IJC
International Journal of Cancer

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

David I. Conway[1], Darren R. Brenner[2], Alex D. McMahon[1], Lorna M.D. Macpherson[1], Antonio Agudo[3], Wolfgang Ahrens[4,5], Cristina Bosetti[6], Hermann Brenner[7], Xavier Castellsague[8], Chu Chen[9], Maria Paula Curado[10], Otávio A. Curioni[11], Luigino Dal Maso[12], Alexander W. Daudt[13], José F. de Gois Filho[14], Gypsyamber D'Souza[15], Valeria Edefonti[16], Eleonora Fabianova[17], Leticia Fernandez[18], Silvia Franceschi[2], Maura Gillison[19], Richard B. Hayes[20], Claire M. Healy[21], Rolando Herrero[22], Ivana Holcatova[23], Vijayvel Jayaprakash[24], Karl Kelsey[25], Kristina Kjaerheim[26], Sergio Koifman[27], Carlo La Vecchia[6], Pagona Lagiou[28], Philip Lazarus[29], Fabio Levi[30], Jolanta Lissowska[31], Daniele Luce[32], Tatiana V. Macfarlane[33], Dana Mates[34], Elena Matos[35], Michael McClean[36], Ana M Menezes[37], Gwenn Menvielle[32], Franco Merletti[38], Hal Morgenstern[39], Kirsten Moysich[24], Heiko Müller[6], Joshua Muscat[40], Andrew F. Olshan[41], Mark P. Purdue[42], Heribert Ramroth[43], Lorenzo Richiardi[38], Peter Rudnai[44], Stimson Schantz[45], Stephen M. Schwartz[9], Oxana Shangina[46], Lorenzo Simonato[47], Elaine Smith[48], Isabelle Stucker[32], Erich M. Sturgis[49], Neonila Szeszenia-Dabrowska[50], Renato Talamini[12], Peter Thomson[51], Thomas L. Vaughan[9], Qingyi Wei[49], Deborah M. Winn[52], Victor Wunsch-Filho[53], Guo-Pei Yu[54,55], Zuo-Feng Zhang[56], Tongzhang Zheng[57], Ariana Znaor[58], Paolo Boffetta[10,59], Shu-Chun Chuang[60], Marianoosh Ghodrat[61], Yuan-Chin Amy Lee[61], Mia Hashibe[61] and Paul Brennan[2]

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

Additional Supporting Information may be found in the online version of this article.

