Role of medical history and medication use in the aetiology of upper aerodigestive tract cancers in Europe: the ARCAGE study.

Role of medical history and medication use in the aetiology of upper aerodigestive tract cancers in Europe: the ARCAGE study

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Abstract

Background: The study aimed to investigate the role of medical history (skin warts, *Candida albicans*, herpetic lesions, heartburn, regurgitation) and medication use (for heartburn; for regurgitation; aspirin) in the aetiology of upper aerodigestive tract (UADT) cancer.
Methods: A multicentre (10 European countries) case–control study [Alcohol-Related CAncers and GEnetic susceptibility (ARCAGE) project].
Results: There were 1779 cases of UADT cancer and 1993 controls. History of warts or *C. albicans* infection was associated with a reduced risk [odds ratio (OR) 0.80, 95% confidence interval (CI) 0.68–0.94 and OR 0.73, 95% CI 0.60–0.89, respectively] but there was no association with herpetic lesions, heartburn, regurgitation or medication for related symptoms. Regurgitation was associated with an increased risk for cancer of the oesophagus (OR 1.47, 95% CI 0.98–2.21). Regular aspirin use was not associated with risk of UADT cancer overall but was associated with a reduced risk for cancer of oesophagus (OR 0.51, 95% CI 0.28–0.96), hypopharynx (OR 0.53, 95% CI 0.28–1.02) and larynx (OR 0.74, 95% CI 0.54–1.01).
Conclusions: A history of some infections appears to be a marker for decreased risk of UADT cancer. The role of medical history and medication use varied by UADT subsites with aspirin use associated with a decreased risk of oesophageal cancer and suggestive of a decreased risk of hypopharyngeal and laryngeal cancers.

Key words
aspirin use epidemiology gastroesophageal reflux medical history medication use upper aerodigestive tract cancer

Introduction

Cancer of the upper aerodigestive tract (UADT) (oral cavity, pharynx, larynx and oesophagus combined) is, globally, the fourth most common cancer and cause of cancer mortality, with an estimated 1 033 004 incident cases and 712 489 deaths in 2008 [1]. While a decrease in mortality was noted in the European Union overall between 1993 and 2004, a persistent rise was observed in central and eastern European countries [2].
Major risk factors for UADT cancer are tobacco consumption, heavy alcohol drinking and poor nutrition, specifically low fruit and vegetable consumption [3–5]. Other possible risk factors include poor oral hygiene, alcohol in mouthwash and genetic factors [6].
Human papillomavirus (HPV) has been shown to play an aetiological role in head and neck cancers irrespective of tobacco and alcohol use [7–10] and may be responsible for the increase in incidence of oropharyngeal squamous cell carcinoma (SCC) [11]. A systematic review by Kreimer et al. [12] of 60 studies estimated that the prevalence of HPV in head and neck SCC specimens was 25.9% (95% CI 24.7–27.2). In clinical practise, only oropharyngeal (tonsil/base of tongue) cancers are tested for HPV [13].
Other aspects of medical history have been investigated, such as self-reported history of warts, herpetic lesions and yeast infection [14–18] and symptoms of gastrointestinal reflux [9, 19], but there have been few studies and the results are inconsistent. The herpes simplex virus (HSV) type 1 has been associated with oral cancer by serological studies, animal models and *in vitro* systems [20]. It is likely that HSV, similar to HPV, is transmitted to the oral cavity by orogenital contact [21]. Infection with *Candida* has been associated with malignant development in the oral cavity by means of endogenous nitrosamine production [15, 22].
Quantitative review of aspirin and cancer risk found reduction in risk for several cancer sites; however, there was evidence of significant heterogeneity between studies, with a stronger reduction in risk in case–control studies compared with cohort studies [23]. Recent analysis of individual patient data from randomised clinical trials of daily aspirin [24] showed a significant reduction in the number of deaths due to cancer. Few studies have investigated the role of nonsteroidal anti-

inflammatory drugs (NSAIDs) specifically for UADT cancer [25–27] and the results are not consistent. Biologically, aspirin and other NSAIDs suppress the production of prostaglandins and thromboxanes by irreversible inactivation of the cyclooxygenase (COX) enzyme that is involved in mechanism of carcinogenesis [28].
The aim of this study, the largest among UADT cancer studies ever conducted in Europe, is to further investigate the effect of previous verrucae/warts infection, HSV and *Candida* infection, symptoms of gastrointestinal reflux and associated use of medication or aspirin on the risk of UADT cancer.

