Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: The ARCAGE study.

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a r t i c l e i n f o

Article history:
Received 17 September 2013
Received in revised form 5 February 2014
Accepted 3 March 2014
Available online 27 March 2014

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Oral Oncology 50 (2014) 616–625
Keywords:
Head and neck neoplasms
Oral health
Oral hygiene
Genetic polymorphisms

a b s t r a c t Objective: We aimed to assess the association of oral health (OH), dental care (DC) and mouthwash with upper-aerodigestive tract (UADT) cancer risk, and to examine the extent that enzymes involved in the metabolism of alcohol modify the effect of mouthwash. Materials and methods: The study included 1963 patients with incident cancer of the oral cavity, oropharynx, hypopharynx, larynx or esophagus and 1993 controls. Subjects were interviewed about their oral health and dental care behaviors (which were converted to scores of OH and DC respectively), as well as smoking, alcohol drinking, diet, occupations, medical conditions and socio-economic status. Blood samples were taken for genetic analyses. Mouthwash use was analyzed in relation to the presence of polymorphisms of alcohol-metabolizing genes known to be associated with UADT. Adjusted odds ratios (ORs) and 95%-confidence intervals [CI] were estimated with multiple logistic regression models adjusting for multiple confounders. Results: Fully adjusted ORs of low versus high scores of DC and OH were 2.36[CI = 1.51–3.67] and 2.22[CI = 1.45–3.41], respectively, for all UADT sites combined. The OR for frequent use of mouthwash use (3 or more times/day) was 3.23[CI = 1.68–6.19]. The OR for the rare variant ADH7 (coding for fast ethanol metabolism) was lower in mouthwash-users (OR = 0.53[CI = 0.35–0.81]) as compared to never-users (OR = 0.97[CI = 0.73–1.29]) indicating effect modification ($p_{heterogeneity}$ = 0.065) while no relevant differences were observed between users and non-users for the variant alleles of ADH1B, ADH1C or ALDH2. Conclusions: Poor OH and DC seem to be independent risk factors for UADT because corresponding risk estimates remain substantially elevated after detailed adjustment for multiple confounders. Whether mouthwash use may entail some risk through the alcohol content in most formulations on the market remains to be fully clarified. Introduction Cancer of the oral cavity, larynx, oropharynx, hypopharynx and esophagus, i.e. upper aerodigestive tract tumors (UADT), account for approximately 129,000 new cancer cases annually in the European Union [1], making them together the 4th and 10th most common cancer site in men and women, respectively. The most important risk factors are consumption of alcohol and tobacco with a greater than multiplicative joint effect [2]. Among never smokers it is likely that alcohol has little or no effect [1,3]. There is also increasing evidence that high consumption of fruits and vegetables are protective [4–8], and emerging evidence for the role of HPV infection in some subsites [9]. Occupational exposures are known risk factors for UADT [10–14]. Low socioeconomic status (SES) and a downward trajectory of social position over the life-course are also both associated with an increased risk after adjustment for confounding factors [15,16]. Both a lack of oral hygiene and poor oral health seem to be risk factors for cancers of the

