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A population-based study of the epidemiology of oral squamous cell carcinoma in the Netherlands 1989–2018, with emphasis on young adults

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Abstract. There has been an increasing trend in oral squamous cell carcinoma (OSCC) in patients under 45 years of age. The aim of this study was to evaluate the burden of OSCC in the Netherlands between 1989 and 2018 among young adults (age 20–34 years) when compared to adults (age 35–44 years), and to describe the burden in older groups as well, utilizing cancer registry data to characterize incidence patterns by age, sex, and risk factors. A total of 18,963 cases of OSCC were reported. The overall incidence rate, as measured by annual percentage change (APC), increased significantly from 1989 to 2010 by 1.3% per year (95% confidence interval (CI) 0.9–1.7%) but decreased thereafter by −0.9% (95% CI −2.5% to 0.7%). Annual incidence increased significantly by 2.4% (95% CI 1.1–3.8%) for patients aged 20–34 years, while it decreased for those aged 35–44 years by −0.9% (95% CI −1.7% to 0.0%). In patients older than 60 years, incidence rates increased overall (60–74 years: APC 1.8%, 95% CI 1.5–2.1%; ≥75 years: APC 1.5%, 95% CI 1.2–1.9%). Overall, 66.5% of patients were smokers and 65.3% were alcohol consumers. The marked differences in incidence within the young age subgroups warrants further investigation to elucidate any likely disparity in biological process and clinical outcomes in these populations.

Key words: oral cancer; young adults; incidence; risk factors; epidemiology; Netherlands.

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The incidence of oral cancer varies considerably internationally, and with its high mortality rate, oral cancer remains a serious problem for global public health. Based on the global estimate of the year 2012, cancer of the oral cavity alone was responsible for 202,000 incident cases[1]. The most recent GLOBOCAN data available (2018) showed that a total of 354,864 new cases of lip and oral cavity cancer were diagnosed worldwide, and the highest incidence rates were reported in

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Melanesia and South-Central Asia[2]. More than 90% of malignant oral tumours are squamous cell carcinoma (SCC), and most patients are male and between 50 and 70 years of age, with a history of (combined) tobacco and alcohol use[3]. However, a trend of increasing numbers of patients with oral squamous cell carcinoma (OSCC) younger than 45 years old has been reported in countries all over the world, except for the Netherlands[4]. This subgroup of young patients has been reported to be different with regard to tumour site, aetiological factors, and sex distribution when compared to the older age groups[4,5].

Tobacco and alcohol use are the most prominent risk factors in 74% of OSCC in the Western countries[6]. Viral infection with human papillomavirus (HPV) has also been suggested as an emerging risk factor that explains the increasing incidence of this disease in the young population, particularly in non-smoker young females[7,8]. Its causal role in OSCC is still controversial because of the very low detection rate. The incidence of HPV positivity among Dutch patients with OSCC varies between 3.2% and 3.7%[9]. Hence, the involvement of HPV infection in OSCC carcinogenesis in the Netherlands seems to be limited.

Until now, there has been a lack of consensus on what age should be considered to define 'young' patients. Various studies have arbitrarily used cut-off values of 35, 40, or 45 years[10–13], unavoidably resulting in varying incidence rates and trends, and making it impossible to compare reported incidences rates of OSCC in young patients.

In the Netherlands, the age range for the adolescent and young adults (AYA) group has been defined as 18–35 years[14], but Dutch epidemiological studies so far have evaluated OSCC incidence rates using an upper age limit of 45 years for young adults[15,16]. In order to provide detailed information on incidence rates of OSCC in particular in young patients in the Netherlands, an analysis was performed of the changes in OSCC trends over the period 1989–2018 in young patients in two age groups: 20–34 years and 35–44 years. Possible trends were also determined for older patients. This study is novel in examining incidence trends in OSCC in the Netherlands for these younger age groups separately. The second research aim was to elucidate differences in smoking and drinking habits at the population-level between OSCC age groups.

Materials and methods

Data source and population

All newly diagnosed patients (age ≥20 years) with oral epithelial carcinoma during the years 1989 to 2018, identified in the Netherlands Cancer Registry (NCR), were included. Comprehensive evaluation of the NCR data has shown that the registry database is complete and recording approximately 98% of all cancers[17]. The current analysis was limited to cases diagnosed with SCC (morphology codes M8050–M8084) based on the International Classification of Diseases for Oncology, third edition (ICD-O-3), localized at the following subsites: mucosa of lip (C00.3–C00.9), oral tongue (C02), gum (C03), floor of mouth (C04), palate (C05.0; C05.8–9), and other or unspecified parts of the oral cavity (C06). Epithelial carcinoma of the external lip (C00.0–2) and salivary gland carcinoma (C07–C08) were not considered. Standard clinical TNM staging is the main tumour staging system used in the NCR and comprises four stages. For the purpose of analysis, the TNM stages were condensed into local disease (stages I and II) and advanced disease (stages III and IV). Incidence rates according to sex by age group were expressed as the European age-standardized rate per 100,000 person-years (ESR), and data were classified into five age groups: young adults (20–34 years), adults (35–44 years), middle-aged adults (45–59 years), early elderly (60–74 years), and late elderly (≥75 years).

As part of a national initiative towards a comprehensive registry, the NCR started to collect data on risk factors in 2015, thus information about smoking and drinking habits was available only for the last 4 years of the study period (2015–2018). Smoking tobacco was defined in terms of cigarettes/cigars, and was reported as smoking status (current/past smoker, and never). Quantification was calculated in pack-years, and 20 pack-years was chosen as the cut-off point for subgrouping the patients. Similarly, patients consuming alcohol were defined as 'current drinker/past drinker' and 'never'. Regarding the amount of alcohol, 20 beverages/week was used as the cut-off point to separate the patients into two groups. This information was extracted from the patient electronic files. To facilitate understanding of the characteristics and risk factors of this disease, differences between younger and older patients with regard to sex, sites and subsites, clinical stages, smoking, and drinking were also analysed for that period.

