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ORIGINAL PAPER

The aetiology of upper aerodigestive tract cancers among young adults in Europe: the ARCAGE study

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Abstract

Background The incidence of cancers of the upper aerodigestive tract (UADT) is increasing throughout the world. To date the increases have been proportionally greatest among young people. Several reports have suggested that they often do not have a history of tobacco smoking or heavy alcohol consumption.

Objective To determine the contribution of lifestyle factors to the etiology of UADT cancers occurring in those aged less than 50 years.

Methods A case–control study was conducted in 10 European countries. Cases were cancers of the oral cavity and pharynx, larynx and esophagus, and hospital or population controls were age and sex matched.

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Results There were 356 cases younger than 50 years and 419 controls. Risk was strongly related to current smoking [odds ratio (OR) 5.5 95%; confidence interval (CI) (3.3, 9.2)], and risk increased with number of pack-years smoked. Risk was also related to alcohol consumption for both current (OR 1.8; 0.97, 3.3) and past (OR 3.4; 1.6, 7.4) drinkers, and risk increased with number of drink-years. Persons frequently consuming fruits and vegetables were at significantly reduced risk.

Conclusions Risk factors already identified as being important for UADT cancers in adults are also important influences on risk in younger adults. The implication of these results is that the public health message in preventing UADT cancers remains the same to young and old alike.

Keywords Epidemiology · Cancer · Oral · Pharynx · Larynx · Tobacco · Alcohol · Diet

Introduction

Cancers of the upper aerodigestive tract (UADT) have been the subject of considerable research interest particularly over the last two decades. Important increases in the incidence of tumor and mortality, particularly from tumors in the oral cavity and pharynx, have been noted [1]. For example, in the United Kingdom, over the period 1990–1999 there has been an average annual increase in incidence of over 2.4% [2]. In some countries, particularly among males in Eastern Europe, the changes have been much more dramatic. For example, in Slovakia rates of oral and pharyngeal cancer in males increased from 4.5 per 100,000 in 1968–1970 to 17.9 per 100,000 in 1987–1989, with even more marked increases in males aged 35–64 years (6.8–47.9 per 100,000) [3]. Overall, in the 25 members state European Union in 2006, there were an estimated 70,200 new cases of cancers of the oral cavity and pharynx registered—representing 3.1% of all cancers [4].

The patterns of changes in incidence and mortality in many countries have suggested a cohort effect and as such the changes observed are currently proportionally greatest among young men [5]. About 6% of oral cancers occur in young people under the age of 45 years [6]. There is relatively little understood about their etiology, since until recently there have been few cases of such cancers among young persons. Several studies, mainly case reports, suggested however that young cases often did not have a history of heavy alcohol or tobacco consumption [7–12]. As a consequence, hypotheses have been proposed that other environmental factors (e.g., occupation, immune defense or viral infection) or genetic factors may be important [13]. Being relatively uncommon has meant that studies to date have had low statistical power to examine risk factors.

We have taken advantage of an international case–control study of UADT cancers: the ARCAGE (Alcohol-Related CAncers and GEnetic Susceptibility) study to determine the importance of lifestyle factors (established as risk factors for UADT cancers at older ages) for these cancers occurring at young ages.

Methods

The ARCAGE project is a large multicenter case–control study conducted in 14 study centers in 10 European countries [14]. Cases are squamous cell carcinomas (SCC) of the upper aerodigestive tract (UADT), i.e., those of the oral cavity, pharynx (other than nasopharynx), larynx, and esophagus (i.e., International Classification of Disease Volume 10 (ICD-10): C01–06, C08–10, C13–15, C32) [15]. Cases were identified from participating hospitals as soon as possible after diagnosis and in no instance later than 6 months after diagnosis. In each center, controls were frequency matched to cases by sex, age (within 5 years), and area of residence. In most centers, controls were frequency matched and chosen among subjects admitted as in-patients or attending as out-patients in the same hospital as the cases. Persons who were admitted with diagnoses related to alcohol, tobacco or dietary factors were excluded. The UK centers used similarly matched population controls.

