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Oral cavity cancer in young, non-smoking, and non-drinking patients: a contemporary review

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Abstract

Oral squamous cell carcinoma (OSCC) in non-smoking and non-drinking (NSND) individuals appears to be distinct from the traditional head and neck squamous cell carcinoma (HNSCC). The incidence of this subset is increasing, as are the number of studies examining its characteristics. NSND OSCC individuals tend to be younger (<45 years) compared to traditional HNSCC patients. The proportion of females in the NSND OSCC cohort is also higher. The tongue is the predominantly affected subsite. Studies have revealed several gene mutations and unique epigenomic profiles but no definitive genetic etiology. Transcriptomic analysis has not found any causative viral agents. Other proposed etiologies include chronic dental trauma, microbiome

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References for this Review were identified through searches of PubMed with various key search terms, including "non-smoking, non-drinking oral cancer", "young oral cancer", "NSND OSCC", "non-smoker OSCC", "non-smoker HNSCC", "non-drinker OSCC", "non-drinker HNSCC", and other similar combinations. No date limitations were applied. Articles were selected via manual review by the authors, and only papers published in English were reviewed. The final reference list was generated to cover the broad spectrum of findings and opinions on the topic discussed.

abnormalities, marijuana consumption, and genetic disorders. There are international efforts to determine the relative prognostic outcome of this unique cohort, but no consensus has been reached. Here, we review the incidence, demographics, subsite, possible etiologies, prognosis, and therapy implications of the NSND OSCC cohort.

Keywords

oral cancer; head and neck cancer; young; non-smokers; non-drinkers

Introduction

Historically, tobacco and alcohol consumption have been the most significant risk factors for the development of head and neck squamous cell carcinoma (HNSCC) .[1,2] Despite the decline in tobacco use in the United States, the annual number of oral cavity and pharynx cancer cases has been steadily increasing.[3–6] This increase is attributed to the human papillomavirus (HPV)-mediated oropharyngeal SCC epidemic in the United States over the past two decades.[4,5] However, there is also an emerging population of younger, non-smoking, non-drinking (NSND) oral squamous cell carcinoma (OSCC) patients without identifiable risk factors.[6] This subset of patients is distinct from the HPV-mediated oropharyngeal SCC patients as shown by a multi-institutional study that confirmed that HPV does not play a significant role in the etiology of oral tongue SCCs.[7]

While the exact cause has yet to be determined, the younger patient population of this distinct clinical entity has sparked interest with increasing publications focused on the topic within the head and neck cancer literature. Of note, these studies are not always directly comparable due to differences in OSCC site selection (eg, tongue), age cutoffs and definitions of non-smoking, non-drinking status. For instance, the criteria for "non-smoking" can vary between studies as never smoking, not currently smoking, or smoking less than a certain number of pack-years in a lifetime. Similarly, the criteria for "non-drinking" could be never drinking or not drinking on a daily basis. Furthermore, some investigators have equated the NSND OSCC patients with younger OSCC patients, but the younger patients in the studies are not all NSND and vice versa. Thus, age is not a perfect proxy for this atypical entity, which is known to lack the traditional risk factors of smoking and drinking. This highlights the need for a consensus on the parameters that define the NSND group for future studies. In this contemporary review, we provide an accessible overview of oral cavity cancer in younger, NSND patients, including a review of the entity's incidence, demographics, subsite involvement, possible etiology, prognosis, and implications for therapy.

Incidence

Because the NSND OSCC entity has not yet been clearly defined (as discussed above), no study has directly analyzed the incidence of NSND OSCC, specifically. However, the available studies have shown an increase in the proportion of NSNDs among OSCC cases, and others have shown an overall rise in OSCC incidence, which suggests an increase in the incidence rates of NSND OSCC. The rising rate of OSCC in younger patients within

the United States population was likely first reported by Shemen et al. in 1984 in a letter to the editor of JAMA stating an unusual increase in the proportion of young men (< 40 years) treated for OSCC at Memorial Sloan-Kettering Cancer Center from 1955 to 1982.[8] Subsequently, Myers et al. from M.D. Anderson reported single institution data that showed an increase in the percentage of young adults with oral tongue SCC from 4% in 1971 to 18% in 1993.[9] In 1996, Atula et al. in Finland were perhaps the first to study the proportional rise of OSCC in younger patients without traditional risk factors at the population level. They noted that the proportion of younger patients with SCC of the oral tongue increased from 3% in the 1950's to 7% in the 1980's.[10] This proportional increase of younger patients with tongue cancer within Nordic countries has subsequently been confirmed with cancer registry data.[11,12] Analysis of data from the Surveillance, Epidemiology and End Results (SEER) database also confirmed the rise of OSCC cases among young individuals in the United States.[3,6,13] Tota et al. found an increased incidence of oral tongue cancer for both men (annual increase 0.7%, $P = 0.02$) and women (annual increase 1.7%, $P < 0.001$) using SEER data from 1973 to 2012.[13] Of note, smoking and drinking status is incompletely reported in the SEER database, which limits the findings of SEER studies to some extent. Finally, a global study using data from 22 international cancer registries consistently found that the incidence increase was higher in women than men (in 11 of the 22 registries studied) and in younger patients less than 45 years old (14 of the 22 registries).[14] Taken together, these studies so far suggest a global increase in incidence of OSCC in younger patients.

Demographics

The characteristics of the "typical" OSCC patient have slowly evolved over the last few decades. While a white male in his seventh decade of life with a long history of tobacco and alcohol abuse continues to be a common OSCC patient in the U.S., OSCC is now presenting frequently in patients without these characteristics. Population level data suggests an increase in the incidence of OSCC in both men and women under the age of 40.[3,6,13] When analyzed as a distinct population, the NSND OSCC patient is three times more likely to be female compared to patients with significant past or current smoking and alcohol use (which, herein, we refer to as the "ever smoker, ever drinker" (ESED) OSCC patients) who are twice as likely to be male.[15–19] There is also a significant age difference in the two presenting populations with some studies suggesting a bimodal age distribution of 40–59 and 70–79 years of age for the NSNDs compared to the single peak of 60–69 years in the ESEDs described by prior authors.[15,20] However, more commonly, authors refer to the NSND OSCC group as being less than 40 or 45 years old.[3,6,9,13,17,21] Multiple studies have described the NSND OSCC patient as more likely to be non-Hispanic white.[3,6,13,20] Indeed, SEER data has shown that the incidence of oral cavity cancer in patients less than 40 is increasing among White individuals only.[3,6,13] Finally, personal income or education level has not shown any association with the development of NSND oral cavity cancer.[20] However, these conclusions may be limited by variations in the definitions of nonsmoking and non-drinking between papers.