Statistical analysis

Trends in the incidence rates for the five age groups were assessed using the annual percentage change (APC) or average annual percentage change (AAPC) and the corresponding 95% confidence interval (CI), with the Joinpoint Regression Analysis program (version 4.6.0.0; National Cancer Institute, http://surveillance.cancer.gov/joinpoint)[18,19]. This analysis program selected the best-fitting log-linear regression model to identify calendar years (i.e. the join points) when APC changed significantly, allowing for the minimum number of join points necessary to fit the data. Since these tumours are relatively rare, separating the groups according to sex led to ESR values of zero, specifically in the youngest female population aged 20–34 years. Therefore, in this subgroup, an ESR of zero was replaced with 0.01, representing the smallest value in comparison with non-zero ESR in the data being analysed.

To investigate differences in patient and tumour characteristics by age category for data from the years 2015–2018, the Kruskal–Wallis test was used for continuous variables (Kolmogorov–Smirnov test, $P < 0.05$) and the Pearson χ^2 test or Fisher's exact test with the Monte Carlo simulation was used for categorical variables. Measured data of continuous variables were presented as the median value with 25th and 75th percentiles (allowing calculation of the interquartile range (IQR)), and count data were presented as the number (%). All statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

Results

Study population

Over the 29-year period, there were 18,963 cases of oral cavity SCC in the Netherlands. The male-to-female ratio was 1.3:1. Overall, 1.3% of patients were aged 20–34 years and 4.8% were aged 35–44 years at the time of diagnosis. Tongue (38.8%) and floor of the mouth (28.6%) OSCC accounted for two-thirds of all cases that occurred in the Netherlands. The results also showed that 53.0% of the OSCC patients presented with a localized stage disease (TNM stages I and II) (Table 1).

Trends in incidence

Figure 1 shows a graphical representation of the join point analysis by age and sex of the OSCC trends (detailed data are

Table 1. General characteristics of 18,963 patients with oral squamous cell carcinoma diagnosed in 1989–2018, by age group.

Variables	Total	Age groups (years)				
		20–34	35–44	45–59	60–74	≥75
Total, *n* (row %)	18,963 (100)	241 (1.3)	912 (4.8)	5690 (30.0)	7792 (41.1)	4328 (22.8)
Sex, *n* (column %)						
Male	10,848 (57.2)	145 (60.2)	587 (64.4)	3617 (63.6)	4753 (61.0)	1746 (40.3)
Female	8115 (42.8)	96 (39.8)	325 (35.6)	2073 (36.4)	3039 (39.0)	2582 (59.7)
Anatomical sites, *n* (column %)						
Tongue [C02.0–C2.3; C02.8–9]	7356 (38.8)	193 (80.1)	498 (54.6)	2186 (38.4)	2887 (37.1)	1592 (36.8)
Gum [C03]	2672 (14.1)	17 (7.1)	80 (8.8)	562 (9.9)	1027 (13.2)	986 (22.8)
Floor of the mouth [C04]	5430 (28.6)	9 (3.7)	227 (24.9)	2064 (36.3)	2436 (31.3)	694 (16.0)
Others/NOS[a] [C00.3–C00.9; C05.0, C05.8–9; C06]	3505 (18.5)	22 (9.1)	107 (11.7)	878 (15.4)	1442 (18.5)	1056 (24.4)
Clinical stage, *n* (column %)						
Local disease (stage I and II)	10,047 (53.0)	159 (66.0)	536 (58.8)	3047 (53.6)	4152 (53.3)	2153 (49.7)
Advanced disease (stage III and IV)	8070 (42.5)	68 (28.2)	330 (36.2)	2414 (42.4)	3331 (42.7)	1927 (44.5)
Unknown	846 (4.5)	14 (5.8)	46 (5.0)	229 (4.0)	309 (4.0)	248 (5.7)

[a] Not otherwise specified.

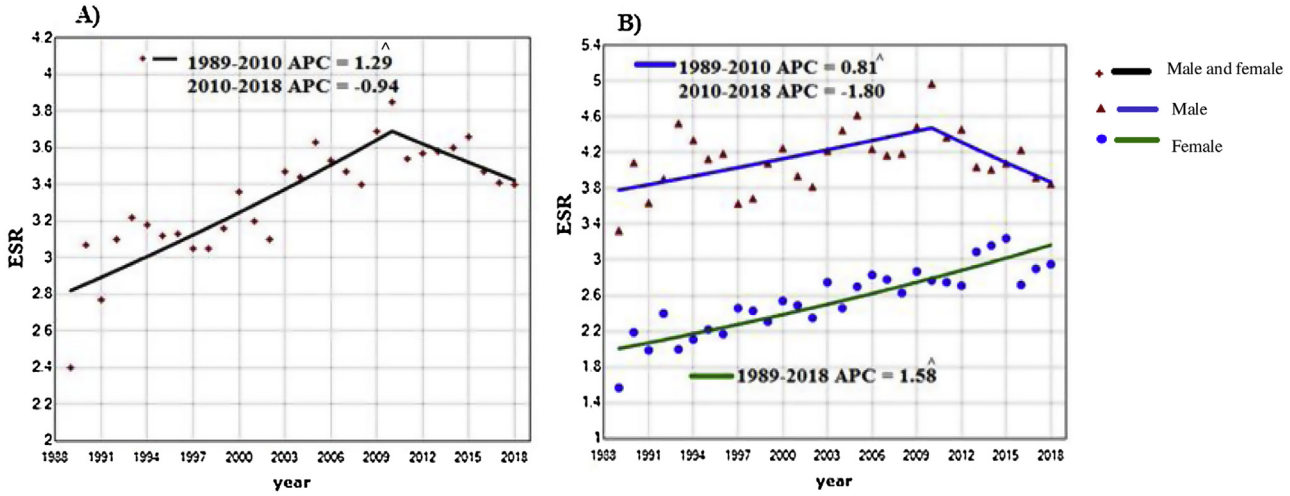

Fig. 1. Join point regression analysis showing the trend in incidence of oral squamous cell carcinoma, 1989–2018. (A) Overall incidence trend for all groups combined. (B) Overall incidence trends by sex. ESR: European age-standardized rate per 100,000 person-years. ^ indicates that the annual percentage change (APC) is significantly different from zero at the alpha = 0.05 level.

provided in **Supplementary Material** Table S1). The results showed that the AAPC of OSCC in the Netherlands increased at a very modest rate (AAPC 0.7%, 95% CI 0.2–1.2%). The overall APC increased significantly from 1989 to 2010 by 1.3% (95% CI 0.9–1.7%) per year and showed a small decline from 2010 to 2018 (APC −0.9%, 95% CI −2.5% to 0.7%) (Fig. 1A).

