuation of the risk associated with low education in relation to head and neck cancer by behavioural factors, and also an as yet unexplained "direct" risk. Causal inference of low educational attainment is considered problematic on two counts –

firstly by the potential for reverse causation (i.e. low educational attainment itself is caused by underlying childhood health that could also be involved in the aetiology of the disease – although in terms of head and neck cancer this seem unlikely), and secondly by unobserved third variables such as IQ or time preference (whether one places emphasis on their present or future wellbeing), rather than educational attainment *per se*.[24]

Our findings should be interpreted in light of several limitations inherent in pooled individual participant data analyses. Our first major concern was the heterogeneity across studies especially given the high number of studies from across the world. Much work has been done by INHANCE to ensure standardisation of case-definition and smoking and alcohol variables within the dataset. Here we endeavoured to standardise education levels using the UNESCO ISCED, which is a recognised instrument for cross-country education analysis[48,49]; and to standardise household income categories into US dollars in absolute terms as reported. Changes in the education systems (albeit unlikely in the relatively short time-frame covered by included studies) and in the absolute value of income over time are nevertheless potential limitations of the data. Heterogeneity was detected in the vast majority of associations and was mitigated as far as possible with random-effects logistic regression models. There were also limitations in the interpretation of our mediation analyses; we assumed no interaction between SES and behavioural factors in the risk of developing head and neck cancer and we assumed there were no unmeasured confounders of the association between behaviours and cancer risk. Therefore, we computed the proportion of the SES effect *not* attributable to behavioural factors.

Our approach, adjusting for several metrics of smoking, tobacco, and alcohol behaviour variables and also including analysis in never smokers, other tobacco users, or alcohol drinkers, attempted to limit the effects of potential residual confounding associated with these behaviours. However, we have to acknowledge the risk of residual confounding remains. Inconsistent results have been reported in the literature with regard to the relationship of between SES and reported smoking behaviours – with higher rates of under-reporting of smoking among men and women with lower education attainment in the United States[50], but no such differences reported in European studies.[51] This could explain some of the differences in attenuation of the head and neck risk associated with education by behaviours we observed between regions. Furthermore, we were also unable to adjust for other potential risk factors, which could explain the association with low educational attainment such as HPV infection or working conditions and/or occupational exposures – the latter previously identified as a potential explanatory factor for socioeconomic inequalities in head and neck[21] and for lung cancer.[52]

We did not identify any substantial differences in results between sources of control subjects which reassures against the risk of selection bias, particularly associated with hospital source controls. Moreover, there was some variability in control matching factors across studies (Table 1). A number of studies matched on neighbourhood, residence, and ethnicity – all which could potentially overmatch on socioeconomic factors and could have led to an underestimate of the SES effect observed. A final limitation of our study was the lack of data from Asia – particularly South East Asia where incidence of head and neck cancer is high.[2] Moreover, we investigated potential publication bias via visual examination of a Funnel plot, which indicated no significant publication bias (Supplementary Figure 3).
In conclusion we found that a third of the risk for head and neck cancer associated with low education was not explained by the major behavioural risk factors, which chimes with previous estimates that 70% of head and neck cancers are "avoidable" by lifestyle changes – particularly smoking and alcohol behaviours.[39,41] Therefore, lifestyle factors need to be considered in their socioeconomic context – both with regard to understanding the disease aetiology, but also in relation to prevention.

The consistent risk associated with low education for head and neck cancer is a cause for concern. The differences in head and neck cancer subsite, age, sex and region – provide some potential direction for future aetiological research to better understand the causes of this disease. The association of low education with head and neck cancer risk even after thorough adjustment for known behavioural risk factors indicates the potential role of yet unidentified risk factors and pathways that are associated with socioeconomic status.

This knowledge could also begin to more explicitly underpin the development of more tailored preventive approaches for head and neck cancer, including risk profiling with SES as developed for other conditions such as cardiovascular disease[53], but thus far largely ignored in relation to head and neck cancer.[54]

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Results

Table 1 Characteristics of individual studies of the INHANCE consortium pooled analysis

Location	INHANCE ID	Region	Period	Sources of controls	Participation rate (%) Cases / Controls	E	I	Cancer (n) Oral cavity	Oropharynx	NOS	Hypopharynx	Larynx	Missing	(n)	(n)
France *	**Paris (1989-1991)**	Europe	1989-1991	H	80 / 86	X		.	.	.	206	322	0	305	528
France *	**Paris (2001-2007)**	Europe	2001-2007	P	82.5 / 80.6	X		468	692	155	413	509	0	3555	2237
Italy (Aviano)	**Aviano**	Europe	1987-1992	H	>95 / 95	X		85	148	33	70	146	0	855	482
Italy multicenter *	**Italy multicenter**	Europe	1990-2005	H	>95 / >95	X		209	359	90	143	460	0	2716	1261
Italy (Milan)	**Milan (1984-1989)**	Europe	1984-1989	H	95 / 95	X		48	34	65	27	242	0	1531	416
Italy (Milan)	**Milan (2006-2009)**	Europe	2006-2009	H	>95 / >95	X		85	21	18	17	229	0	755	370
Switzerland (Lausanne)	**Switzerland**	Europe	1996-1999	H	>95 / >95	X		138	151	7	96	124	0	883	516
Germany (Heidelberg)	**Germany-Heidelberg**	Europe	1998-2000	P	96 / 62	X		.	.	.	.	246	6	769	252
Central Europe *	**Central Europe**	Europe	1998-2003	H	96 / 97	X		196	98	32	52	384	0	907	762
Western Europe *	**Western Europe**	Europe	2000-2005	H & P	82 / 68	X		482	439	106	154	539	8	1993	1728
Germany (Saarland)	**Germany-Saarland**	Europe	2001-2003	P	94 / not known	X		15	30	9	13	27	0	94	94
US Multicentre *	**USmulticenter**	North America	1983-1984	P	75 / 76	X		386	389	218	121	.	0	1268	1114
USA (New York) *	**New York Multicenter**	North America	1981-1990	H	91 / 97	X		536	502	64	62	286	0	1610	1450
USA (Seattle)	**Seattle (1985-1995)**	North America	1985-1995	P	54&63 / 63&61†	X		224	174	14	.	.	0	615	412
USA (Iowa)	**Iowa**	North America	1993-2006	H	87 / 92	X	X	254	150	38	11	95	8	760	556
USA (North Carolina)	**Norh Carolina (1994-**	North America	1994-1997	H	88 / 86	X		42	44	25	17	52	0	202	180
USA (Baltimore)	**Baltimore**	North America	2000-2005	H	100 / 100	X	X	46	108	.	6	49	0	200	209
USA (Tampa)	**Tampa**	North America	1994-2003	H	98 / 90	X		22	57	65	1	63	5	899	213
USA (Boston)	**Boston**	North America	1999-2003	P	89 / 49	X	X	139	247	43	44	111	1	659	585
USA (Houston)	**Houston**	North America	2001-2006	H	95 / >80	X	X	238	387	10	38	154	2	866	829
USA (Buffalo)	**Buffalo**	North America	1982-1998	H	50 / 50	X	X	218	141	36	46	191	0	1254	632
USA (Baltimore)	**HOTSPOT**	North America	2009-2012	H	>85 / >80	X	X	.	71	.	.	.	0	71	71
USA (North Carolina)	**North Carolina (2002-**	North America	2002-2006	P	82 / 61	X	X	194	372	251	70	481	0	1396	1368
USA (Los Angeles)	**Los Angeles**	North America	1999-2004	P	49 / 68	X	X	53	156	112	17	90	0	1040	428
USA (Seattle)	**Seattle-Leo**	North America	1983-1987	P	81 / 75	X		183	151	47	61	209	6	547	657
USA (New York)	**MSKCC**	North America	1992-1994	H	>95 / >95	X	X	72	13	2	11	42	25	171	165
Puerto Rico	**Puerto Rico**	South/Central America	1992-1995	P	71 / 83	X	X	94	143	57	57	.	0	521	351
Latin America *	**Latin America**	South/Central America	2000-2003	H	95 / 86	X		459	395	240	180	860	66	1706	2200
Brazil (Sao Paulo)	**SaoPaulo**	South/Central America	2002-2007	H	>95 / >95	X		769	326	64	180	574	9	1670	1922
International *	**Intl Multicenter**	Global	1992-1997	H	89 / 87	X		828	347	135	.	.	262	1732	1572
China (Beijing)	**Beijing**	Asia	1988-1989	H	100 / 100	X		404	.	.	.	.	0	404	404
TOTAL	Total							6887	6145	1936	2113	6485	398	31954	23964