UADT, independently from smoking and alcohol consumption [17–21]. Frequent use of mouthwash may be a risk factor due to the alcohol contained in many formulations [22,23]. Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH) and is further metabolized to acetic acid by aldehyde dehydrogenase (ALDH). Polymorphic variants of the genes ADH1B, ADH1C and ADH7 encoding for rapid metabolism of ethanol have been shown to decrease the risk of UADT [24–28] indicating that fast metabolism of ethanol reduces its carcinogenic effect. In a genome-wide association study comprising over 8000 cases and 11,000 controls (including our ARCAGE – Alcohol-Related Cancers And Genetic-susceptibility in Europe – study participants), variants in all 4 genes were robustly associated with UADT, with the association for the ADH1B gene variant (rs1229984) being particular prominent among heavy drinkers [25]. Similarly, we hypothesize that an effect of mouthwash may be modified by ADH genes, in particular by the ADH1B variant rs1229984. The evidence for the risk associated with alcohol-containing mouthwashes is limited. Although a recent meta-analysis showed no statistically significant association between mouthwash-use and oral cancer [29], nevertheless, this issue may still be considered as controversial [30]. While one recent case-control study found a positive association between daily mouthwash use and UADT with, both, alcohol-containing and non-alcoholic mouthwashes [20], another recent study used non-alcoholic mouthwash users as the reference and observed threefold risks among nonusers and users of alcohol-containing mouthwashes [21]. The objective of this analysis is to disentangle the effects of mouthwash from major potential confounding factors such as smoking and alcohol and to investigate the role of mouthwash and oral health/dental care more comprehensively [31]. We aim to use a novel approach, developing two composite weighted scores were constructed using indicators of oral health and dental care that were associated with UADT in previous studies. In addition, we investigate the potential risk due to frequent use of mouthwash and its potential effect modification by genetic variants that have been shown to modify the risk of UADT in heavy alcohol drinkers. Materials and methods Briefly, the ARCAGE multicenter case-control study for 13 centers (cf. Table 1) in 9 European countries collected extensive lifestyle data including oral health (OH) and dental care (DC) [32]. The study was approved by the ethical review board of the coordinating center, IARC, and the respective local boards in all centers. All subjects signed an informed consent form. With a common protocol, cases were defined as those patients newly diagnosed with primary squamous cell tumors of the UADT between 2002 and 2005. Diagnoses included malignant cancers of the oral cavity (ICD-O-3 topography: C00-06), oropharynx (C09, 10), hypopharynx (C12, 13), pharynx (C14), larynx (C32), or esophagus (C15). Controls were frequency-matched to cases by sex and age (5-year groups). In the UK centers, population controls were randomly selected from the same medical practice list as the corresponding cases. In all other countries patients admitted to the same hospitals as the cases for a wide spectrum of medical conditions not associated with alcohol consumption and smoking were selected as controls [32]. Subjects were interviewed face-to-face by trained interviewers about socio-demographic characteristics, anthropometric measures, smoking and alcohol consumption, frequency of intake of selected foods, a detailed occupational history and a medical and dental history including oral hygiene habits. We used the number of years of fulltime education (school, high school, university) as a measure of socio-economic status (SES). Lifetime smoking history of cigarettes, cigars, and pipes was used to calculate ‘pack-years’. Lifetime duration of drinking and average daily alcohol consumption over the lifetime (drinks/day) was assessed for all beverage categories. Daily consumption was converted into standard units with one drink corresponding to 8 g of ethanol. Weekly consumption of fruits and vegetables recorded by a food frequency questionnaire was categorized by countryspecific tertiles [32]. In the absence of any previous established scoring system, a priori we constructed a composite weighted score of oral health (OH) based on the following three variables that repeatedly were reported as being associated with one or more UADT sites. The categories were chosen to ensure equal distribution of study subjects while the weights (in brackets) were assigned according to the strength of associations in previous studies without knowing the corresponding risk estimates in our data: 1. Wearing of dentures (none = 0; partial denture in upper or lower jaw = 1; partial denture in both jaws = 2; complete denture in one jaw = 3; complete denture in both jaws = 4). 2. Age at starting to wear dentures (no denture = 0; denture at age 55 years or older = 1; denture at age 35–54 years = 2; denture at age below 35 years = 3). 3. Frequency of gum bleeding from brushing teeth (sometimes or never = 0; always or almost always = 1; zero in subjects wearing complete dentures in both jaws). Weights were added up over these variables to give a maximum score of seven for the poorest OH level. History of oral, pharyngeal or laryngeal biopsies, while included in the questionnaire (and analyzed separately), were not included in the OH score as we could not rule out that part of the biopsies reported by cases were disease-related. The composite weighted score of dental care (DC) was constructed a priori in a similar way as the OH score based on the following three variables: 1. Frequency of tooth cleaning (at least twice/day = 0; once/ day = 1; 1–4 times/week = 2; less often or never = 3). 2. Use of toothbrush, toothpaste or dental floss (two or three of these = 0; only one of these three = 1; none of these = 2). 3. Frequency of visiting a dentist (at least once/year = 0; every 2– 5 years = 1; less than every 5 years = 2; never = 3). The maximum DC score of eight indicated poor DC. Mouthwash use was not included in the DC score as previous studies suggested that frequent mouthwash use carried a potential risk rather than a benefit for UADT. Those with complete upper and lower dentures were not scored and excluded. Composite weighted scores were grouped into four categories such that OH and DC scores of zero served as the reference. The other categories were defined such that each included a meaningful number of subjects while keeping the range between low and high scores as wide as possible. The sample size was chosen to allow identification of a twofold relative risk for rare exposures with 1% prevalence, or a 50% risk increase for more common exposures of at least 5% prevalence. Regarding an assessment of gene-environment interaction, the sample size was chosen to allow identification of a twofold relative risk for polymorphisms with a population prevalence of 5% or more. For inter-country comparisons, the sample size was chosen to allow detection of effect modification between countries for the common risk factors (e.g. 10% or more), which have a moderate increased risk of between 2- and 2.5-fold. The study was designed to provide a sufficient number of cases to enable subgroup analyses. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated by unconditional logistic regression using the PROC LOGISTIC function of the SAS software package, Version 9.2. The strength and robustness of the association between indicators of the OH and DC scores and UADT were explored by consecutive inclusion of potential confounders in the statistical model to examine attenuation of the ORs. The basic model 1 (OR_1) includes sex, age (9 categories) and study center (using dummy variables). As additional variables, model 2 (OR_2) includes smoking status (never, former, current smoking), tobacco consumption (packyears), duration of alcohol drinking (6 dummy variables for duration: 1–9 years, 10–19 years, 20–29 years, 30–39 years, 40+ years, unknown) and frequency of alcohol drinking. Frequency of drinking was weighted by multiplying the number of drinks/week by years of alcohol drinking. We imputed 44 missing values for frequency by the median (of cases and controls) within each drinking duration category. Further adjustment for education was included in model 3 (OR_3) using two dummy variables (intermediate/upper secondary school [corresponding to 8–13 years of school], university degree). Model 4 (OR_4) extended model 3 by adding two tertiles of frequency of fruit and vegetable intake, respectively (two dummy variables each). In sensitivity analyses, we stratified by sex and by subsite of UADT (esophagus; hypopharynx and larynx; oral cavity and oropharynx). We analyzed 4 SNPs from the genes ADH1B (rs1229984), ADH1C (rs698), ADH7 (rs1573496) and ALDH2 (rs4767364) assuming a dominant model. All four SNPs have been conclusively shown to be associated with a risk of UADT, with the most comprehensive evidence from a recent genome-wide study of UADT that involved over 8000 cases and 11,000 controls including the ARCAGE study. Of particular interest was the greater effect among alcohol users that was observed with the ADH1B variant rs1229984, implying a gene-environment interaction [25]. We hypothesized that the association with these SNPs may be more pronounced in mouthwash users, in particular for ADH1B (rs1229984). Results The overall response proportion was 80% in cases and 66% in controls. The study group comprised 1963 cases and 1993 controls after exclusion of