Grant sponsor(s): UICC Yamagiwa-Yoshida Memorial International Cancer Study grant; International Agency for Research on Cancer, Lyon, France Visiting Scientist Award; INHANCE Pooled Data Coordination Grant sponsor: NCI; Grant number: R03CA113157; and Grant sponsor: NIDCR; Grant number: R03DE016611; Individual Studies funded by the following: Aviano, Milan (1984-1989) Study, Milan (2006-2009) Study and Italy Multicenter Study Grant sponsors: Italian Association for Research on Cancer (AIRC); Grant number: 10068; Grant sponsor: Italian Ministry of Research; Grant number: PRIN 2009 X8YCBN; Grant sponsor: Swiss League against Cancer and the Swiss Research against Cancer/Oncosuisse, Switzerland; Grant numbers: KFS-700 and OCS-1633; Central Europe Study Grant sponsor: World Cancer Research Fund and the European Commission INCO-COPERNICUS Program Central Europe; Grant number: IC15-CT98-0332; Western Europe Study Grant sponsors: European Commission's 5th Framework Programme; Grant number: QLK1-2001-00182, and RegionPiemonte and Padova University; Grant number: CPDA057222; Germany-Saarland Study Grant sponsor: Ministry of Science, Research and Arts Baden-Wurttemberg; Germany-Heidelberg Study Grant sponsor: German Ministry of Education and Research; Grant number: 01GB9702/3; France (2001-2007) Study Grant sponsors: French National Cancer Institute (INCA); French Agency for Food, Environmental and Occupational Health and Safety (ANSES); French Association for Research on Cancer (ARC); Fondation pour la Recherche Médicale (FRM); French Institute for Public Health Surveillance (InVS); Fondation de France; Ministry of Health; International Multicenter Study Grant sponsor: Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government; Grant numbers: FIS 97/0024, FIS 97/0662 and BAE 01/5013, and International Union Against Cancer (UICC) and Yamagiwa-Yoshida Memorial International Cancer Study Grant; Boston Study Grant sponsor: NIH US; Grant numbers: R01CA078609 and R01CA100679; Baltimore Study Grant sponsor: NIDCR; Grant number: DE016631; HOTSPOT Study Grant sponsor: Johns Hopkins Richard Gelb Cancer Prevention Award; New York Multicenter Study Grant sponsor: National Institutes of Health (NIH) US; Grant numbers: P01CA068384 and R01DA026815; Seattle (1985-1995) Study Grant sponsor: NIH US; Grant numbers: R01CA048996 and R01DE012609; Iowa Study Grant sponsor: NIH US; Grant numbers: NIDCR R01DE11979, NIDCR R01DE13110 and NIH FIRCA TW01500 and Veterans affairs Merit Review Funds; North Carolina (1994–1997) Study Grant sponsor: NIH, US; Grant number: R01CA061188 and Grant sponsor: National Institute of Environmental Health Sciences; Grant number: P30ES010126; North Carolina (2002–2012) Study Grant sponsor: NIH, US; Grant number: R01CA90731; Seattle-Leo Study Grant sponsor: NIH; Grant number: R01CA030022; Tampa Study Grant sponsor: NIH, US; Grant numbers: P01CA068384, K07CA104231 and R01DE013158; Los Angeles Study Grant sponsor: NIH, US; Grant numbers: P50CA090388, R01DA011386, R03CA077954, T32CA009142, U01CA096134 and R21ES011667 and the Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center; Houston Study Grant sponsor: NIH, US; Grant numbers: R01ES011740 and R01CA100264; Puerto Rico Study Grant sponsor: NIH NCI and NIDCR intramural programs; MSKCC Study Grant sponsor: NIH, US; Grant number: R01CA051845; Latin America Study Grant sponsors: Fondo para la investigación Cientifica y Tecnologica (FONCYT) Argentina, IMIM (Barcelona), and Fundaçao de Amparo à Pesquisa no Estado de Sao Paulo (FAPESP); Grant number: 01/01768-2; and Grant sponsor: European Commission; Grant number: IC18-CT97-0222; Sao Paulo Study Grant sponsor: Fundaçao de Amparo à Pesquisa no Estado de Sao Paulo (FAPESP); Grant number: 10/51168-0

DOI: 10.1002/ijc.29063

History: Received 24 Oct 2013; Accepted 20 Mar 2014; Online 4 July 2014

Correspondence to: David I. Conway, University of Glasgow Dental School, 378 Sauchiehall Street, Glasgow G2 3JZ, United Kingdom, Tel.: ++44(0)141 211 9750, E-mail: david.conway@glasgow.ac.uk