E - education data; I - household income data; X - data present; H - hospital-based controls; P - population-based controls; OC/OP NOS - oral cavity and / or oropharynx not specified

*** - multicenter study**

† - 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

‡ - All studies frequency matched controls to cases minimally on age and sex. Additional frequency matching factors included: center/city/region (France 2001-2007, Central Europe, Latin America, Sao Paulo, Western Europe, International Multicenter), Hospital (France 1989-1991, New York Multicenter, Sao Paulo), Neighbourhood (Los Angeles, Boston), ethnicity (Central Europe, Tampa, Houston, Latin America, US Multicenter, Western Europe, North Carolina (2002-2006), HOTSPOT), Residence (Germany Saarland), HPV status (Baltimore)

Table 2a **Distribution of INHANCE Consortium head and neck cancer cases and control-subjects by selected demographic, behavioural, study design characteristics, and tumour subsite by sex**

		Sex								All			
		Women				Men				Overall			
		Controls		Cases		Controls		Cases		Controls		Cases	
Variable		(n=9210)		(n=5070)		(n=22744)		(n=18894)		(n=31954)		(n=23964)	
		n	%	n	%	n	%	n	%	n	%	n	%
Age (years)	< 50	2265	24.59	964	19.01	4939	21.72	3566	18.87	7204	22.54	4530	18.9
	50 +	6945	75.41	4106	80.99	17805	78.28	15328	81.13	24750	77.46	19434	81.1
Global region	Europe	4072	44.21	1601	31.58	12242	53.83	8354	44.22	16314	51.05	9955	41.54
	North America	3479	37.77	2295	45.27	6927	30.46	6011	31.81	10406	32.57	8306	34.66
	South/Central America	1142	12.4	706	13.93	2955	12.99	3911	20.7	4097	12.82	4617	19.27
	Other	517	5.61	468	9.23	620	2.73	618	3.27	1137	3.56	1086	4.53
Country income inequality	Lower <6	758	8.23	518	10.22	2155	9.48	2087	11.05	2913	9.12	2605	10.87
(ratio income share	Mid 6-8	2031	22.05	643	12.68	5632	24.76	3323	17.59	7663	23.98	3966	16.55
richest 20% : poorest 20%)	Higher >8	4532	49.21	2955	58.28	9559	42.03	9718	51.43	14091	44.1	12673	52.88
	missing	1889	20.51	954	18.82	5398	23.73	3766	19.93	7287	22.8	4720	19.7
Education (ISCED)	Low (0 - 1)	3183	34.56	1718	33.89	7118	31.3	7517	39.79	10301	32.24	9235	38.54
	Intermediate (2 - 4)	2899	31.48	1862	36.73	7340	32.27	6508	34.44	10239	32.04	8370	34.93
	High (5 - 6)	2993	32.5	1349	26.61	7934	34.88	4201	22.23	10927	34.2	5550	23.16
	missing	135	1.47	141	2.78	352	1.55	668	3.54	487	1.52	809	3.38
Annual household income	1 (<$15,000)	557	6.05	443	8.74	1011	4.45	1113	5.89	1568	4.91	1556	6.49
(US $)	2 ($15,000 - <$30,000)	252	2.74	161	3.18	577	2.54	429	2.27	829	2.59	590	2.46
	3 ($30,000 - $45,000)	237	2.57	133	2.62	616	2.71	388	2.05	853	2.67	521	2.17
	4 ($45,000 - <$60,000)	193	2.1	111	2.19	425	1.87	325	1.72	618	1.93	436	1.82
	5 ($60,000 +)	481	5.22	247	4.87	1496	6.58	1047	5.54	1977	6.19	1294	5.4
	missing	7490	81.32	3975	78.4	18619	81.86	15592	82.52	26109	81.71	19567	81.65
Study design	Hospital-based	6295	68.35	3311	65.31	14800	65.07	12847	68	21095	66.02	16158	67.43
	Population-based	2915	31.62	1759	34.69	7944	34.92	6047	31.99	10859	33.97	7806	32.56
Time of study recruitment	Pre-2000 studies	4712	51.16	2466	48.64	11066	48.65	7874	41.67	15778	49.38	10340	43.15
	2000-onward studies	4498	48.81	2604	51.36	11678	51.34	11020	58.31	16176	50.61	13624	56.84
Subsite of tumour	Oral cavity			2122	41.85			4765	25.22			6887	28.74
	Oropharynx			1237	24.4			4908	25.98			6145	25.64
	OC/OP NOS			240	4.73			1873	9.91			2113	8.82
	Hypophayrnx			535	10.55			1401	7.42			1936	8.08
	Larynx			843	16.63			5642	29.86			6485	27.06
	Mixed			75	1.48			256	1.35			331	1.38
	Missing			18	0.36			49	0.26			67	0.28

Table 2b **Distribution of INHANCE Consortium head and neck cancer cases and control-subjects by Smoking, alcohol, and dietary variables by sex**

		Sex								All			
		Women				Men				Overall			
		Controls		Cases		Controls		Cases		Controls		Cases	
Variable		(n=9210)		(n=5070)		(n=22744)		(n=18894)		(n=31954)		(n=23964)	
		n	%	n	%	n	%	n	%	n	%	n	%
Smoking (pack-years)	0 <=10	1223	13.28	410	8.09	3162	13.9	1044	5.53	4385	13.72	1454	6.07
	10-<=20	758	8.23	435	8.58	2923	12.85	1453	7.69	3681	11.52	1888	7.88
	20-<=30	508	5.52	496	9.78	2562	11.26	2271	12.02	3070	9.61	2767	11.55
	30-<=40	386	4.19	534	10.53	2205	9.69	2867	15.17	2591	8.11	3401	14.19
	40-<=50	252	2.74	488	9.63	1551	6.82	2534	13.41	1803	5.64	3022	12.61
	> 50	385	4.18	1008	19.88	2882	12.67	6086	32.21	3267	10.22	7094	29.6
	missing	60	0.65	57	1.12	533	2.34	822	4.35	593	1.86	879	3.67
Other Tobacco status	Never	4669	50.69	1058	20.87	5222	22.96	953	5.04	9891	30.95	2011	8.39
	Ever	1544	16.76	685	13.51	7849	34.51	4409	23.34	9393	29.4	5094	21.26
	Current	1589	17.25	2491	49.13	6650	29.24	10787	57.09	8239	25.78	13278	55.41
	missing	1408	15.29	836	16.49	3023	13.29	2745	14.53	4431	13.87	3581	14.94
Alcohol drinking status	Never	4074	44.23	1765	34.81	3457	15.2	1399	7.4	7531	23.57	3164	13.2
	Ever	5081	55.17	3256	64.22	19211	84.47	17362	91.89	24292	76.02	20618	86.04
	missing	55	0.6	49	0.97	76	0.33	133	0.7	131	0.41	182	0.76
Alcohol (drinks / day)	Never	4082	44.32	1767	34.85	3476	15.28	1404	7.43	7558	23.65	3171	13.23
	0 to < 1	3293	35.75	1527	30.12	6899	30.33	2907	15.39	10192	31.9	4434	18.5
	1 to < 3	1196	12.99	797	15.72	5772	25.38	3856	20.41	6968	21.81	4653	19.42
	3 to < 5	200	2.17	323	6.37	2642	11.62	2716	14.37	2842	8.89	3039	12.68
	5 to	109	1.18	427	8.42	3293	14.48	7119	37.68	3402	10.65	7546	31.49
	missing	330	3.58	229	4.52	662	2.91	892	4.72	992	3.1	1121	4.68
Fruit consumption	< 1	1368	14.85	1203	23.73	3974	17.47	4762	25.2	5342	16.72	5965	24.89
(pieces / week)	1 to 3	1454	15.79	741	14.62	3817	16.78	2803	14.84	5271	16.5	3544	14.79
	3 to 7	1883	20.45	745	14.69	4158	18.28	2380	12.6	6041	18.91	3125	13.04
	≥ 7	1806	19.61	620	12.23	3757	16.52	1887	9.99	5563	17.41	2507	10.46
	missing	2699	29.31	1761	34.73	7038	30.94	7062	37.38	9737	30.47	8823	36.82
Vegetable consumption	< 1	1382	15.01	997	19.66	3960	17.41	4180	22.12	5342	16.72	5177	21.6
(pieces / week)	1 to 3	1613	17.51	845	16.67	3924	17.25	3051	16.15	5537	17.33	3896	16.26
	3 to 7	1757	19.08	802	15.82	3735	16.42	2474	13.09	5492	17.19	3276	13.67
	≥ 7	1910	20.74	809	15.96	4216	18.54	2251	11.91	6126	19.17	3060	12.77
	missing	2548	27.67	1617	31.89	6909	30.38	6938	36.72	9457	29.6	8555	35.7