Subsite Involvement

The oral tongue tends to be the most common oral cavity subsite in NSND OSCC patients.[15–17,20,22] A study examining only young patients (18 – 39 years) with HNSCC found NSND patients to be significantly more likely to have oral tongue tumors (57% vs. 24%, $P < .001$).[18] In a retrospective analysis of 881 patients, Perry et al. found a statistically significant difference in tumor location within the oral cavity between non-smokers and those who currently or previously smoked. Tumors of the lateral tongue were proportionately more common in nonsmokers (66%) than current or ex-smokers (35%) (p <.001).[22] This was replicated by Li et al. who reported that virtually all 53 non-smokers with OSCC had tumors arising from the lateral border of the tongue.[23] Similarly, a cohort study by Dahlstrom et al. with 172 NSND patients found the most common subsites to be oral tongue, mandibular alveolus, buccal, and maxilla. Notably, floor of mouth malignancies were particularly rare (1.4%) in the NSND group compared to the ESED group (24.9%).[20] These studies are supported by the previously mentioned SEER studies, which show that the number of younger patients with OSCC of the tongue specifically has been increasing in the United States since that database was created in the 1970s.[3,6,13] Ultimately, the oral tongue appears to be the most common subsite for younger, NSND OSCC patients. However, it is important to note that the precise definition of anatomical subsites can vary between providers and institutions, leading to possible variation in the distribution of anatomic locations of lesions reported between articles.

Etiology

Despite increasing efforts to study the new entity, the exact cause of OSCC in younger, NSND patients remains unknown. The upcoming sections explore possible etiologies including dental trauma, genomics, viruses, microbiome, and toxins.

Dental Trauma

Both preclinical and clinical studies have demonstrated the positive association between wound repair, chronic inflammation and the development of cancer.[24,25] Molecular analyses have highlighted similar gene expression and molecular pathway activation between wound healing and tumorigenesis.[24,26] Moreover, chronic trauma triggers inflammation that result in oxidative DNA damage, which increases the possibility of malignant transformation of cells.[27,28]

As tumors of the oral cavity commonly arise from sites of potential chronic dental trauma (CDT), such as the lateral tongue, CDT has been proposed as a possible etiology of oral cancer in patients lacking the classical risk factors such as smoking and drinking.[22,29] CDT may be due to ill-fitting dentures, broken or sharp teeth, faulty dental restorations, or dental implants.Dahlstrom et al[20] compared 172 NSND head and neck squamous cell carcinoma (HNSCC) patients with 1131 ESED HNSCC patients. Based on their demographics data, they concluded that the oral cavity subsite in NSND HNSCC patients depended on age and gender, with oral tongue cancer more common in women under 50 years and gingivobuccal cancer in women 70 years or older. CDT from ill-fitting dentures primarily affect the gingivobuccal area and thus, has been proposed as an etiology for

gingivobuccal cancer in elderly NSND OSCC patients.[22,27,29] To our knowledge, there are no animal models that study the pathophysiology of chronic oral trauma leading to OSCC development. Investigations thus far are limited to retrospective studies. To further elucidate the relationship between CDT and OSCC, thorough documentation of dental trauma history in patients with OSCC is needed, as well as animal models to study the causative role of CDT.

Genomics

The atypical non-smoking OSCC entity appears to have a distinct epigenetic profile that distinguishes it from the traditional OSCC. Brennan et al. performed unsupervised clustering on the methylation profiles of 528 HNSCC patients and identified five distinct subtypes: one HPV positive subtype, two smoking-related subtypes, and two atypical subtypes.[30] One of the atypical subtypes was genomically stable with widespread DNA hypermethylation-related gene silencing, hence called 'CpG island methylator phenotype' (CIMP)-atypical subtype. The CIMP-atypical subtype was composed of more non-smokers than the other subtypes and was 98% HPV-negative. They also found that the CIMP-atypical subgroup had enrichment of genes in the interferon (IFN) pathways and an overexpression of CD274 (PD-L1) and PDCD1LG2 (PD-L2). Enrichment in the genetic signature for IFN-γ response and immune checkpoint ligands, such as PD-L1, in NSND OSCC tumors have been seen in other studies as well.[31,32] Given that IFNs are strong modulators of antiviral immunity, viral etiologies have been proposed for the atypical OSCC group.[33,34] Investigations into viral etiologies are discussed in later sections.

Analysis of the CIMP-atypical tumors found an increased incidence of mutations in the gene encoding caspase 8 (*CASP8*).[30] In fact, nearly all of the TCGA HNSCC tumors that harbored *CASP8* mutations segregated to the CIMP-atypical subgroup. *CASP8* is a critical component of the apoptosis and necroptosis cascades and contributes to the death-inducing signaling complex.[35] Loss of *CASP8* expression has been documented in other cancers, including small-cell lung cancer, brain tumors, neuroendocrine cancers, and more.[36] Prior whole exome sequencing of patients with HPV-negative OSCC found that these tumors frequently present with *CASP8* mutations that co-occur with *FAT1* mutations.[37] These data point to a unique pathway by which NSND patients may develop OSCC that requires further exploration and validation.

Of note, conflicting data exists for copy number analysis and mutational burden profiles of NSND OSCC patients. Pickering et al. performed whole-exome sequencing and copy-number analysis of oral tongue tumors from 29 non-smoking young patients (ages <45 years old) and 86 older patients who have a history of smoking (ages >45 years old). Their data revealed similar gene-specific mutations and copy-number alteration frequencies between the two groups, despite differences in smoking prevalence.[38] Based on their data, the mutational signature from tobacco smoking is not prominent in tumors of the tongue. Li et al., also performed exome sequencing of tumor DNA and similarly found no difference in overall mutational burden between smoking (n= 36) and non-smoking (n=53) OSCC groups.[23] However, there exist other studies that suggest nonsmokers harbor fewer mutations compared to smokers.[30,39,40]

Regarding the *TP53* gene, some studies found *TP53* expression to be comparable between the two groups, while other studies concluded that p53 abnormalities are less frequent in OSCCs of young patients.[23,41,42] Non-smoking patients with *TP53* mutations had higher tumor-node-metastasis (TNM) stage, worse tumor differentiation, earlier recurrence, and poorer survival than those without mutations.[43] Other cell cycle proteins such as p21, Rb and MDM2 were also not found to be differentially expressed.[41] In one study comparing NSND (n = 59) to ESED (n = 117) patients using a targeted panel of 68 genes, the NSND cohort had a greater proportion of *CDKN2A* mutations, *EGFR* amplifications, and *BRCA2* deletions (11.9% vs 1.7%, p =0.007).[44] *PIK3CA* mutation, *CDKN2A* deletion, and *EGFR* amplification were significantly associated with worse survival in univariate analyses. However, none of these gene mutations was significant in multivariable survival analysis accounting for clinicopathologic variables.[44]

In summary, there has been much progress to genomically characterize NSND OSCC as distinctly different from the traditional OSCC, but the available studies are not all consistent and no definitive genetic etiology has been identified. On an epigenetic level, there seems to be widespread CpG island methylation and gene silencing. On a genomic mutational level, there are differences in specific gene mutational frequencies, such as *CASP8*. Interestingly, genomic analysis of OSCC tumors from non-smokers showed evidence of a more robust IFN-γ response and activation of immune checkpoint ligands, pointing to the possibility of viruses as the pathogenic cause of OSCC.