Trends by age at diagnosis

When age-specific trends were explored, linear increases in age-standardized rate during the study period were most pronounced in the age groups of 20–34, 60–74, and ≥75 years (**Supplementary Material** Table S1). Across these subgroups, the greatest increases were observed among individuals aged 20–34 years (APC 2.4%, 95% CI 1.2–3.8%) and those aged 60–74 years (APC 1.8%, 95% CI 1.5–2.1%). In the 45–59 years age group, the incidence rate levelled off at APC of 0.2% (95% CI −0.9% to 1.3%). Among individuals aged 35–44 years, a non-statistically significant decrease in incidence rate was observed (APC −0.9%, 95% CI −1.7% to 0.0%), ranging from 1.5 per 100,000 in 1989 to 1.1 per 100,000 in 2018.

Trends by sex

A clear difference in the incidence trends according to sex was observed during the total period, with a significant APC increase of 1.6% (95% CI 1.2–1.9%) in females and a stable trend in males with an AAPC of 0.1% (95% CI −0.6% to 0.7%) (Fig. 1B). For the age group of 20–34 years, join point regression analysis showed a steeper increase over time with an AAPC of 3.0% (95% CI 0.8–5.3%) in males and an upward but non-significant trend among females (Fig. 2A). Trends towards an increase were observed in all age subgroups except those aged 35–44 years: there the annual rate of incidence declined similarly for males and females (AAPC of −0.9%, 95% CI −2.0% to 0.2% and −0.8%, 95% CI −2.2% to 0.6%, respectively), although this was non-significant (Fig. 2B). In males aged 45–59 years, distinct and significant trends were noted for different time periods, starting with a steep increase (1989–1993: APC of 9.9%, 95% CI 2.8–17.6%), followed by a period with a modest decline (1993–2010: APC of −0.5%, 95% CI −1.4% to 0.3%) and finally a strong decline (2010–2018: APC of −4.7%, 95% CI −6.9% to −2.5%) (Fig. 3A). Females aged 45–59 years also showed an initial rise in the incidence

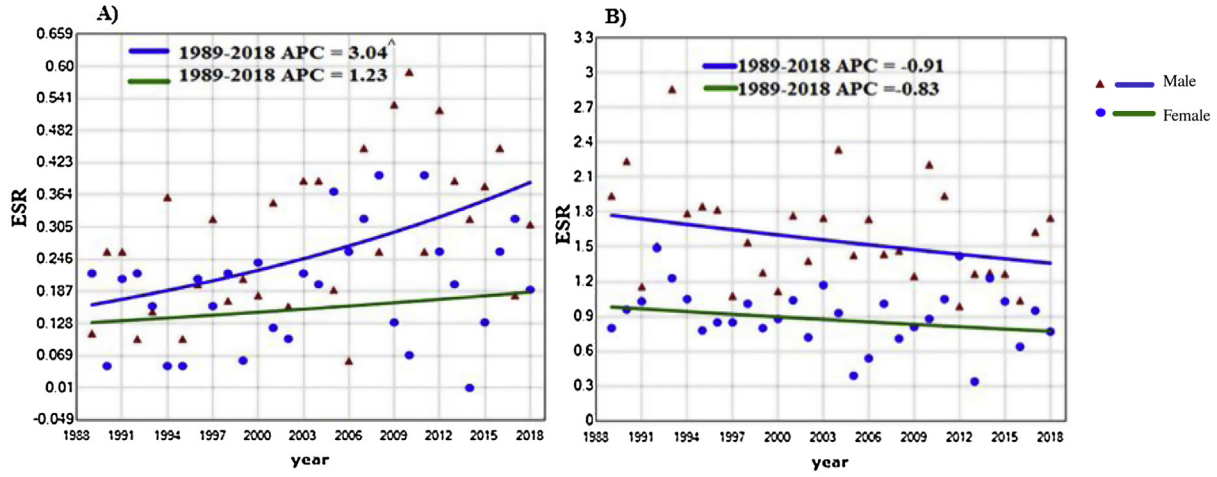

Fig. 2. (A) Join point regression model for age group 20–34 years. (B) Join point regression model for age group 35–44 years. ESR: European age-standardized rate per 100,000 person-years. ^ indicates that the annual percentage change (APC) is significantly different from zero at the alpha = 0.05 level.