Methods
The Alcohol-Related CAncers and GEnetic Susceptibility (ARCAGE) project is a large multicentre case–control study conducted in 14 European centres (in 10 countries) and coordinated by the International Agency for Research on Cancer (IARC) (http://www.iarc.fr/). It was designed to examine the environmental and genetic risk factors for UADT cancers in adults [29]. Cases are cancers of the UADT, i.e. those of the oral cavity, pharynx (other than nasopharynx), larynx and oesophagus [i.e. International Classification of Disease, Revision 10 (ICD-10: http://www.who.int/classifications/icd/en/) C01-06, C08-10, C13-15, C32]. Cases were identified from participating hospitals as soon as possible after the diagnosis was made, and in no instance later than 6 months after diagnosis.
In each centre, controls were frequency-matched to cases by sex and age (within 5 years). In most centres, controls were chosen from subjects admitted as inpatients or attending outpatient departments in the same hospital as the cases. Admission diagnoses related to alcohol, tobacco or dietary factors were excluded. Only controls with a recently diagnosed disease were accepted; patients who have been in the hospital for >1 week were not included to avoid oversampling of long-stay patients. The proportion of controls within a specific diagnostic group did not exceed 33% of the total. The UK centres used population controls who were randomly chosen from the same family medical practise list as the corresponding case. Specifically, for each case, a total of 10 controls were selected. The potential controls were approached in random order and, in case of non-participation of the first potential control, the second one was approached and so on until one agreed to participate.
The ARCAGE project was approved by the Ethical Review Board of IARC, as well as the respective local boards in the individual participating centres. All subjects provided written informed consent for their participation in the study. Both cases and controls were interviewed, during which time they completed a common lifestyle questionnaire. The questionnaire collected details on sociodemographic factors and anthropometry, smoking history, alcohol consumption, dietary habits (consumption of fruits, vegetables and meat), oral health, medical history and medication use. Specifically, participants were asked if, throughout their lives, they had ever had any of the following:

- Skin warts/verrucae, *C. albicans*/thrush or herpetic lesions/cold sores. Information was also obtained on infection location, i.e. hands, feet, head and neck, genital region or other (open question).
- Heartburn or regurgitation (including frequency and age of commencement) and medication use for these conditions.
- Regular aspirin use (at least once a week for a year). Information was obtained on duration of use. The Paris centre did not collect information on medical history as described above, however participants were asked whether they regularly had migraines and, in case of a positive reply, to indicate the names and duration of drugs used.

STATA 11.0 for Windows [30] was used for statistical data analysis. Unconditional logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for UADT cancer. Multinomial regression models (mlogit procedure in STATA) were used to estimate the ORs for each cancer site. The models were adjusted for the following variables: centre, sex, age,

education, smoking (pack-years), alcohol consumption (alcohol drink-years), fruit intake (frequency) and body mass index (BMI). Further analysis was carried out adjusting history of skin warts/verrucae, *C. albicans*/thrush or herpetic lesions/cold sores for each other in addition to other adjustment variables. Heartburn or regurgitation was also adjusted for aspirin use, in addition to other adjustment variables.

Results

The overall participation rate was 82% among cases and 68% among controls. However, participation rate was low among population controls (26%–35%). In some centres, cases and controls explicitly refused any recording of information and therefore were not included into the participants' database, leading to an overestimated participation rate [29].

The distribution of the hospital controls by diagnostic group was as follows: acute gastrointestinal conditions (19%), injuries (17%), eye, ear or related conditions (14%), musculoskeletal, connective tissue and skin disorders (13%), genitourinary system conditions (10%), respiratory diseases (9%), neurological conditions and behavioural disorders (5%), abnormal laboratory tests or unspecified symptoms and signs or other complaints leading to seeking medical advice (4%), benign neoplasms (3%), circulatory system diseases (3%), endocrine conditions (1%), infectious diseases and congenital malformations (2%) [29]. Only 32 (2%) hospital controls had diseases of the skin and subcutaneous tissue.

In total, there were 1779 cases of UADT cancers (all SCC) available for current analysis and 1993 controls (Table 1).

Table 1.

Distribution of UADT cases and controls by centre and subsite

Centre	Controls	Cases	Cases by subsite (all SCC)					
			Oral cavity	Oropharynx	Hypopharynx	OP NOS[a]	Larynx	Oesophagus
Czech Republic—Prague	187	163	5	49	11	8	41	49
Germany—Bremen	328	277	53	96	40	6	72	10
Greece—Athens	194	211	51	14	1	34	102	9
Italy—Aviano	151	145	48	34	9	1	36	17
Italy—Padova	130	128	26	24	13	0	51	14
Italy—Turin	198	157	65	28	9	2	41	12
Ireland—Dublin	19	33	7	6	5	0	5	10
Norway—Oslo	184	137	39	45	11	1	30	11
UK—Glasgow	91	86	15	23	8	21	18	1
UK—Manchester	186	141	63	40	9	9	20	0
UK—Newcastle	113	67	17	7	4	9	19	11
Spain—Barcelona	166	184	42	34	17	3	79	9
Croatia—Zagreb	46	50	30	12	6	0	2	0
France—Paris	234	323	49	62	40	18	154	0
TOTAL	2227	2102	510	474	183	112	670	153

SCC, squamous cell carcinoma; UADT, upper aerodigestive tract.

a Oral, pharynx not otherwise specified.

The prevalence of skin warts/verrucae was 36% among cases and 45% among controls, *C. albicans*/thrush 16% and 23%, respectively and herpetic lesions (cold sores) 38% and 43%, respectively (Table 2). Having had warts/verrucae or *C. albicans*/thrush infection was associated with a reduced risk for UADT cancers (OR 0.80, 95% CI 0.68–0.94 and OR 0.73, 95% CI 0.60–0.89, respectively) but there was no association with herpetic lesions (OR 0.96, 95% CI 0.82–1.12)

(Table 2). When considered by location, a reduced risk was found for foot skin warts/verrucae (OR 0.70, 95% CI 0.53–0.93), head and neck (OR 0.67, 95% CI 0.49–0.90) and genitals (OR 0.31, 95% CI 0.10–0.90). For history of *C. albicans*/thrush infection, reduced risk was noted for infection in the genitals (OR 0.67, 95% CI 0.49–0.92) and nonsignificant reduced risk for infection in the mouth (OR 0.86, 95% CI 0.59–1.24). Further analysis adjusting history of skin warts/verrucae, *C. albicans*/thrush or herpetic lesions/cold sores for each other in addition to other adjustment variables did not show substantial change in risk estimate (Table 2).