Viruses

Given the relatively young age and lack of tobacco and alcohol carcinogen exposure in the unique OSCC entity, viral etiologies have been explored. As previously mentioned, this is supported by the finding that multiple IFN-γ pathway genes are upregulated in tumors of young patients, and interferons are strong modulators of antiviral immunity.[23,33,34] Viruses, such as the Epstein–Barr Virus (EBV) and HPV, have a well-established association with head and neck cancer. In a meta-analysis of 13 case-control studies, She et al. found an association between EBV infection and OSCC with an odds ratio of 5.03 (95% CI 1.80–14.01).[45] Additional mechanistic research into how EBV infection induces OSCC tumorigenesis is required, but current studies implicate EBNA-1, EBER-2, and especially LMP-1 as oncoproteins.[46]

HPV has been implicated as a clear driver of tumor formation in oropharyngeal SCC, however its role is not clear in the NSND OSCC group.[47–49] HPV infection can result in *p16INK4a* (p16) overexpression on immunohistochemistry. In one study, NSND OSCC was found to have more frequent and greater p16 expression compared to OSCC in smokers/drinkers, and p16 expression was correlated with a worse prognosis in these NSND OSCC patients.[48] While the overexpression of p16 is supportive of HPV infection, it does not confirm HPV infection, as there are other mechanisms that can result in p16 overexpression. Zafereo et al. found that 30% of oral cavity SCC patients had p16 overexpression, with more prominent expression in younger patients with oral tongue tumors. However, in situ hybridization analysis found that very few tumors were HPV-positive.[50] Another study by Lingen et al. utilizing RT-PCR corroborated these findings and found that only 5.9%

of OSCC tumors were positive for HPV-E6/7, with 3.7% positive for HPV16, and 2.2% positive for any other HPV variant.[7]

More specifically, in NSND patients with OSCC, Laco et al. published an analysis comparing OSCC and oropharyngeal SCC (OPSCC) finding that p16 expression was detected in 29% of OSCC tumors compared to 100% of OPSCC tumors in this patient population of individuals with no history of smoking or chronic alcohol abuse.[51] Furthermore, only 25% of NSND OSCC tumors had high risk (HR) HPV DNA and only 13% had HPV DNA.[51] These findings are supported by a more recent analysis by Perot et al. showing HR-HPV DNA is present in only 4.4% (3/68) of OSCC samples analyzed. Only 1 of these samples actually had the presence of viral transcripts.[52] Thus, despite the potential correlation of p16 overexpression and prognosis of NSND OSCC[48], there is little evidence to suggest HPV has a role in carcinogenesis within NSND OSCC.[49]

Traditionally, α-HPV has been thought to be a driver of carcinogenesis in HNSCC, but recent data suggest that beta-papillomaviruses (β-HPV) may possibly play a role in inducing tumorigenesis but may not be as essential for tumor maintenance.[53] Perot et al. found that 41.2% of OSCC samples had HPV DNA, and 90.9% of these DNA samples belonged to β-HPV. Indeed, one study of HPV in HNSCC found that β1-HPV-5 was associated with oral cavity, oropharyngeal, and laryngeal SCC.[53] β-HPV naturally can be found in various parts of the human body as a commensal, including the skin. β-HPV has been implicated to have a role in skin carcinogenesis that can lead to cancers like cutaneous SCC, especially in immunosuppressed or immunocompromised individuals.[54] More preclinical and clinical studies are needed to investigate the role of β-HPV in OSCC carcinogenesis.

Even after using three different algorithms (MapSplice, PathSeq and Trinity) to probe the genomic and epigenomic landscape of oral tongue tumors from smoking and non-smoking patients, no causative viral agents were identified.[23] Because viral genome integration has not been detected in NSND OSCC tumors, prior authors have hypothesized a "hit and run" viral mechanism. The "hit and run" theory proposes that oncogenic viruses can integrate into the host cell genome, triggering epigenome deregulation. The epigenome deregulation leads to gene expression changes that can result in carcinogenesis. Subsequently, the viral genome is lost in host cell progeny and thus becomes undetectable at the time of clinical diagnosis.[23,55] Further investigations to detect epigenetic signatures of previous viral infections may be able to support the "hit and run" hypothesis.

Fanconi anemia

Fanconi anemia (FA) is a group of genetic disorders characterized by defects in the cells' normal response to DNA damage. FA can be inherited as autosomal recessive, autosomal dominant, or X-linked recessive depending on the mutations involved.[56] FA results in congenital defects, endocrine abnormalities, bone marrow failure, and a predisposition to developing acute myelogenous leukemia (AML), as well as a multitude of solid malignancies. There is a greater than 500-fold increase in the incidence of HNSCC in FA patients relative to the general population.[57] FA has been proposed as a possible etiology in NSND OSCC patients because patients with FA are more likely than the general public to develop OSCC in young adulthood without smoking or drinking risk factors.[58] Due to the

heterogeneity in symptoms of FA, some FA patients can present with a milder phenotype and go undiagnosed. In the population of younger, NSND OSCC patients, it can be useful to screen for anemia, endocrine disorders, or congenital defects to evaluate for FA.[59] Moreover, if available, genetic testing for FA can help provide definitive diagnosis while offering a possible explanation for the origin of a patient's HNSCC.[56] Additional studies on NSND patients with FA may elucidate the influence of FA on OSCC carcinogenesis.

Microbiome

Although smoking and drinking have been long known to disrupt the oral microbiome, there is a paucity of studies linking the microbiome to the NSND OSCC entity. The microbiome has been an increasingly important topic in the field of cancer biology, and the oral microbiome is particularly relevant to OSCC pathology. Smoking is thought to make the oral microbiome more pro-inflammatory while also depleting commensal bacteria. Specifically, an increase in *Fusobacterium*, *Mogibacterium*, and *Tannerella* were observed with a loss of *Neisseria*, which are commensal bacteria that can have protective effects on oral mucosa.[60] Alcohol usage increases OSCC-associated bacteria, such as the *Campylobacter* species.[50] Smoking in conjunction with alcohol use was found to produce increased acetaldehyde in saliva, which is associated with carcinogenesis.[60] Additional factors that can alter the oral microbiota and potentially contribute to OSCC formation include viral (eg, HPV) infections and certain sexual behaviors.[55] Given this, the oral microbiome has been hypothesized to have a major role in the pathogenesis of OSCC in NSND patients as well.