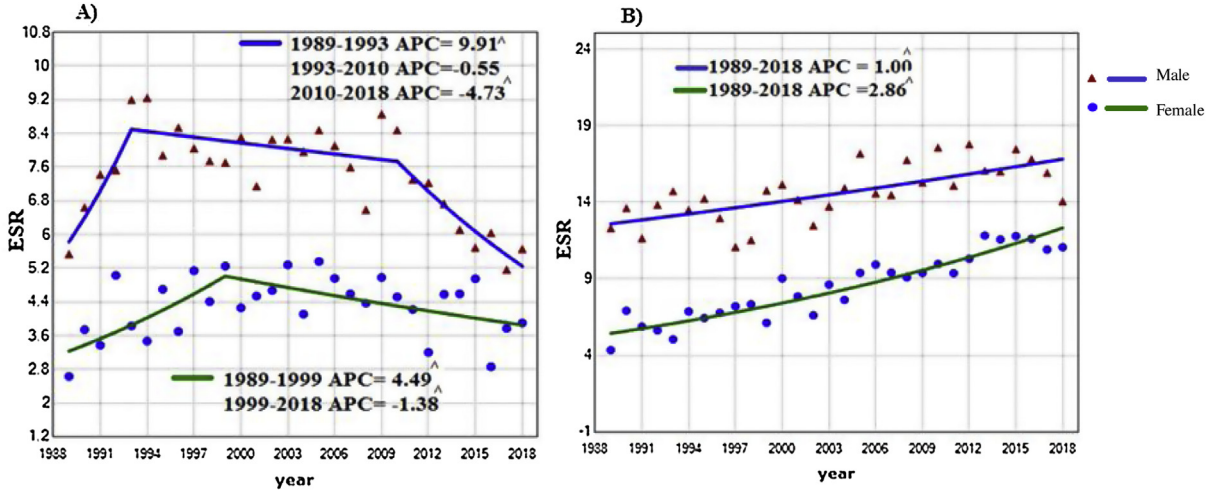

Fig. 3. (A) Join point regression model for age group 45–59 years. (B) Join point regression model for age group 60–74 years. ESR: European age-standardized rate per 100,000 person-years. ^ indicates that the annual percentage change (APC) is significantly different from zero at the alpha = 0.05 level.

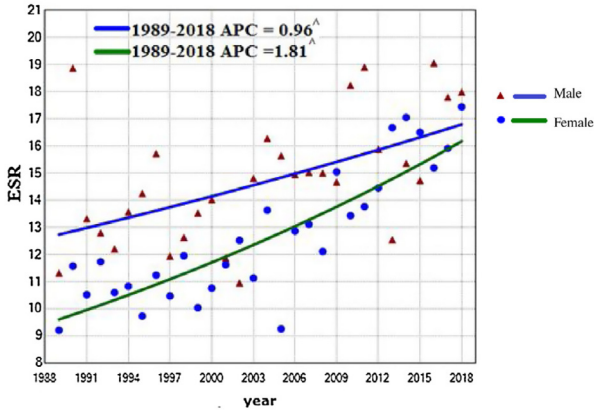

Fig. 4. Join point regression model for age group ≥75 years. ESR: European age-standardized rate per 100,000 person-years. ^ indicates that the annual percentage change (APC) is significantly different from zero at the alpha = 0.05 level.

(1989–1999: APC of 4.5%, 95% CI 0.9–8.2%), followed by a decline (1999–2018: APC of −1.4%, 95% CI −2.7% to −0.1%). The increase in those aged ≥60 years was stronger in females than males, particularly for females younger than 75 years in the entire period (1989–2018) (Fig. 3B, Fig. 4).

Mobile tongue is the most commonly affected site

The most common OSCC site in all age groups was the mobile tongue (42.5%, $P < 0.001$), ranging from 88.6% in patients less than 35 years old to 37.9% in patients aged ≥75 years (Table 2). Differences according to sex were noted particularly among patients under

Table 2. Characteristics of oral squamous cell carcinoma patients and differences in individual risk factors according to age group, for the years 2015–2018.

Variables	All ages	Age groups (years)					*P*-value
		20–34	35–44	45–59	60–74	≥75	
Total, *n* (row %)	3351 (100)	35 (1.0)	96 (2.9)	724 (21.6)	1591 (47.5)	905 (27.0)	
Sex, *n* (column %)							<0.001*
Male	1817 (54.2)	21 (60)	60 (62.5)	430 (59.4)	921 (57.9)	385 (42.5)	
Female	1534 (45.8)	14 (40)	36 (37.5)	294 (40.6)	670 (42.1)	520 (57.5)	
Anatomical sites, *n* (column %)							<0.001**
Mobile tongue	1425 (42.5)	31 (88.6)	68 (70.8)	348 (48.1)	635 (39.9)	343 (37.9)	
Gum	567 (16.9)	1 (2.9)	8 (8.3)	77 (10.6)	240 (15.1)	241 (26.6)	
Floor of the mouth	712 (21.2)	0 (0)	7 (7.3)	182 (25.1)	415 (26.1)	108 (11.9)	
Others/NOS[a]	647 (19.3)	3 (8.6)	13 (13.5)	117 (16.2)	301 (18.9)	213 (23.5)	
Clinical stage, *n* (column %)							0.002*
Local (stage I and II)	1817 (54.2)	21 (60)	65 (67.7)	427 (59.0)	860 (54.1)	444 (49.1)	
Advanced (stage III and IV)	1470 (43.9)	13 (37.1)	30 (31.3)	286 (39.5)	702 (44.1)	439 (48.5)	
Unknown	64 (1.9)	1 (2.9)	1 (1.0)	11 (1.5)	29 (1.8)	22 (2.4)	
Smoking status, *n* (column %)							<0.001*
Current or past	2227 (66.5)	15 (42.9)	56 (58.3)	525 (72.5)	1190 (74.8)	441 (48.7)	
Never	432 (12.9)	7 (20)	16 (16.7)	81 (11.2)	137 (8.6)	191 (21.1)	
Unknown	692 (20.6)	13 (37.1)	24 (25)	118 (16.3)	264 (16.6)	273 (30.2)	
Pack-years among current/past smokers, *n* (column %)							<0.001**
1–20 pack-year	300 (13.5)	11 (73.3)	19 (33.9)	85 (16.2)	139 (11.7)	46 (10.4)	
≥21 pack-year	914 (41.0)	0 (0)	11 (19.6)	223 (42.5)	522 (43.9)	158 (35.8)	
Unknown	1013 (45.5)	4 (26.7)	26 (46.4)	217 (41.3)	529 (44.4)	237 (53.7)	
Median (P25–P75)[b]	37 (21–50)	4 (2–10)	20 (12–25)	32 (20–40)	40 (25–50)	37.5 (23–55.5)	<0.001***
Alcohol status, *n* (column %)							<0.001**
Current or past	2189 (65.3)	21 (60)	62 (64.6)	501 (69.2)	1155 (72.6)	450 (49.7)	
Never	146 (4.4)	2 (5.7)	3 (3.1)	30 (4.1)	44 (2.7)	67 (7.4)	
Unknown	1016 (30.3)	12 (34.3)	31 (32.3)	193 (26.7)	392 (24.6)	388 (42.9)	
Number of alcoholic beverages per week for current/past drinker, *n* (column %)							<0.001**
>0–20	1057 (48.3)	16 (76.2)	29 (46.8)	210 (41.9)	518 (44.8)	284 (63.1)	
≥21	733 (33.5)	2 (9.5)	14 (22.6)	193 (38.5)	445 (38.5)	79 (17.6)	
Unknown	399 (18.2)	3 (14.3)	19 (30.6)	98 (19.6)	192 (16.6)	87 (19.3)	
Median (P25–P75)[b]	14 (6–28)	3 (2–14)	10 (2–28)	18 (7–42)	14 (7–28)	7 (2–14)	<0.001***