Table 2.
Skin warts/verrucae, *Candida albicans*/thrush, Herpetic lesions (cold sore) and UADT cancer risk

Characteristics	Cases[a]	Controls[a]	OR (95% CI)[b]
	N (%)	*N* (%)	
Skin warts/verrucae			
Never	1119 (63.80)	1077 (55.75)	1.00
Ever	635 (36.20)	890 (45.25)	0.80 (0.68, 0.94)
Skin warts/verrucae (location)[c]			
Hands	433 (24.69)	559 (28.42)	0.84 (0.70–1.01)
Feet	125 (7.13)	230 (11.69)	0.70 (0.53–0.93)
Head & Neck	109 (6.21)	172 (8.74)	0.67 (0.49–0.90)
Genitals	6 (0.34)	15 (0.76)	0.31 (0.10–0.90)
C. albicans/thrush			
Never	1457 (83.83)	1507 (76.85)	1.00
Ever	281 (16.17)	454 (23.15)	0.73 (0.60–0.89)
C. albicans/thrush (location)[c]			
Genitals	93 (5.35)	173 (8.82)	0.67 (0.49–0.92)
Mouth	80 (4.60)	101 (5.15)	0.86 (0.59–1.24)
Herpetic lesions (cold sore)			
Never	1075 (61.75)	1118 (56.84)	1.00
Ever	666 (38.25)	849 (43.16)	0.96 (0.82–1.12)
Herpetic lesions (location)[c]			
Lip	600 (34.46)	773 (39.30)	0.97 (0.83–1.14)
Genitals	12 (0.69)	14 (0.71)	1.06 (0.44–2.50)
Additional model[d]			
Skin warts/verrucae	612 (36.15)	874 (45.31)	0.81 (0.69–0.96)
C. albicans/thrush	273 (16.13)	446 (23.12)	0.76 (0.62–0.94)
Herpetic lesions (cold sore)	652 (38.51)	841 (43.60)	0.99 (0.84–1.16)

CI, confidence interval; OR, odds ratio; UADT, upper aerodigestive tract.
a Numbers do not add up to total due to missing values.
b Adjusted for centre, age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago.
c Reference category ‘never’; Categories are not mutually exclusive.
d Reference category ‘never’; Adjusted for each other in addition to b.

Heartburn was reported by 48% of cases and 48% of controls, while regurgitation was reported by 19% of cases and 20% of controls. Symptoms of gastro-oesophageal reflux were not associated with risk of UADT cancer (OR for heartburn 0.90, 95% CI 0.77–1.04 and OR for regurgitation 0.88, 95% CI 0.73–1.07, respectively) (Tables 3 and 4). There was no change in risk with longer duration of heartburn. Younger age at the onset of heartburn symptoms (<25 years), shorter (<10 years) or longer (≥35 years) time between heartburn symptoms start and diagnosis and medication

use for heartburn were associated with reduced risk (OR 0.68, 95% CI 0.54–0.89; OR 0.76, 95% CI 0.58–0.98; OR 0.74, 95% CI 0.57–0.95; and OR 0.81, 95% CI 0.68–0.96, respectively). There was no association with regurgitation frequency, age at regurgitation onset, time between regurgitation symptoms start and diagnosis or medication use of regurgitation (Table 4). Additional adjustment for aspirin use did not show change in risk estimates (Tables 3 and 4).

Table 3.
Heartburn and UADT cancer risk

Characteristics	Cases[a] *N* (%)	Controls[a] *N* (%)	OR (95% CI)[b]	OR (95% CI)[c]
Heartburn				
Never	932 (52.54)	1040 (52.34)	1.00	1.00
Ever	842 (47.46)	947 (47.66)	0.90 (0.77–1.04)	0.89 (0.71–1.09)
Heartburn frequency				
No heartburn	932 (53.29)	1040 (52.66)	1.00	1.00
Less than once per week	350 (20.01)	424 (21.47)	0.85 (0.70–1.04)	0.85 (0.70–1.04)
Once per week	116 (6.63)	117 (5.92)	0.99 (0.72–1.35)	0.98 (0.72–1.34)
2–6 times per week	160 (9.15)	203 (10.28)	0.81 (0.62–1.05)	0.80 (0.62–1.04)
At least once a day	191 (10.92)	191 (9.67)	0.97 (0.75–1.25)	0.96 (0.75–1.25)
Age began suffering from heartburn (years)				
No heartburn	932 (55.44)	1040 (53.75)	1.00	1.00
<25	159 (9.46)	207 (10.70)	0.68 (0.54–0.89)	0.68 (0.52–0.88)
25–34	205 (12.20)	239 (12.35)	0.89 (0.70–1.13)	0.88 (0.69–1.13)
35–44	169 (10.05)	191 (9.87)	0.89 (0.68–1.16)	0.88 (0.68–1.15)
45+	216 (12.85)	258 (13.33)	0.95 (0.75–1.21)	0.95 (0.75–1.21)
Time between heartburn start and diagnosis (years)				
No heartburn	932 (55.44)	1040 (53.75)	1.00	1.00
0–9	152 (9.04)	215 (11.11)	0.76 (0.58–0.98)	0.75 (0.57–0.98)
10–21	200 (11.90)	237 (12.25)	0.97 (0.76–1.24)	0.97 (0.76–1.23)
22–34	215 (12.79)	228 (11.78)	0.96 (0.76–1.23)	0.96 (0.75–1.22)
35+	182 (10.83)	215 (11.11)	0.74 (0.57–0.95)	0.74 (0.57–0.95)
Medication for heartburn				
No heartburn	932 (53.01)	1040 (52.58)	1.00	1.00
No	343 (19.51)	320 (16.18)	1.06 (0.86–1.30)	1.05 (0.85–1.30)
Yes	483 (27.47)	618 (31.24)	0.81 (0.68–0.96)	0.81 (0.68–0.96)