[1] Glasgow Dental School, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom
[2] International Agency for Research on Cancer, Lyon, France
[3] Unit of Nutrition, Environment and Cancer Epidemiology Research Program, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain
[4] BIPS-Institute for Epidemiology and Prevention Research, Bremen, Germany
[5] Institute for Statistics, University of Bremen, Germany
[6] Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri,", Milan, Italy
[7] German Cancer Research Center, Heidelberg, Germany
[8] Institut Catala d'Oncologia (ICO), IDIBELL, CIBER-ESP, L'Hospitalet de Llobregat, Barcelona, Catalonia, Spain
[9] Fred Hutchinson Cancer Research Center, Seattle, WA
[10] International Prevention Research Institute, Lyon, France
[11] Hospital Heliopolis, Sao Paulo, Brazil
[12] Epidemiology and Biostatistics Unit, Centro di Riferimento Oncologico IRCCS, Aviano, Italy
[13] Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil
[14] Instituto do Cancer Arnaldo Viera de Carvalho, Sao Paulo, Brazil
[15] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
[16] Department of Clinical Sciences and Community Health, University of Milan, Italy
[17] Regional Authority of Public Health, Banska Bystrica, Slovakia
[18] Institute of Oncology and Radiobiology, Havana, Cuba
[19] The Ohio State University, Comprehensive Cancer Center, Columbus, OH
[20] Division of Epidemiology, New York University, School of Medicine, NY
[21] Trinity College School of Dental Science, Dublin, Ireland
[22] Prevention and Implementation Group, International Agency for Research on Cancer, Lyon, France
[23] First Faculty of Medicine, Institute of Hygiene and Epidemiology, Charles University, Prague, Czech Republic
[24] Roswell Park Cancer Institute, Buffalo, NY
[25] Brown University, Providence, Rhode Island
[26] Cancer Registry of Norway, Oslo, Norway
[27] Escola Nacional de Saude Publica, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil
[28] University of Athens School of Medicine, Athens, Greece
[29] Washington State University College of Pharmacy, Spokane, WA
[30] Institut de Médecine Sociale et Préventive (IUMSP), Centre Hospitalier Universitaire Vaudois et Université de Lausanne, Lausanne, Switzerland
[31] Department of Cancer Epidemiology and Prevention, The M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
[32] Inserm, Center for Research in Epidemiology and Population Health (CESP), U1018, Occupational and Environmental Determinants of Health, Villejuif, France
[33] University of Aberdeen Dental School, Aberdeen, United Kingdom
[34] National Institute of Public Health, Bucharest, Romania
[35] Institute of Oncology Angel H. Roffo, University of Buenos Aires, Argentina
[36] Boston University School of Public Health, Boston, MA
[37] Universidade Federal de Pelotas, Brazil
[38] Department of Medical Sciences, University of Turin, Italy
[39] Departments of Epidemiology and Environmental Health Sciences, School of Public Health and Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI
[40] Penn State College of Medicine, Hershey, PA
[41] Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC
[42] National Cancer Institute, Bethesda, MD
[43] Institute of Public Health, University of Heidelberg, Germany
[44] National Institute of Environmental Health, Budapest, Hungary
[45] New York Eye and Ear Infirmary, NY
[46] Cancer Research Centre, Moscow, Russia
[47] Department of Molecular Medicine, Laboratory of Public Health and Population Studies, University of Padova, Italy
[48] College of Public Health, University of Iowa
[49] UT-M.D. Anderson Cancer Center, Houston, TX
[50] Institute of Occupational Medicine, Lodz, Poland
[51] University of Newcastle, United Kingdom
[52] National Cancer Institute, National Institutes of Health, Bethesda, MD
[53] Department of Epidemiology, Faculdade de Saude Publica, Universidade de Sao Paulo, Brazil
[54] New York Medical College, Valhalla, NY
[55] Peking University Medical Informatics Center, Beijing, China
[56] UCLA School of Public Health, Los Angeles, CA
[57] Yale University, New Heaven, CT
[58] Croatian National Cancer Registry, Croatian National Institute of Public Health, Zagreb, Croatia

[59] The Tisch Cancer Institute, Mount Sinai School of Medicine, NY
[60] Division of Health Policy Translation, Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan
[61] University of Utah School of Medicine, Salt Lake City, UT

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 behavioral 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 behaviors; and it remained elevated among never users of tobacco and nondrinkers (OR = 1.61; 95% CI = 1.13 – 2.31). More of the estimated education effect was not explained by cigarette smoking and alcohol behaviors: 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 versus 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 behavioral risk factors for these cancers and which varies across cancer sites, sexes, countries and country income inequality levels.

What's new?
Head and neck cancer is among the most common and increasing cancers in the world. Besides smoking, alcohol drinking, and human papilloma virus infections, low socioeconomic status has been implicated as one of the most important risk factors for this cancer type. This large multinational study authoritatively confirmed that lower education status and lower income are associated with increased risk for head and neck cancer development. Smoking and alcohol consumption could not entirely explain the risk associated with low socioeconomic factors, and therefore, as the authors argue, need to be more explicitly recognized in the etiology associated with head and neck cancer.

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 hypothesized an association with alcohol and an infection (syphilis).[1]

Today, head and neck cancer—comprising tumors 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] 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.[10]

While smoking and alcohol behaviors have long been recognized as the major risk factors for head and neck cancer,[11] and more recently the role of genetic variants[12] and human papillomavirus (HPV) infection[13] 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.[14] 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 to 50%.[15–17] 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 behavioral risk factors. In addition, while country income inequality has consistently been associated with numerous negative health outcomes[18] 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

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[19,20] (Supporting Information Table S1). 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 Supporting Information Methods). We excluded lymphomas, sarcomas and cancers of the nasopharynx and salivary glands.