prevalent cases, subjects with tumors of the salivary glands, carcinoma in situ and non-UADT as well as controls with non-eligible diseases (Table 1). The majority of the cases (48%) had tumors of the mouth and oropharynx, followed by hypopharynx and larynx (36%) and esophagus (12%). The site of origin was not assigned in 5% because the tumor had overlapping sites. Table 2 shows the distribution of known risk factors and their adjusted ORs. Our data corroborated the dose–effect relationship of smoking and alcohol consumption with UADT risk. SES and consumption of fruits and vegetables were inversely associated with risk of these tumors after adjustment for smoking and alcohol. Table 3 displays the risk estimates for each indicator of OH and DC and the impact of adjustment on these estimates. Indicators of oral health Wearing dentures was associated with an elevated risk, with complete dentures in both (upper and lower) jaws carrying the highest risk (OR_1 = 2.60; CI = 2.15–3.15). The risk estimate was substantially reduced after adjustment for smoking and alcohol (OR_2) while further adjustment for education and diet had little impact (OR_4 = 1.73; CI = 1.39–2.15). Similarly, age when starting to wear dentures was under 55 years was associated with an elevated risk by about 40%. However, frequent gum bleeding when cleaning teeth was associated with no noticeable risk differences. Indicators of dental care Compared to subjects cleaning their teeth at least twice per day the risk estimates increased with decreasing frequency of tooth cleaning. Subjects cleaning their teeth less than once per week showed the highest risk estimate (OR_1 = 3.51; 95%CI = 2.55–4.83) but adjustment attenuated this effect substantially (OR_4 = 1.37; 95%CI = 0.95–1.99). Similarly, the elevated risk for not using a toothbrush (OR_1 = 1.96; 95%CI = 0.94–4.06) came close to unity after adjustment (OR_4 = 1.15; 95%CI = 0.48–2.80). Neither non-use of toothpaste nor non-use of dental floss showed a marked increased risk after adjustment for confounding. Risk estimates decreased with increasing frequency of visiting a dentist during the last 20 years. Compared to participants who were seeing the dentist at least once a year, participants who never visited the dentist had an estimated OR_4 of 1.93 (95%CI = 1.48–2.51). Frequent use of mouthwash (three and more times/day) was positively associated with UADT as compared to never use with adjustment for confounders increasing the risk estimate further (OR_4 = 3.23; CI = 1.68–6.19). While this effect was strong, only 1.8% of cases and 0.8% of controls reported such frequent use. The risk was most pronounced for oral cavity (OR_4 = 3.53; CI = 1.65–7.57) and pharyngeal cancers (OR_4 = 3.50; CI = 1.55– 7.89). When restricting the analysis to non-smokers or to non-drinkers, the risk persisted. Only four (3.1%) of 128 non-drinking cases and three (1.2%) of 254 non-drinking controls reported frequent use of mouthwash, resulting in an OR_4 of 4.42 (CI = 0.79–24.75). Frequent mouthwash users did not differ from less frequent users in terms of amount of drinking and smoking, frequency of toothbrushing or use of toothpaste or dental floss. Although frequent mouthwash users were more likely to wear complete dentures (28.9% versus 17.5%), the risk estimates for frequent mouthwash use were elevated in both those wearing complete dentures (OR_4 = 7.27; 95%CI = 1.32–40.0) and among those not wearing complete dentures (OR_4 = 2.57; 95%CI = 1.24–5.33). Weighted scores of oral health and dental care ORs for OH/DC scores are reported in Table 4. Good OH scores 1–4 did not noticeably elevate risk for UADT cancer while scores 5, 6 and 7 did increase risk. Poor OH (score = 7) was associated with a more than twofold risk of developing UADT after adjustment for confounding factors (OR_4 = 2.22; 95%CI = 1.45–3.41). Even a moderate lack of DC (score = 1) was associated with an elevated risk of developing UADT after adjustment (OR_4 = 1.36; 95%CI = 1.07–1.72). ORs increased substantially with increasing DC score reaching their maximum for scores 5–8 (OR_1 = 6.01; 95%CI = 4.07–8.87). Smoking and alcohol were the main confounders (OR_2 = 2.77; 95%CI = 1.79–4.27) while further adjustment for SES and diet had little impact (OR_4 = 2.36; 95%CI = 1.51–3.67). We carried out sensitivity analyses using the numeric scores without categorisation. This resulted in unstable risk estimates due to small numbers in some strata, but the overall trend of increasing risk with increasing score was confirmed for both scores. Subgroup analyses showed consistent risk elevations for OH/DC across all subsites of UADT (Table 5). We observed a more than twofold though statistically nonsignificant increased risk for frequent mouthwash use even in the subgroup of cases and controls with the best OH score (score = 0) (OR_4 = 2.33; 95%CI = 0.72–7.47). Genetic markers As expected, and in line with results from the larger GWA study [25], strongly significant inverse associations were observed for the rare variants of ADH1B (OR = 0.55; 95%CI = 0.41–0.74) and ADH7 (OR = 0.79; 95%CI = 0.64–0.98) (Fig. 1). Both of these rare variants code for fast alcohol metabolism. Correspondingly, a positive association was observed for the rare variant of ADH1C that codes for slow ethanol metabolism (OR = 1.23; 95%CI = 1.04–1.46). A moderate non-significantly increased risk was seen for the ALDH2 variant (OR = 1.07; 95%CI = 0.91–1.27) (not included in Fig. 1). No strong effect modification by any of these variants was observed after stratifying by the level of alcohol consumption. Similarly, the strong effect modification seen in the larger GWA analysis for ADH1B [25] was not replicated here, indicating that the sample size with ARCAGE alone is likely to be insufficient to robustly detect effect modifications. Further, the only indication for effect modification observed after stratifying for mouthwash use was for the ADH7 variant ($p_{heterogeneity}$ = 0.065). When this analysis was restricted to subjects who consumed less than 5 drinks/month the reduced risk for the ADH7 variant persisted among mouthwash users as compared to non-users but the risk estimates became rather unstable, because this restriction reduced the sample size by 74%. Given that no clear effect modification was observed for alcohol use in this analysis or the larger GWA analysis for the ADH7 variant, it is unclear to what extent this could represent real effect modification and not just random fluctuation. Discussion Our study showed that both poor oral health and poor dental care were associated with increased risk of UADT cancer independently of other known risk factors. Semi-quantitative scores of OH and DC revealed a dose–effect relationship with the risk of UADT tumors. Frequent use of mouthwashes (3+ times/day) was associated with an elevated risk of developing UADT cancer. The strengths of our study include: (i) statistical power – this is one of the largest case-control studies to-date which has investigated the etiology of UADT cancer associated with oral health and dental care factors; (ii) strict inclusion criteria – limited to histologically confirmed incident cases; and (iii) thorough adjustment for multiple confounding variables including smoking, alcohol, consumption of fresh fruits and vegetables as well as SES [8,15,16,33,34]. Nevertheless, there are some methodological issues associated with our study. The ARCAGE study relied mainly on hospital controls in all but the UK centers. Hospital controls were chosen to achieve better participation because blood samples had to be taken, but this choice may be more vulnerable to selection bias. To minimize such bias, only those with conditions not related to tobacco smoking, alcohol intake or diet were eligible as controls [8]. However, lower socioeconomic groups have a higher risk of hospital admission [35]. Our study may therefore underestimate the association between UADT and OH/DC since both are associated with low SES. Residual confounding by tobacco smoking, alcohol drinking, and possibly other factors such as poor diet also cannot be ruled out as adjustment had an important effect on most risk estimates. Moreover, some misclassification of these confounders cannot be ruled out which could have led to incomplete adjustment. However, residual confounding should be limited since associations persisted in stratified analyses and since we were able to carefully adjust for alcohol and tobacco for which histories detailed every change in their consumption. Alcohol and tobacco consumption of our controls was comparable to other case-control studies [6,19,36–39]. We performed sensitivity analyses and used alternative modeling strategies to assess the robustness of our findings. A hierarchical model with random center effects gave quite similar risk estimates as our modeling strategy using traditional logistic regression including a dummy variable each center. Also, the introduction of a multiplicative interaction term (pack-years * duration of alcohol consumption) did not have any noticeable effect on the risk estimates. Given the magnitude and the level of lower confi- dence limit of the fully adjusted risk estimates, it therefore seems unlikely that our findings are completely due to residual confounding or inadequate adjustment. The association between poor OH and DC and UADT cancer was attenuated but not eliminated after full adjustment. Furthermore, despite methodological differences, our findings are corroborated by many previous studies [19,21,40–42,17,18,43–50]. As these studies used retrospective designs they are all vulnerable to reporting bias which might explain some of the apparent consistency across studies. However, such reporting bias (e.g. due to underreporting of smoking by cases) would primarily