CI, confidence interval; OR, odds ratio; UADT, upper aerodigestive tract.
a Numbers do not add up to total due to missing values.
b Adjusted for centre, age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago.
c Adjusted for aspirin use (never/ever) in addition to b.

Table 4.
Regurgitation and UADT cancer risk

Characteristics	Cases[a] *N* (%)	Controls[a] *N* (%)	OR (95% CI)[b]	OR (95% CI)[bc]
Regurgitation				
Never	1439 (81.39)	1588 (80.53)	1.00	1.00
Ever	329 (18.61)	384 (19.47)	0.88 (0.73–1.07)	0.88 (0.71–1.10)

Characteristics	Cases[a]	Controls[a]	OR (95% CI)[b]	OR (95% CI)[bc]
	N (%)	*N* (%)		
Regurgitation frequency				
Never	1439 (81.95)	1588 (80.86)	1.00	1.00
Less than once per week	163 (9.28)	181 (9.22)	0.96 (0.74–1.25)	0.96 (0.74–1.25)
Once per week	34 (1.94)	47 (2.39)	0.70 (0.42–1.16)	0.70 (0.42–1.17)
2–6 times per week	46 (2.62)	59 (3.00)	0.72 (0.46–1.15)	0.71 (0.45–1.12)
At least once a day	74 (4.21)	89 (4.59)	0.91 (0.62–1.32)	0.91 (0.63–1.33)
Age regurgitation began (years)				
No regurgitation	1439 (83.61)	1588 (82.07)	1.00	1.00
55+	53 (3.08)	81 (4.19)	0.74 (0.49–1.13)	0.75 (0.49–1.14)
45–54	52 (3.02)	65 (3.36)	0.91 (0.60–1.40)	0.93 (0.61–1.42)
35–44	61 (3.54)	65 (3.36)	0.97 (0.64–1.47)	0.96 (0.63–1.47)
25–34	55 (3.20)	67 (3.46)	0.86 (0.56–1.32)	0.86 (0.53–1.31)
<25	61 (3.54)	69 (3.57)	0.75 (0.49–1.13)	0.74 (0.48–1.12)
Time between regurgitation start and diagnosis (years)				
No regurgitation	1439 (83.61)	1588 (82.07)	1.00	1.00
0–6	64 (3.72)	93 (4.81)	0.70 (0.48–1.02)	0.71 (0.49–1.03)
7–17	63 (3.66)	85 (4.39)	0.96 (0.65–1.43)	0.97 (0.66–1.44)
18–31	80 (4.65)	87 (4.50)	0.87 (0.61–1.25)	0.87 (0.61–1.26)
32+	75 (4.36)	82 (4.24)	0.86 (0.59–1.25)	0.85 (0.58–1.24)
Medication for regurgitation				
No regurgitation	1439 (82.18)	1588 (80.90)	1.00	1.00
No	216 (12.34)	229 (11.67)	0.92 (0.73–1.17)	0.92 (0.73–1.17)
Yes	96 (5.48)	146 (7.44)	0.76 (0.55–1.04)	0.76 (0.55–1.04)

CI, confidence interval; OR, odds ratio; UADT, upper aerodigestive tract.
a Numbers do not add up to total due to missing values.
b Adjusted for centre, age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago.
[c]Adjusted for aspirin use (never/ever) in addition to b.

Regular aspirin use (at least once a week for a year) was reported by 13% of cases and 16% of controls and was associated with borderline reduced risk of UADT cancer (OR 0.87, 95% CI 0.70–1.09) (Table 5). There was no difference in risk by age when regular aspirin use stopped and duration of use; however, there was a decrease in risk among those who started using aspirin regularly at 55–64 years of age (OR 0.60, 95% CI 0.40–0.89) in comparison to those who never used aspirin at least once a week for a year. Cases were more likely to have stopped taking aspirin regularly within a year before interview (OR 0.68, 95% CI 0.51–0.91). When considering aspirin use for migraines (Paris centre only), a reduced risk was observed for aspirin use (OR 0.22, 95% CI 0.10–0.51). When considered by duration of use, significant decrease in risk was observed for whose who used aspirin for migraines for <5 years (OR 0.26, 95% CI 0.10–0.65) and for those who used it for 5–30 years (OR 0.13, 95% CI 0.02–0.80) compared with those with no migraines.