Table 3 **Adjusted Odds Ratios and 95%Confidence Intervals for the association between head and neck cancer overall and education level / monthly household income**

	Controls	Cases	1. Minimally adjusted Adjusted for age, sex and center†				Controls	Cases	2. Adjusted for age, sex, center, smoking†				Controls	Cases	3. Adjusted for age, sex, center, smoking and alcohol†			
	number		OR	LCI	UCL	n studies, p het	number		OR	LCI	UCL	n studies, p het	number		OR	LCI	UCL	n studies, p het
Education Level																		
Low	10301	9235	2.50	2.02	3.09	28, <.0001	10039	8748	1.87	1.53	2.29	27, <.0001	7680	7142	1.46	1.16	1.82	25, <.0001
Mid	10238	8370	1.80	1.57	2.07	30, <.0001	10046	8105	1.42	1.24	1.63	29, <.0001	6755	6331	1.32	1.15	1.53	26, <.0001
High	10925	5550	1.00				10778	5463	1.00				7184	3930	1.00			
Monthly Income																		
1	1568	1556	2.44	1.62	3.67	8, <0.0001	1544	1532	1.69	1.27	2.26	8, 0.016	733	1048	1.56	1.29	1.88	8, 0.53
2	828	590	1.60	1.11	2.32	8, 0.001	815	583	1.26	0.90	1.75	8, 0.0023	363	379	1.11	0.90	1.37	8, 0.54
3	853	521	1.31	0.93	1.84	9, 0.0009	846	520	1.14	0.80	1.62	9, 0.0018	436	383	1.10	0.80	1.53	9, 0.48
4	618	436	1.15	0.82	1.61	9, 0.0003	614	435	1.02	0.73	1.44	9, 0.0015	425	341	0.94	0.64	1.37	9, 0.0034
5	1976	1294					1967	1284					1516	1082				

	Controls	Cases	4. Adjusted for age, sex, center, smoking, alcohol and diet†				Controls	Cases	5. Adjusted for age, sex, center, smoking, alcohol, diet and Tb†				Controls	Cases	6. Adjusted for age, sex, center, in never smokers/Tb/alcohol users†			
	number		OR	Lower CI	Upper CI	n studies, p het	number		OR	Lower CI	Upper CI	n studies, p het	number		OR	Lower CI	Upper CI	n studies, p het
Education Level																		
Low	5697	4932	1.43	1.13	1.81	19, <.0001	5013	4395	1.34	1.04	1.73	16, <.0001	1784	774	1.61	1.13	2.31	23, 0.1751
Mid	3690	3639	1.33	1.11	1.59	19, <.0001	3107	3240	1.22	1.03	1.46	16, <.0001	1476	372	1.10	0.90	1.34	26, 0.6039
High	4646	2342	1.00				4136	2149	1.00				1453	349	1.00			

N - number of subjects; OR - Odds Ratio; CI - 95% Confidence Interval; n - number of studies; p het - p-value for heterogeneity;

† Unconditional logistic regression (random-effects model); ref - reference category

1 Adjusted for: age, sex, center

2 Adjusted for: 1 + smoking status, smoking pack years (continuous), cigarettes per day, duration of smoking (years)

3 Adjusted for: 2 + drinking status, alcohol frequency, years of drinking

3x Adjusted for: 3 + interaction between years of smoking and years of drinking

4 Adjusted for: 3 + fruit consumption, vegetable consumption

5 Adjusted for: 4 + Tb - tobacco use: duration of pipe smoking, duration of cigar smoking, use of snuff, use of chewing tobacco

6 Adjusted for: age, sex, center in never smokers, never tobacco users, and never alcohol drinkers

Table 4 Subgroup analyses – Random-effects unconditional logistic regression models: adjusted Odds Ratios and 95%Confidence Intervals in (1) minimally adjusted models and (2) models adjusted for significant behavioural factors for the association of low relative to high educational attainment in head and neck cancer subsites by: sex, age-group, over-time, source of control, cancer subsite, global region, and country income inequality.

	Minimally adjusted Adjusted for age, sex and center†					Adjusted for age, sex, center and smoking and alcohol†$					%unexplained by smoking and alcohol‡
Education low vs high	**OR**	**Lower CI**	**Upper CI**	**n, p het***	**p het****	**OR**	**Lower CI**	**Upper CI**	**n, p het***	**p het****	**%**
Men	2.58	2.07	3.21	28, <.0001	0.097	1.44	1.16	1.80	25, <.0001	0.757	28.1
Women	1.89	1.41	2.54	24, <.0001		1.34	0.90	2.00	20, 0.008		38.0
< 50 years	2.19	1.68	2.85	25, 0.02	0.495	1.22	0.89	1.67	22, 0.033	0.123	18.3
50 + years	2.47	1.98	3.09	28, <.0001		1.65	1.32	2.05	27, <.0001		43.9
Pre-2000 studies	2.55	1.83	3.56	15, <.0001	0.924	1.27	0.88	1.82	13, <.0001	0.176	17.4
2000-onward studies	2.50	1.97	3.16	13, <.0001		1.70	1.37	2.11	12, 0.0099		46.7
Population controls	3.25	2.25	4.68	9, <.0001	0.058	1.62	1.17	2.23	7, 0.019	0.539	27.4
Hospital controls	2.16	1.75	2.66	19, <.0001		1.42	1.08	1.85	19, <.0001		36.0
Oral cavity	2.06	1.64	2.58	26, <.0001	0.043	1.33	1.02	1.75	25, <.0001	0.387	31.2
Oropharynx	2.34	1.66	3.31	24, 0.012		1.88	1.23	2.88	23, 0.085		65.7
Oral cavity /oropharynx NOS	2.21	1.76	2.78	26, <.0001		1.44	1.12	1.85	25, 0.0034		36.5
Hypopharynx	3.80	2.60	5.54	23, 0.00016		2.00	1.33	3.01	20, 0.024		35.8
Larynx	2.99	2.19	4.07	25, <.0001		1.69	1.24	2.32	22, <.0001		34.9
Europe	2.20	1.55	3.11	13, <.0001	0.047	1.30	0.88	1.93	10, <.0001	0.630	25.1
North America	3.00	2.05	4.39	13, <.0001		1.57	1.12	2.19	13, 0.0037		28.4
South/Central America	2.37	1.93	2.91	4, 0.37		1.68	1.31	2.16	4, 0.45		49.8
Lower income inequal country	2.22	1.33	3.73	6, <.0001	0.040	1.30	0.67	2.53	5, <.0001	0.002	24.4
Mid income inequal country	1.40	0.90	2.18	9, <.0001		1.17	0.77	1.78	7, 0.00018		42.3
Higher income inequal country	2.75	2.08	3.62	17, <.0001		1.65	1.27	2.15	17, <.0001		37.3

comparison lowest to highest education level; † Unconditional logistic regression.; OR - Odds Ratio; CI - Confidence Interval; n - number of studies

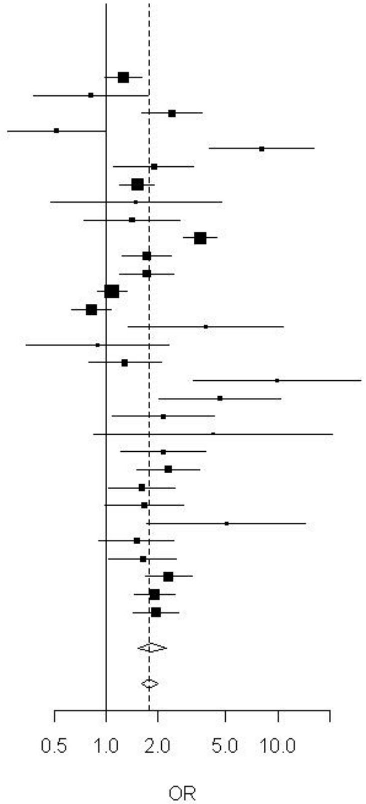
$ Adjusted for: smoking status, smoking pack years (continuous), cigarettes per day, smoking duration (years), drinking status, alcohol frequency, alcohol duration (years)

p het * - p-value for heterogeneity within subgroups; p het ** - p-value for heterogeneity across subgroups;