Education data were standardized using the International Standard Classification of Education (ISCED 97)[21]; and grouped into three 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 standardized as far as possible (given the original study questionnaire categorization) by grouping comparable levels based on the strata used in the original study questionnaires (Supporting Information Table S2), 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 modeling strategy see Supporting Information Methods. We then estimated the summary effect estimates using a meta-analysis approach: by pooling study-specific risk estimates with random effects models.[22] For additional details on meta-analytic approaches and evaluation of heterogeneity see Supporting Information 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 (Supporting Information Methods). We also conducted a sensitivity analysis using a complete observation only dataset where no missing data existed across any variable in all studies 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 behavioral 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 behavioral risk factors referred to as attributable fraction for covariates.[23] 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 Tables (2 and 3). The distribution of selected behavioral 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 (Supporting Information Table S3).

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 4). These associations were increasingly attenuated when models sequentially adjusted for lifestyle behaviors (Table 4); 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 4). The model adjusting for smoking and alcohol (Table 4 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 >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 4).

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; Supporting Information Table S4).

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 behaviors. These results vary slightly from Table 4 due to using the data from the lowest and highest strata available

Epidemiology

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

Location	INHANCE ID	Reigon	Period	Source of controls	Participation rate (%) Cases/ Controls	E I	Oral cavity	Oropharynx	Cancer (n) NOS	Hypopharynx	Larynx	Missing	(*n*)	(*n*)
France[1]	**Paris (1989-1991)**	Europe	1989-1991	H	80/86	X	.	.	.	206	322	0	305	528
France[1]	**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[1]	**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[1]	**Central Europe**	Europe	1998-2003	H	96/97	X	196	98	32	52	384	0	907	762
Western Europe[1]	**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[1]	**US Multicentre**	North America	1983-1984	P	75/76	X	386	389	218	121	.	0	1268	1114
USA(New York)[1]	**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+[2]	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 (1994-1997)**	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)	**HOYSPOT**	North America	2009-2012	H	>85 / >80	X X		71	.	.	.	0	71	71
USA (North Carolina)	**North Carolina (2002-2006)**	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[1]	**Latin America**	South/Central America	2000-2003	H	95/86	X	459	395	240	180	860	66	1706	2200

Epidemiology

Table 1. Characteristics of individual studies of the INHANCE consortium pooled analysis (Continued)

Location	INHANCE ID	Reigon	Period	Source of controls	Participation rate (%) Cases/ Controls	E	I	Oral cavity	Oropharynx	Cancer (n) NOS	Hypopharynx	Larynx	Missing	(n)	(n)
Brazil (Sao Paulo)	**Sao Paulo**	South/Central America	2002-2007	H	>95 / >95	X		769	326	64	180	574	9	1670	1922
International[1]	**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	31,954	23,964

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
[1]- multicenter study
[2]- Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995
[3]- 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)[19]

(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 (Supporting Information Figs. S1 and S2). 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 behaviors 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 5). 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 behaviors 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 5).

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 than with European studies. There was full attenuation of this risk association by adjustment for smoking and alcohol behaviors 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 5).

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 with other regions (Supporting Information Table S5). The proportion of the risk left unexplained by smoking and alcohol behaviors by subsite and region was highly variable.

The risk associated with lower educational attainment varied across global regions by sex and age subgroups (Supporting Information Table S6). 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 behaviors these differences do not remain significant as the elevated risk associations among women in both North and South/Central America were attenuated.

Epidemiology

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

Variable		Sex								All			
		Women				Men				Overall			
		Controls (n=9210)		Cases (n=5070)		Contorls (*n*=22,744)		Cases (*n*=18894)		Controls (*n*=31,954)		Cases (*n*=23,964)	
		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 (ratio income share richest 20% : poorest 20%)	Lower <6	758	8.23	518	10.22	2155	9.48	2087	11.05	2913	9.12	2605	10.87
	Mid 6-8	2031	22.05	643	12.68	5632	24.76	3323	17.59	7663	23.98	3966	16.55
	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 (US $)	1 (<$15,000)	557	6.05	443	8.74	1011	4.45	1113	5.89	1568	4.91	1556	6.49
	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
	Poulation-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

Epidemiology

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

Variable	Sex								All			
	Women				Men				Overall			
	Controls (n=9210)		Cases (n=5070)		Contorls (*n*=22,744)		Cases (*n*=18894)		Controls (*n*=31,954)		Cases (*n*=23,964)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
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