One study analyzed the mRNA expression of the oral microbiome in non-smoking, HPV-negative OSCC patients and found more virulence factor transcripts associated with *Fusobacterium* along with greater biosynthesis, chemotaxis, iron transport, and more activities in the tumor site.[61] Additionally, a study of 16S rRNA in non-smoking, HPV-negative OSCC by Ganly et al. found enrichment of *Fusobacterium, Prevotella*, and *Alloprevotella* (all periodontal pathogens) compared to healthy controls.[62] The authors also observed a loss of commensal bacteria in OSCC patients regardless of alcohol consumption.[62] The influence of the microbiome and potential mechanism by which the enriched pathogens contribute to OSCC formation in NSND have not yet been determined.

Overall, there is a paucity of data evaluating the oral microbiome of NSND OSCC patients, but existing analyses suggest that multiple factors can disrupt the oral microbiome in both smokers and non-smokers, resulting in an enrichment in pathogenic bacteria, such as *Fusobacterium*. Additional studies that directly compare smoking and drinking OSCC samples to NSND OSCC samples are necessary to evaluate the role of the microbiome in the oncogenesis of NSND OSCC.

Marijuana

Marijuana is another potential risk factor of HNSCC, in general, that has been under investigation. The cigarette-adjusted risk of general HNSCC for marijuana users was 2.6, with an observed dose-response relation.[63] A cross-sectional study of 530 oral cavity and oropharyngeal SCC patients found that 13.2% were marijuana users, and 2.3% of patients were solely marijuana and not tobacco smokers.[64] One case-control analysis of 173 HNSCC

found an increased risk of HNSCC in marijuana users compared to never users (OR 2.6, CI 1.1–6.6) after adjusting for age, sex, race, education, alcohol consumption, and cigarette smoking.[65] The oral microbiome may also be involved in marijuana's influence on OSCC formation, and in tongue SCC samples from marijuana users (not adjusting for cigarette smoking or alcohol usage), a reduction of *Capnocytophaga, Fusobacterium*, and *Porphyromonas* and elevation of *Rothia* was observed.[66] Interestingly, the reduction in *Fusobacterium* observed in this study was in direct contrast to the elevation observed in other microbiome analyses of the oral cavity for patients with OSCC.[61,62]

The role of marijuana in the NSND OSCC group is not yet clear. Dahlstrom et al. report in their analysis of 67 NSND and 48 ESED OSCC patients, only 3% of NSND patients were positive for serum Δ9-tetrahydrocannabinol, the active ingredient of marijuana, compared to 6% of ESED patients, suggesting that marijuana is unlikely to be the etiology of carcinogenesis in NSND OSCC patients.[20] Additionally, a case-control study of 407 cases of OSCC and 615 controls concluded that after adjustment for alcohol consumption, cigarette smoking, and other possible confounding factors, the adjusted odds ratio for risk of OSCC after marijuana use was not statistically significant.[67] These results suggest that marijuana use on its own may not be relevant to OSCC development in NSND patients.

Betel Quid

Betel nut or quid is a prevalent recreational substance globally, especially in South and Southeast Asian countries, that has been linked to OSCC carcinogenesis. Betel nut chewing on its own without tobacco additives is a well-established risk factor for OSCC and thus, will not be the focus of this review.[62,63] Yet, it is prudent to note its importance as a risk factor for OSCC in NSND patients, especially in Southeast Asia. A meta-analysis of Southeast Asian studies of OSCC risk factors found that betel quid chewing in non-smoking and non-drinking patients, had a pooled odds ratio of 7.90 (95% CI 6.1–9.30).[64] These data suggest that betel quid chewing, especially in regions of high prevalence, can partially explain the etiology of NSND OSCC.

Prognosis

A consensus has yet to be reached for the prognosis of OSCC NSND patients compared to those with traditional smoking and drinking risk factors. Many groups have used age to identify the atypical cohort, with individuals <40 or <45 years identified as part of this group. A number of retrospective studies suggest worse oncologic outcomes for younger OSCC patients compared to older patients,[68–72] while other studies conclude that younger patients have better survival.[68,73–75] That said, a growing number of studies are seeing no difference in survival outcomes of young vs old patients.[69,76–79] Although it is true that patients in the NSND OSCC group tend to be younger on average than the patients in the traditional OSCC group, not all young patients <45 years lack smoking and drinking history. Thus, studies that divide the cohorts based on age still have a significant proportion of the young cohort patients with smoking and drinking history. Similarly, there is also a significant number of older OSCC patients without smoking and drinking history. A comparison of patients with smoking and drinking history to those who lack smoking and

drinking risk factors can be difficult due to lack of thorough documentation. Herein, we describe the studies that compare OSCC patients with traditional smoking and drinking risk factors to those who do not have the risk factors. These studies are summarized in Table 1.

The majority of studies comparing the prognosis of NSND vs ESED OSCC patients found that NSND patients have better or similar survival outcomes.[44,48,80–86] Andersen et al. compared the survival of never-smokers (n=240) to current (n=1138)/former smokers (n=339) with OSCC.[80] After adjusting for excessive alcohol consumption, they found that overall survival (OS) was worse for current smokers (hazard ratio [HR] 1.83, 95% CI 1.38–2.42) and former smokers (HR 1.32, 95% CI 0.98–1.77) compared to never-smokers. Similarly, disease-free survival (DFS) was worse for current smokers (HR 1.32, 95% CI 1.04–1.68) and former smokers (HR 1.17, 95% CI 0.90–1.51) compared to never-smokers. Furthermore, the effect was dose dependent; with a higher accumulated tobacco exposure correlating with poorer OS and DFS. Similarly, a study looking at 646 NSND OSCC patients compared to ESED OSCC patients, matched for age, gender, occupation, education level, residence, BMI, TNM stage, and pathological type, found that NSND patients had improved all-cause mortality and oral cancer-specific mortality.[83]

A number of studies suggest NSND patients have similar outcomes as ESED patients.[17,44,48,85,86] Dediol et al. defined NSND as patients who smoked less than 10 pack-years and did not drink alcohol on a daily basis. Their multivariable analysis showed no difference in DSS, recurrence or metastasis based on smoking or drinking status. However, HPV and p16 expression were negative predictive factors.[48] Similarly, Bachar et al. studied patients with oral tongue SCC who had heavy tobacco smoking and alcohol abuse history compared to those without and found no difference in 5-year local and regional control rates or 5-year OS.[86] Those with heavy smoking and drinking history did, however, have significantly greater tumor depth of invasion and higher tumor grade. Interestingly, when further partitioning the NSND group by age, young (<40 years) NSND patients had significantly worse OS and DFS compared to young ESED patients. Of note, they defined the risk factor group as those who smoked daily and drank alcohol for >3 drinks/day. Studies have used different smoking and drinking cutoffs to categorize NSND, which could contribute to differing study outcomes. Several studies set 100 cigarettes as the threshold; those who have smoked less than 100 cigarettes in their lifetime are categorized as never-smoker.[44,82–84] It may be difficult to consistently use this criteria in future retrospective work because the number of lifetime cigarettes is difficult to ascertain from medical records.