For the current analysis, we have considered cases aged less than 50 years with cancers of the oral cavity, larynx,

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pharynx, or esophagus. Cases and controls were interviewed face-to-face and completed a questionnaire that collected details on socio-demographic factors and anthropometry, smoking history, alcohol drinking, dietary habits (consumption of fruits, vegetables, and meats), and oral health.

For analysis, "ever" tobacco smoking was defined as smoking cigarettes, cigars, pipe, or any tobacco product at least once per week for a year. Smokers were classified as current smokers unless they had stopped smoking at least 12 months before interview in which case they were defined as former smokers. Ages of starting and stopping tobacco smoking were determined. Pack-years of cigarette equivalents was calculated as the number of packs/day multiplied by years smoked, where a pack was considered as a standard volume of 20 cigarettes.

In relation to alcohol consumption, study subjects were first asked: "Have you ever drunk alcoholic beverages?" and questions on alcohol frequency and duration. Ages of starting and stopping alcohol drinking were determined. Alcohol drink-years were calculated, similar to pack-years of smoking, as the number of drinks/day multiplied by years. A volume of 18 ml pure ethanol was considered a standard drink for all types of alcoholic beverages that generally correspond to 330 ml of beer, 150 ml of wine, and 36 ml of hard liquor.

Body mass index (BMI) was calculated as weight (in kg) 2 years prior to interview divided by squared height (m^2) and was categorized using WHO standards [16]. Dietary habits were assessed using a semi-quantitative food frequency questionnaire, specifically developed for ARCAGE, recording the frequency (per month, per week or per day, as appropriate) of consumption of 22 food items or groups that have been previously reported to be related to UADT cancer risk.

Logistic regression adjusted for age, gender, education, and center was used to model the relationship between case/control status and potential risk factors, and associations are expressed as odds ratio (OR) with 95% confidence intervals (CI). For each analysis, persons with all necessary data were included. The number of persons with missing data for each variable is specified in Tables 2, 3, 4, and 5. Factors that showed a statistically significant association in univariate analysis were entered into a multivariate model. A backward stepwise regression procedure was used to identify the final model. Adjusted measures of the population attributable fraction from the logistic regression model were calculated as described by Greenland and Drescher [17].

STATA statistical software was used for all analyses [18].

Results

There were 2,304 cases and 2,227 controls recruited to ARCAGE, which represented a participation rate of 82 and 68%, respectively [14]. There were 356 cases and 419 controls younger than 50 years (Table 1). The largest number of cases were recruited in France ($n = 90$), Italy

Table 1 Distribution of UADT cases and controls aged < 50 years by center and subsite

Center	Controls	Cases	Cases by subsite						
			Oral cavity	Oro pharynx	Hypo pharynx	OP NOS[a]	Larynx	Esophagus	Overlapping
CZECH REPUBLIC—Prague	26	21	1	7	2	1	4	6	–
GERMANY—Bremen	58	47	14	17	9	1	5	1	–
GREECE—Athens	38	35	9	3	–	7	15	1	–
ITALY—Aviano	16	13	6	3	–	1	1	2	–
ITALY—Padova	21	16	5	5	3	–	2	1	–
ITALY—Turin	42	24	13	5	2	1	2	–	1
IRELAND—Dublin	10	4	1	1	1	–	1	–	–
NORWAY—Oslo	37	17	6	5	1	–	3	2	–
UK—Glasgow	13	14	2	6	–	1	4	–	1
UK—Manchester	24	23	10	7	3	1	2	–	–
UK—Newcastle	12	9	3	1	1	–	3	1	–
SPAIN—Barcelona	37	29	6	11	3	–	6	3	–
CROATIA—Zagreb	9	14	7	5	2	–	–	–	–
FRANCE—Paris	76	90	13	17	13	5	42	–	–
Total	419	356	96	93	40	18	90	17	2

[a] Oral, pharynx not otherwise specified

($n = 53$), Germany (47), and the United Kingdom ($n = 46$). There were approximately equal number of cases of cancers of the oral cavity ($n = 96$), oropharynx ($n = 93$), and larynx ($n = 90$) with smaller number of cases of cancer of the hypopharynx ($n = 40$) and esophagus ($n = 17$). There were 18 cases in which the specific site within the oral cavity or pharynx was not specified and two cases where the tumor overlapped two sites. The cases were predominantly male (290 male cases vs. 66 female cases) and, overall, 60% of cases were diagnosed between ages 45–49 years, 27% between ages 40–44 years and 13% before age 40 years. The cases were of lower social status than controls (8% university education/professional employment, 67% secondary school education/non-manual employment, 25% only primary school education/unskilled employment versus 17, 69 and 15%, respectively among controls: $p < 0.001$).