affect factors known to be associated with UADT cancer like smoking and alcohol but not necessarily DC or OH, and so strong associations of DC and OH with UADT cancer may not be explained by reporting bias. Some previous studies assessed OH by clinical examination, but they did not describe precisely how the various indicators were combined into a single variable. Nevertheless, aggregate variables of OH were consistently associated with elevated risks of head and neck cancers. Inspection of the mouth was not undertaken in the ARCAGE study. Instead, from self-reported data, we developed a composite weighted score for OH and for DC, respectively, in order to obtain robust semi-quantitative variables that capture the various dimensions of oral health and dental care. To our knowledge, a similar but much more simple approach has only been used once [21]. The score allows for subgroup analyses and for the assessment of dose–effect relationships. Both scores showed consistent associations with the tumor sites investigated in our study and may thus serve as a useful tool in future assessments. In agreement with previous IARC studies [19] we found the strongest association with frequent mouthwash use (3+ times/day) for oral cavity and pharyngeal cancers. However, this is based on 36 (17/17 + 2) cases and 16 controls only. In their meta-analysis Gandini et al. observed a dose–effect relationship with increasing frequency of mouthwash use, but the corresponding risk estimates were unstable and not statistically significant [29]. The Carolina Head and Neck Cancer Study did not observe such an association [50] while Winn et al. observed an elevated risk only for the use of mouthwash containing alcohol [44]. Eliot et al. [20] reported an elevated risk of head and neck carcinomas for frequent use of both, alcohol-containing and alcohol-free mouthwashes. However, the validity of this distinction based on self-reports may be questionable. The same is true for a recent study from Taiwan [21]that observed an elevated risk for alcohol-containing relative to alcohol-free mouthwashes. These results were quite unstable due to a very small reference group. Unfortunately our questionnaire did not allow us to distinguish between both types of mouthwashes. An in-depth analysis of a Puerto Rican case-control study of oral and pharyngeal cancer [51] showed no overall increased risk but revealed an effect of alcohol-containing mouthwash in women and in subjects who neither drank alcohol nor smoked cigarettes. Our study supports these findings as well as the results of subgroup analyses among alcohol abstainers from the recent study by Guha et al. [19] suggesting mouthwash to be a risk factor for the development of UADT cancer, which may act through the alcohol contained in most formulations on the market [22]. Given alcohol consumption among never smokers appears to have little or no risk for head and neck cancers [2,3] we may expect that similarly, any risk associated with alcohol from mouthwash use may be restricted to smokers. The sample size of our current study was, however, too limited to test such a hypothesis. Further, similar to our previous study [2] that have identified effect modification between alcohol metabolizing genes and alcohol consumption, we investigated whether any effect modification existed between alcohol and acetaldehyde genes known to be associated with head and neck cancers and mouthwash use. On the one hand, the apparent effect modification by the variant ADH7 would support a carcinogenic effect of mouthwash but it is surprising that the effect is stronger than in heavy drinkers. In retrospect, it is likely that the sample size for this study (up to 1353 cases and 1488 controls with genetic and mouthwash data available) was too limited to robustly detect effect modification. On the other hand, the results on the small group of users of mouthwash 3+ times/day might indicate some underlying oral disease as people with oral problems are more likely to use mouthwash [52]. It should be noted that study subjects who used mouthwash 3+ times/day were more likely to wear dentures. Although cases were recruited within 6 months of diagnosis, it is indeed possible that some cases had started chemotherapy before they were interviewed. Therefore, reverse causation cannot be excluded since UADT cancer patients are often prescribed mouthwashes like chlorhexidine for prevention of mouth infection. Also the lack of association in the more informative group of regular users (1–2 times/day) does not support the hypothesis of an association. Neither does the similar magnitude of an effect on oral cavity/oropharynx and hypopharynx/larynx. In conclusion our study provides further evidence for an elevated risk of UADT cancer associated with poor oral health and poor dental care that is not explained by smoking, alcohol or other confounding factors. Excessive use (3+ times/day) of mouthwash also increased risk for UADT cancer but the question whether this effect is mediated by alcohol content or just due to bias or reverse causation cannot be decided with our data. UADT cancer prevention strategies may want to consider promoting oral health and dental care, regularly attending the dentist, good personal oral hygiene practices. Funding This work was supported by the European Community (5th Framework Programme) [grant number QLK1-CT-2001-00182], University of Athens Medical School and Bureau of Epidemiologic Research Academy of Athens, for the Athens center; Padova University (Contract No. CPDA057222) for the Padova center; Compagnia San Paolo, AIRC, and Piedmont Region for the Turin center. The Estonian study was supported by Targeted Financing from Estonian Government: SF0180142, European Union through the European Regional Development Fund in the frame of Centre of Excellence in Genomics and 7FP Project ECOGENE. Conflict of interest statement None declared. Acknowledgements The authors thank the patients and their families for their participation and gratefully acknowledge the study interviewers and our clinical colleagues in hospitals and primary care who supported this study. GJM and TVM partly worked on this study while at the University of Manchester. We acknowledge the help of Dr. Ann-Marie Biggs, Professor Martin Tickle and Professor Phil Sloan in study conduct in the Manchester center. We are grateful for the editorial support by Ina Alvarez in revising previous versions of this manuscript. References

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Table 1
Characteristics of study subjects of the ARCAGE study included in the analysis of oral health and dental care.

