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Rediscussing the Role of Traditional Risk Factors in Young Adults With Oral Squamous Cell Carcinoma

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Abstract. *Background/Aim: The current literature conjectures that oral squamous cell carcinoma (OSCC) in younger patients is an entirely separate entity with a different risk profile. We aimed to uncover the potential risk factors of OSCC and evaluated the long-term outcome in such patients. Patients and Methods: This hospital-based case–control study included 40 patients with OSCC and 40 controls under the age of 46 years. Survival was analyzed via Kaplan–Meier estimates, including a follow-up of up to 24.3 years. Results: The patients with OSCC were prone to smoking and drinking heavily and even suffered secondary organ damage to the lungs and the liver at this young age. Early diagnosed as well as surgically treated patients had superior 5-year recurrence-free and overall survival. Conclusion: Young patients with OSCC were found to have a traditional risk profile. Secondary organ damage to the liver and the lungs might be considered as a risk indicator. The meticulous screening of every age group with this risk profile is key to early diagnosis and acceptable treatment results.*

While most studies addressing risk factors in patients with head and neck squamous cell carcinoma (HNSCC) recently have tended to focus on human papillomavirus (HPV), patients with HNSCC and especially those with oral squamous cell carcinoma (OSCC) still consist mostly of older male individuals with habits of heavy alcohol and tobacco consumption (1-4).

In these cases, the most typical mechanism of carcinogenesis remains field cancerization, including the involvement of macroscopically normal tissue, caused by exposure to harmful substances, thus leading to multi-step tumorigenesis and progression over an extended period. This has also been shown to exist on a molecular level (5-7).

Consequently, because of the characteristic risk factors of drinking and smoking, OSCC is generally considered a preventable disease (8). Over the past decades, a significant number of studies have been carried out which surprisingly demonstrated an increase in OSCC in young adults worldwide (3, 9-11). Younger adults without typical risk factors seem to be affected, which is emotionally distressing for the patients, their families, and healthcare professionals. Mostly, the term 'young' is defined as being under 40 or 45 years old (3, 12). This finding surprisingly coincided with a decrease in the aforementioned classic risk factors and led several authors to conclude that HNSCC in a younger population can or should be seen as an entirely different entity (3, 7, 12-16). The frequent lack of traditional risk factors such as alcohol and tobacco consumption in a population under 30 years old was already described in 1975 by Byers for SCCs of the tongue (17). This observation was also made by Kuriakose *et al*., who reported an association of OSCC with the female gender and fewer risk factors in younger adults (18). This finding was again confirmed by Harris *et al*., who found that nonsmokers and nondrinkers in a more heterogeneous group with HNSCC are more likely to be younger and predominantly female in contrast to their

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alcohol- and tobacco-consuming counterparts (16). In the wake of this, a wide variety of other co- or alternative risk factors such as HPV status, nutrition, genetic alterations, long-term irritation, immunosuppression, hormonal status, and other comorbidities are being discussed, but none have been proven to play a superior role in the development of HNSCC or OSCC (3, 6, 7, 12, 14, 19-21).

However, the role of classic risk factors for HNSCC in younger patients and the impact of other parameters have been discussed controversially in the literature, especially since some studies failed to demonstrate significant differences between OSCC in older and younger patients (22, 23). While minor molecular differences are likely to exist, the data are still too sparse to draw definitive conclusions (24). Another major problem in defining risk factors for OSCC arises from its inclusion in the heterogeneous group of HNSCC and a lack of adequate subcategorization (7, 19, 25-27). HPV-positive as well as HPV-negative SCCs, for instance, tend to originate from different tissues and therefore favor distinct locations (12, 28). The former, for example, are associated with lymphoepithelial tissue, such as the base of the tongue and the pharynx, whereas HPV seems not to be typical in OSCC (12, 26). This emphasizes the need for anatomically focused risk assessment studies.