Tobacco smoking

Current smoking was strongly related to risk of UADT cancer when compared to never smokers (Table 2) [OR 5.5 95% CI (3.3, 9.2)]. Risk increased monotonically with number of pack-years smoked, with OR > 9 for twenty-six or more pack-years. In comparison with current smokers, those who had given up for more than 10 years had a risk (OR 0.2; 0.1, 0.3) that was similar to those who had never smoked [OR 0.2; 0.1, 0.3)]. Risk was also strongly related to the measure of addiction—namely how soon after waking the first cigarette was smoked. Compared to never smokers, those whose first cigarette was within the first 30 min of waking had the highest risk (within 5 min of waking (OR 9.9; 5.1, 19.4), within 6–30 min [OR 7.2; 3.9, 13.3)].

Alcohol consumption

Risk was also strongly related to alcohol consumption (Table 3). There was excess risk, relative to people who had never consumed alcohol, for both current (OR 1.8; 0.97, 3.3) and past (OR 3.4; 1.6, 7.4) alcohol drinkers. Risk increased monotonically with number of alcohol drink-years. In comparison with those who were current drinkers those who had stopped within the past 9 years had a significant excess risk (OR 2.4; 1.1, 5.2), while there was no significant difference in risk for those who had given up

Table 2 Smoking and UADT cancer risk in adults aged < 50 years

Characteristics	Cases *n* (%)	Controls *n* (%)	OR (95% CI)[a]
Smoking			
Never smoker	26 (7.30)	129 (30.79)	1.00
Past	32 (8.99)	72 (17.18)	1.78 (0.95, 3.34)
Current	298 (83.71)	218 (52.03)	5.53 (3.31, 9.22)
Pack-years			
Never	26 (7.30)	129 (30.86)	1.00
<14	47 (13.20)	102 (24.40)	2.34 (1.32, 4.16)
14–25	76 (21.35)	83 (19.86)	4.24 (2.40, 7.49)
26–39	100 (28.09)	57 (13.64)	9.00 (4.89, 16.55)
40+	107 (30.06)	47 (11.24)	10.09 (5.19, 19.61)
Missing	–	1	
Time since stopped smoking			
Current	298 (83.71)	218 (52.03)	1.00
>1–4 years	11 (3.09)	14 (3.34)	0.52 (0.22, 1.21)
5–9 years	10 (2.81)	10 (2.39)	0.85 (0.32, 2.26)
10–35 years	11 (3.09)	48 (11.46)	0.16 (0.08, 0.34)
Never smoker	26 (7.30)	129 (30.79)	0.18 (0.11, 0.30)
First cigarette after waking up			
Never smoker	26 (10.74)	129 (45.58)	1.00
After 60 min	28 (11.57)	42 (14.84)	3.04 (1.52, 6.09)
Within 31–60 min	22 (9.09)	31 (10.95)	4.52 (2.09, 9.75)
Within 6–30 min	83 (34.30)	49 (17.31)	7.16 (3.85, 13.30)
Within 5 min	83 (34.30)	32 (11.31)	9.88 (5.05, 19.35)
Missing	–	3	
Not collected[b]	90	76	
Past smoker	24	57	

[a] Adjusted for age (years, continuous), gender, alcohol consumption, education, and center