Over the last several decades, significant efforts have been made to understand the prognosis of OSCC patients who lack smoking and drinking risk factors. Most of these studies so far are retrospective and suggest similar or better prognosis in the NSND group compared to the ESED group (Table 1).

Implications for therapy

As NSND patients with OSCC represent a growing population, there is a need to determine if special consideration should be given to optimize treatment modalities. Prior analysis of "CIMP-atypical" HNSCC patients found greater tumor infiltrating leukocytes in this subset,

suggesting immunotherapy may be a useful approach to therapy for these patients.[30] These tumors also showed an enrichment in PD-L1 expression, pointing to checkpoint blockade of the PD-1/PD-L1 axis as a therapy that could be tested.[30,87] However, the increased inflammation may also point to enhanced immune resistance. Ultimately, as the NSND OSCC population grows, rigorous clinical studies of different treatment protocols compared to the existing standard of care are necessary to validate new therapeutic approaches.

Conclusions

Decades of work have been dedicated to characterizing and understanding the NSND OSCC entity. OSCC in the NSND population is becoming increasingly prevalent and presents more commonly in younger patients compared to other OSCC counterparts. Here, we have reviewed traits of the NSND OSCC patient population, key characteristics of the pathology, and different proposed etiologies, including genetic mutations, viral infection, dental trauma, microbiome differences, Fanconi anemia, and recreational drug consumption. We highlight the need for consensus in the specific definition of the NSND OSCC cohort to allow for consistency and comparability of data. The more we can understand about the characteristics of the NSND OSCC entity, the better we can tailor treatments and preventative measures in the future.

Acknowledgements:

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Data Availability:

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References

1. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988;48(11):3282–3287. [PubMed: 3365707]

2. Hashibe M, Brennan P, Benhamou S, 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(10):777–789. doi:10.1093/jnci/djk179 [PubMed: 17505073]

3. Shiboski CH, Schmidt BL, Jordan RCK. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer. 2005;103(9):1843–1849. doi:10.1002/cncr.20998 [PubMed: 15772957]

4. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110(7):1429–1435. doi:10.1002/cncr.22963 [PubMed: 17724670]

5. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–4301. doi:10.1200/JCO.2011.36.4596 [PubMed: 21969503]

6. Patel SC, Carpenter WR, Tyree S, et al. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. J Clin Oncol. 2011;29(11):1488–1494. doi:10.1200/JCO.2010.31.7883 [PubMed: 21383286]

7. Lingen MW, Xiao W, Schmitt A, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49(1):1–8. doi:10.1016/j.oraloncology.2012.07.002 [PubMed: 22841678]

8. Shemen LJ, Klotz J, Schottenfeld D, Strong EW. Increase of tongue cancer in young men. JAMA. 1984;252(14):1857. [PubMed: 6471315]

9. Myers JN, Elkins T, Roberts D, Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg. 2000;122(1):44–51. doi:10.1016/S0194-5998(00)70142-2 [PubMed: 10629481]

10. Atula S, Grénman R, Laippala P, Syrjänen S. Cancer of the tongue in patients younger than 40 years. A distinct entity? Arch Otolaryngol Head Neck Surg. 1996;122(12):1313–1319. doi:10.1001/archotol.1996.01890240021006 [PubMed: 8956742]

11. Annertz K, Anderson H, Biörklund A, et al. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer. 2002;101(1):95–99. doi:10.1002/ijc.10577 [PubMed: 12209594]

12. Annertz K, Anderson H, Palmér K, Wennerberg J. The increase in incidence of cancer of the tongue in the Nordic countries continues into the twenty-first century. Acta Otolaryngol. 2012;132(5):552–557. doi:10.3109/00016489.2011.649146 [PubMed: 22339663]

13. Tota JE, Anderson WF, Coffey C, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. Oral Oncol. 2017;67:146–152. doi:10.1016/j.oraloncology.2017.02.019 [PubMed: 28351569]

14. Ng JH, Iyer NG, Tan MH, Edgren G. Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. Head Neck. 2017;39(2):297–304. doi:10.1002/hed.24589 [PubMed: 27696557]

15. DeAngelis A, Breik O, Koo K, et al. Non-smoking, non-drinking elderly females, a 5 year follow-up of a clinically distinct cohort of oral squamous cell carcinoma patients. Oral Oncol. 2018;86:113–120. doi:10.1016/j.oraloncology.2018.09.004 [PubMed: 30409291]

16. Koo K, Barrowman R, McCullough M, Iseli T, Wiesenfeld D. Non-smoking non-drinking elderly females: a clinically distinct subgroup of oral squamous cell carcinoma patients. Int J Oral Maxillofac Surg. 2013;42(8):929–933. doi:10.1016/j.ijom.2013.04.010 [PubMed: 23702369]

17. 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(4):499–503. doi:10.1002/hed.21220 [PubMed: 19691028]

18. Wiseman SM, Swede H, Stoler DL, et al. Squamous cell carcinoma of the head and neck in nonsmokers and nondrinkers: an analysis of clinicopathologic characteristics and treatment outcomes. Ann Surg Oncol. 2003;10(5):551–557. doi:10.1245/aso.2003.09.010 [PubMed: 12794022]

19. Kruse AL, Bredell M, Grätz KW. Oral squamous cell carcinoma in non-smoking and nondrinking patients. Head & Neck Oncology. 2010;2(1):24. doi:10.1186/1758-3284-2-24 [PubMed: 20920351]

20. 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(1):75–84. doi:10.1002/hed.20664 [PubMed: 17694557]

21. Campbell BR, Netterville JL, Sinard RJ, et al. Early onset oral tongue cancer in the United States: a literature review. Oral Oncol. 2018;87:1–7. doi:10.1016/j.oraloncology.2018.10.009 [PubMed: 30527223]

22. Perry BJ, Zammit AP, Lewandowski AW, et al. Sites of origin of oral cavity cancer in nonsmokers vs smokers: possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus. JAMA Otolaryngol Head Neck Surg. 2015;141(1):5–11. doi:10.1001/jamaoto.2014.2620 [PubMed: 25375930]

23. Li R, Faden DL, Fakhry C, et al. Clinical, genomic, and metagenomic characterization of oral tongue squamous cell carcinoma in patients who do not smoke. Head Neck. 2015;37(11):1642–1649. doi:10.1002/hed.23807 [PubMed: 24954188]

24. Schäfer M, Werner S. Cancer as an overhealing wound: an old hypothesis revisited. Nat Rev Mol Cell Biol. 2008;9(8):628–638. doi:10.1038/nrm2455 [PubMed: 18628784]