The remaining uncertainties and occasional cases of fatal and emotionally burdening courses in young patients, which cannot be explained sufficiently with the current knowledge, led to the conduction of this investigation. The aim of this study was to evaluate relevant risk factors in younger patients with OSCC and evaluate long-term survival in this patient cohort.

Patients and Methods

This study was approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany (EA2/107/19).

Of the 590 patients with OSCC treated at the Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, from 1993 to 2006, all those under the age of 46 years were selected. Their medical history was analyzed retrospectively regarding tumor localization, histological diagnosis, classification according to tumor size, node status, and metastasis (TNM), survival, recurrence, and risk factors. Comorbidities such as cardiovascular, pulmonary, or liver diseases as well as diabetes mellitus, immunodeficiency, and allergies were documented. A family history of malignant tumors was also taken into account. The following exogenous factors were considered: History of smoking, drug and alcohol consumption, and poor oral hygiene. The control group was matched by age and gender and selected out of a patient population of 2006 that was hospitalized with diagnoses not related to malignancies. Treatment decisions were made on an interdisciplinary basis after clinical and radiological staging was performed and after histological confirmations of OSCC diagnoses were made. The following parameters were defined to alleviate comparability between the test and control groups.

The body mass index (BMI) was used to define the nutritional level of the patients according to the definition of the World Health Organization (29). The follow-up period for survival analysis lasted until December 2018. As the tumor location was defined according to the anatomical origin, overlapping areas in certain patients were included. Histological analysis was performed by the Department of Pathology of the Charité – Universitätsmedizin Berlin. The tumors were classified according to the fifth edition of the TNM Atlas of the Union Internationale Contre le Cancer (30). Cancer recurrence was screened until January 31, 2013, whereas overall survival (OS) was traced until December 7, 2018. Patients without signs of recurrence until that date were defined as free of recurrence. Based on the parameters defined by the World Health Organization, which were applied to the German federal health study of 2006, smokers were divided into 'heavy' smokers (20 or more cigarettes per day), 'moderate' smokers (11-20 cigarettes per day), and 'light' smokers (less than 10 cigarettes per day) (31). Grouping according to pack-years was impossible because of insufficient documentation and the retrospective character of the study.

To define alcohol consumption, a modified and simplified classification described by Baker *et al.* was used (32). The definition comprised 'daily or almost daily/very frequent' consumption (5 times per week or more), 'moderately frequent' consumption (no more than 4 times per week), and abstinence (no alcohol consumption). Further, alcohol consumption was subcategorized into the consumption of beverages with high alcohol concentration (15% or more), moderate concentration (5-15%), and low concentration (5%). Alcoholism was defined as the consumption of at least 60 g alcohol per day in males and 40 g per day in females or was included as such in the case of the documented psychiatric diagnosis (33). The combination of alcohol and tobacco was also taken into consideration.

Socioeconomic status had to be defined retrospectively. Patients with academic professions that required a university or college degree were defined as having high socioeconomic status, whereas patients who worked in professions that necessitated the equivalent of a high-school certificate were defined as having medium socioeconomic status. Those with professions requiring basic or lesser school education were defined as having low socioeconomic status. Unemployed patients were categorized in a separate group. In some cases, a retrospective definition of socioeconomic status was not possible.

In 17 cases, p16 status as a surrogate parameter for HPV was analyzed retrospectively since this was not a standard procedure at the time. All statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM, Armonk, NY, USA). The descriptive analysis of the categorical variables was carried out *via* frequency count and cross-tabulation. Associations among the categorical variables were examined using Pearson's chi-square test. Overall and recurrence-free survival were described by Kaplan–Meier curves. For comparisons of the Kaplan–Meier curves, the log-rank test was used. From these curves, 5-year survival rates with two-sided 95% confidence intervals were derived. In this exploratory study, no level of significance was specified, and all the *p*-values are exploratory.