* χ^2 test.
** Fisher's exact test.
*** Kruskal–Wallis test; $P < 0.05$ is statistically significant.
[a] Not otherwise specified.
[b] Median with interquartile range (25th percentile–75th percentile).

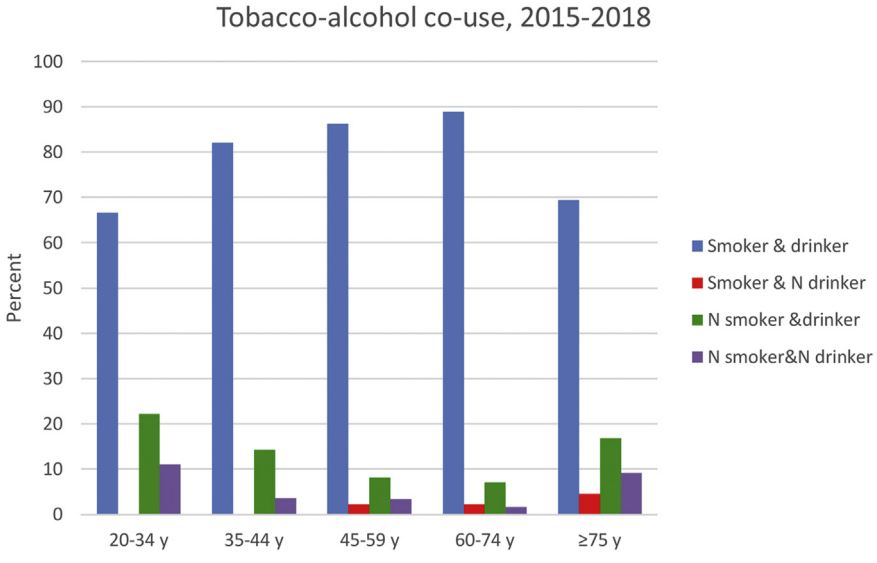

Fig. 5. Percentage of patients who were current/past tobacco and/or alcohol users across the different age groups (N: never).

45 years of age. Among those younger than 35 years old, 86% of females and 91% of males were diagnosed with mobile tongue carcinoma, whilst in those aged 35–44 years, females were more frequently affected with tongue carcinoma (78%) than males (67%) (data not shown).

Risk factors

Overall, the study revealed that 66.5% of the patients with OSCC were current/past tobacco smokers and 65.3% were current/past alcohol drinkers; 55% reported both (Table 2). Of the patients aged 20–34 years, 71% were current/past tobacco and/or current/past alcohol users. Similar patterns were observed for the other age groups (Fig. 5). Among the elderly group, the majority of the patients in the age group 60–74 years had a background of heavy smoking; this group had the highest pack-years, with a median of 40 pack-

years (IQR 25–50 pack-years; $P < 0.001$). It is also apparent from Table 2 that the group with the highest level of present/past alcohol consumption was patients aged 45–59 years (median 18, IQR 7–42 alcoholic beverages per week).

Discussion

The key finding in this study was a significant increase in the annual incidence of OSCC in the group of patients aged 20–34 years, and a decline in the age group 35–44 years. This finding differs from previous publications, which have concluded an overall downward or stable trend in young Dutch patients[15,16]. This is mainly because the prior studies collectively categorized young adults into one cohort aged less than 45 years. When this definition was applied in the present study, the findings were in accordance with those previous reports (APC −0.1%). This shows that the estimation of incidence rates may be quite sensitive to grouping during analysis, and reveals that the subclassification of the young age group into two cohorts in this study was rather powerful and allowed an important trend in the youngest 20–34 years group to be revealed, which would otherwise have been masked by the much larger number of patients in the 35–44 years subgroup. The increasing incidence in the youngest age group, which was only statistically significant in males, seems to be consistent with other studies from various regions of the world, although age subgroup classifications have differed slightly. In the USA, Chen et al.[20] reported a nearly four-fold increase in OSCC incidence in males aged 30–39 years between the 1960s and the mid-1980s. A study from Ahmedabad, India, covering the years 1985 to 2010, also showed an increase in oral cancer incidence in males[21]. The largest increase of more than 30 times was recorded in the youngest age group (males <35 years old)[21]. Data from Taiwan showed a progressive increase in oral cancer in males aged 30–39 years, but not in those aged 20–29 years[22]. A German analysis over a 20-year period revealed a significant increase in OSCC incidence among patients aged 30–39 years, with a male-to-female ratio of 3.8:1[23].