[b] Not all data were collected in the Paris center

Table 3 Alcohol consumption and UADT cancer risk in adults aged < 50 years

Characteristics	Cases *n* (%)	Controls *n* (%)	OR (95% CI)[a]
Alcohol consumption			
Never	19 (5.34)	59 (14.11)	1.00
Past	53 (14.89)	27 (6.46)	3.42 (1.59, 7.37)
Current	284 (79.78)	332 (79.43)	1.80 (0.97, 3.34)
Missing	–	1	
Alcohol drink-years			
Never	19 (5.48)	59 (14.53)	1.00
<20	64 (18.44)	151 (37.19)	1.23 (0.63, 2.38)
20–39	41 (11.82)	57 (14.04)	1.77 (0.85, 3.70)
40–59	37 (10.66)	41 (10.10)	2.01 (0.93, 4.34)
60–79	35 (10.09)	24 (5.91)	3.41 (1.49, 7.77)
80+	151 (43.52)	74 (18.23)	3.92 (1.96, 7.83)
Missing	9	13	
Time since stopped drinking			
Current	284 (81.61)	332	1.00
>1–9 years	26 (7.47)	10	2.38 (1.08, 5.23)
10+ years	20 (5.75)	16	1.17 (0.57, 2.41)
Never drunk alcohol	19 (5.17)	59	0.55 (0.30, 1.03)
Missing	7	2	
How often drink alcohol before noon			
Never	13 (5.39)	49 (14.98)	1.00
Never before noon	117 (48.55)	219 (66.97)	1.71 (0.80, 3.67)
Less 1 per month	18 (7.47)	15 (4.59)	3.26 (1.15, 9.27)
1–4 per month	9 (3.73)	10 (3.06)	1.54 (0.46, 5.12)
1–3 per week	17 (7.05)	9 (2.75)	4.19 (1.32, 13.31)
Most days or every day	67 (27.80)	25 (7.65)	4.52 (1.87, 10.92)
Missing	25	16	
Not collected[b]	90	76	

[a] Adjusted for age (years, continuous), gender, smoking, education, and center

[b] Not all data were collected in the Paris center

more than 10 years previously. There was a strong relationship between risk and a measure of addiction—how often alcohol was consumed before noon. Relative to persons who never drank alcohol those who did so before noon on most or every day had a greater than four-fold increased risk (OR 4.5; 1.9, 10.9).

Diet

In relation to BMI 2 years prior to diagnosis (or a matched time before interview for controls) and relative to persons with a BMI higher than 30.0 kg m^{-2}), persons who were underweight (BMI < 18.4 kg m^{-2}) had a significantly increased risk of UADT cancer (OR 4.2; 1.4, 12.2) (Table 4). Aspects of diet were strongly related to risk (Table 4). In comparison with those who consumed fruits less than once per week those who consumed them at least once per week (OR 0.5, 0.3, 1.1) or several times per day 0.3 (0.1, 0.5) had reduced risk. A similar pattern was evident for vegetable and salad consumption. Risk of UADT cancers was significantly in excess among persons consuming beef (OR 1.8; 1.1, 3.1).

Oral health

In comparison with those who never visited a dentist, those who did (however infrequently) had a decreased risk of UADT, with the lowest risk evident in those who visited at least every year. (OR 0.2; 0.1, 0.4) (Table 5). Risk of UADT cancers was increased in those with dentures (OR 1.5; 0.96, 2.5), with frequent use of mouthwash (at least twice per day vs. never: OR 1.7; 0.7, 4.0), while a decreased risk was associated with toothbrushing (at least twice a day vs. once a day or less: OR 0.66 (0.43, 1.01), although these relationships were not statistically significant.

Multivariate model

The final multivariable analysis included the following factors: smoking status (never/ever), alcohol drink-years (never or less than 40 vs. 40+), and fruit consumption

Table 4 UADT cancer risk in relation to prior BMI and diet in adults aged < 50 years