25. Hussain SP, Hofseth LJ, Harris CC. Radical causes of cancer. Nat Rev Cancer. 2003;3(4):276–285. doi:10.1038/nrc1046 [PubMed: 12671666]

26. Arwert EN, Hoste E, Watt FM. Epithelial stem cells, wound healing and cancer. Nat Rev Cancer. 2012;12(3):170–180. doi:10.1038/nrc3217 [PubMed: 22362215]

27. Singhvi HR, Malik A, Chaturvedi P. The Role of Chronic Mucosal Trauma in Oral Cancer: A Review of Literature. Indian J Med Paediatr Oncol. 2017;38(1):44–50. doi:10.4103/0971-5851.203510 [PubMed: 28469336]

28. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. International Journal of Cancer. 2007;121(11):2381–2386. doi:10.1002/ijc.23192 [PubMed: 17893868]

29. Yesensky JA, Hasina R, Wroblewski KE, et al. Role of dental hardware in oral cavity squamous cell carcinoma in the low-risk nonsmoker nondrinker population. Head Neck. 2018;40(4):784–792. doi:10.1002/hed.25059 [PubMed: 29356169]

30. Brennan K, Koenig JL, Gentles AJ, Sunwoo JB, Gevaert O. Identification of an atypical etiological head and neck squamous carcinoma subtype featuring the CpG island methylator phenotype. EBioMedicine. 2017;17:223–236. doi:10.1016/j.ebiom.2017.02.025 [PubMed: 28314692]

31. Farshadpour F, Roepman P, Hordijk GJ, Koole R, Slootweg PJ. A gene expression profile for non-smoking and non-drinking patients with head and neck cancer. Oral Dis. 2012;18(2):178–183. doi:10.1111/j.1601-0825.2011.01861.x [PubMed: 22035108]

32. Foy JP, Bertolus C, Michallet MC, et al. The immune microenvironment of HPV-negative oral squamous cell carcinoma from never-smokers and never-drinkers patients suggests higher clinical benefit of IDO1 and PD1/PD-L1 blockade. Annals of Oncology. 2017;28(8):1934–1941. doi:10.1093/annonc/mdx210 [PubMed: 28460011]

33. Goodbourn S, Didcock L, Randall RE. Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. J Gen Virol. 2000;81(Pt 10):2341–2364. doi:10.1099/0022-1317-81-10-2341 [PubMed: 10993923]

34. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev. 2001;14(4):778–809, table of contents. doi:10.1128/CMR.14.4.778-809.2001 [PubMed: 11585785]

35. Tummers B, Green DR. Caspase-8: regulating life and death. Immunol Rev. 2017;277(1):76–89. doi:10.1111/imr.12541 [PubMed: 28462525]

36. Stupack DG. Caspase-8 as a Therapeutic Target in Cancer. Cancer Lett. 2013;332(2):133–140. doi:10.1016/j.canlet.2010.07.022 [PubMed: 20817393]

37. Hayes TF, Benaich N, Goldie SJ, et al. Integrative genomic and functional analysis of human oral squamous cell carcinoma cell lines reveals synergistic effects of FAT1 and CASP8 inactivation. Cancer Lett. 2016;383(1):106–114. doi:10.1016/j.canlet.2016.09.014 [PubMed: 27693639]

38. Pickering CR, Zhang J, Neskey DM, 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(14):3842–3848. doi:10.1158/1078-0432.CCR-14-0565 [PubMed: 24874835]

39. Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science. 2011;333(6046):1154–1157. doi:10.1126/science.1206923 [PubMed: 21798897]

40. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011;333(6046):1157–1160. doi:10.1126/science.1208130 [PubMed: 21798893]

41. Regezi JA, Dekker NP, McMillan A, et al. p53, p21, Rb, and MDM2 proteins in tongue carcinoma from patients < 35 versus > 75 years. Oral Oncol. 1999;35(4):379–383. doi:10.1016/s1368-8375(98)00126-2 [PubMed: 10645402]

42. Sorensen DM, Lewark TM, Haney JL, Meyers AD, Krause G, Franklin WA. Absence of p53 mutations in squamous carcinomas of the tongue in nonsmoking and nondrinking patients younger than 40 years. Arch Otolaryngol Head Neck Surg. 1997;123(5):503–506. doi:10.1001/archotol.1997.01900050051006 [PubMed: 9158397]

43. Heaton CM, Durr ML, Tetsu O, van Zante A, Wang SJ. TP53 and CDKN2a mutations in never-smoker oral tongue squamous cell carcinoma. Laryngoscope. 2014;124(7):E267–273. doi:10.1002/lary.24595 [PubMed: 24431303]

44. Koo K, Mouradov D, Angel CM, et al. Genomic Signature of Oral Squamous Cell Carcinomas from Non-Smoking Non-Drinking Patients. Cancers (Basel). 2021;13(5):1029. doi:10.3390/cancers13051029 [PubMed: 33804510]

45. She Y, Nong X, Zhang M, Wang M. Epstein-Barr virus infection and oral squamous cell carcinoma risk: A meta-analysis. PLoS One. 2017;12(10):e0186860. doi:10.1371/journal.pone.0186860 [PubMed: 29065191]

46. Rahman R, Gopinath D, Buajeeb W, Poomsawat S, Johnson NW. Potential Role of Epstein-Barr Virus in Oral Potentially Malignant Disorders and Oral Squamous Cell Carcinoma: A Scoping Review. Viruses. 2022;14(4):801. doi:10.3390/v14040801 [PubMed: 35458531]

47. Andrews E, Seaman WT, Webster-Cyriaque J. Oropharyngeal carcinoma in non-smokers and non-drinkers: a role for HPV. Oral Oncol. 2009;45(6):486–491. doi:10.1016/j.oraloncology.2008.07.008 [PubMed: 19027350]

48. Dediol E, Sabol I, Virag M, Grce M, Muller D, Manojlovi S. HPV prevalence and p16INKa overexpression in non-smoking non-drinking oral cavity cancer patients. Oral Diseases. 2016;22(6):517–522. doi:10.1111/odi.12476 [PubMed: 26993152]

49. Salem A Dismissing links between HPV and aggressive tongue cancer in young patients. Annals of Oncology. 2010;21(1):13–17. doi:10.1093/annonc/mdp380 [PubMed: 19825879]

50. Zafereo ME, Xu L, Dahlstrom KR, et al. Squamous cell carcinoma of the oral cavity often overexpresses p16 but is rarely driven by human papillomavirus. Oral Oncol. 2016;56:47–53. doi:10.1016/j.oraloncology.2016.03.003 [PubMed: 27086486]

51. Laco J, Vosmikova H, Novakova V, et al. The role of high-risk human papillomavirus infection in oral and oropharyngeal squamous cell carcinoma in non-smoking and nondrinking patients: a clinicopathological and molecular study of 46 cases. Virchows Arch. 2011;458(2):179–187. doi:10.1007/s00428-010-1037-y [PubMed: 21221634]