	Men				Women				All			
	Cases		Controls		Cases		Controls		Cases		Controls	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	59.7	(9.5)	59.9	(10.5)	60.4	(12.0)	59.6	(13.8)	59.8	(10.1)	59.8	(11.8)
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Center												
Prague	159	(10.3)	154	(10.7)	31	(7.3)	33	(6.0)	190	(9.7)	187	(9.4)
Bremen	236	(15.3)	264	(18.3)	51	(12.1)	64	(11.6)	287	(14.6)	328	(16.5)
Athens	192	(12.5)	143	(9.9)	47	(11.1)	51	(9.3)	239	(12.2)	194	(9.7)
Aviano	119	(7.7)	118	(8.2)	32	(7.6)	33	(6.0)	151	(7.7)	151	(7.6)
Padova	109	(7.1)	97	(6.7)	26	(6.2)	33	(6.0)	135	(6.9)	130	(6.5)
Turin	123	(8.0)	144	(10.0)	43	(10.2)	54	(9.8)	166	(8.5)	198	(9.9)
Dublin	33	(2.1)	6	(0.4)	11	(2.6)	13	(2.4)	44	(2.2)	19	(1.0)
Oslo	121	(7.9)	109	(7.6)	51	(12.1)	75	(13.6)	172	(8.8)	184	(9.2)
Glasgow	61	(4.0)	52	(3.6)	32	(7.6)	39	(7.1)	93	(4.7)	91	(4.6)
Manchester	104	(6.7)	122	(8.5)	45	(10.7)	64	(11.6)	149	(7.6)	186	(9.3)
Newcastle	71	(4.6)	95	(6.6)	17	(4.0)	18	(3.3)	88	(4.5)	113	(5.7)
Barcelona	168	(10.9)	101	(7.0)	27	(6.4)	65	(11.8)	195	(9.9)	166	(8.3)
Zagreb	45	(2.9)	37	(2.6)	9	(2.1)	9	(1.6)	54	(2.8)	46	(2.3)
Subsite												
Mouth/oropharynx	680	(44.1)			254	(60.2)			934	(47.6)		
Hypopharynx/larynx	619	(40.2)			79	(18.7)			698	(35.6)		
Esophagus	173	(11.2)			61	(14.5)			234	(11.9)		
Overlapping multiple sites	69	(4.5)			28	(6.6)			97	(4.9)		
All	1541	(100.0)	1442	(100.0)	422	(100.0)	551	(100.0)	1963	(100.0)	1993	(100.0)

Table 2
Distribution of known risk factors of UADT and corresponding ORs with 95%-confidence intervals.

	Cases		Controls		OR_1	95%-CI	OR_2	95%-CI
	N	(%)	*N*	(%)				
Smoking status[a]								
Never [c]	217	(11.1)	733	(36.8)	1.00	(ref.)	1.00	(ref.)
Former	472	(24.0)	688	(34.5)	2.25	(1.84–2.75)	2.02	(1.64–2.49)
Current	1274	(64.9)	572	(28.7)	8.45	(6.96–10.26)	6.66	(5.45–8.14)
Pack-years[a]								
Never [c]	217	(11.1)	733	(36.8)	1.00	(ref.)	1.00	(ref.)
(0–20)	341	(17.4)	570	(28.6)	2.14	(1.73–2.63)	2.04	(1.65–2.53)
[20–40)	650	(33.1)	416	(20.9)	5.98	(4.86–7.35)	4.98	(4.02–6.16)
[40–60)	427	(21.8)	180	(9.0)	9.72	(7.61–12.42)	7.34	(5.69–9.46)
[60– max]	316	(16.1)	91	(4.6)	14.69	(10.91–19.77)	10.41	(7.65–14.17)
Missing	12	(0.6)	3	(0.2)	15.73	(4.33–57.13)	14.60	(3.97–53.67)
Alcohol drinking (frequency)[b]								
Never [c]	128	(6.5)	254	(12.7)	1.00	(ref.)	1.00	(ref.)
<1 drink/day	516	(26.3)	798	(40.0)	1.35	(1.04–1.74)	1.02	(0.77–1.36)
1–2 drinks/day	500	(25.5)	586	(29.4)	2.03	(1.54–2.66)	1.25	(0.93–1.68)
3–4 drinks/day	325	(16.6)	199	(10.0)	4.13	(3.04–5.61)	1.93	(1.38–2.71)
5 drinks/day	463	(23.6)	122	(6.1)	9.81	(7.12–13.52)	3.95	(2.79–5.60)
Missing	31	(1.6)	34	(1.7)	1.85	(1.08–3.20)	1.28	(0.71–2.29)
Alcohol drinking (duration)[b]								
Never [c]	128	(6.5)	254	(12.7)	1.00	(ref.)	1.00	(ref.)
1–9 years	39	(2.0)	62	(3.1)	1.34	(0.84–2.15)	1.02	(0.62–1.70)
10–19 years	92	(4.7)	117	(5.9)	1.76	(1.22–2.54)	1.22	(0.82–1.81)
20–29 years	292	(14.9)	250	(12.5)	2.58	(1.92–3.47)	1.59	(1.15–2.20)
30–39 years	587	(29.9)	506	(25.4)	2.52	(1.93–3.30)	1.43	(1.06–1.92)
40+ years	810	(41.3)	775	(38.9)	2.23	(1.71–2.90)	1.28	(0.96–1.72)
Missing [c]	15	(0.8)	29	(1.5)	1.23	(0.63–2.41)	0.79	(0.38–1.66)
Education								
General secondary school	719	(36.6)	517	(25.9)	1.00	(ref.)	1.00	(ref.)
Intermediate or advanced secondary school	1147	(58.4)	1274	(63.9)	0.63	(0.53–0.75)	0.77	(0.64–0.93)
University degree	97	(4.9)	202	(10.1)	0.32	(0.24–0.43)	0.60	(0.44–0.82)
Fruit intake (tertiles)								
low [c]	963	(49.1)	596	(29.9)	1.00	(ref.)	1.00	(ref.)
Medium	707	(36.0)	899	(45.1)	0.49	(0.42–0.56)	0.65	(0.55–0.76)
High	293	(14.9)	498	(25.0)	0.34	(0.29–0.41)	0.53	(0.43–0.64)
Vegetable intake (tertiles)								
low [c]	932	(47.5)	703	(35.3)	1.00	(ref.)	1.00	(ref.)
Medium	858	(43.7)	1042	(52.3)	0.64	(0.56–0.73)	0.75	(0.64–0.87)
High	173	(8.8)	248	(12.4)	0.49	(0.39–0.62)	0.60	(0.47–0.78)
All	1963	(100.0)	1993	(100.0)				