Characteristics	Cases *n* (%)	Controls *n* (%)	OR (95% CI)[a]
BMI 2 years previously			
30.0–53.0	29 (11.07)	67 (19.76)	1.00
25.0–29.9	77 (29.39)	112 (33.04)	2.02 (1.11, 3.66)
18.5–24.9	141 (53.82)	147 (43.36)	2.59 (1.47, 4.55)
13.0–18.4	15 (5.73)	13 (3.83)	4.18 (1.44, 12.16)
Missing	4	4	
Not collected[b]	90	76	
Fruits			
Never or less than once/week	45 (12.78)	17 (4.09)	1.00
Once/week	40 (11.36)	32 (7.69)	0.52 (0.23, 1.15)
Several times/week	116 (32.95)	107 (25.72)	0.54 (0.27, 1.08)
Once/day	70 (19.89)	120 (28.85)	0.33 (0.16, 0.67)
Several times/day	81 (23.01)	140 (33.65)	0.26 (0.13, 0.52)
Missing	4	3	
Vegetables (potatoes excluded)			
1 time/week or less	35 (9.94)	23 (5.56)	1.00
Several times/week	149 (42.33)	132 (31.88)	0.58 (0.30, 1.13)
1 time/day	82 (23.30)	124 (29.95)	0.43 (0.21, 0.86)
Several times/day	86 (24.43)	135 (32.61)	0.37 (0.17, 0.77)
Missing	4	5	
Salad			
Never or less than 1 time/week	54 (20.30)	46 (13.49)	1.00
1 time/week	40 (15.04)	44 (12.90)	0.74 (0.38, 1.42)
Several times/week	120 (45.11)	141 (41.35)	0.80 (0.47, 1.37)
At least 1 time/day	52 (19.55)	110 (32.26)	0.50 (0.27, 0.92)
Missing	–	2	
Not collected[b]	90	76	
Beef			
Never or less than 1 time/week	55 (20.91)	102 (29.82)	1.00
1 time/week	97 (36.88)	127 (37.13)	1.27 (0.77, 2.10)
Several times/week or more often	111 (42.21)	113 (33.04)	1.81 (1.06, 3.09)
Missing	3	1	
Not collected[b]	90	76	
Ham, salami, sausages			
Never or less than 1 time/week	36 (13.53)	64 (18.82)	1.00
1 time/week	53 (19.92)	76 (22.35)	1.19 (0.63, 2.26)
Several times/week	101 (37.97)	122 (35.88)	1.39 (0.78, 2.47)
At least 1 time/day	76 (28.57)	78 (22.94)	1.49 (0.77, 2.89)
Missing	–	3	
Not collected[b]	90	76	

[a] Adjusted for age (years, continuous), gender, smoking, alcohol consumption, education, and center

[b] Not all data were collected in the Paris center

frequency (adjusted for age, gender, education and center). The population attributable fraction (PAF) was calculated for these variables in the final model. This showed a PAF for smoking-related factors of 70% (95% CI 54, 80%), alcohol-related factors 36% (95% CI 23, 47%), and low fruit consumption 39% (95% CI 20, 54%). For the combination of these factors, the PAF was 88% (95% CI 0.80, 93%).

Discussion

This multi-center study, the largest to date conducted on the etiology of upper aerodigestive tract cancers in young adults, has produced clear and consistent conclusions. The risk factors already identified as being important for such cancers in adults generally also influence the risk in younger adults. Risk is increased by tobacco smoking (and

Table 5 Oral health and UADT risk in adults aged < 50 years

Characteristics[a]	Cases *n* (%)	Controls *n* (%)	OR (95% CI)[a]
Dentures			
No	193 (72.83)	294 (86.22)	1.00
Yes	72 (27.17)	47 (13.78)	1.54 (0.96, 2.47)
Missing	1	2	
Not collected[b]	90	76	
Tooth brushing			
Once a day or less often	124 (49.80)	108 (32.63)	1.00
2 Times/day or more often	125 (50.20)	223 (67.37)	0.66 (0.43, 1.01)
Missing	16	12	
Not collected[b]	90	76	
Mouthwash use			
Never	151 (58.08)	199 (58.53)	1.00
<Once a day	61 (23.46)	91 (26.76)	1.02 (0.66, 1.60)
Once a day	29 (11.15)	34 (10.00)	1.22 (0.65, 2.30)
2 Times a day or more often	19 (7.31)	16 (4.71)	1.70 (0.73, 3.95)
Missing	6	3	
Not collected[b]	90	76	
Dental attendance			
Never	43 (16.48)	16 (4.83)	1.00
<Every 5 years	73 (27.97)	74 (22.36)	0.28 (0.13, 0.60)
Every 2–5 years	66 (25.29)	63 (19.03)	0.42 (0.19, 0.90)
At least every year	79 (30.27)	178 (53.78)	0.16 (0.07, 0.35)
Missing	5	12	
Not collected[b]	90	76	

[a] Adjusted for age (years, continuous), gender, smoking, alcohol consumption, education, and center

[b] Not all data were collected in the Paris center

increases with amount smoked), alcohol consumption (and increases with amount drunk), a lack of fruit and vegetables and markers of poor oral health (not visiting a dentist regularly).