Table 5.
Aspirin use and UADT cancer risk

Characteristics	Cases[a]	Controls[a]	OR (95% CI)[b]
	N (%)	*N* (%)	
Aspirin use (at least once a week for a year)			
Never	1527 (86.66)	1649 (83.71)	1.00

Characteristics	Cases[a]	Controls[a]	OR (95% CI)[b]
	N (%)	*N* (%)	
Ever	235 (13.34)	321 (16.29)	0.87 (0.70–1.09)
Age began using (years)			
Never	1527 (87.46)	1649 (84.13)	1.00
<45	79 (4.52)	91 (4.64)	1.11 (0.78–1.58)
45–54	49 (2.81)	64 (3.27)	0.77 (0.50–1.20)
55–64	54 (3.09)	90 (4.59)	0.60 (0.40–0.89)
65+	37 (2.12)	66 (3.37)	0.93 (0.57–1.50)
Age stopped using (years)			
Never	1527 (89.25)	1649 (85.53)	1.00
<45	18 (1.05)	20 (1.04)	1.46 (0.70–3.04)
45–54	26 (1.52)	38 (1.97)	0.80 (0.44–1.45)
55–64	66 (3.86)	89 (4.62)	0.70 (0.48–1.02)
65+	74 (4.32)	132 (6.85)	0.78 (0.55–1.16)
Duration of use (years)			
Never	1527 (89.30)	1649 (85.53)	1.00
<5	80 (4.68)	127 (6.59)	0.81 (0.58–1.13)
5–9	42 (2.46)	65 (3.37)	0.78 (0.49–1.22)
10+	61 (3.57)	87 (4.51)	0.78 (0.53–1.15)
Time between start using and diagnosis (years)			
Never	1527 (87.61)	1649 (84.39)	1.00
1–3	43 (2.47)	70 (3.58)	0.80 (0.51–1.25)
4–9	57 (3.27)	96 (4.91)	0.73 (0.49–1.08)
10–21	53 (3.04)	70 (3.58)	0.82 (0.54–1.25)
22+	63 (3.61)	69 (3.53)	1.13 (0.76–1.70)
Time since stopped using (years)			
Never	1527 (89.25)	1649 (85.53)	1.00
<1	109 (6.37)	190 (9.85)	0.68 (0.51–0.91)
1–4	42 (2.45)	52 (2.70)	0.97 (0.59–1.60)
5+	33 (1.93)	37 (1.92)	1.20 (0.69–2.09)
Migraines and aspirin use[c]			
No migraines	305 (94.43)	195 (85.15)	1.00
Aspirin	15 (4.64)	32 (13.97)	0.22 (0.10–0.51)
Other medication	3 (0.93)	2 (0.87)	0.33 (0.03–4.34)
Migraines and aspirin use (duration of use, years)[c]			
No migraines	305 (94.43)	195 (85.15)	1.00
<5	12 (3.72)	22 (9.61)	0.26 (0.10–0.65)
5–30	3 (0.93)	10 (4.34)	0.13 (0.02–0.80)
Other medication	3 (0.93)	2 (0.87)	0.33 (0.03–4.31)

CI, confidence interval; OR, odds ratio; UADT, upper aerodigestive tract.
a Numbers do not add up to total due to missing values.
b Adjusted for centre, age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago.
c France (Paris) centre only.

When considered by type of UADT cancer, regular aspirin use was associated with a reduced risk for cancer of the oesophagus (OR 0.51, 95% CI 0.28–0.96) and a nonsignificant reduced risk for

cancer of hypopharynx (OR 0.53, 95% CI 0.28–1.02) and larynx (OR 0.74, 95% CI 0.54–1.01) (Table 6).

Table 6.
ORs by cancer subsite and medical history and medication use

Variable	Subsite (all SCC)[a]						
	Oral cavity	Oropharynx	Hypopharynx	OP NOS[b]	Larynx	Oesophagus	*P*-value[c]
Skin warts/verrucae	0.76 (0.60–0.95)	0.88 (0.70–1.22)	0.62 (0.42–0.92)	0.53 (0.32–0.87)	0.85 (0.67–1.06)	0.85 (0.59–1.24)	0.291
Candida albicans/thrush	0.64 (0.48–0.87)	0.91 (0.68–1.22)	0.58 (0.33–1.03)	0.53 (0.27–1.03)	0.89 (0.67–1.19)	0.47 (0.26–0.83)	0.086
Herpetic lesions	0.97 (0.77–1.23)	0.97 (0.76–1.23)	1.00 (0.69–1.47)	0.87 (0.54–1.39)	0.98 (0.78–1.23)	0.94 (0.65–1.35)	0.997
Heartburn	0.88 (0.70–1.09)	0.89 (0.71–1.12)	0.64 (0.44–0.93)	0.78 (0.50–1.24)	1.05 (0.84–1.30)	0.87 (0.61–1.24)	0.253
Regurgitation	0.89 (0.67–1.18)	0.76 (0.56–1.04)	0.62 (0.37–1.06)	1.07 (0.62–1.86)	0.94 (0.72–1.24)	1.47 (0.98–2.21)	0.065
Medication for heartburn	0.78 (0.61–1.00)	0.78 (0.60–1.01)	0.45 (0.28–0.72)	0.88 (0.54–1.45)	0.96 (0.76–1.22)	0.72 (0.48–1.08)	0.076
Medication for regurgitation	0.76 (0.48–1.25)	0.91 (0.56–1.47)	0.62 (0.24–1.59)	0.67 (0.24–1.89)	0.78 (0.49–1.25)	0.81 (0.38–1.75)	0.977
Aspirin use	1.04 (0.76–1.41)	1.05 (0.76–1.46)	0.53 (0.28–1.02)	1.29 (0.70–2.35)	0.74 (0.54–1.01)	0.51 (0.28–0.96)	0.042

OR, odds ratio; SCC, squamous cell carcinoma.
a ORs from multinomial model adjusted for age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago (note: not adjusted for centre).
b Oral, pharynx not otherwise specified.
c *P*-value for equality of ORs across subsites.