There is general agreement that the mobile tongue is the most common site for OSCC in young adults[24]. This matches the findings of the present study: 88.6% of patients aged 20–34 years and 70.8% of those aged 35–44 years old, but less than 50% in each of the older age groups had cancer in this region. Previous studies found that white females younger than 45 years were more commonly affected with mobile tongue carcinoma than males[4,5]. This was confirmed in the current study population aged 35–44 years, but not in those under 35 years of age. A direct comparison between the present study results and those in the published reports with the aim of confirming whether there is a specific age and sex–subsite association is difficult given the difference in grouping intervals. Further, it was observed that the proportionate share of mobile tongue cancer became less with increasing age, reaching the lowest percentage in patients older than 75 years. However, this is also a reflection of the increasing number of tumours at other sites, since the number of tongue cancers in those ≥75 years was still quite high: 21.6% ($n = 1592$) of all reported tongue cancers compared with 9.4% ($n = 691$) in those 20–44 years old. The increasing incidence of OSCC in young adults makes it paramount for dentists and general practitioners to consider tongue SCC in this age group as is now done for the adult and elderly populations, and necessitates prompt referral in the case of suspicion of a non-healing ulcerative and indurated lesion of the tongue to improve the possibility of early detection.

Of note, the mobile tongue has been reported as the most prevalent affected site with SCC in the non-smoker, non-drinker young population, especially in females[25,26]. A recent study subjected samples of tongue SCC from young and old patients to whole-exome sequencing and copy-number analysis[27]. The study revealed similar genetic mutations in both groups irrespective of smoking status[27]. Additionally, the robust mutation signatures of smoking that were reported with lung and laryngeal carcinoma were not observed. Therefore, smoking has been suggested as a promotor of tongue carcinoma, rather than a direct causative factor[27]. This could be the case for our young samples that showed high percentages of tobacco and alcohol users, in which these risk factors may act as a promotor while other unknown factor(s) play a role in the exclusive presentation of SCC in the mobile tongue in this cohort of patients. It is also possible that less exposure time to tobacco/alcohol allows more mobile tongue carcinoma, and less smoking-related sites. As a matter of fact, although the present study does not prove any causal age and site associations since risk factor data were only available for a short time frame (4 years), it represents an important step towards increasing awareness.

This study showed an enigmatic change in trend pattern of OSCC among males aged 45–59 years: the incidence rate increased steeply from 1989 to 1993, then declined slowly during 1993–2010 and dropped from 2010 to 2018. In fact, the overall reduction in OSCC annual incidence in the Netherlands by −0.9% after 2010 appears solely attributable to the overall annual incidence in the male patients (2010–2018: APC = −1.8%), which in turn is largely accounted for by the trend in males aged 45–59 years. So far, published data from the Netherlands have shown only the overall APC for this age group during the period of interest, if any. With the use of the join point regression model, the present study showed further details and revealed a significant decrease in the annual incidence in recent calendar years. It is well documented that people in their 50 s are at greater risk of developing OSCC, but why this particular group shows such a pattern is not clear[28]. Some may assume this to be a depiction of the decline in smoking prevalence in the Netherlands; however, since the consumption of cigarettes and other tobacco products has decreased (from 35% in 1995 to 23% in 2014) quite equally in all age groups, this seems an unlikely explanation[29–31]. It is postulated that one possible reason underlying this finding could be the better awareness and higher alertness level among patients and dentists, which may have enhanced opportunities for early detection and treatment at pre-cancer stages.

Based on solid observational studies performed since the 1970s, tobacco smoking and alcohol drinking have been identified as major risk factors for OSCC, with a well-defined dose–response relationship[32,33]. Despite the still inconsistent evidence regarding the independent causal association between these factors and OSCC, evidence for the carcinogenic effect of heavy drinking has been considered sufficient, regardless of smoking status[34]. One study found that the association between ever smoking and the risk of head and neck cancer among females (odd ratio (OR) 2.33, 95% CI 1.56–3.49) was stronger than that among males (OR 1.65, 95% CI 1.14–2.39), while meta-analyses have found that the effects of smoking are more profound on larynx and pharynx cancer than on oral cavity cancer[35–37]. Although it is generally suggested that at least 21 years of exposure to a high dose of tobacco and alcohol is required to cause malignant transformation, others have shown that the

risk increases monotonically with the level of exposure, rather than the duration or the age when the habit began[8,38–40]. Intriguingly, it has been reported that the interaction between smoking and drinking significantly increases the risk of cancer by five-fold in a synergic fashion, even with a moderate consumption level[41]. In this study, a 2–4-fold increase in risk of OSCC with ever smoking or drinking only was noted, while a 13-fold increase in risk was found with simulations of exposure to both habits.

How do these findings relate to the results? For the youngest patient group aged 20–34 years, it can be questioned whether the occurrence of OSCC is sporadic or hereditary[42]. The study data demonstrated that more than half of the patients within this stratum had a background of tobacco and alcohol co-use, although the total exposure time was limited. Although data are still conflicting about the aetiology of OSCC in young patients, this study appears to support the assumption that these traditional risk factors play an essential role in oral carcinogenesis in the young groups as they do in the elderly ones. It has been suggested that smoking and alcohol consumption at a very young age play a crucial role in the development of oral malignancy[12,39,43]. Early life exposure to environmental carcinogenic factors has been shown to increase susceptibility to cancer formation, inflicting a high rate of cell proliferation and incompetent DNA repair in the young individual[44,45]. Nonetheless, it is highly unlikely that the patients in the youngest age group will be exposed for at least 21 years to one or both risk factors, the time frame considered to be required for developing malignancies. Some publications have suggested a causal link between the observed trend and HPV infection, especially because this age group is known to be sexually active. In Brazil, 32% of young patients with OSCC were found to be HPV-positive[46]. The frequency of HPV in OSCC has been assessed in the Netherlands in a study in which the presence of HPV16 infection in 31 young patients was compared with that in two independent cohorts of older patients[9]. Biologically active HPV16 was only detected in one sample (3.2%) in the young patients, indicating a lack of evidence on the direct oncogenic role of HPV during oral carcinogenesis in this cohort[9]. Hence, HPV testing is not routinely recommended for Dutch OSCC patients. Other studies have investigated the association between familial history of cancer and OSCC, but the results have been inconclusive[47,48]. All of these controversies have led some authors to conclude that the aetiology of OSCC in the young group of patients is most likely multifactorial[49,50]. Together, these data suggest that the young patient groups are either more susceptible to the classic risk factors and/or other factors may play a role as well.