OR_1: adjusted for age (9 categories), sex and study center.
OR_2: adjusted as OR_1; plus smoking status (never, former, current), plus cumulative tobacco consumption (pack-years), plus alcohol drinking duration (1–9 years, 10–19 years, 20–29 years, 30–39 years, 40+ years, missing), plus a cumulative alcohol consumption (alcohol drinking frequency weighted by duration of the drinking period).
[a] OR_2 not adjusted for cumulative tobacco consumption.
[b] OR_2 not adjusted for cumulative alcohol consumption.
[c] Reference category (ref.).

Table 3
Distribution of indicators of oral hygiene, dental care and oral health with corresponding ORs and 95%-confidence intervals.

	Cases	(%)	Contr.	(%)	OR_1	95%-CI	OR_2	95%-CI	OR_3	95%-CI	OR_4	95%-CI
Wearing dentures												
None [a]	974	(49.6)	1226	(61.5)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Partial (one jaw)	136	(6.9)	163	(8.2)	1.13	(0.88–1.45)	1.03	(0.78–1.36)	1.02	(0.77–1.34)	1.03	(0.78–1.36)
Partial (lower and upper jaw)	152	(7.7)	154	(7.7)	1.35	(1.05–1.72)	1.29	(0.98–1.69)	1.27	(0.97–1.67)	1.24	(0.94–1.66)
Complete (one jaw)	246	(12.5)	184	(9.2)	1.84	(1.48–2.28)	1.29	(1.01–1.64)	1.25	(0.98–1.59)	1.22	(0.96–1.56)
Complete (lower and upper jaw)	445	(22.7)	251	(12.6)	2.60	(2.15–3.15)	1.81	(1.46–2.25)	1.76	(1.42–2.19)	1.73	(1.39–2.15)
Missing	10	(0.5)	15	(0.8)								
Age at starting to wear dentures												
No denture [a]	974	(49.6)	1226	(61.5)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
55 years or older	259	(13.2)	269	(13.5)	1.28	(1.03–1.58)	1.09	(0.86–1.39)	1.07	(0.84–1.36)	1.05	(0.83–1.34)
35–54 years	477	(24.3)	321	(16.1)	1.97	(1.66–2.34)	1.50	(1.24–1.82)	1.46	(1.20–1.77)	1.44	(1.19–1.75)
Below 35 years	203	(10.3)	146	(7.3)	1.95	(1.53–2.47)	1.41	(1.08–1.84)	1.38	(1.06–1.80)	1.35	(1.03–1.77)
Missing	50	(2.5)	31	(1.6)								
Gum bleeding [complete dentures excluded]												
Never [a]	719	(47.4)	824	(47.3)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Sometimes	517	(34.1)	726	(41.7)	0.79	(0.68–0.92)	0.95	(0.80–1.13)	0.95	(0.80–1.13)	0.94	(0.79–1.12)
Almost always	85	(5.6)	94	(5.4)	1.03	(0.75–1.41)	1.15	(0.81–1.63)	1.16	(0.81–1.65)	1.07	(0.75–1.53)
Missing	197	(13.0)	98	(5.6)								
Teeth cleaning [complete dentures excluded]												
Twice/day [a]	622	(41.0)	1043	(59.9)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Once/day	464	(30.6)	442	(25.4)	1.69	(1.42–2.01)	1.36	(1.12–1.65)	1.35	(1.11–1.64)	1.25	(1.03–1.53)
1–4x/week	172	(11.3)	128	(7.3)	2.18	(1.68–2.83)	1.53	(1.14–2.05)	1.49	(1.11–2.00)	1.39	(1.03–1.87)
Less than once/week or never	153	(10.1)	69	(4.0)	3.51	(2.55–4.83)	1.61	(1.12–2.31)	1.56	(1.08–2.25)	1.37	(0.95–1.99)
Missing	107	(7.0)	60	(3.4)								
Use of toothbrush [complete dentures excluded]												
Yes [a]	1308	(86.2)	1639	(94.1)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
No	20	(1.3)	12	(0.7)	1.96	(0.94–4.06)	1.27	(0.54–3.01)	1.26	(0.53–3.00)	1.15	(0.48–2.80)
Missing	190	(12.5)	91	(5.2)								
Use of toothpaste [complete dentures excluded]												
Yes [a]	1279	(84.3)	1626	(93.3)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
No	47	(3.1)	24	(1.4)	2.26	(1.36–3.74)	1.40	(0.79–2.48)	1.38	(0.78–2.45)	1.33	(0.75–2.37)
Missing	192	(12.6)	92	(5.3)								
Use of dental floss [complete dentures excluded]												
Yes [a]	180	(11.9)	349	(20.0)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
No	1136	(74.8)	1296	(74.4)	1.57	(1.28–1.93)	1.26	(1.00–1.57)	1.24	(0.99–1.55)	1.20	(0.95–1.50)
Missing	202	(13.3)	97	(5.6)								
Visiting a dentist												
Every year [a]	583	(29.7)	965	(48.4)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Every 2–5 years	401	(20.4)	423	(21.2)	1.68	(1.40–2.01)	1.32	(1.08–1.61)	1.30	(1.07–1.59)	1.25	(1.02–1.53)
less than every 5 years	577	(29.4)	405	(20.3)	2.67	(2.22–3.20)	1.64	(1.34–2.01)	1.59	(1.29–1.95)	1.52	(1.23–1.87)
Never	345	(17.6)	176	(8.8)	3.87	(3.08–4.88)	2.13	(1.65–2.76)	2.02	(1.56–2.63)	1.93	(1.48–2.51)
Missing	57	(2.9)	24	(1.2)								
Frequency of mouthwash												
Never [a]	1199	(61.1)	1218	(61.1)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
less than daily	407	(20.7)	447	(22.4)	0.94	(0.80–1.10)	1.04	(0.87–1.25)	1.05	(0.88–1.26)	1.06	(0.89–1.27)
1–2 times/day	290	(14.8)	300	(15.1)	1.02	(0.84–1.23)	1.01	(0.81–1.25)	1.03	(0.83–1.27)	1.06	(0.86–1.32)
3 and more times/day	36	(1.8)	16	(0.8)	2.31	(1.27–4.21)	2.91	(1.52–5.57)	3.01	(1.56–5.79)	3.23	(1.68–6.19)
Missing	31	(1.6)	12	(0.6)								