Results

This study comprised 40 cases suffering OSCC under the age of 46 and their controls, which had been matched according to age and sex. The general characteristics are summarized in Table I. The mean age was 41.5 years, ranging from 27 to 45

Table I. *Synopsis of general characteristics of cases and controls.*

Variable		Case (n=40)	Control (n=40)	OR (95% CI)	*p*-Value
Gender, n (%)	Male	30 (75.0%)	28 (70.0%)	Ref	
	Female	10 (25.0%)	12 (30.0%)	0.778 (0.291-2.082)	0.618
Mean age±SD, years	Male	40.5 ±4.4	40.0 (5.3)		
	Female	39.2 ±3.8	36.8 (5.5)		
BMI, kg/m^2	<18.5	5 (12.8%)	1 (3.8%)	Ref	
	18.5-25	22 (56.4%)	15 (57.7%)	0.293 (0.031-2.769)	0.284
	25-30	7 (17.9%)	9 (34.6%)	0.156 (0.015-1.653)	0.123
	≥30	5 (12.8%)	1 (3.8%)	1.000 (0.048-20.829)	0.999
Socioeconomic status, n (%)	Unemployed	5 (12.5%)	3 (7.5%)	Ref	
	Low	14 (35.0%)	12 (30.0%)	0.700 (0.138-3.558)	0.668
	Middle	13 (32.5%)	23 (57.5%)	0.339 (0.070-1.654)	0.181
	High	1 (2.5%)	1 (2.5%)	0.600 (0.027-13.582)	0.752
	Unknown	7 (17.5%)	1 (2.5%)	NA	
Smoking status, n (%)	Nonsmoker	7 (17.5%)	11 (27.5%)	Ref	
	<10 cig./day	1 (2.5%)	11 (27.5%)	0.143 (0.015-1.363)	0.091
	11-20 cig./day	6 (15.0%)	12 (30.0%)	0.786 (0. 201-3.071)	0.729
	20 cig./day	27 (65.0%)	6 (15.0%)	6.810 (1.859-24.948)	**0.004**
Lung disease	COPD	6 (15%)	0 (0%)	NA	
Alcohol consumption, n (%)	Never	4 (10%)	3 (7.5%)	Ref	
	1-4 Times/week	11 (27.5%)	36 (90%)	0.229 (0.044-1.184)	0.079
	>5 Times/week	25 (62.5%)	1 (2.5%)	18.750 (1.543-227.8)	**0.021**
	Alcoholism	16 (40%)	0 (0%)	NA	
Alcohol content of beverages, n (%)	Nondrinker	4 (10.0%)	2 (5.0%)	Ref	
	≤5%	20 (50.0%)	11 (27.5%)	0.909 (0.143-5.781)	0.920
	5-15%	7 (17.5%)	24 (60.0%)	0.146 (0.022-0.970)	**0.049**
	≥15%	9 (22.5%)	3 (7.5%)	1.500 (0.176-12.775)	0.711
Smoking/alcohol	≤10 cig./moderate	7 (17.5%)	22 (55.0%)	Ref	
	>10 cig./moderate	8 (20%)	17 (42.5%)	1.479 (0.447-4.889)	0.522
	≤10 cig./daily	1 (2.5%)	0 (0.0%)	NA	
	>10 cig./daily	24 (60%)	1 (2.5%)	75.4 (8.6-663.1)	**<0.001**
Liver disease	Total	15 (37.5%)	1 (2.5%)	23.4 (2.9-188.4)	**0.003**
	Steatohepatitis, n	12	1		
	Liver cirrhosis, n	3	0		
Other factors, n (%)	Allergies	10 (25%)	13 (32.5%)	0.692 (0.261-1.835)	0.459
	Heart disease	8 (20%)	9 (22.5%)	0.861 (0.295-2.518)	0.786
	Immunodeficiency	2 (5%)	1 (2.5%)	2.053 (0.179-23.589)	0.563
	Drug abuse	3 (7.5%)	3 (7.5%)	1.00 (0.189-5.280)	0.999
	Insufficient oral hygiene	13 (32.5%)	11 (27.5%)	1.269 (0.487-3.311)	0.625