Discussion

Our results from this large pooled analysis indicate that low SES is a strong risk factor for head and neck cancer. We found that variation in the influence of SES 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 recognized lifestyle behavioral 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 behaviors reduced the increased risk associated with low educational attainment by around two-thirds, leaving a potentially unexplained risk, suggesting that low SES confers risk that operates through pathways other than through these risk behaviors. 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 SES may help explain the global differences we observed. North[24] and South[25] 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.[26,27] 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.[24,28] 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.[19,29] These differences were considered to be potentially due to variation in the tobacco carcinogen content of cigarettes (which have also changed over time)[30] or could be due to other aspects of smoking behavior 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[29,31], 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

Table 3. Distribution of INHANCE Consortium head and neck cancer cases and control-subjects by Smoking, alcohol, and dietary variables by sex

Variable		Sex								All			
		Women				Men				Overall			
		Controls (*n*=9210)		Cases (*n*=5070)		Controls (*n*=22,744)		Cases (*n*=18,894)		Controls (*n*=31,954)		Cases (*n*=23,964)	
		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
	01 to <1	3293	35.75	1527	30.12	6899	30.33	2907	15.39	10192	31.9	4434	18.5
	11 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 (Pieces/week)	<1	1368	14.85	1203	23.73	3974	17.47	4762	25.2	5342	16.72	5965	24.89
	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

Epidemiology

Table 3. Distribution of INHANCE Consortium head and neck cancer cases and control-subjects by Smoking, alcohol, and dietary variables by sex (Continued)

Variable		Sex								All			
		Women				Men				Overall			
		Controls (*n*=9210)		Cases (*n*=5070)		Controls (*n*=22,744)		Cases (*n*=18,894)		Controls (*n*=31,954)		Cases (*n*=23,964)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Vegetable consumption (pices/week)	<1	1382	15.01	997	19.66	3960	17.41	4180	22.12	5342	16.72	5177	21.6
	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

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.[29] 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[13] compared with Europe[32–34] or South America[33] – 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.[13]

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.[35] 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 behaviors, 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.[13]

The causal mechanisms between low educational attainment or income and disease are *via* behavioral lifestyle factors[36] and/or through psychosocial, material and life-course pathways.[37] We have observed both an attenuation of the risk associated with low education in relation to head and neck cancer by behavioral factors and also an as yet unexplained "direct" risk. Causal inference of low educational attainment is considered problematic on two counts—first, 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*.[38]

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 standardization of case-definition and smoking and alcohol variables within the dataset. Here we endeavored to standardize education levels using the UNESCO ISCED, which is a recognized instrument for cross-country education analysis[39,40]; and to standardize household income categories into US dollars in absolute terms as reported. Changes in the education systems (albeit unlikely in the relatively short time-

Table 4. Adjusted Odds Rations and 95% confidence intervals for the association between head and neck 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,<0.0001	10039	8748	1.87	1.53	2.29	27, <0.0001	7680	7142	1.46	1.16	1.82	25 <0.0001
Mid	10238	8370	1.80	1.57	2.07	30,<0.0001	10046	8105	1.42	1.24	1.63	29, <0.0001	6755	6331	1.32	1.15	1.53	26 <0.0001
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				
	Control	Cases	4. Adjusted for age, sex, center, smoking, alcohol and diet†				Control	Cases	5. Adjusted for age, sex, center, smoking, alcohol, diet and Tb†				Control	Cases	6. Adjusted for age, sex, center, in never smokers/Tb/alcohol users†			
	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	5697	4932	1.43	1.13	1.81	19,<0.0001	5013	4395	1.34	1.04	1.73	16, <0.0001	1784	774	1.61	1.13	2.31	23,0.1751
Mid	3690	3639	1.33	1.11	1.59	19,<0.0001	3107	3240	1.22	1.03	1.46	16, <0.0001	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;
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
3× 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
†Unconditional logistic regression (random-effects model); ref - reference category