Analysis by type of controls (hospital or population) showed a significantly decreased risk associated with heartburn (OR 0.57, 95% CI 0.39–0.86) and use of medication for heartburn (OR 0.55, 95% CI 0.37–0.80) when restricted to population controls. There was no association observed for hospital controls ($P = 0.021$ and 0.057 for difference in estimates between types of control, respectively) (Table 7). When hospital controls with diseases of the skin and subcutaneous tissue were excluded from the analysis for skin warts/verrucae, the OR estimate did not change substantially (OR 0.83, 95% CI 0.70–0.99).

Table 7.
ORs by centres with population and hospital controls

Variable	Centres using hospital controls			Centres using population controls (UK only)			*P*-value
	Cases[a]	Controls[a]	OR (95% CI)[b]	Cases[a]	Controls[a]	OR (95% CI)[b]	
	N (%)	*N* (%)		*N* (%)	*N* (%)		
Skin warts/verrucae							
Never	949 (65.0)	904 (57.32)	1.00	170 (57.82)	173 (44.36)	1.00	0.150
Ever	511 (35.0)	673 (42.68)	0.84 (0.71–1.00)	124 (42.18)	217 (55.64)	0.58 (0.40–0.85)	
Candida albicans/thrush							
Never	1207 (83.59)	1191 (75.81)	1.00	250 (85.03)	316 (81.03)	1.00	0.822
Ever	237 (16.41)	380 (24.19)	0.72 (0.58–0.90)	44 (14.97)	74 (18.97)	0.76 (0.45–1.29)	
Herpetic lesions							0.584

Variable	Centres using hospital controls			Centres using population controls (UK only)			*P*-value
	Cases[a]	Controls[a]	OR (95% CI)[b]	Cases[a]	Controls[a]	OR (95% CI)[b]	
	N (%)	*N* (%)		*N* (%)	*N* (%)		
Never	928 (64.13)	903 (57.26)	1.00	147 (50.0)	215 (55.13)	1.00	
Ever	519 (35.87)	674 (42.74)	0.94 (0.79–1.23)	147 (50.0)	175 (44.87)	1.11 (0.77–1.60)	
Heartburn							
Never	784 (52.97)	847 (54.66)	1.00	148 (50.34)	166 (42.78)	1.00	0.021
Ever	696 (47.03)	725 (45.34)	0.98 (0.83–1.16)	146 (49.66)	222 (57.22)	0.57 (0.39–0.86)	
Regurgitation							
Never	1189 (80.66)	1273 (80.32)	1.00	250 (85.03)	315 (81.40)	1.00	0.490
Ever	285 (19.34)	312 (19.68)	0.94 (0.76–1.16)	44 (14.97)	72 (18.60)	0.71 (0.43–1.17)	
Medication for heartburn							
Never	1082 (73.91)	1137 (71.46)	1.00	193 (65.65	223 (57.62)	1.00	0.057
Ever	382 (26.09)	454 (28.54)	0.87 (0.72–1.05)	101 (34.35)	164 (42.38)	0.55 (0.37–0.80)	
Medication for regurgitation							
Never	1378 (94.58)	1466 (93.02)	1.00	277 (94.22)	351 (90.70)	1.00	0.717
Ever	79 (5.42)	110 (6.98)	0.84 (0.59–1.19)	17 (5.78)	36 (9.30)	0.72 (0.36–1.45)	
Aspirin use							
Never	1298 (88.42)	1364 (86.22)	1.00	229 (77.89)	285 (73.45)	1.00	0.603
Ever	170 (11.58)	218 (13.78)	0.91 (0.70–1.16)	65 (22.11)	103 (26.55)	0.93 (0.60–1.46)	

CI, confidence interval; OR, odds ratio.
a Numbers do not add up to total due to missing values.
b Adjusted for centre, age, gender, education, smoking (pack-years), alcohol drinking (drink-years), fruit consumption and body mass index 2 years ago.

Discussion

This international multicentre case–control study is the largest to date investigating the role of medical history and medication use in the aetiology of UADT cancers. A history of infections such as warts/verrucae or *C. albicans* infection/thrush was associated with decreased risk of UADT cancer, while there was no association found for herpetic lesions, symptoms of gastro-oesophageal reflux or regular aspirin use. However, the associations varied by subsite within the UADT.
Considering methodological quality, firstly, the study has included cancers over several sites in the UADT. While these are a heterogeneous group of neoplasms, they have similar aetiologies: Regular alcohol consumption and tobacco smoking are established causes of these cancers [3, 4]. However, to investigate potential aetiological differences, we conducted additional analyses by subsite. Secondly, while this study was conducted in 10 countries across Europe, all participating centres followed a similar protocol and used the same questionnaire. This enabled us to take into account in the analyses potential confounding factors such as smoking, alcohol intake, fruit consumption and BMI. Thirdly, while the overall sample size was large, the study did not have the statistical power to examine whether the effects varied between countries. Finally, because three centres (in a single country) used population controls, we carried out additional analysis separately for hospital and population controls.
Our results show that having a history of warts/verrucae was associated with a reduced risk for UADT cancers, irrespective of location. This effect was more evident for cancers of oral cavity, hypopharynx and oral/pharynx cancers with site ‘not otherwise specified’. The effect was also similar for all UADT subsites, but was more evident in centres with population controls. A possible explanation for this is that eligible control admission diagnoses included skin diseases for hospital controls. However, the proportion of hospital controls with diseases of the skin and subcutaneous tissue was small and exclusion of hospital controls with these diseases did not substantially change