BMI: Body mass index; cig.: cigarette(s); COPD: chronic obstructive pulmonary disease; OR: odds ratio; SD: standard deviation. Statistically significant *p*-values are shown in bold.

years, in the cases and 41 years, ranging from 23 to 45 years, in the controls. The case group consisted of 30 males and 10 females, whereas the control group comprised 28 males and 12 females. The mean age when diagnosed with OSCC was 42.5 years in males and 39 years in females. The BMI was equally distributed in the cases and controls, but the case group comprised more underweight (n=5, 12.5%) and obese (n=5, 12.5%) patients compared to the control group (n=1, 3.8%, and n=1, 3.8%, respectively). Of the 10 females in the case group, seven were smokers, of whom six consumed more than 20 cigarettes per day; 21 out of the 26 male smokers in this group showed the same behavior. None of the smokers in the case group consumed 10 cigarettes per day or less. In the control group, five female and six male patients consumed up to 10 cigarettes per day, nine males and three females consumed up to 20 cigarettes per day, and six males but no females consumed more than 20 cigarettes per day.

The characteristics of the case group are summarized in Table II, including location, tumor size, and nodal status. The majority of carcinomas were staged as T4 when initially diagnosed, and 57.5% were classified as stage IV tumors according to the Union for International Cancer Control (30). In addition, 70% of all tumors were staged as grade 2; 45% were diagnosed with N0 and 40% with N2 status. Lastly, 31

Table II. *Distribution of tumor-specific characteristics in the case group (n=40).*

Variable		Frequency, n (%)
Location	Floor of the mouth	19 (47.5%)
	Tongue	19 (47.5%)
	Palate	2 (5%)
	Anterior (premolar)	31 (77.5%)
	Posterior (molar/postmolar)	9 (22.5%)
TNM Classification*	T1	9 (22.5%)
T-Stage	T2	11 (27.5%)
	T3	3 (7.5%)
	T4	17 (42.5%)
N-Stage	N0	18 (45%)
	N1	3 (7.5%)
	N2	16 (40%)
	N3	3 (7.5%)
M-Stage	Mx	12 (30%)
	M0	27 (67.5%)
	M1	1 (2.5%)
Staging*	I	6 (15%)
	II	9 (22.5%)
	III	2 (5%)
	IV	23 (57.5%)
Grading	1	4 (10%)
	2	28 (70%)
	3	8 (20%)

*Union for International Cancer Control TNM Classification of Malignant Tumours, fifth edition (30).

out of 33 smokers in the OSCC group continued smoking after their initial cancer diagnosis.

In 17 cases, HPV status (p16 surrogate marker) was analyzed retrospectively, of which one case showed HPV positivity. Around 41% of the cases suffered from cancer recurrence or secondary metastases within the first 5 years after diagnosis, all of which occurred in the first 3 years. The 5-year recurrence-free survival was 67% for tumor stages I and II [95% confidence intervaI (CI)=40.6-85.4%3 and 24% (95% CI=11.2-44.2%) for stages III and IV. When comparing patients who had received surgical therapy with those who had not, 5-year recurrence-free survival was 54% (95% CI=35.4-70.8%) and only 8% (95% CI=1.2-41.3%), respectively. Consequently, recurrence-free survival for those with tumor stages I and II as well as for those who had undergone surgery was significantly higher than for those with stages III and IV (p=0.015) and for patients who had not (p=0.0005).