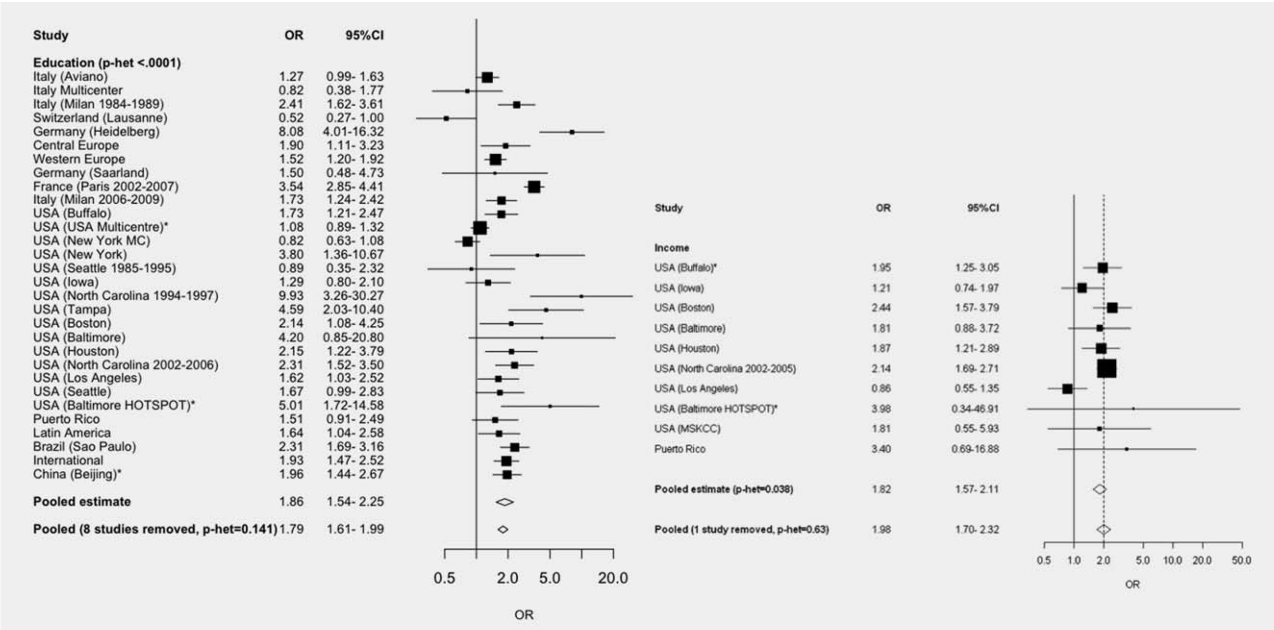

Figure 1. The risk of head and neck cancer associated with low relative to high education and low income relative to high income adjusted for smoking and alcohol behaviors, by study and pooled. OR: odds ratios; 95%CI: 95% confidence intervals *USA Multicenter, Baltimore HOTSPOT, China (Beijing) no lowest group, second group (1v2 or 2v5). Squares: study specific OR; Size of the squares: determined by the inverse of the variance of the log OR. Horizontal lines: study specific 95% CI; Diamond: summary estimate combining the study specific estimates with random-effects models adjusted for age, sex, center, smoking [smoking status, smoking pack years (continuous), cigarettes per day] and alcohol (alcohol drinking status and alcohol frequency); Width of diamond: summary estimate 95% CI Solid vertical line-OR of 1; Dashed vertical line-summary OR, "X studies removed refers to when studies leading to heterogeneity were removed.

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 behavioral factors in the risk of developing head and neck cancer and we assumed there were no unmeasured confounders of the association between behaviors and cancer risk. Therefore, we computed the proportion of the SES effect not attributable to behavioral factors.

Our approach, adjusting for several metrics of smoking, tobacco and alcohol behavior 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 behaviors. 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 behaviors, with higher rates of under-reporting of smoking among men and women with lower education attainment in the United States,[41] but no such differences reported in European studies.[42] This could explain some of the differences in attenuation of the head and neck risk associated with education by behaviors 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[17] and for lung cancer.[43]

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 neighborhood, 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 (Supporting Information Fig. S3).