the OR estimate. These findings contradict previous studies, which have not reported any associations: Maden et al. [21] reported an OR of 1.30, 95% CI (0.7–2.4) for oral cancer in men for common warts and an OR of 0.9, 95% CI (0.2–2.4) for genital warts; Talamini et al. [17] reported an OR for oral cancer of 1.0, 95% CI (0.5–2.3) for hand and feet warts and an OR of 0.5, 95% CI (0.1–1.6) for other sites; Garrote et al. [16] reported an OR of 1.04, 95% CI (0.43–2.50) for warts on hands and feet and an OR of 0.72, 95% CI (0.44–1.18) for other sites for cancer of the oral cavity and oropharynx.

The explanation for a reduced risk of warts on UADT cancer is not clear. The effect was evident for all locations, despite the fact that the warts are caused by different types of HPV. For example, common warts are caused mostly by HPV types 2 and 4, while anogenital warts are commonly caused by HPV types 6 and 11. HPV types 16, 18 and others have been associated with cancer [12].

A history of *C. albicans* (thrush) infection in our study was also associated with a reduced risk for UADT cancers, irrespective of location. This effect was more evident for cancers of oral cavity and oesophagus. Talamini et al. [17] in contrast found a significant risk for cancers of the oral cavity and oropharynx (OR 6.5, 95% CI 1.2–34.4) for oral candidosis and an increased but not significant risk (OR 2.0, 95% CI 0.7–5.8) for candidosis in other body sites, however Garrote et al. [16] found no association. While thrush is an acute infection, it has been suggested that malignant transformation of oral leukoplakia may be elicited by particular biotypes of *C. albicans* and that yeasts could play a causal role in oral cancer by means of endogenous nitrosamine production [15].

In agreement with previous studies [14, 17, 21, 31], we did not find a significant association between previous herpetic infection and UADT cancers. However, two studies have reported significant protective effect: Garrote et al. [16] (OR 0.36 95% CI 0.17–0.75) for herpetic lesions and cancer of oral cavity and oropharynx and Rosenquist et al. [26] for a history of herpes labialis for oral cancer (OR 0.5, 95% CI 0.3–0.9). It has been previously suggested that patients with oral cancer have an increased immune response to HSV [20]. Laboratory experiments have shown that HSV can be carcinogenic or cocarcinogenic [32]. However, later epidemiological studies did not support these observations.

Overall, we did not find an association for symptoms of gastro-oesophageal reflux (heartburn or regurgitation) and risk of UADT cancer, which is similar to results reported by D'Souza et al. [9] for oropharyngeal cancer (OR 1.0, 95% CI 0.5–1.7). However, regurgitation was associated with a nonsignificant increased risk for cancer of oesophagus. A study in Sweden [19] of 189 cases of oesophageal SCC and 820 controls did not find an association with symptoms of reflux, irrespective of the frequency, severity or duration of the symptoms (OR 1.1, 95% CI 0.7–1.9). However, strong relationships have been reported between gastro-oesophageal reflux and oesophageal adenocarcinoma [18, 19]. Analysis by type of controls (hospital or population) showed a significantly decreased risk associated with heartburn and medication for heartburn, only when using population controls. This may be accounted for by the increased morbidity among hospital controls masking such an association. However, in this study 45% of hospital controls and 57% of population controls reported heartburn.

While our study overall did not show a significant association between regular aspirin use and risk of UADT cancer, when considered by subsite, aspirin was associated with a reduced risk for cancer of oesophagus and a nonsignificant reduced risk for cancers of hypopharynx and larynx. This finding supports results of a review of aspirin and cancer risk [23], which showed that aspirin use was associated with a reduced risk of cancer of the oesophagus. Combined data from three Italian case–control studies showed that aspirin use was associated with reduced risk of cancers of the UADT (OR 0.33, 95% CI 0.13–0.82 for duration of use of >5 years) [25]. Analysis of individual patient data from eight randomised trials of daily aspirin versus no aspirin [24] showed a significant reduction in death due to cancer (OR 0.79, 95% CI 0.68–0.92). There were no data reported specifically on head and neck cancer, but there was a nonsignificant decrease in risk of death due to oesophageal cancer [hazard ratio (HR) 0.78 (95% CI 0.27–2.23) for 0–5 years of follow-up and HR 0.43 (95% CI 0.11–1.72) for 5 years follow-up or longer]. The overall protective effect of aspirin

was more evident for adenocarcinomas (HR 0.53, 95% CI 0.35–0.81 for 5 years of follow-up or longer). The protective effect of aspirin in this combined analysis did not appear to increase at doses >75 mg daily.

In the current study, we did not collect information on dose and defined regularly as at least once per week for a year. We also did not collect information on reasons for regularly taking aspirin. Aspirin is widely used for pain relief and also most commonly used for primary and secondary prevention of vascular disease. However, its use is associated with gastrointestinal and extracranial bleeds. When recruiting hospital controls, admission diagnoses related to alcohol, tobacco or dietary practises were excluded, but diagnoses related to musculoskeletal, gastrointestinal and circulatory diseases were included [29]. It may be therefore that aspirin use is particularly high in the hospital control populations chosen and this might artificially increase the observed protective effect. We therefore carried out a separate analysis for centres with population- and hospital-based controls and found no statistically significant difference in risk associated with aspirin use. We also noted that a higher proportion of controls stopped taking aspirin within a year before interview compared with cases.