OS analysis was performed, categorizing the tumor stages into early (stages I and II, n=15) and advanced (stages III and IV, n=25), as well as differentiating between resected (surgery was performed, n=28) and unresected (no surgery was performed, n=12) findings. After a follow-up of up to 24.3 years, the median survival of patients with tumor stage I or II was 19.3 years and only 4.6 years for patients suffering from tumor stage III or IV. The median survival of patients who had undergone surgery was 14 years. On the other hand, in patients who had not undergone surgical treatment, the median survival was only 1.8 years. The 5-year survival for those with early tumor stages was 86.7% (95% CI=59.5-96.6%) and 26.7% (95% CI=12.8-47.4%) for those with advanced stages. Patients who underwent surgical therapy had a 5-year survival of 64% (95% CI=45.4-79.6%), those with unresected tumors only 12.5% (95% CI=2.0-49.8%). The survival analysis is illustrated in Figure 1. Of the 25 patients diagnosed with OSCC stage III or IV, three received surgical treatment, as did 11 out of the 15 patients diagnosed with stage I or II cancer.

The proportion of smokers was similar in both groups, with 82.5% (n=32) smokers in the case group and 72.5% (n=29) in the control group, but the percentage of heavy smokers in the case group, on the other hand, exceeded those found in the control group. No 'light' smokers were found among the patients with OSCC. Only two of the smokers (6%) quit after their initial cancer diagnosis; 15% (n=6) of the patients with OSCC already suffered from chronic obstructive pulmonary disease (COPD), all of whom were categorized as 'heavy' smokers In the case and control groups, a correlation between level of occupational status and smoking status was found: The higher the socioeconomic status, the less likely the patients were to smoke heavily or at all, and *vice versa*. Professional exposure to harmful substances was not identified as an influential factor.

The proportion of patients who consumed alcohol was almost equally high, with 90% in the case group versus 92.5% in the control group. The overwhelming majority (62.5%) of alcohol-consuming patients in the case group were 'daily drinkers,' whereas only one patient (2.5%) in the control group showed the same behavior. The majority of patients in the control group (90%) were 'moderately frequent' consumers. Furthermore, the frequent consumption of liquor was significantly higher in the case group (25%) compared with the control group (none), in which only 5% stated drinking beverages with high alcohol content occasionally. Independently of the alcohol content, patients with OSCC consumed alcohol significantly more frequently than their controls; 40% of the cases were categorized as alcoholics in contrast to those in the control group, in which none were diagnosed as such. Similarly, 32.5% of the cases suffered from liver disease (none in the control group); 76.9% of those with liver disease had hepatic steatosis, whereas the remainder suffered from liver cirrhosis. Both diseases coincided with heavy consumption of beverages with high alcohol content.

Combined smoking and frequent alcohol consumption was observed in 60% of the cases but only in 2.5% of the controls. Furthermore, 50% of the frequent drinkers in the case group were also heavy smokers. Most of the patients in the control group 'occasionally' combined drinking and smoking. Further potential risk factors including allergies,