The current study found that the overall annual incidence showed a marked increase in females in the adult and elderly age groups when compared to males, particularly in patients older than 60 years. Possible contributing causes may be that 22% of Dutch females have been reported to be heavy drinkers compared to 14% of males (especially those older than 55 years)[51], that Dutch females smoke almost as much as Dutch males[52], and finally that the odds ratio for the development of head and neck cancer is apparently higher for females than for males[35]. These findings, combined with a longer life-expectancy for females, may explain the increased APC values for females when compared to males in the elderly population.

This novel and large study has described the trends in age- and sex-specific incidence rates for OSCC in the Netherlands using the join point regression program, with the goal of highlighting details for those patients younger than 45 years. The study provides an in-depth update of the trends in Dutch OSCC incidence based on the most recent data, and the relevance of the well-known risk factors for OSCC were evaluated at a population level, which allowed additional differences between age groups to be explored. The findings should be understood in the context of some limitations. Firstly, the risk factor analysis was based on the available data for only 4 years, and consequently these findings cannot be related to changes in incidence rates over time. Secondly, because lifestyle habits were only available at the time of diagnosis of the tumour, nothing can be said about the causal link; this was just to illustrate the differences by age group. Finally, there was some missing information regarding smoking and alcohol drinking. The findings with regard to these factors should thus be regarded as a first indication only.

In summary, patients aged 20–34 years appear to be a distinct group when compared to those aged 35–44 years, as the incidence rate of OSCC increased in the 20–34 years group, but decreased in those aged 35–44 years. This may suggest focusing on other avenues of research into carcinogenesis, such as potential genetic differences between these two young age group strata. Such research may help in gaining a greater understanding and delineation of the risk factors, and consequently may guide diverse OSCC prevention plans. The estimated overall incidence rate showed an increase in females when compared to males, in particular in the older females, which could be explained at least in part by behavioural factors and longevity. Finally, the cessation of risk habits remains an important factor to reduce the burden of oral cancer.

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Competing interests

None.

Ethical approval

None.

Patient consent

Not required.

Data availability

Data can be made available upon reasonable request to the NCR (data application number K18.196).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2021.03.006.

References

1. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA Cancer J Clin* 2017;**67**:51–64.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.
3. Choi S, Myers JN. Molecular pathogenesis of oral squamous cell carcinoma: implications for therapy. *J Dent Res* 2008;**87**:14–32.
4. Hussein AA, Helder MN, de Visscher JG, Leemans CR, Braakhuis BJ, de Vet HCW, et al. Global incidence of oral and oropharynx cancer in patients younger than 45 years