Conclusions

In this largest study conducted on the role of infections on UADT cancers, we have reported that some infections appear to be a marker for decreased risk. The role of medical factors and medication use varied with UADT subsites with aspirin use associated with a decreased risk of oesophageal cancer and suggestive of a decreased risk of hypopharyngeal and laryngeal cancers. These findings are important in terms of understanding the aetiology of UADT cancers and should be a priority for further investigation using collaboration between major studies (e.g. INHANCE [33]).

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Disclosure

The authors declare no conflicts of interest.

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References

1. Ferlay J, Shin HR, Bray F et al. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer 2010; http://globocan.iarc.fr (7 July 2011, date last accessed).
2. Garavello W, Bertuccio P, Levi F et al. The oral cancer epidemic in central and eastern Europe. Int J Cancer 2010; 127: 160–171.
3. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83—Tobacco Smoke and Involuntary Smoking. Lyon, France: IARC-publisher 2004.

4. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 96. Alcohol Consumption and Ethyl Carbamate. Lyon, France: IARC-publisher 2010.
5. Lagiou P, Talamini R, Samoli E et al. Diet and upper-aerodigestive tract cancer in Europe: the ARCAGE study. Int J Cancer 2009; 124: 2671–2676.
6. Warnakulasuriya S. Causes of oral cancer—an appraisal of controversies. Br Dent J 2009; 207: 471–475.
7. Franceschi S, Mun˜ oz N, Bosch XF et al. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. Cancer Epidemiol Biomarkers Prev 1996; 5: 567–575.
8. Gillison ML, Koch WM, Capone RB et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000; 92: 709–720.
9. D'Souza G, Kreimer AR, Viscidi R et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007; 356: 1944–1956.
10. Rotnaglova E, Tachezy R, Salakova´ M et al. HPV involvement in tonsillar cancer: prognostic significance and clinically relevant markers. Int J Cancer 2011; 129: 101–110.
11. Mehanna H, Jones TM, Gregoire V, Ang KK. Oropharyngeal carcinoma related to human papillomavirus. BMJ 2010; 340: c1439
12. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005; 14: 467–475.
13. Thavaraj S, Stokes A, Guerra E et al. Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice. J Clin Pathol 2011; 64: 308–312; [Epub ahead of print 2011 February 23].
14. Kabat GC, Hebert JR, Wynder EL. Risk factors for oral cancer in women. Cancer Res 1989; 49: 2803–2806.
15. Krogh P. The role of yeasts in oral cancer by means of endogenous nitrosation. Acta Odontol Scand 1990; 48: 85–88.
16. Garrote FL, Herrero R, Reyes RM et al. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. Br J Cancer 2001; 85: 46–54.
17. Talamini R, Vaccarella S, Barbone F et al. Oral hygiene, dentition, sexual habits and risk of oral cancer. Br J Cancer 2000; 83: 1238–1242.
18. Duan L, Wu AH, Sullivan-Halley J, Bernstein L. Antacid drug use and risk of esophageal and gastric adenocarcinomas in Los Angeles County. Cancer Epidemiol Biomarkers Prev 2009; 18: 526–533.
19. Lagergren J, Bergstro¨m R, Lindgren A, Nyre´net O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825–831.
20. Steele C, Shillitoe EJ. Viruses and oral cancer. Crit Rev Oral Biol Med 1991; 2: 153–175.
21. Maden C, Beckmann AM, Thomas DB et al. Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. Am J Epidemiol 1992; 135: 1093–1102.
22. Hooper SJ, Wilson MJ, Crean SJ. Exploring the link between microorganisms and oral cancer: a systematic review of the literature. Head Neck 2009; 31: 1228–1239.
23. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. Cancer Causes Control 2006; 17: 871–888.
24. Rothwell PM, Fowkes FG, Belch JF et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011; 377: 31–41.
25. Bosetti C, Talamini R, Franceschi S et al. Aspirin use and cancers of the upper aerodigestive tract. Br J Cancer 2003; 88: 672–674.
26. Rosenquist K, Wennerberg J, Schildt EB et al. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol 2005; 125: 1327–1336.
27. Friis S, Poulsen A, Pedersen L et al. Use of nonsteroidal anti-inflammatory drugs and risk of oral cancer: a cohort study. Br J Cancer 2006; 95: 363–365.
28. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 2002; 94: 252–266.
29. Lagiou P, Georgila C, Minaki P et al. Alcohol-related cancers and genetic susceptibility in Europe: the ARCAGE project: study samples and data collection. Eur J Cancer Prev 2009; 18: 76–84.
30. StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.
31. Winn DM, Blot WJ, McLaughlin JK et al. Mouthwash use and oral conditions in the risk of oral and pharyngeal cancer. Cancer Res 1991; 51: 3044–3047.
32. Shillitoe EJ, Silverman S Jr. Oral cancer and herpes simplex virus—a review. Oral Surg Oral Med Oral Pathol 1979; 48: 216–224.
33. Conway DI, Hashibe M, Boffetta P. Enhancing epidemiologic research on head and neck cancer: INHANCE—The international head and neck cancer epidemiology consortium. Oral Oncol 2009; 45: 743–746