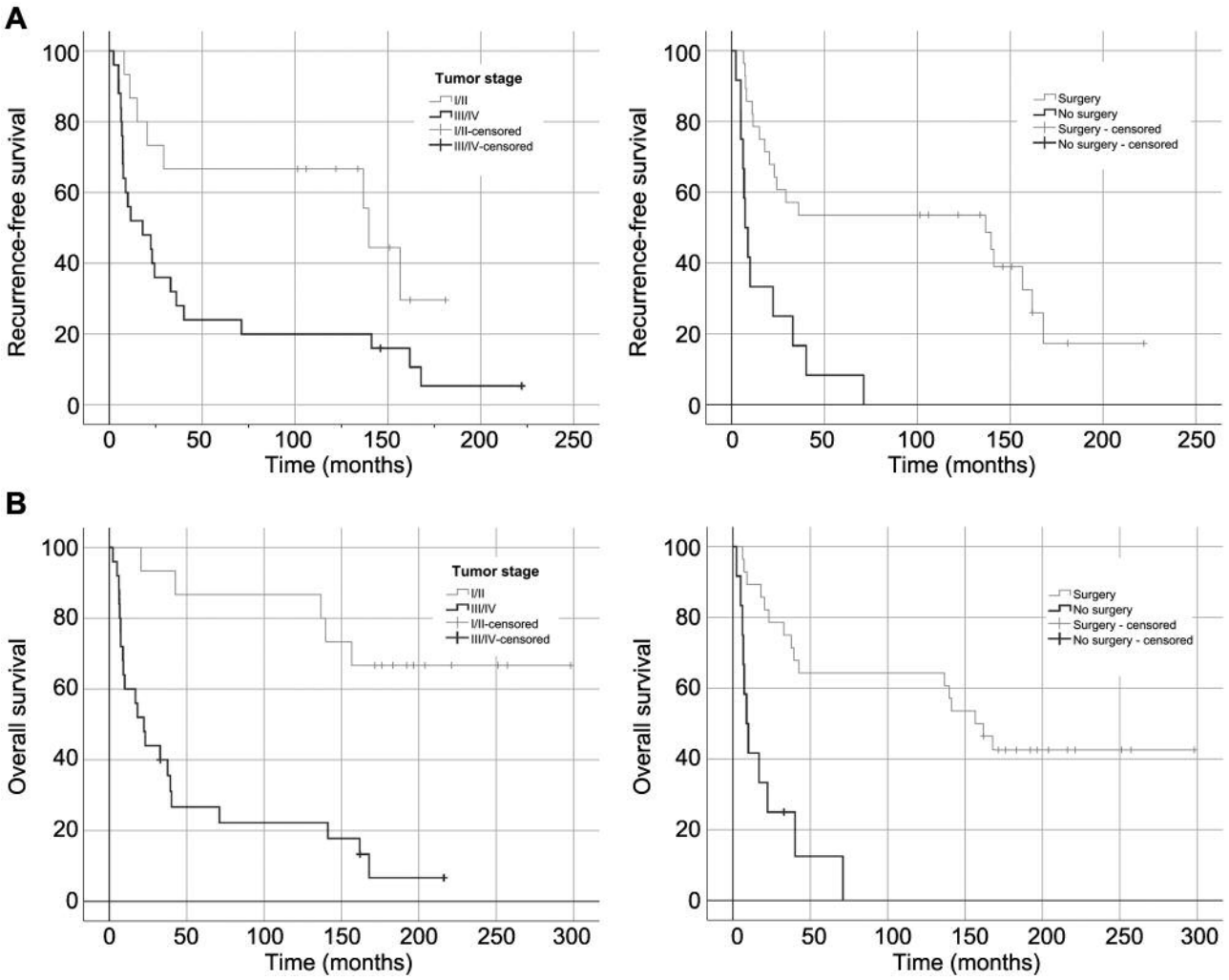

Figure 1. *Kaplan–Meier estimates for recurrence-free (A) and overall (B) survival in relation to the tumor stage (left), and surgical approach (right).*

cardiovascular diseases, immunodeficiency, drug abuse, and poor oral hygiene were not found to lead to statistically significant differences between the case and control groups.

Discussion

Despite the increasing focus on HNSCC in younger adults and reports about growing prevalence in this specific patient cohort, OSCC in young patients is still a rare disease. This is especially the case when differentiating among the various subtypes of the heterogeneous group of head and neck cancers, which originate from different anatomical areas and tissues (14, 34). When trying to evaluate specific risk factors, this must be considered to avoid flawed conclusions for the sake of higher sample sizes. In our study, we focused only on OSCC, and even at a high-volume hospital, the sample size of cases with OSCC under the age of 46 years did not exceed 40 patients in a 13-year period. Nevertheless, the findings were remarkably striking.

In the overwhelming majority of studies conducted in the past years, the authors concluded that traditional risk factors played a decreasing role in younger patients suffering from OSCC, and several authors stated that females were more frequently affected in this age group (15, 16, 27, 35, 36). However, these claims have been challenged in more recent studies (22, 23). Furthermore, the literature indicates that in younger patients, the ratio of males to females is approximately 1:1 (23). In contrast, the gender distribution in our study showed a ratio of 3:1 (75% males and 25% females), which represents the traditional pattern (14).