OR_1: adjusted for age (9 categories), sex and study center.
OR_2: adjusted as OR_1; plus smoking status (never, former, current), plus cumulative tobacco consumption (pack-years), plus alcohol drinking duration (1–9 years, 10–19 years, 20–29 years, 30–39 years, 40+ years, missing), plus a cumulative alcohol consumption (alcohol drinking frequency weighted by duration of the drinking period).
OR_3: adjusted as OR_2 plus SES/professional education (primary school/worker, further school/clerks, University degree/manager).
OR_4: adjusted as OR_3plus consumption of fruits and vegetables (country-specific tertiles each).
[a] Reference category (ref.).

Table 4
Distribution of indices for oral health and dental care with corresponding ORs and 95%-confidence intervals.

	Cases	(%)	Contr.	(%)	OR_1	95%-CI	OR_2	95%-CI	OR_3	95%-CI	OR_4	95%-CI
Oral Health Score[b]												
OH Score = 0 [a]	829	(42.2)	1122	(56.3)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
OH-Score = 1–4	293	(14.9)	370	(18.6)	1.15	(0.96–1.38)	1.00	(0.82–1.23)	0.99	(0.81–1.21)	0.97	(0.79–1.19)
OH-Score = 5,6	508	(25.9)	334	(16.8)	2.32	(1.94–2.77)	1.62	(1.33–1.97)	1.57	(1.29–1.92)	1.53	(1.25–1.87)
OH-Score = 7	97	(4.9)	41	(2.1)	3.95	(2.68–5.83)	2.34	(1.54–3.57)	2.27	(1.49–3.47)	2.22	(1.45–3.41)
Missing[d]	236	(12.0)	126	(6.3)								
Dental Care Score [complete dentures excluded][c]												
DC Score = 0 [a]	298	(19.2)	675	(38.7)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
DC Score = 1	269	(17.7)	390	(22.4)	1.69	(1.36–2.09)	1.45	(1.15–1.83)	1.45	(1.15–1.83)	1.36	(1.07–1.72)
DC Score = 2–4	619	(40.8)	521	(29.9)	3.17	(2.58–3.90)	2.04	(1.63–2.56)	2.01	(1.60–2.53)	1.88	(1.49–2.37)
DC Score = 5–8	109	(7.2)	49	(2.8)	6.01	(4.07–8.87)	2.77	(1.79–4.27)	2.68	(1.73–4.15)	2.36	(1.51–3.67)
Missing[e]	223	(14.7)	107	(6.1)								

OR_1: adjusted for age (9 categories), sex and study center.
OR_2: adjusted as OR_1; plus smoking status (never, former, current), plus cumulative tobacco consumption (pack-years), plus alcohol drinking duration (1–9 years, 10–19 years, 20–29 years, 30–39 years, 40+ years, missing), plus a cumulative alcohol consumption (alcohol drinking frequency weighted by duration of the drinking period).
OR_3: adjusted as OR_2 plus SES/professional education (primary school, further school, University degree).
OR_4: adjusted as OR_3 plus consumption of fruits and vegetables (country-specific tertiles each).

[a] Reference category (ref.).
[b] Oral Health Score is the sum of the three following items:
Denture: No denture = 0, Partial denture (one jaw) = 1, Partial denture (upper and lower jaw) = 2, Complete denture (one jaw) = 3, Complete denture (upper and lower jaw) = 4.
Age at starting to wear dentures: No denture = 0, 55 years or older = 1, 35–54 years = 2, below 35 years = 3.
Gum bleeding: never/sometimes and complete denture in the upper and lower jaw = 0, almost always = 1.
[c] Dental Care Score is the sum of the three following items:
Frequency of tooth cleaning: At least twice/day = 0, once/day = 1, 1–4 times/week = 2, less or never = 3.
Use of toothbrush, toothpaste and dental floss: Two or three of these = 0, only one of these three = 1, none of these three = 2.
Frequency of visiting a dentist: At least once/year = 0, every 2–5 years = 1, less than every 5 years = 2, never = 3.
[d] Missing value for denture or age at start.
[e] Missing value for at least one item.

Table 5
Odds ratios for indices of oral health and dental care with corresponding 95%-confidence intervals.