52. Pérot P, Falguieres M, Arowas L, et al. Investigation of viral etiology in potentially malignant disorders and oral squamous cell carcinomas in non-smoking, non-drinking patients. PLOS ONE. 2020;15(4):e0232138. doi:10.1371/journal.pone.0232138 [PubMed: 32348362]

53. Agalliu I, Gapstur S, Chen Z, et al. Associations of Oral α-, β-, and γ-Human Papillomavirus Types With Risk of Incident Head and Neck Cancer. JAMA Oncology. 2016;2(5):599–606. doi:10.1001/jamaoncol.2015.5504 [PubMed: 26794505]

54. Bandolin L, Borsetto D, Fussey J, et al. Beta human papillomaviruses infection and skin carcinogenesis. Reviews in Medical Virology. 2020;30(4):e2104. doi:10.1002/rmv.2104 [PubMed: 32232924]

55. Foy JP, Bertolus C, Boutolleau D, et al. Arguments to Support a Viral Origin of Oral Squamous Cell Carcinoma in Non-Smoker and Non-Drinker Patients. Frontiers in Oncology. 2020;10. Accessed July 28, 2022. https://www.frontiersin.org/articles/10.3389/fonc.2020.00822

56. Mehta PA, Ebens C. Fanconi Anemia. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews®. University of Washington, Seattle; 1993. Accessed August 4, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1401/

57. Furquim CP, Pivovar A, Amenábar JM, Bonfim C, Torres-Pereira CC. Oral cancer in Fanconi anemia: Review of 121 cases. Crit Rev Oncol Hematol. 2018;125:35–40. doi:10.1016/j.critrevonc.2018.02.013 [PubMed: 29650274]

58. Kutler DI, Patel KR, Auerbach AD, et al. Natural History and Management of Fanconi Anemia Patients with Head and Neck Cancer: A 10-year Follow-up. Laryngoscope. 2016;126(4):870–879. doi:10.1002/lary.25726 [PubMed: 26484938]

59. Beddok A, Krieger S, Castera L, Stoppa-Lyonnet D, Thariat J. Management of Fanconi Anemia patients with head and neck carcinoma: Diagnosis and treatment adaptation. Oral Oncol. 2020;108:104816. doi:10.1016/j.oraloncology.2020.104816 [PubMed: 32480311]

60. Sami A, Elimairi I, Stanton C, Ross RP, Ryan CA. The Role of the Microbiome in Oral Squamous Cell Carcinoma with Insight into the Microbiome–Treatment Axis. Int J Mol Sci. 2020;21(21):8061. doi:10.3390/ijms21218061 [PubMed: 33137960]

61. Yost S, Stashenko P, Choi Y, et al. Increased virulence of the oral microbiome in oral squamous cell carcinoma revealed by metatranscriptome analyses. Int J Oral Sci. 2018;10(4):1–10. doi:10.1038/s41368-018-0037-7 [PubMed: 29343681]

62. Ganly I, Yang L, Giese RA, et al. Periodontal pathogens are a risk factor of oral cavity squamous cell carcinoma, independent of tobacco and alcohol and human papillomavirus. International Journal of Cancer. 2019;145(3):775–784. doi:10.1002/ijc.32152 [PubMed: 30671943]

63. Sturgis EM, Wei Q, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. Seminars in Oncology. 2004;31(6):726–733. doi:10.1053/j.seminoncol.2004.09.013 [PubMed: 15599850]

64. Houle A, Callahan NF. Head and Neck Squamous Cell Carcinoma in Marijuana Users. Journal of Oral and Maxillofacial Surgery. 2020;78(10):e89. doi:10.1016/j.joms.2020.07.176

65. Zhang ZF, Morgenstern H, Spitz MR, et al. Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck1. Cancer Epidemiology, Biomarkers & Prevention. 1999;8(12):1071–1078.

66. Newman T, Krishnan LP, Lee J, Adami GR. Microbiomic differences at cancer-prone oral mucosa sites with marijuana usage. Sci Rep. 2019;9(1):12697. doi:10.1038/s41598-019-48768-z [PubMed: 31481657]

67. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana Use and Risk of Oral Squamous Cell Carcinoma. Cancer Research. 2004;64(11):4049–4054. doi:10.1158/0008-5472.CAN-03-3425 [PubMed: 15173020]

68. Komolmalai N, Chuachamsai S, Tantiwipawin S, et al. Ten-year analysis of oral cancer focusing on young people in northern Thailand. J Oral Sci. 2015;57(4):327–334. doi:10.2334/josnusd.57.327 [PubMed: 26666856]

69. Kaminagakura E, Vartanian JG, da Silva SD, dos Santos CR, Kowalski LP. Case-control study on prognostic factors in oral squamous cell carcinoma in young patients. Head Neck. 2010;32(11):1460–1466. doi:10.1002/hed.21347 [PubMed: 20175200]

70. Farquhar DR, Tanner AM, Masood MM, et al. Oral tongue carcinoma among young patients: An analysis of risk factors and survival. Oral Oncol. 2018;84:7–11. doi:10.1016/j.oraloncology.2018.06.014 [PubMed: 30115478]

71. Garavello W, Spreafico R, Gaini RM. Oral tongue cancer in young patients: a matched analysis. Oral Oncol. 2007;43(9):894–897. doi:10.1016/j.oraloncology.2006.10.013 [PubMed: 17307026]

72. Vargas H, Pitman KT, Johnson JT, Galati LT. More aggressive behavior of squamous cell carcinoma of the anterior tongue in young women. Laryngoscope. 2000;110(10 Pt 1):1623–1626. doi:10.1097/00005537-200010000-00009 [PubMed: 11037814]

73. van Monsjou HS, Lopez-Yurda MI, Hauptmann M, van den Brekel MWM, Balm AJM, Wreesmann VB. Oral and oropharyngeal squamous cell carcinoma in young patients: the Netherlands Cancer Institute experience. Head Neck. 2013;35(1):94–102. doi:10.1002/hed.22935 [PubMed: 22431238]

74. 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;4:28. doi:10.1186/1758-3284-4-28 [PubMed: 22647235]

75. Ho HC, Lee MS, Hsiao SH, et al. Squamous cell carcinoma of the oral cavity in young patients: a matched-pair analysis. Eur Arch Otorhinolaryngol. 2008;265 Suppl 1:S57–61. doi:10.1007/s00405-007-0496-5 [PubMed: 17957378]

76. Morris LGT, Patel SG, Shah JP, Ganly I. Squamous cell carcinoma of the oral tongue in the pediatric age group: a matched-pair analysis of survival. Arch Otolaryngol Head Neck Surg. 2010;136(7):697–701. doi:10.1001/archoto.2010.94 [PubMed: 20644066]