versus older patients: a systematic review. *Eur J Cancer* 2017;**82**:115–27.
5. Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, Hackman T, et al. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. *J Clin Oncol* 2011;**29**:1488–94.
6. Chattopadhyay I, Verma M, Panda M. Role of oral microbiome signatures in diagnosis and prognosis of oral cancer. *Technol Cancer Res Treat* 2019;**18**:1533033819867354.
7. Bleyer A. Cancer of the oral cavity and pharynx in young females: increasing incidence, role of human papilloma virus, and lack of survival improvement. *Semin Oncol* 2009;**36**:451–9.
8. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people—a comprehensive literature review. *Oral Oncol* 2001;**37**:401–18.
9. Braakhuis BJ, Rietbergen MM, Buijze M, Snijders PJ, Bloemena E, Brakenhoff RH, et al. TP53 mutation and human papilloma virus status of oral squamous cell carcinomas in young adult patients. *Oral Dis* 2014;**20**:602–8.
10. What should the age range be for AYA oncology? *J Adolesc Young Adult Oncol* 2011;**1**:3–10.
11. Iype EM, Pandey M, Mathew A, Thomas G, Sebastian P, Nair MK. Oral cancer among patients under the age of 35 years. *J Postgrad Med* 2001;**47**:171–6.
12. Iamaroon A, Pattanaporn K, Pongsiriwet S, Wanachantararak S, Prapayasatok S, Jittidecharaks S, et al. Analysis of 587 cases of oral squamous cell carcinoma in northern Thailand with a focus on young people. *Int J Oral Maxillofac Surg* 2004;**33**:84–8.
13. Blanchard P, Belkhir F, Temam S, El Khoury C, De Felice F, Casiraghi O, et al. Outcomes and prognostic factors for squamous cell carcinoma of the oral tongue in young adults: a single-institution case-matched analysis. *Eur Arch Otorhinolaryngol* 2017;**274**:1683–90.
14. Stark D, Bielack S, Brugieres L, et al. Teenagers and young adults with cancer in Europe: from national programmes to a European integrated coordinated project. *Eur J Cancer Care* 2016;**25**:419–27.
15. Braakhuis BJ, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. *Oral Oncol* 2014;**50**:670–5.
16. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. *Int J Cancer* 2016;**139**:574–83.
17. Nederlandse Kanker Registratie. Integraal Kankercentrum Nederland. http://www.cijfersoverkanker.nl [Accessibility verified].
18. Joinpoint Regression Program. *Statistical Methodology and Applications Branch, Surveillance Research Program*. National Cancer Institute; 2018 [Accessibility verified July, 2018]https://surveillance.cancer.gov/joinpoint/.
19. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;**19**:335–51.
20. Chen JK, Eisenberg E, Krutchkoff DJ, Katz RV. Changing trends in oral cancer in the United States, 1935 to 1985: a Connecticut study. *J Oral Maxillofac Surg* 1991;**49**:1152–8.
21. Gupta PC, Ray CS, Murti PR, Sinha DN. Rising incidence of oral cancer in Ahmedabad city. *Indian J Cancer* 2014;**51**(Suppl 1): S67–72.
22. Lin YS, Jen YM, Wang BB, Lee JC, Kang BH. Epidemiology of oral cavity cancer in Taiwan with emphasis on the role of betel nut chewing. *ORL J Otorhinolaryngol Relat Spec* 2005;**67**:230–6.
23. Udeabor SE, Rana M, Wegener G, Gellrich NC, Eckardt AM. Squamous cell carcinoma of the oral cavity and the oropharynx in patients less than 40 years of age: a 20-year analysis. *Head Neck Oncol* 2012;**4**.
24. Sasaki T, Moles DR, Imai Y, Speight PM. Clinico-pathological features of squamous cell carcinoma of the oral cavity in patients <40 years of age. *J Oral Pathol Med* 2005;**34**:129–33.
25. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker–never drinkers: a descriptive epidemiologic study. *Head Neck* 2008;**30**:75–84.
26. Harris SL, Kimple RJ, Hayes DN, Couch ME, Rosenman JG. Never-smokers, never-drinkers: unique clinical subgroup of young patients with head and neck squamous cell cancers. *Head Neck* 2010;**32**:499–503.
27. Pickering CR, Zhang J, Neskey DM, Zhao M, Jasser SA, Wang J, et al. Squamous cell carcinoma of the oral tongue in young non-smokers is genomically similar to tumors in older smokers. *Clin Cancer Res* 2014;**20**:3842–8.
28. Ridge JA, Mehra R, Lango M, Galloway T. Head and Neck Tumors, cancer management. *online] Cancernetwork* 2016 [Accessibility verified May 31, 2019]https://www.cancernetwork.com/cancer-management/head-and-neck-tumors.
29. Janssen F, van Poppel F. The adoption of smoking and its effect on the mortality gender gap in Netherlands: a historical perspective. *Biomed Res Int* 2015;**2015**:370274.
30. International Tobacco Control Project. ITC Netherlands National Report June 2010. University of Waterloo, Ontario, Canada; STIVORO (Dutch Expert Centre on Tobacco Control), The Hague, The Netherlands. https://itcproject.org/findings/reports/itc-netherlands-national-report-waves-1-to-3-2008-2009-june-2010/ [Accessibility verified November, 2018].
31. International Tobacco Control Project. ITC Netherlands National Report September 2015. Findings from the Wave 1 to 8 Surveys (2008–2014). University of Waterloo, Waterloo, Ontario, Canada. https://itcproject.org/findings/reports/itc-netherlands-national-report-waves-1-to-8-2008-2014-sept-2015/ [Accessibility verified November, 2018].
32. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;**48**:3282–7.
33. Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis* 1972;**25**:711–6.
34. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007;**8**:292–3.
35. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 2007;**99**:777–89.
36. Boing AF, Antunes JLF, de Carvalho MB, de Gois JF, Kowalski LP, Michaluart P, et al. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? *J Epidemiol Community Health* 2011;**65**:709–14.
37. Maasland DHE, van den Brandt PA, Kremer B, Goldbohm RA, Schouten LJ. Alcohol consumption, cigarette smoking and the risk of subtypes of head–neck cancer: results from the Netherlands Cohort Study. *BMC Cancer* 2014;**14**.
38. Lipkin A, Miller RH, Woodson GE. Squamous cell carcinoma of the oral cavity, pharynx, and larynx in young adults. *Laryngoscope* 1985;**95**(7 Pt 1):790–3.
39. Macfarlane TV, Macfarlane GJ, Oliver RJ, Benhamou S, Bouchardy C, Ahrens W, et al. The aetiology of upper aerodigestive tract cancers among young adults in Europe: the ARCAGE study. *Cancer Causes Control* 2010;**21**:2213–21.
40. Morse DE, Psoter WJ, Cleveland D, Cohen D, Mohit-Tabatabai M, Kosis DL, et al. Smoking and drinking in relation to oral cancer and oral epithelial dysplasia. *Cancer Causes Control* 2007;**18**:919–29.
41. Castellsague X, Quintana MJ, Martinez MC, Nieto A, Sanchez MJ, Juan A, et al. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. *Int J Cancer* 2004;**108**:741–9.
42. van Monsjou HS, Wreesmann VB, van den Brekel MW, Balm AJ. Head and neck squamous cell carcinoma in young patients. *Oral Oncol* 2013;**49**:1097–102.

43. Rodriguez T, Altieri A, Chatenoud L, Gallus S, Bosetti C, Negri E, et al. Risk factors for oral and pharyngeal cancer in young adults. *Oral Oncol* 2004;**40**:207–13.
44. Barton HA, Cogliano VJ, Flowers L, Valcovic L, Setzer RW, Woodruff TJ. Assessing susceptibility from early-life exposure to carcinogens. *Environ Health Perspect* 2005;**113**:1125–33.
45. Ginsberg GL. Assessing cancer risks from short-term exposures in children. *Risk Anal* 2003;**23**:19–34.
46. Kaminagakura E, Villa LL, Andreoli MA, Sobrinho JS, Vartanian JG, Soares FA, et al. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. *Int J Cancer* 2012;**130**:1726–32.
47. Copper MP, Jovanovic A, Nauta JJP, Braakhuis BJM, Devries N, Vanderwaal I, et al. Role of genetic factors in the etiology of squamous cell carcinoma of the head and neck. *Arch Otolaryngol* 1995;**121**:157–60.
48. Foulkes WD, Brunet JS, Kowalski LP, Narod SA, Franco EL. Family history of cancer is a risk factor for squamous cell carcinoma of the head and neck in Brazil: a case–control study. *Int J Cancer* 1995;**63**:769–73.
49. Atula S, Grenman R, Laippala P, Syrjanen S. Cancer of the tongue in patients younger than 40 years—a distinct entity? *Arch Otolaryngol* 1996;**122**:1313–9.
50. Son YH, Kapp DS. Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. *Cancer* 1985;**55**:441–4.
51. Comijs HC, Aartsen MJ, Visser M, Deeg DJH. Alcoholgebruik onder 55-plussers in Nederland. *Tijdschrift voor Gerontologie en Geriatrie* 2012;**43**:115–26.
52. *WHO Report on the Global Tobacco Epidemic, 2008: the MPOWER package*. Geneva: World Health Organization; 2008.

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