The majority of patients in our study were of normal weight in both groups. However, the case group presented a

higher number of malnourished or obese patients, which presumably results from lifestyle differences, such as frequent heavy smoking and drinking habits. High alcohol consumption was shown to be associated with higher BMI values, and the affected individuals presented a tendency toward poor diet and smoking (37, 38). In advanced cases, on the other hand, malnourishment and low BMI pose a serious threat to overall health and can have negative effects on tumor therapy (39, 40). Tobacco smoking can be associated with low socioeconomic status and higher BMI but also coincided with lower BMI in other studies (41-43). A poor diet, low in fruit and vegetables, has been correlated with oral cancer, and it has been shown that a Mediterranean diet favorably affects the risk of upper aerodigestive tract cancer (44, 45). Considering the significantly higher number of cases with pathological BMI in our young patients with cancer, nutrition might be an influential factor. Unfortunately, the retrospective setting of this study did not deliver sufficient data to substantiate this.

The tongue and the floor of the mouth were the most frequently affected sites in this study. This does not directly correspond to claims of a trend toward higher incidence of SCC of the tongue (36, 46, 47). Some data hints that in the younger population, tongue carcinoma of the lateral border accounts for more than 70% of OSCC but is quite rare in older patients (26%) (48). In this study, these cases accounted only for 32.5% of OSCC in patients under the age of 46 years. To the best of our knowledge, no study has been able to find relevant risk factors correlated with this proclaimed predominance of OSCC in the tongue (27, 48). Immunodeficiency, exposure to other pollutants, and drug abuse have been described as possible risk factors (3, 44, 48). None of these factors had a measurable impact in our study, but we cannot rule out that this might be due to the limited number of cases. In addition, p16 positivity was only found in one of the cases, and in contrast to oropharyngeal squamous cell carcinoma (OPSCC), its role in OSCC remains unclear since HPV-DNA positivity does not necessarily play a tumor-promoting role; nor does it represent a highly reliable diagnostic tool (8, 34, 49, 50).

As previously stated, the documented rise in OSCC in younger adults is repeatedly mentioned with the decline of traditional risk factors such as tobacco smoking and alcohol consumption. While the moderate consumption of alcohol and tobacco was present in both the case and control groups, the excessive abuse of both substances was primarily found in the former. The number of heavy smokers was four times higher in the case group compared with their controls (81.8% vs. 20.7%, respectively; $p<0.001$). Furthermore, female smokers in the case group did not rank behind their male smoking counterparts, with a percentage of heavy female smokers of 86%. This stands in stark contrast to the previously cited literature, especially since none of the female smokers in the control group could be categorized as such. After initial diagnosis, 77.5% of the patients with OSCC continued smoking, which indicates reduced disease awareness and mirrors the proportion of low-level education or socioeconomic status, which is correlated with smoking status. Even more striking is the fact that 15% of the cases (n=6) also suffered from COPD, further emphasizing excessive tobacco consumption, which is generally accepted as the primary risk factor for COPD (51, 52). Particularly because all of the COPD cases were 'heavy' smokers, we suggest that this results from smoking-related accelerated lung aging since the mean age of high prevalence is generally much higher (53, 54). In contrast, none of the controls suffered from secondary pulmonary damage because of moderate tobacco consumption. Therefore, secondary COPD caused by heavy smoking can also be seen as a risk indicator for OSCC in young patients.

Analogously, the frequent consumption of beverages with high alcohol content, such as liquor, in the case group exceeded that of the control group by far. The difference of frequent (daily) drinkers between cases (62.5%; n=25) and controls (2.5%, n=1) was statistically significant ($p<0.001$). This is correlated with the very high proportion of alcoholism among the cases of 40% (n=16). In addition, 25% of the cases stated that they consumed high-proof alcohol on a daily basis, whereas none of the controls declared likewise ($p<0.001$). Moreover, 32.5% (n=15, Table I) of the patients in the case group suffered from alcohol-associated liver comorbidities; 80% (n=12) statosis hepatis vs. 20% (n=3) liver cirrhosis, both associated with alcohol consumption. In contrast, only one patient in the control group was affected. This statistically significant difference ($p=0.003$) leads us to conclude that secondary liver disease might also serve as a risk indicator for OSCC in younger patients.