There are several methodological issues to consider in interpreting the results. First, the study has included cancers over several sites in the upper aerodigestive tract. We therefore conducted an additional analysis to determine whether there was any evidence of heterogeneity of our results for tobacco, alcohol, and diet. Risks were similar across sites except that heavy smoking (14+ pack-years) was particularly associated with cancers of the larynx (OR 13.10; 5.03, 34.09: oropharynx OR 3.14; 1.70, 5.81: oral cavity OR 2.55; 1.43, 4.56). Second, although this study was conducted across 10 countries in Europe, we do not have sufficient number of subjects to determine whether the effects are consistent across countries nor of the effects of multiple exposures to these factors. Third, this study has not assessed total dietary intake and thus we have not been able to examine the effects of individual foods and nutrients in the context of the whole diet.

Previous studies have come to inconsistent conclusions on the etiology of UADT in young people. Some, particularly smaller studies, have highlighted that many young patients have not been exposed to the traditional risk factors or that the risk estimates are smaller (e.g., [19]). However, other studies have found that most patients do smoke tobacco, drink alcohol, and have a poor quality diet [20]. In the current study, 94% of cases were either current or former smokers and 95% reported alcohol consumption. In a study in Northern Italy and Switzerland of patients with oral and pharyngeal cancers below 46 years, Rodriguez et al. [21] reported multivariate ORs of 20.7 and 4.9 for heavy smokers and drinkers, respectively. They reported a population attributable risk for smoking, alcohol, and low vegetable consumption of 85%. This study has confirmed these findings and, in addition, has shown that measures of addiction to alcohol and tobacco are strong markers of risk. It also has demonstrated for tobacco smoking that 10 years after stopping, risk has returned to around the levels seen in those who have never smoked.

Some of the results found in the current study may seem initially surprising. For example, the risk of UADT cancers is higher in past compared to current drinkers and those who have given up recently are at higher risk. This is likely to be explained by the fact that those previous drinkers who try to abstain from alcohol completely may be the ones who have previously had high levels of consumption. This has been observed, more generally, in studies of alcohol consumption and mortality [22]. It may also reflect aspects

of reporting such that cases, who may still be drinking, report that they have given up.

We found an increased risk (OR 1.7), but not statistically significant, for mouthwash use. There have been some studies which have suggested that frequent use of mouthwash is a risk factor for cancers of the oral cavity and that this risk is mediated through the alcohol content of the mouthwash [23, 24]. However, recent reviews have not agreed on whether the available epidemiological evidence supports such an association [25, 26]. A further, artefactual reason for observing an association with mouthwash is that it is a proxy for alcohol and tobacco use and is used to disguise the oral malodour associated with their use. Indeed one such study in women found that cases were likely to use mouthwash specifically for this reason [27]. We have no such data in this study to evaluate this and it remains the most likely reason for our observed association. Consistent with other studies, we find that regular attendance at the dentist is a marker of low risk.

An important question is why some people develop UADT cancer at a young age while others, also exposed to the traditional risk factors, do not. It may be that the level of exposure is high and the current study provides support for this. Second, the effects of exposure may be modified by genetic factors. An important role of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) has been postulated [28] and we have previously shown in this and two other studies that gene variants of the ADH gene [rs1229984 (ADH1B) and rs1573496 (ADH7)] were protective against UADT cancers [29]. There are also other risk factors for oral cancer, such as Human Papillomavirus [30], which have not been considered in this study.

In summary, this study has shown that young persons with UADT cancers across European centers have high exposure to the traditional risk factors of tobacco smoking, alcohol drinking, and poor diet. Each of these risk factors was strongly related to risk. The implication of these results is that the public health message in preventing UADT cancers remains the same to young and old alike.