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 behavioral risk factors, which chimes with previous estimates that 70% of head and neck cancers are "avoidable" by lifestyle changes—particularly smoking and alcohol behaviors.[29,31] Therefore, lifestyle factors need to be considered in their socioeconomic context—both with

Epidemiology

Table 5. 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[1]					Adjusted for age, sex, center and smoking and alcohol[1,2]					% unexplained by smoking and alocohol[3]
Education low vs high	OR	Lower Cl	Upper Cl	*n,p* het *	*p* het**	OR	Lower Cl	Upper Cl	*n*, *p* het*	*p* het**	%
Men	2.58	2.07	3.21	28, <0.0001	0.097	1.44	1.16	1.80	25, <0.0001	0.757	28.1
Women	1.89	1.41	2.54	24,<0.0001		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, <0.0001		1.65	1.32	2.05	27, <0.0001		43.9
Pre-2000 stidies	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, <0.0001		1.70	1.37	2.11	12, 0.0099		46.7
Population controls	3.25	2.25	4.68	9, <0.0001	0.058	1.62	1.17	2.23	7, 0.019	0.539	27.4
Hospital controls	2.16	1.75	2.66	19, <0.0001		1.42	1.08	1.85	19, <0.0001		36.0
Oral cavity	2.06	1.64	2.58	26, <0.0001	0.043	1.33	1.02	1.75	25, <0.0001	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, <0.0001		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, <0.0001		1.69	1.24	2.32	22, <0.0001		34.9
Eurpoe	2.20	1.55	3.11	13, <0.0001	0.047	1.30	0.88	1.93	10, <0.0001	0.630	25.1
North America	3.00	2.05	4.39	13, <0.0001		1.57	1.12	2.19	13, 0.0037		28.4
South /central America	2.37	1.93	2.91	4, 0.37	0 040	1.68	1.31	2.16	4, 0.45		49.8
Lower income inequalcountry	2.22	1.33	3.73	6, <0.0001	0 040	1.30	0.67	2.53	5, < 0.0001	0.002	24.4
Mid income inequal country	1.40	0.90	2.18	9, <0.0001		1.17	0.77	1.78	7, 0.00018		42.3
Higher income inequal country	2.75	2.08	3.62	17, <0.0001		1.65	1.27	2.15	17, <0.0001		37.3

comparison lowest to highest education level;
[1]Unconditional logistic regression.; OR - Odds Ratio; CI - Confidence Interval; n - number of studies; NOS - Not Otherwise Specified
[2]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;
[3]Proportion remaining after attributable fraction of covariates removed 100-(OR1-OR2/OR1-1)×100)

Epidemiology

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 behavioral risk factors indicates the potential role of yet unidentified risk factors and pathways that are associated with SES.

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,[44] but thus far largely ignored in relation to head and neck cancer.[45]

Acknowledgements

No funder had any role in the study design; data collection, analysis or interpretation; in the writing of the report; or in the decision to submit the article for publication. The views expressed are those of the authors and not necessarily those of any of the funders or organizations they represent.