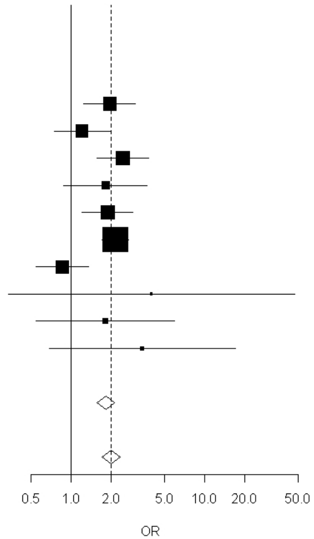
Difference in models expressed as a percentage computed to quantify amount of effect associated with low education explained by smoking and alcohol behaviours; ‡ proportion remaining after attributable fraction of covariates removed 100-(OR1-OR2/OR1-1)x100)

Figure 1 **The risk of head and neck cancer associated with low relative to high education and low income relative to high income adjusted for smoking and alcohol behaviours, by study, and pooled.**

Study	OR	95%CI
Education		
Italy (Aviano)	1.27	0.99- 1.63
Italy Multicenter	0.82	0.38- 1.77
Italy (Milan 1984-1989)	2.41	1.62- 3.61
Switzerland (Lausanne)	0.52	0.27- 1.00
Germany (Heidelberg)	8.08	4.01-16.32
Central Europe	1.90	1.11- 3.23
Western Europe	1.52	1.20- 1.92
Germany (Saarland)	1.50	0.48- 4.73
France (Paris 1989-1991)	1.42	0.75- 2.68
France (Paris 2002-2007)	3.54	2.85- 4.41
Italy (Milan 2006-2009)	1.73	1.24- 2.42
USA (Buffalo)	1.73	1.21- 2.47
USA (USA Multicentre)*	1.08	0.89- 1.32
USA (New York MC)	0.82	0.63- 1.08
USA (New York)	3.80	1.36-10.67
USA (Seattle 1985-1995)	0.89	0.35- 2.32
USA (Iowa)	1.29	0.80- 2.10
USA (North Carolina 1994-1997)	9.93	3.26-30.27
USA (Tampa)	4.59	2.03-10.40
USA (Boston)	2.14	1.08- 4.25
USA (Baltimore)	4.20	0.85-20.80
USA (Houston)	2.15	1.22- 3.79
USA (North Carolina 2002-2006)	2.31	1.52- 3.50
USA (Los Angeles)	1.62	1.03- 2.52
USA (Seattle)	1.67	0.99- 2.83
USA (Baltimore HOTSPOT)*	5.01	1.72-14.58
Puerto Rico	1.51	0.91- 2.49
Latin America	1.64	1.04- 2.58
Brazil (Sao Paulo)	2.31	1.69- 3.16
International	1.93	1.47- 2.52
China (Beijing)*	1.96	1.44- 2.67
Pooled estimate (p-het <.0001)	1.86	1.54- 2.25
Pooled (8 studies removed, p-het=0.141)	1.79	1.61- 1.99



Study	OR	95%CI
Income		
USA (Buffalo)*	1.95	1.25- 3.05
USA (Iowa)	1.21	0.74- 1.97
USA (Boston)	2.44	1.57- 3.79
USA (Baltimore)	1.81	0.88- 3.72
USA (Houston)	1.87	1.21- 2.89
USA (North Carolina 2002-2005)	2.14	1.69- 2.71
USA (Los Angeles)	0.86	0.55- 1.35
USA (Baltimore HOTSPOT)*	3.98	0.34-46.91
USA (MSKCC)	1.81	0.55- 5.93
Puerto Rico	3.40	0.69-16.88
Pooled estimate (p-het=0.038)	1.82	1.57- 2.11
Pooled (1 study removed, p-het=0.63)	1.98	1.70- 2.32



OR - Odds Ratios; 95%CI - 95% Confidence Intervals *USA Multicenter, Baltimore HOTSPOT, China (Beijing) no lowest group, second group (1v2 or 2v5)
Squares - study specific odds ratios; Size of the squares - determined by the inverse of the variance of the log OR
Horizontal lines - study specific 95% Confidence Intervals; Diamond - summary estimate combining the study specific estimates with random-effects models adjusted for age, sex, centre, smoking (smoking status, smoking pack years (continuous), cigarettes per day), and alcohol (alcohol drinking status, and alcohol frequency); Width of diamond – summary estimate 95% Confidence Interval Solid vertical line - odds ratio of 1; Dashed vertical line - summary odds ratio, "X studies removed refers to when studies leading to heterogeneity were removed.

Supplementary

Supplementary Table 1 - Reference list of pooled studies

Supplementary Table 2 - Household income categorisation

Supplementary Table 3 - Distribution of selected behavioural factors by education attainment in the study population

Supplementary Table 4 - Adjusted Odds Ratios and 95%Confidence Intervals for the association between head and neck cancer overall and education level monthly household income using complete observation only dataset

Supplementary Table 5 - Subgroup analyses – Adjusted Odds Ratios and 95%Confidence Intervals in (1) minimally adjusted models and (2) models adjusted for smoking and alcohol – for the association of low relative to high educational attainment in head and neck cancer subsites for global regions by: sex, and age-group

Supplementary Table 6 - Subgroup analyses – Adjusted Odds Ratios and 95%Confidence Intervals in (1) minimally adjusted models and (2) models adjusted for smoking and alcohol – for the association of low relative to high educational attainment in global regions by: sex, and age-group.

Supplementary Figure 1 - Galbraith plot of the studies included in the overall income analysis. (Studies contributing to Heterogeneity: Los Angeles)

Supplementary Figure 2 - Galbraith plot of the studies included in the overall education analysis. (Studies contributing to Heterogeneity Germany – Heidelberg, Italy Multicenter, Switzerland, NY-1, NC-2, Tampa, France 2001-2007, Italy-Aviano).

Supplementary Methods

Supplementary Table 1 **Reference list of pooled studies**

INHANCE STUDY ID	**Original publication reference**
Aviano	Negri E, La Vecchia C, Franceschi S, Tavani A. Attributable risk for oral cancer in northern Italy. Cancer Epidemiol Biomarkers Prev.1993;2:189-93.
Baltimore	D'souza G, Kreimer AR, Viscidi R et al. Case-control study of human papilloma virus and oropharyngeal cancer. N Engl J Med. 2007; 10;356: 1944-56.
Beijing	Zheng TZ, Boyle P, Hu HF et al. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer causes control. 1990; 1: 235-41.
Boston	Peters ES, McClean MD, Liu M, et al. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. Cancer Epidemiol Biomarkers Prev.2005;14:476-82.
Buffalo	Jayaprakash V, Rigual NR, Moysich KB et al. Chemoprevention of Head and Neck Cancer With Aspirin. Arch Otolaryngol Head Neck Surg. 2006; 132:1231-6.
Central Europe	Hashibe M, Boffetta P, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D, Janout V, Fabiánová E, Bencko V, Moullan N, Chabrier A, Hung R, Hall J, Canzian F, Brennan P. Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev. 2006;15:696-703.
Germany-Heidelberg	Dietz A, Ramroth H, Urban T, Ahrens W, Becher H. Exposure to cement dust, related occupational groups and laryngeal cancer risk: results of a population based case-control study. Int J Cancer.2004;108:907-11.
Germany-Saarland	Twardella D, Loew M, Rothenbacher D, Stegmaier C, Ziegler H, Brenner H. The diagnosis of a smoking-related disease is a prominent trigger for smoking cessation in a retrospective cohort study. J Clin Epidemiol. 2006;59:82-9.
HOTSPOT	Publication in progress
Houston	Zhang Z, Shi Q, Liu Z, Sturgis EM, Spitz MR, Wei Q. Polymorphisms of methionine synthase and methionine synthase reductase and risk of squamous cell carcinoma of the head and neck: a case-control analysis. Cancer Epidemiol Biomarkers Prev.2005;14:1188-93.
International Multicenter	Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, Rajkumar T, Sridhar H, Rose B, Pintos J, Fernández L, Idris A, Sánchez MJ, Nieto A, Talamini R, Tavani A, Bosch FX, Reidel U, Snijders PJ, Meijer CJ, Viscidi R, Muñoz N, Franceschi S; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and the risk of Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst.2003;95:1772-83.