Frequency of mouthwash			Mouth/oropharynx				Hypopharynx/larynx				Esophagus				Multiple sites			
	Contr.	(%)	Cases	(%)	OR_4	95%-CI	Cases	(%)	OR_4	95%-CI	Cases	(%)	OR_4	95%-CI	Cases	(%)	OR_4	95%-CI
Never [a]	1218	(61.1)	547	(58.6)	1.00	(ref.)	431	(61.7)	1.00	(ref.)	159	(67.9)	1.00	(ref.)	62	(63.9)	1.00	(ref.)
Less than daily	447	(22.4)	209	(22.4)	1.10	(0.89–1.38)	133	(19.1)	0.99	(0.76–1.29)	45	(19.2)	1.14	(0.77–1.70)	20	(20.6)	0.94	(0.51–1.72)
1–2 times/day	300	(15.1)	152	(16.3)	1.11	(0.86–1.44)	104	(14.9)	1.08	(0.80–1.47)	21	(9.0)	0.76	(0.44–1.33)	13	(13.4)	0.99	(0.48–2.03)
3 and more times/day	16	(0.8)	17	(1.8)	3.53	(1.65–7.57)	17	(2.4)	3.50	(1.55–7.89)	0	(0.0)	–	(–)	2	(2.1)	3.89	(0.59–25.52)
Missing	12	(0.6)	9	(1.0)			13	(1.9)			9	(3.8)			0	(0.0)		
Oral Health Score																		
OH Score = 0 [a]	1122	(56.3)	443	(47.4)	1.00	(ref.)	253	(36.2)	1.00	(ref.)	99	(42.3)	1.00	(ref.)	34	(35.1)	1.00	(ref.)
OH-Score = 1–4	370	(18.6)	141	(15.1)	0.94	(0.73–1.21)	102	(14.6)	1.00	(0.74–1.36)	39	(16.7)	1.05	(0.68–1.64)	11	(11.3)	0.63	(0.30–1.36)
OH-Score = 5,6	334	(16.8)	216	(23.1)	1.31	(1.03–1.68)	217	(31.1)	1.94	(1.48–2.55)	47	(20.1)	1.08	(0.70–1.67)	28	(28.9)	1.98	(1.04–3.75)
OH-Score = 7	41	(2.1)	47	(5.0)	2.00	(1.21–3.31)	28	(4.0)	2.14	(1.18–3.88)	12	(5.1)	2.43	(0.98–5.99)	10	(10.3)	2.56	(0.96–6.84)
Missing [b]	126	(6.3)	87	(9.3)			98	(14.0)			37	(15.8)			14	(14.4)		
Dental Care Score																		
DC Score = 0 [a]	675	(38.7)	163	(22.1)	1.00	(ref.)	81	(15.5)	1.00	(ref.)	46	(24.1)	1.00	(ref.)	8	(11.8)	1.00	(ref.)
DC Score = 1	390	(22.4)	138	(18.7)	1.37	(1.02–1.83)	90	(17.2)	1.49	(1.04–2.16)	28	(14.7)	0.72	(0.41–1.26)	13	(19.1)	2.33	(0.89–6.11)
DC Score = 2–4	521	(29.9)	308	(41.8)	1.95	(1.47–2.59)	219	(42.0)	2.00	(1.40–2.86)	62	(32.5)	1.21	(0.72–2.03)	30	(44.1)	3.60	(1.43–9.06)
DC Score = 5–8	49	(2.8)	46	(6.2)	2.23	(1.29–3.84)	45	(8.6)	2.89	(1.57–5.32)	13	(6.8)	1.95	(0.81–4.69)	5	(7.4)	3.54	(0.84–14.84)
Missing [c]	107	(6.1)	82	(11.1)			87	(16.7)			42	(22.0)			12	(17.6)		

OR_4: adjusted for age (9 categories), sex and study center; plus smoking status (never, former, current), plus cumulative tobacco consumption (pack-years), plus alcohol drinking duration (1–9 years, 10–19 years, 20–29 years, 30–39 years, 40+ years, missing), plus a cumulative alcohol consumption (alcohol drinking frequency weighted by duration of the drinking period), plus SES/professional education (primary school, further school, University degree), plus consumption of fruits and vegetables (country-specific tertiles each).
[a] Reference category (ref.).
[b] Missing value for denture or age at start.
[c] Missing value for at least one item.

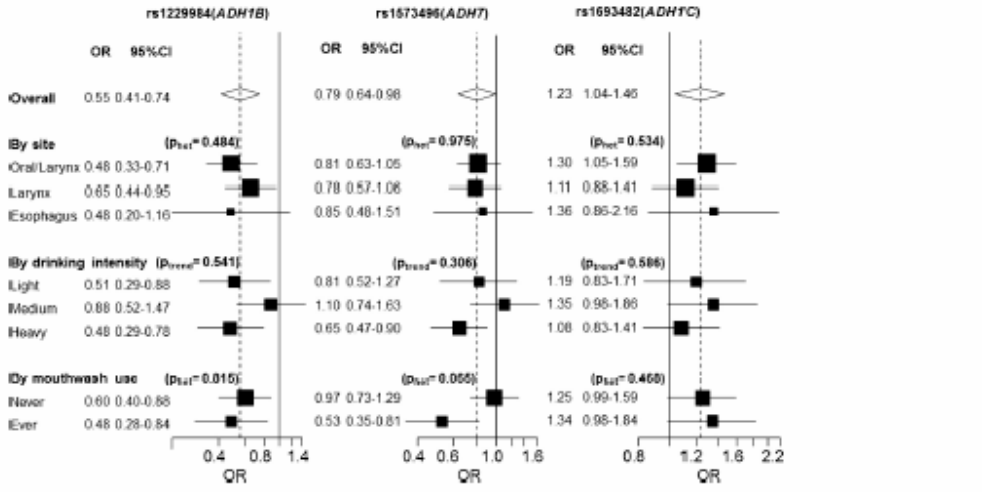

Figure 1. Odds ratio (OR) of upper aero-digestive cancer by rs1229984 (ADH1B), rs1573496 (ADH7) and rs1693482 (AHD1C) genotype. Rare allele carriers (dominant model) versus common allele homozygous genotype. ORs are standardized by age, sex, centre, cumulative alcohol consumption and, when relevant, smoking. *P* values for heterogeneity are derived from a Chi Square statistic with 2df. *P* values for trend test are derived from a Chi Square statistic with 1df.