Epidemiology

References

1. Singer C. A study of some factors in the aetiology of oral carcinoma. *Q J Med* 1911;5:15–57.
2. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010. Available at: http://globocan.iarc.fr. Accessed on July 2013.
3. Curado MP, Hashibe M. Recent changes in the epidemiology of head and neck cancer. *Curr Opin Oncol* 2009;21:194–200.
4. Braakhuis BJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: increasing incidence, but not in young adults. *Oral Oncol* 2009;45:85–89.
5. Hammarstedt, Dahlstrand H, Lindquist D, et al. The incidence of tonsillar cancer in Sweden is increasing. *Acta Otolaryngol* 2007;127:988–92.
6. Conway DI, Stockton DL, Warnakulasuriya KA, et al. Incidence of oral and oropharyngeal cancer in United Kingdom (1990–1999): recent trends and regional variation. *Oral Oncol* 2006;42:586–92.
7. Junor EJ, Kerr GR, Brewster DH. Oropharyngeal cancer fastest increasing cancer in Scotland. *BMJ* 2010;340:c2512.
8. Conway DI, Brewster DH, McKinney PA, et al. Widening socioeconomic inequalities in oral cancer incidence in Scotland, 1976-2002. *Br J Cancer* 2007;96:818–20.
9. Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papilloma virus-related and –unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612–19.
10. Sethi S, Ali-Fehmi R, Franceschi S, et al. Characteristics and survival of head and neck cancer by HPV status: a cancer registry-based study. *Int J Cancer* 2012;131:1179–86.
11. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48:3282–7.
12. Canova C, Hashibe M, Simonato L, et al. Genetic associations of 115 polymorphisms with cancers of the upper aerodigestive tract across 10 European countries: the ARCAGE project. *Cancer Res* 2009;69:2956–65.
13. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356:1944–56.
14. Conway DI, Petticrew M, Marlborough H, et al. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. *Int J Cancer* 2008;122:2811–9.
15. Conway DI, McKinney PA, McMahon AD, et al. Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. *Eur J Cancer* 2010;46:588–98.
16. Boing AF, Ferreira Antunes JL, de Carvalho MB, et al. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? *J Epidemiol Community Health* 2011;65:709–14.
17. Menvielle G, Luce D, Goldberg P, et al. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. *Int J Epidemiol* 2004;33:799–806.
18. Pickett KE, Shona K, Brunner E, et al. Wider income gaps, wider waistbands. An ecological study of obesity and income inequality. *J Epidemiol Community Health* 2005;59:670–4.
19. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 2007;99:777–89.
20. Conway DI, Hashibe M, Boffetta P, et al. Enhancing epidemiologic research on head and neck cancer: INHANCE-The international head and neck cancer epidemiology consortium. *Oral Oncol* 2009;45:743–6.
21. UNESCO. International Standard Classification of Education. Paris: UNESCO, 1997.
22. Riley RD, Lambert PC, Abo-Zaid. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340. DOI: 10.1136/bmj.c221.
23. Morgenstern H. Attributable fractions. In: Boslaugh S, ed. Encyclopaedia of epidemiology, vol. 1. Thousand Oaks, CA: Sage Publications, 2008. 55–63.
24. Escabedo LG, Peddicord JP. Smoking prevalence in US birth cohorts: the influence of gender and education. *Am J Public Health* 1996;86:231–6.
25. Szklo AS, de Almeida LM, Figueiredo VC, et al. A snapshot of the striking decrease in cigarette smoking prevalence in Brazil between 1989 and 2008. *Prev Med* 2012;54:162–7.
26. Flinte AJ, Novotny TE. Poverty status and cigarette smoking prevalence in the United States, 1983-1993: the independent risk of being poor. *Tob Control* 1997;6:14–18.
27. Zhu BP, Giovino GA, Mowery PD, et al. The relationship between cigarette smoking and education revisited: implications for categorizing persons' educational status. *Am J Public Health* 1996;86:1582–9.
28. Escabedo LG, Anda RF, Smith PF, et al. Sociodemographic characteristics of cigarette smoking initiation in the United States. *JAMA* 1990;264:1550–5.
29. Hashibe M, Brennan P, Chuang SC, Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18:541–50.
30. Gray N, Zaridze D, Robertson C, et al. Variation within global cigarette brands in tar, nicotine, and certain nitrosamines: analytic study. *Tob Control* 2000;9:351.
31. Anantharaman D, Marron M, Lagiou P, et al. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. *Oral Oncol* 2011;47:725–31.
32. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 2003;95:1772–83.
33. Ribeiro KB, Levi JE, Pawlita M, et al. Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. *Int J Epidemiol* 2011;40:489–502.
34. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
35. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst* 2004;96:99–106.
36. Rose G. Strategy of preventive medicine. Oxford: Oxford University Press, 1992.
37. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol* 2001;30:668–77.
38. Kawachi I, Adler NE, Dow WH. Money, schooling, and health: Mechanisms and causal evidence. *Ann N Y Acad Sci* 2010;1186:56–68.
39. Steedman H, McIntosh S. Measuring low skills in Europe: how useful is the ISCED framework? *Oxford Econ Papers* 2001;53:564–81.

40. Van der Heyden JH, Schaap MM, Kunst AE, et al. Socioeconomic inequalities in lung cancer mortality in 16 European populations. *Lung Cancer* 2009;63:322–30.
41. Wagenknecht LE, Burke GL, Perkins LL, et al. Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. *Am J Public Health* 1992;82:33–36.
42. Cavelaars AE, Kunst AE, Geurts JJ, et al. Educational differences in smoking: international comparison. *BMJ* 2000;320:1102–7.
43. Menvielle G, Boshuizen H, Kunst AE, et al. Occupational exposures contribute to educational inequalities in lung cancer incidence among men: evidence from the EPIC prospective cohort study. *Int J Cancer* 2010;126:1928–35.
44. National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: NICE, 2010.
45. Speight PM, Palmer S, Moles DRl. The cost-effectiveness of screening for oral cancer in primary care. *Health Technol Assess* 2006;10:1–144.