Iowa	Smith EM, Hoffman HT, Summersgill KS, Kirchner HL, Turek LP, Haugen TH. Human papillomavirus and risk of oral cancer. Laryngoscope.1998;108:1098Â¡V103.
Italy Multicenter	Bosetti C, Gallus, S, Trichopoulou A, Talamini R, Franceschi S, Negri E, et al. Influence of the Meditterranean diet on the risk of cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev.2003; 12: 1091-4.
Latin America	Szymańska K, Hung RJ, Wünsch-Filho V, Eluf-Neto J, Curado MP, Koifman S, Matos E, Menezes A, Fernandez L, Daudt AW, Boffetta P, Brennan P. Alcohol and tobacco, and the risk of cancers of the upper aerodigestive tract in Latin America: a case-control study. Cancer Causes Control.2011;22:1037-46.
Los Angeles	Cui Y, Morgenstern H, Greenland S, et al. Polymorphism of xeroderma pigmentosum group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. Int J Cancer.2006;118:714-20.
Milan (1984-1989)	Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res.1990;50:6502-7
Milan (2006-2009)	Publication in progress
MSKCC	Schantz SP, Zhang ZF, Spitz MS, Sun M, Hsu TC. Genetic susceptibility to head and neck cancer: interaction between nutrition and mutagen sensitivity. Laryngoscope.1997;107:765-81.
North Carolina (1994-1997)	Olshan AF, Weissler MC, Watson MA, Bell DA. GSTM1, GSTT1, GSTP1, CYP1A1, and NAT1 polymorphisms, tobacco use, and the risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev.2000;9:185-91.
North Carolina (2002-2006)	Divaris K, Olshan AF, Smith J, Bell ME, Weissler MC, Funkhouser WK, Bradshaw PT. Oral health and risk for head and neck squamous cell carcinoma: the Carolina Head and Neck Cancer Study. Cancer Causes Control. 2010; 4:567-75.
NY Multicenter	Muscat JE, Richie JP Jr., Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. Cancer Res.1996;56:5192-97.
Paris (2002-2005)	Luce D, Stücker I; ICARE Study Group. Investigation of occupational and environmental causes of respiratory cancers (ICARE): a multicenter, population-based case-control study in France. BMC Public Health. 2011;11:928.
Paris (1989-1991)	Menvielle G, Luce D, Goldberg P, Leclerc A. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. Int J Epidemiol. 2004; 33 (4): 799-806.
Puerto Rico	Hayes RB, Bravo-Otero E, Kleinman DV, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. Cancer Causes Control.1999;10:27-33.

Sao Paulo	Boing AF, Ferreira Antunes JL, de Góis Filho JF, Kowalski LP, Michaluart P Jr; Head and Neck Genome Project/GENCAPO, Eluf-Neto J, Boffetta P, Wünsch-Filho V. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? J Epidemiol Community Health. 2010; 65:709-14.
Seattle (1985-1995)	Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res.2004;64:4049-54.
Seattle-Leo	Rogers MA, Thomas DB, Davis S, Vaughan TL, Nevissi AE. A case-control study of element levels and cancer of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev. 1993 Jul-Aug;2(4):305-12.
Switzerland	Levi F, Pasche C, La Vecchia C, et al. Food groups and risk of oral and pharyngeal cancer. Int J Cancer 1998;77:705-9.
Tampa	Elahi A, Zheng Z, Park J, Eyring K, McCaffrey T, Lazarus P. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis.2002;23:1229-34.
US Multicenter	Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res.1988; 48:3282.
Western Europe	Lagiou P, Georgila C, Minaki P, Ahrens W, Pohlabeln H, Benhamou S, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane TV, Macfarlane GJ, Talamini R, Barzan L, Canova C, Simonato L, Lowry R, Conway DI, McKinney PA, Znaor A, McCartan BE, Healy C, Nelis M, Metspalu A, Marron M, Hashibe M, Brennan PJ. Alcohol-related cancers and genetic susceptibility in Europe: the ARCAGE project: study samples and data collection. Eur J Cancer Prev.2009;18:76-84.

Supplementary Table 2 **Household income categorisation**

Study	Codes				
	1	2	3	4	5
Iowa	< $20,000	-	$20,000- $39,999	$40,000- $59,999	≥$60,000
Los Angeles	< $10,000 or $10,000- $19,999	$20,000- $29,999	$30,000-$39,999	$40,000- $59,999	$60,000- $79,999 or 80,000- $99,999 or ≥$100,000
Houston (MD Anderson)	< $15,000	$15,000-$19,000 or $20,000- $24,999	$25,000- $34,999	$35,000- $49,999	$50,000- $74,999 or 75,000- $99,999 or over $100,000
Puerto Rico	< $15,000	more than $20,000	more than $25,000 or more than $30,000 or more than $35,000	more than $40,000 or more than $45,000	more than $50,000
Boston (Harvard)	$9,000 or $9,000- $14,999	$15,000-$19,999 or $20,000-$24,999 or $25,000-$29,999	$30,000-$39,999	$40,000-$49,999	$50,000-$79,999 or 80,000-$99,999 or 100,000
MSKCC	under $13,000	$13,000- $22,999 or 23,000 - $32,999	$33,000 - $42,999	$43,000 - $52,999	$53,000-$62,999 or over $63,000
Buffalo	<16,000	16000-29,999	≥ 30,000	-	-
UNC - pop-based	< $5,000 or $5,001- $10,000 or $10,001- $20,000	$20,001-$30,000	$30,000-$40,000	$40,001-$50,000	$50,001-$60,000 or $60,001-$70,000 or $70,001- $80,000 or ≥$80,001
Baltimore	< $ 20, 000	$ 20,001- $30,000	$30,001-$40,000	$40,001-$50,000	≥ $ 50,001
HOTSPOT	-	<30,000	30,000-49,999	50,000-100,000	>100,000

Supplementary Table 3 Distribution of selected behavioural factors by educational attainment in the study population

		Lower		Mid		Higher		p for chi-sq / anova
		n	%	n	%	n	%	
Cigarette smoking status	Never	5488	28.09	4601	24.72	5683	34.49	<.0001
	Former	6042	30.93	5471	29.4	5428	32.94	
	Current	7470	38.24	8179	43.95	5237	31.78	
	missing	536	2.74	358	1.92	129	0.78	
Cigarette pack-years	mean	28.1		29.8		22.4		<.0001
Cigarette smoking (pack years)	0	5490	28.1	4601	24.72	5683	34.49	
	0 <=10	1642	8.4	1828	9.82	2243	13.61	
	10-<=20	1919	9.82	1844	9.91	1649	10.01	
	20-<=30	2123	10.87	2043	10.98	1501	9.11	
	30-<=40	2175	11.13	2165	11.63	1492	9.06	
	40-<=50	1814	9.29	1723	9.26	1149	6.97	
	> 50	3641	18.64	3950	21.23	2534	15.38	
	missing	732	3.75	455	2.45	226	1.37	
Alcohol drinking status	Never	4130	21.14	3427	18.42	2901	17.61	<.0001
	Ever	15312	78.38	15103	81.16	13538	82.16	
	missing	94	0.48	79	0.42	38	0.23	
Years of drinking	mean	33.76		32.78		32.78		<.0001
Alcohol (drinks / day)	Never	4153	21.26	3431	18.44	2908	17.65	<.0001
	0 to < 1	2627	13.45	5163	27.74	6620	40.18	
	1 to < 3	3689	18.88	4076	21.9	3611	21.92	
	3 to < 5	2384	12.2	2028	10.9	1338	8.12	
	5 to	5844	29.91	3274	17.59	1531	9.29	
	missing	839	4.29	637	3.42	469	2.85	
Fruit consumption (pieces / week)	< 1	4317	22.1	3550	19.08	3218	19.53	<.0001
	1 to 3	3470	17.76	2548	13.69	2645	16.05	
	3 to 7	3473	17.78	2654	14.26	2887	17.52	
	≥ 7	2807	14.37	2688	14.44	2448	14.86	
	missing	5469	27.99	7169	38.52	5279	32.04	
Vegetable consumption (pieces / week)	< 1	4372	22.38	3197	17.18	2734	16.59	<.0001
	1 to 3	3662	18.74	2873	15.44	2712	16.46	
	3 to 7	3241	16.59	2568	13.8	2816	17.09	
	≥ 7	3154	16.14	2892	15.54	3028	18.38	
	missing	5107	26.14	7079	38.04	5187	31.48	
Region	Europe	10946	56.03	9146	49.15	5602	34	<.0001
	North America	1117	5.72	7296	39.21	10225	62.06	
	South/Central America	6018	30.8	1530	8.22	575	3.49	
	Other	1455	7.45	637	3.42	75	0.46	