Alcohol consumption in Germany is high and especially critical in children and adolescents. A recent press release of the German Federal Statistical Office stated that the number of hospital admissions caused by alcohol intoxication in children and adolescents between 10 and 17 years has more than doubled since 2000 (55). Furthermore, the German Cancer Research Center stated in 2017 that 18% of the male and 14% of the female population consumed critical quantities of alcohol (56). Taking this into account, we must state that the percentage of cases with alcoholism in our group of young patients with OSCC is more than twice as high. Earlier and heavier alcohol abuse in adolescents and even children might nonetheless be a relevant factor. This might shorten the necessary period of exposure for tumor development in a growing body, especially when combined with other carcinogens, such as tobacco, *e.g.* in the form of frequent passive smoking (20, 27, 48).

In particular, the combination of alcohol and tobacco is known to have potentiating effects on carcinogenesis (2, 8, 57). Our results reflect this long-known observation; in the

case group, 60% of the smokers consumed alcohol frequently (n=24), whereas only 2.5% (n=1) of the controls had the same heavy consumer behavior ($p<0.001$). Furthermore, 65% (n=26) of the patients with OSCC also smoked more than 20 cigarettes per day, in contrast to only 15% (n=6; odds ratio =5.958, 95% CI=1.670-21.254) in the control group. While general smoking and drinking habits were present in both groups, the case group showed predominantly abusive consumer behavior. A frequent argument against traditional risk factors in young patients is the lack of time for exposure. Upon reviewing the demonstrated results, this might not be the case if the intensity is high enough or similar doses are consumed in a shorter period.

Despite good accessibility to the oral cavity and the exclusion of oropharyngeal OPSCC, OSCC is frequently diagnosed in advanced stages mostly because of patient ignorance, as well as initial misdiagnosis (8, 58). Our findings reflect this general problem, which is all the more important since OS analysis over a period of up to almost 25 years as well as recurrence-free survival demonstrated unfavorable outcomes of advanced stages and especially devastating results of tumors that were not treated surgically. The high rate of delayed diagnosis (stage IV) is even greater than that described in the current literature and demonstrates a lack of early cancer detection in the younger population (59). In part, this might be because the general risk for OSCC might be underestimated by patients and healthcare professionals. This underlines the importance of early diagnosis and decisive surgical treatment since the outcome in patients who did not undergo surgery was tantamount to a death sentence in our patient cohort.

We conclude that the role of traditional risk factors should not be underestimated in young adults with OSCC. The abusive consumption of harmful substances might especially be a potent accelerator for carcinogenesis. In contrast to most studies, our results lead to the conclusion that secondary organ damage such as COPD and liver cirrhosis or alcohol-induced steatohepatitis can also be considered risk indicators for OSCC in the younger patient population. The influence of other risk factors cannot be evaluated sufficiently given the limited sample size. Therefore, larger prospective multicenter studies that respect the different HNSCC subtypes must be conducted to specify these findings and shed light on still-unanswered questions. Long-term survival analysis over a period of up to 25 years underlined the unfavorable outcome of advanced cancer, especially for patients who had not undergone surgical treatment. Accordingly, these findings call for routine oral cancer screening in younger patients with high-risk behavior and, in particular, secondary organ damage. Furthermore, the discrepancy between the relatively short recurrence-free survival and OS demonstrates the importance of close aftercare and follow-up for recurrence.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: J.R., N.N. and C.D. Data collection and curation: M.M., N.N., D.T., J.W. and S.K. Data analysis and interpretation: K.N., N.N., K.J. and C.D. Resources and supervision: J.R., M.H. and K.J. Writing the original article: N.N. Editing: N.N., J.W., S.K. and D.T. All Authors revised the final article and approved its publication.

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