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References

1. Warnakulasuriya S (2009) Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 45:309–316
2. Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, Macpherson LM (2006) Incidence of oral and oropharyngeal cancer in United Kingdom (1990–1999)—recent trends and regional variation. Oral Oncol 42:586–592
3. Plesko I, Macfarlane GJ, Evstifeeva TV, Obsitnikova A, Kramarova E (1994) Oral and pharyngeal cancer incidence in Slovakia 1968–1989. Int J Cancer 56:481–486
4. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18:581–592
5. Macfarlane GJ, Boyle P, Evstifeeva TV, Robertson C, Scully C (1994) Rising trends of oral cancer mortality among males worldwide: the return of an old public health problem. Cancer Causes Control 5:259–265
6. Llewellyn CD, Johnson NW, Warnakulasuriya KA (2001) Risk factors for squamous cell carcinoma of the oral cavity in young people—a comprehensive literature review. Oral Oncol 37: 401–418
7. Carniol PJ, Fried MP (1982) Head and neck carcinoma in patients under 40 years of age. Ann Otol Rhinol Laryngol 91:152–155
8. Son YH, Kapp DS (1985) Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. Cancer 55:441–444
9. Cusumano RJ, Persky MS (1988) Squamous cell carcinoma of the oral cavity and oropharynx in young adults. Head Neck Surg 10:229–234
10. Sankaranarayanan R, Mohideen MN, Nair MK, Padmanabhan TK (1989) Aetiology of oral cancer in patients less than or equal to 30 years of age. Br J Cancer 59:439–440
11. Iype EM, Pandey M, Mathew A, Thomas G, Sebastian P, Nair MK (2001) Oral cancer among patients under the age of 35 years. J Postgrad Med 47:171–176
12. Harris SL, Kimple RJ, Hayes DN, Couch ME, Rosenman JG (2009) Never-smokers, never-drinkers: unique clinical subgroup of young patients with head and neck squamous cell cancers. Head Neck
13. Hirota SK, Braga FP, Penha SS, Sugaya NN, Migliari DA (2008) Risk factors for oral squamous cell carcinoma in young and older Brazilian patients: a comparative analysis. Med Oral Patol Oral Cir Bucal 13:E227–E231
14. Lagiou P, Georgila C, Minaki P et al (2009) Alcohol-related cancers and genetic susceptibility in Europe: the ARCAGE project: study samples and data collection. Eur J Cancer Prev 18:76–84
15. International Classification of Disease Volume 10 (ICD-10) http://www.who.int/classifications/icd/en/
16. World Health Organisation (WHO) (2000) Obesity: preventing and managing the global epidemic. WHO, Geneva
17. Greenland S, Drescher K (1993) Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 49:865–872
18. StataCorp (2009) Stata statistical software: release 10.1. StataCorp LP, College Station

19. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya KA (2003) Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol 39:106–114
20. Mackenzie J, Ah-See K, Thakker N et al (2000) Increasing incidence of oral cancer amongst young persons: what is the aetiology? Oral Oncol 36:387–389
21. Rodriguez T, Altieri A, Chatenoud L et al (2004) Risk factors for oral and pharyngeal cancer in young adults. Oral Oncol 40:207–213
22. Doll R, Peto R, Boreham J, Sutherland I (2005) Mortality in relation to alcohol consumption: a prospective study among male British doctors. Int J Epidemiol 34:199–204
23. Wynder EL, Kabat G, Rosenberg S, Levenstein M (1983) Oral cancer and mouthwash use. J Natl Cancer Inst 70:255–260
24. Winn DM, Blot WJ, McLaughlin JK et al (1991) Mouthwash use and oral conditions in the risk of oral and pharyngeal cancer. Cancer Res 51:3044–3047
25. Carretero Pelaez MA, Esparza Gomez GC, Figuero Ruiz E, Cerero Lapiedra R (2004) Alcohol-containing mouthwashes and oral cancer. Critical analysis of literature. Med Oral 9(120–3): 116–120
26. McCullough MJ, Farah CS (2008) The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes. Aust Dent J 53:302–305
27. Kabat GC, Hebert JR, Wynder EL (1989) Risk factors for oral cancer in women. Cancer Res 49:2803–2806
28. Yokoyama A, Omori T (2003) Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol 33:111–121
29. Hashibe M, McKay JD, Curado MP et al (2008) Multiple ADH genes are associated with upper aerodigestive cancers. Nat Genet 40:707–709
30. Herrero R, Castellsague X, Pawlita M et al (2003) Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 95: 1772–1783