Supplementary Table 4 **Adjusted Odds Ratios and 95%Confidence Intervals for the association between head and neck cancer overall and education level monthly household income using complete observation only dataset**

	Controls	Cases	1. Minimally adjusted Adjusted for age, sex and center†				2. Adjusted for age, sex, center, smoking†				3. Adjusted for age, sex, center, smoking and alcohol†				4. Adjusted for age, sex, center, smoking, alcohol and diet†				5. Adjusted for age, sex, center, smoking, alcohol, diet and Tb†			
	n		OR	LCI	UCI	n studies, p het	OR	LCI	UCI	n studies, p het	OR	LCI	UCI	n studies, p het	OR	LCI	UCI	n studies, p het	OR	LCI	UCI	n studies, p het
Education Level																						
Low	5013	4395	2.12	1.59	2.84	16, <.0001	1.61	1.27	2.03	16, <.0001	1.37	1.04	1.80	16, <.0001	1.35	1.05	1.73	16, <.0001	1.34	1.04	1.73	16, <.0001
Mid	3107	3240	1.69	1.35	2.11	16, 0.0001	1.39	1.16	1.66	16, <.0001	1.25	1.05	1.50	16, <.0001	1.23	1.03	1.47	16, <.0001	1.22	1.03	1.46	16, <.0001
High	4136	2149	1.00				1.00				1.00				1.00				1.00			
Monthly Income																						
1	733	1048	2.77	1.24	6.21	4, <.0001	1.93	1.10	3.38	4, 007	1.54	1.09	2.16	4, 0.20	1.60	1.20	2.12	4, 0.31	1.62	1.19	2.19	4, 0.28
2	363	379	1.63	1.14	2.32	4, 0.16	1.18	0.92	1.51	4, 0.68	1.03	0.80	1.33	4, 0.65	1.05	0.81	1.37	4, 0.59	1.06	0.82	1.39	4, 0.58
3	436	383	1.48	1.17	1.87	4, 0.52	1.16	0.90	1.51	4, 0.97	1.06	0.81	1.38	4, 0.98	1.09	0.83	1.43	4, 0.98	1.09	0.84	1.43	4, 0.98
4	425	341	1.47	1.17	1.85	4, 0.67	1.23	0.96	1.58	4, 0.83	1.17	0.91	1.51	4, 0.59	1.19	0.92	1.54	4,0.56	1.19	0.92	1.55	4, 0.59
5	1516	1082	1.00				1.00				1.00				1.00				1.00			

N - number of subjects; OR - Odds Ratio; CI - 95% Confidence Interval; n - number of studies; p het - p-value for heterogeneity; † Unconditional logistic regression (random-effects model); ref - reference category

* fixed-effects model p-value for heterogeneity (p het) > 0.05

1 Adjusted for: age, sex, center

2 Adjusted for: 1 + smoking status, smoking pack years (continuous), cigarettes per day, duration of smoking (years)

3 Adjusted for: 2 + drinking status, alcohol frequency, years of drinking

3x Adjusted for: 3 + interaction between years of smoking and years of drinking

4 Adjusted for: 3 + fruit consumption, vegetable consumption

5 Adjusted for: 4 + Tb - tobacco use: duration of pipe smoking, duration of cigar smoking, use of snuff, use of chewing tobacco

Supplementary Table 5 Subgroup analyses - Adjusted Odds Ratios and 95%Confidence Intervals in (1) minimally adjusted models and (2) models adjusted for smoking and alcohol - for the association of low relative to high educational attainment in head and neck cancer subsites for global regions by: sex, and age-group

Education low vs high (cases / controls)		Oral cavity				het	Oropharynx				het	OC/OP NOS				het	Hypopharynx				het	Larynx				het
		OR	LCI	UCI	n, p-het*		OR	LCI	UCI	n, p-het*		OR	LCI	UCI	n, p-het*		OR	LCI	UCI	n, p-het*		OR	LCI	UCI	n, p-het*	
(i) Adjusted for age, sex and center† OR (95% CI)																										
All (n / n)		2.06	1.64	2.58	26, <.0001		2.34	1.66	3.31	24, 0.012		2.21	1.76	2.78	26, <.0001		3.80	2.60	5.54	23, 0.00016		2.99	2.19	4.07	25, <.0001	
Region	Europe (n / n)	1.50	1.03	2.19	11, <.0001	0.123	2.05	1.40	2.99	11, <.0001	0.703	2.56	1.46	4.50	10, 0.032	0.897	4.04	2.38	6.85	10, 0.0004	0.821	2.17	1.41	3.33	12, <.0001	0.008
	North America	2.59	1.75	3.82	13, 0.0008		2.38	1.59	3.56	13, 0.00032		2.17	1.42	3.31	11, 0.26		3.49	1.65	7.37	11, 0.007		4.73	2.77	8.09	11, <.0001	
	South/Central America	2.18	1.63	2.92	4, 0.50		2.64	1.64	4.23	4, 0.23		2.45	0.51	11.91	3, 0.049		3.54	1.83	6.84	2, 0.488		2.60	1.05	6.43	2, 0.011	
Sex	Men	2.21	1.77	2.77	26, 0.0004	0.089	2.43	1.89	3.13	26, <.0001	0.002	2.44	1.67	3.56	24, 0.079	0.903	4.28	2.80	6.53	21, <.0001	0.008	2.87	2.10	3.92	25, <.0001	0.813
	Women	1.57	1.14	2.18	23, 0.012		1.33	1.00	1.77	21, 0.93		2.53	1.63	3.93	18, 0.61		1.52	0.81	2.87	18, 0.97		3.07	1.94	4.88	20, 0.0090	
Age-group	Young < 50 years	1.64	1.10	2.43	22, 0.085	0.274	2.59	1.86	3.61	21, 0.57	0.475	2.57	1.58	4.20	18, 0.99	0.999	2.48	1.35	4.57	16, 0.99	0.209	2.99	2.06	4.33	21, 0.33	0.792
	Older 50 + years	2.11	1.70	2.62	26, 0.0002		2.23	1.75	2.84	26, <.0001		2.23	1.54	3.22	23, 0.052		3.96	2.65	5.91	23, 0.00071		2.80	2.04	3.84	25, <.0001	
(ii) Adjusted for age, sex, center and smoking and alcohol OR (95% CI)																										
All		1.33	1.02	1.75	25, <.0001		1.88	1.23	2.88	23, 0.085		1.44	1.12	1.85	25, 0.0034		2.00	1.33	3.01	20, 0.024		1.69	1.24	2.32	22, <.0001	
Region	Europe	1.10	0.69	1.75	10, <.0001	0.259	1.51	0.99	2.30	10, 0.0053	0.734	2.62	1.69	4.06	9, 0.82	0.427	2.23	1.28	3.88	8, 0.055	0.394	1.29	0.79	2.10	9, <.0001	0.292
	North America	1.34	0.91	1.98	13, 0.15		1.30	0.91	1.85	13, 0.16		1.70	1.00	2.88	11, 0.422		1.69	0.72	4.00	10, 0.042		2.24	1.36	3.70	11, 0.011	
	South Central America	1.77	1.24	2.53	4, 0.042		1.70	0.89	3.23	4, .018		1.40	0.18	11.22	3, 0.011		1.91	0.87	4.22	2, 0.529		1.94	0.74	5.09	2, 0.021	
Sex	Men	1.33	1.03	1.72	25, 0.0098	0.740	1.57	1.21	2.04	24, 0.0073	0.079	1.67	1.16	2.40	22, 0.41	0.137	2.14	1.33	3.46	18, 0.010	0.313	1.57	1.15	2.14	22, <.0001	0.920
	Women	1.18	0.61	2.28	19, 0.0014		0.98	0.64	1.50	17, 0.91		3.41	1.43	8.13	17, 0.82		1.15	0.38	3.48	12, 1.00		1.52	0.88	2.64	11, 0.41	
Age-group	Young < 50 years	0.73	0.46	1.17	15, .025	0.012	0.73	0.46	1.17	15, 0.25	0.007	1.23	0.54	2.84	14, 0.99	0.434	0.80	0.27	2.37	13, 1.00	0.101	1.82	0.87	3.80	13, 0.037	0.719
	Older 50 + years	1.43	1.13	1.80	25, 0.053		1.43	1.13	1.80	25, 0.054		1.81	1.10	2.97	20, 0.096		2.14	1.36	3.35	19, 0.41		1.57	1.14	2.18	22, <.0001	

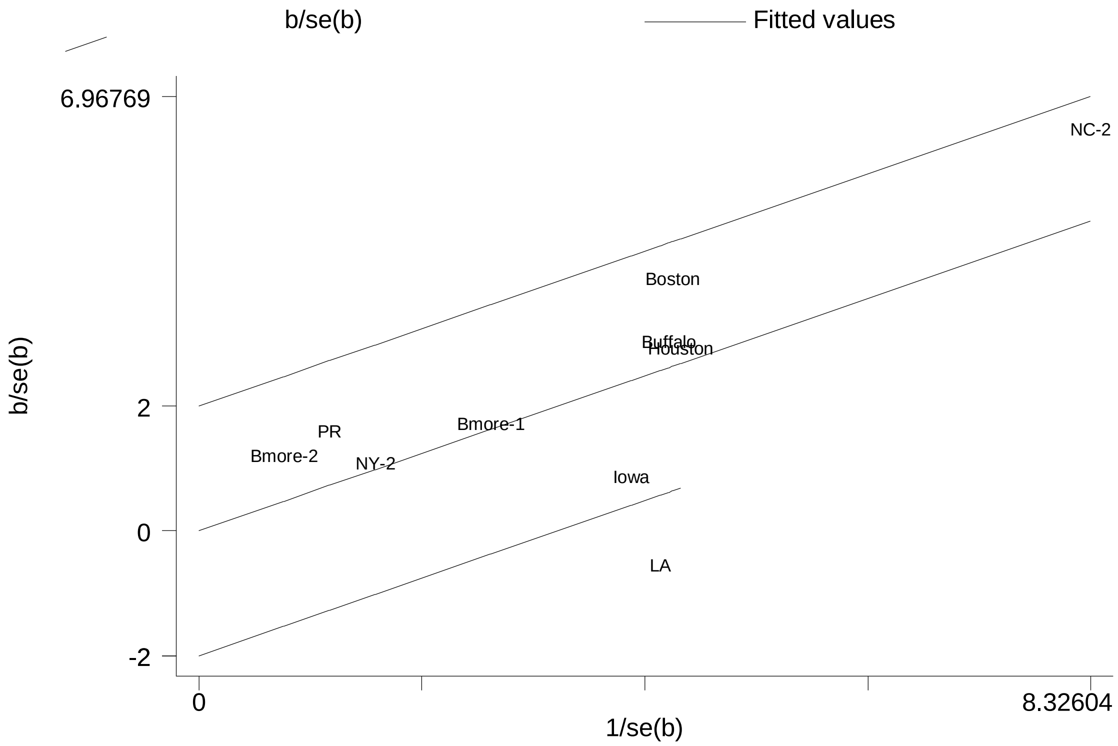
† - unconditional logistic regression (random-effects model)
OR - Odds Ratio; UCI - Upper 95% Confidence Interval; LCI - Lower 95% Confidence Interval; n = number of studies
p het * - p-value for heterogeneity within subgroups; p het ** - p-value for heterogeneity across subgroups
1. Adjusted for: age, sex, centre
2. Adjusted for: 1. + smoking status, smoking pack years (continuous), cigarettes per day, smoking duration (years), drinking status, alcohol frequency, alcohol duration (years)

Supplementary Table 6 **Subgroup analyses - Adjusted Odds Ratios and 95%Confidence Intervals in (1) minimally adjusted models and (2) models adjusted for smoking and alcohol - for the association of low relative to high educational attainment in global regions by: sex, and age-group**

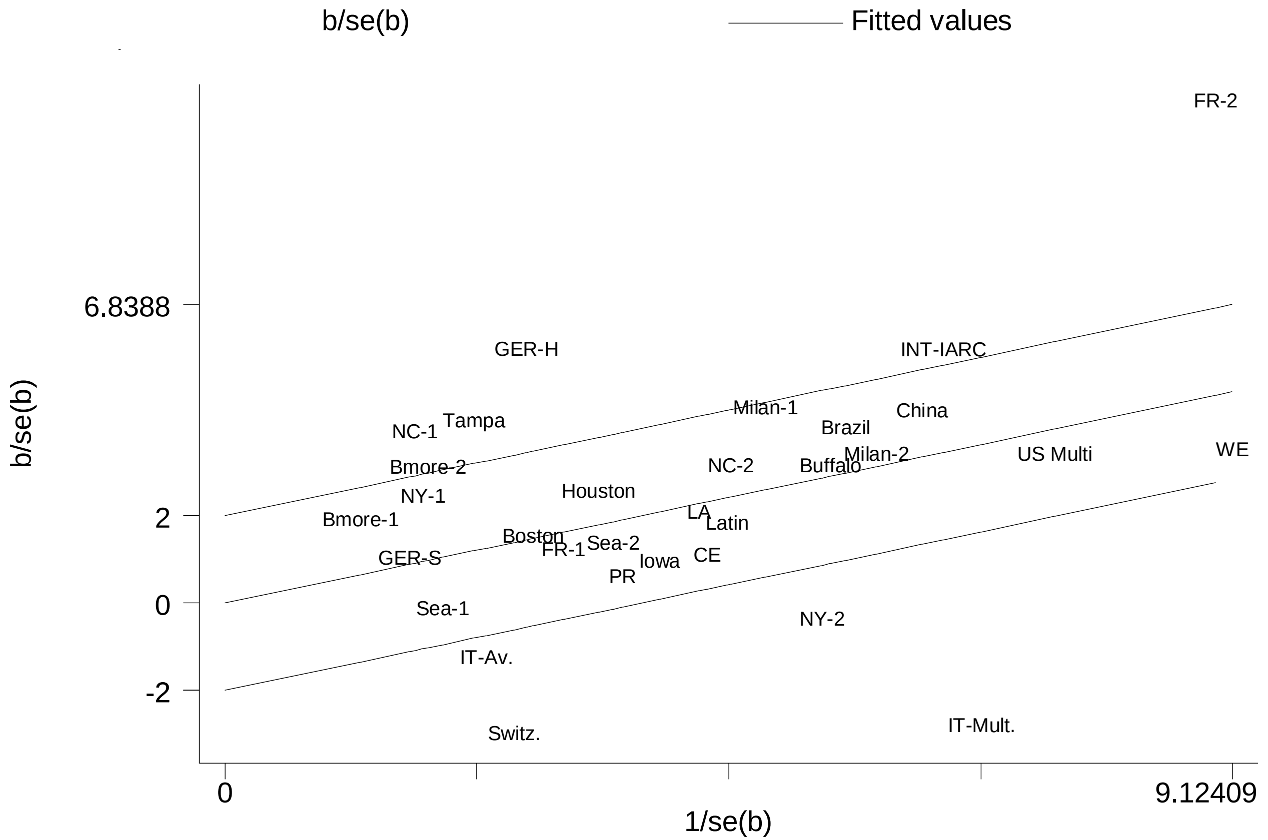
Education low vs high (n cases / controls)		Europe					North America					South/Central America				
		OR	LCI	UCI	n, p-het*	p-het**	OR	LCI	UCI	n, p-het*	p-het**	OR	LCI	UCI	n, p-het*	p-het**
(i) Adjusted for age, sex and center† OR (95% CI)																
All (n / n)		2.20	1.55	3.11	13, <.0001		3.00	2.05	4.39	13, <.0001		2.37	1.93	2.91	4, 0.37	
Sex	Men (n / n)	2.34	1.64	3.34	13, <.0001	0.044	3.00	2.04	4.40	13, <.0001	0.508	2.41	1.93	3.01	4, 0.42	0.585
	Women	1.32	0.86	2.03	10, 0.00042		2.44	1.52	3.94	12, 0.0065		2.10	1.35	3.26	4, 0.42	
Age-group	Young < 50 years	2.24	1.40	3.58	12, <.0001	0.816	1.94	1.24	3.05	11, 1.00	0.142	1.93	1.25	2.99	4, 0.91	0.318
	Older 50 + years	2.09	1.48	2.97	13, <.0001		3.06	2.03	4.60	13, <.0001		2.48	1.97	3.11	4, 0.42	
(ii) Adjusted for age, sex, center and smoking and alcohol†$ OR (95% CI)																
All		1.30	0.88	1.93	10, <.0001		1.57	1.12	2.19	13, 0.0037		1.68	1.31	2.16	4, 0.45	
Sex	Men	1.35	0.92	1.99	10, <.0001	0.385	1.45	1.07	1.97	13, 0.048	0.795	1.60	1.19	2.16	4, 0.35	0.455
	Women	0.97	0.51	1.83	8, 0.0046		1.60	0.81	3.14	10, 0.22		2.40	0.86	6.64	3, 0.22	
Age-group	Young < 50 years	1.04	0.65	1.66	10, 0.034	0.431	1.03	0.52	2.03	7, 0.81	0.241	1.27	0.73	2.22	3, 0.59	0.337
	Older 50 + years	1.33	0.90	1.98	10, <.0001		1.64	1.12	2.38	13, 0.0017		1.74	1.26	2.40	4, 0.32	

† - unconditional logistic regression (random-effects model)
OR - Odds Ratio; UCI - Upper 95% Confidence Interval; LCI - Lower 95% Confidence Interval; n = number of studies
p het * - p-value for heterogeneity within subgroups; p het ** - p-value for heterogeneity across subgroups
1. Adjusted for: age, sex, centre
2. Adjusted for: 1. + smoking status, smoking pack years (continuous), cigarettes per day, smoking duration (years), drinking status, alcohol frequency, alcohol duration (years)

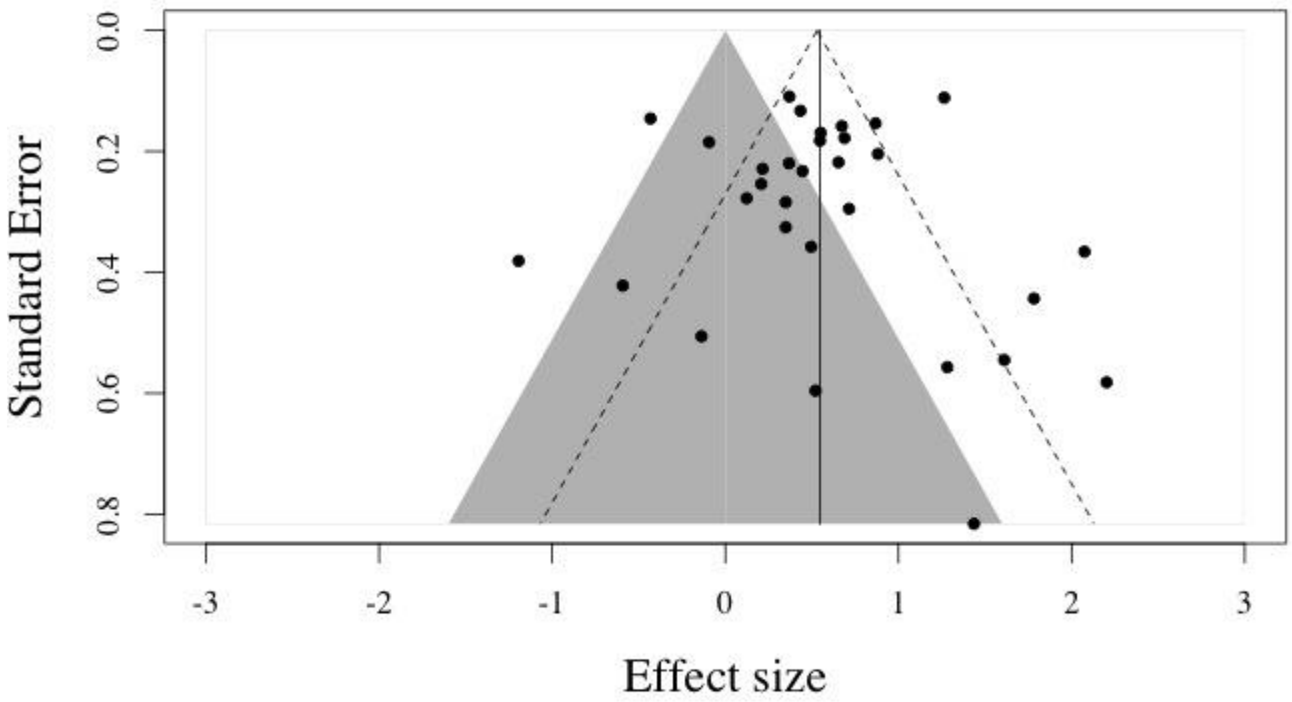
Supplementary Figure 1 **Galbraith plot of the studies included in the overall income analysis. (Studies contributing to Heterogeneity: Los Angeles)**



Supplementary Figure 2 **Galbraith plot of the studies included in the overall education analysis. (Studies contributing to Heterogeneity Germany- Heidelberg, Italy Multicenter, Switzerland, NY-1, NC-2, Tampa, France-2 2001-2007, Italy-Avino)**



Supplementary Figure 3 **Funnel plot of estimates around the summary estimate (vertical line) of the effect of low vs high educational attainment**



Supplementary Methods

ICD Codes : The case subjects had histologically confirmed diagnoses of cancers of the oral cavity (ICD-10 C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8, and C06.9; 2); oropharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0-C10.4, C10.8, C10.9; 3); hypopharynx (C12.9, C13.0-C13.2, C13.8, and C13.9; 4); oral cavity, oropharynx not otherwise specified (C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, C14.8; 5) larynx (C32.0-C32.3, C32.8-C32.9).

Modelling approach We started with a minimally adjusted model including age, sex and centre/location (for multi-centered studies) and increased model complexity to evaluate the relative contribution of risk factors to the association between education and income and head and neck cancer. Our "full model" used in all subgroup analyses consisted of adjusting for age, sex, cigarette smoking status, cigarettes per day while smoking, duration of smoking (years) and cumulative cigarette smoking (in pack-years)[-collectively smoking variables henceforth labelled "smoking"], alcohol consumption status, drinks per day while drinking and duration of alcohol (years)[1] [-alcohol"]. We included variables for fruit and vegetable consumption (based on centre-specific quartiles)[2] [-"diet"]; and other tobacco use (snuff, chewing tobacco, pipes, and cigars) status and duration of use where studies collected this information [-"other tobacco"], although we did not include Asian tobacco-related behaviours such as betel chewing in this analysis.

Subgroup analyses We conducted subgroup analysis by smoking status; drinking status; cancer subsite; geographic region (Europe, North America, South/Central America, and Other regions including Africa, Asia, and Australia – results for the Other regions grouping due to limited sample size); age-group (<50 years vs. ≥50 years); and country income inequality (using ratios of income share of richest 20% of the country's population to income share of poorest 20% grouped into tertiles– low income inequality <6; mid income inequality 6-8; higher income inequality

>8).[3,4] We also conducted sensitivity analyses by control type (population-based vs. hospital-based) and year that the study was conducted (before vs. after 2000).

Meta-analytic techniques and evaluation of heterogeneity Heterogeneity was evaluated for each of the summary estimates based on a test of the Cochrane Q statistic. Where there was evidence of heterogeneity across studies, we evaluated the source of heterogeneity by meta-regression using control type, prevalence of ever smoking among controls, median year of the study period and global region as predictors in the model. If the heterogeneity could not be accounted for by the different study characteristics, an influence analysis was conducted to evaluate the source of heterogeneity from single studies by examining Galbraith plots and the contribution of each study to the Q-statistic.Comparisons within studies in which one or more of the exposure categories had no subjects were excluded from that comparison group in the pooled analysis as the OR could not be estimated. This lead to different numbers of studies across the pooled comparison groups.

Supplementary Methods References

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4. United Nations Development Program. Human development report. New York: Oxford University Press, 2003.