77. Pytynia KB, Grant JR, Etzel CJ, Roberts D, Wei Q, Sturgis EM. Matched analysis of survival in patients with squamous cell carcinoma of the head and neck diagnosed before and after 40 years of age. Arch Otolaryngol Head Neck Surg. 2004;130(7):869–873. doi:10.1001/archotol.130.7.869 [PubMed: 15262765]

78. Verschuur HP, Irish JC, O'Sullivan B, Goh C, Gullane PJ, Pintilie M. A matched control study of treatment outcome in young patients with squamous cell carcinoma of the head and neck. Laryngoscope. 1999;109(2 Pt 1):249–258. doi:10.1097/00005537-199902000-00015 [PubMed: 10890775]

79. Cariati P, Cabello-Serrano A, Perez-de Perceval-Tara M, Monsalve-Iglesias F, Martínez-Lara I. Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital. Med Oral Patol Oral Cir Bucal. 2017;22(6):e679–e685. doi:10.4317/medoral.21755 [PubMed: 29053649]

80. Andersen AO, Jensen JS, Jakobsen KK, et al. The impact of tobacco smoking on survival of patients with oral squamous cell carcinoma: a population-based retrospective study. Acta Oncol. 2022;61(4):449–458. doi:10.1080/0284186X.2022.2033830 [PubMed: 35114883]

81. Adeoye J, Hui L, Tan JY, Koohi-Moghadam M, Choi SW, Thomson P. Prognostic value of non-smoking, non-alcohol drinking status in oral cavity cancer. Clin Oral Investig. 2021;25(12):6909–6918. doi:10.1007/s00784-021-03981-x

82. Yang Z, Du W, Zhang X, et al. Nonsmoking and Nondrinking Oral Squamous Cell Carcinoma Patients: A Different Entity. Frontiers in Oncology. 2021;11. Accessed July 28, 2022. https://www.frontiersin.org/articles/10.3389/fonc.2021.558320

83. Bao X, Liu F, Chen Q, et al. Propensity score analysis exploring the impact of smoking and drinking on the prognosis of patients with oral cancer. Head Neck. 2020;42(8):1837–1847. doi:10.1002/hed.26099 [PubMed: 32031313]

84. Fang QG, Shi S, Liu FY, Sun CF. Squamous cell carcinoma of the oral cavity in ever smokers: a matched-pair analysis of survival. J Craniofac Surg. 2014;25(3):934–937. doi:10.1097/SCS.0000000000000710 [PubMed: 24820715]

85. Fan Y, Zheng L, Mao MH, et al. Survival analysis of oral squamous cell carcinoma in a subgroup of young patients. Asian Pac J Cancer Prev. 2014;15(20):8887–8891. doi:10.7314/apjcp.2014.15.20.8887 [PubMed: 25374224]

86. Bachar G, Hod R, Goldstein DP, et al. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol. 2011;47(1):45–50. doi:10.1016/j.oraloncology.2010.11.003 [PubMed: 21167767]

87. Brennan K, Shin JH, Tay JK, et al. NSD1 inactivation defines an immune cold, DNA hypomethylated subtype in squamous cell carcinoma. Sci Rep. 2017;7(1):17064. doi:10.1038/s41598-017-17298-x [PubMed: 29213088]

Highlights

- Incidence of nonsmoking/nondrinking related oral cancer is increasing

- Patients tend to be younger and have more females than traditional cohort

- The etiology of this atypical subset of oral cancers is not known

- Consensus definitions for this emerging subset are needed

Table 1-

Summary of studies comparing prognosis of OSCC in non-smokers and nondrinkers vs. smokers and drinkers

Author	No. of Subjects	Definition of NSND	Anatomical Subsites in Non-Smokers	Analysis	Conclusions	Reported Data
Andersen et al. (PMID: 35114883) 2022	Never smokers (n =240) Former smoker (n = 339) Current smoker (n = 1138)	Non-smoker = never smoked a cigarette No analysis of drinking	Tongue = 53.8% Gingiva = 21.3% Floor of mouth = 7.9% Other = 15.8% Unknown = 1.3%	Kaplan-Meier Log-rank test Multivariable Cox regression	- Non-smokers have better OS and DFS - Dose dependent relationship between accumulated amount of tobacco use and survival estimates	5-year OS HR (95% CI) Never smoker 1 (ref) Current smoker 1.83 (1.38–2.42) Former smoker 1.32 (0.98–1.77) 5-year DFS HR (95% CI) Never smoker 1 (ref) Current smoker 1.32 (1.04–1.68) Former smoker 1.17 (0.90–1.51)
Adeoye et al. (PMID: 33991259) 2021	NSND (n=171) ESED (n=142)	Non-smoker = no history of tobacco smoking Non-drinker = no history of alcohol consumption	Tongue = 52.6% Gingiva = 22.8% Floor of mouth = 1.8% Buccal = 18.7% Retromolar = 2.3% Hard palate = 1.8%	Kaplan-Meier Log-rank test Multivariable Cox regression	- NSND have better OS - No difference in RFS and DSS	5-year OS HR (95% CI) ESED 1 (ref) NSND 0.47 (0.29–0.75) 5-year DFS HR (95% CI) ESED 1 (ref) NSND 1.14 (0.42–3.05)
Yang et al. (PMID: 34262853) 2021	NSND (n = 86) E SED (n = 267)	Non-smoker = 100 cigarettes in lifetime Non-drinker = drank wine no more than once every 2 weeks	Tongue = 43% Gingiva = 26.7% Floor of mouth = 7% Buccal = 23.3%	Kaplan-Meier Log-rank test Multivariable Cox regression	- NSND have better LRC and DSS	5-year LRC NSND 48% ESED 38% (p=0.048) 5-year DSS NSND 56% ESED 39% (p=0.047)
Koo et al. (PMID: 33804510) 2021	NSND (n = 59) E SED (n = 117)	Non-smoker = <100 cigarettes in lifetime Non-drinker = <1 standard drink per week	Subsites not reported	Kaplan-Meier Log-rank test Multivariable Cox regression	- No difference in OS	5-year OS HR (95% CI) ESED 1 (ref) NSND 1.1 (0.6–2.1)
Bao et al. (PMID: 32031313) 2020	NSND (n = 646) ESED (n = 519)	Non-smoker = <10 pack-years of cigarette use Non-drinker = <7 drinks per week continuously for at least 1 year	Subsites not reported	Kaplan-Meier Log-rank test Multivariable Cox regression	- NSND have better OS and DSS	All-cause death HR (95% CI) NSND 1 (ref) ESED 1.897 (1.138–3.165) Oral cancer-specific death HR (95% CI) NSND 1 (ref) ESED 1.764 (1.043–2.983)
DeAngelis et al. (PMID: 30409291) 2018	NSND (n=70) ESED (n=217)	Non-smoker = <5 cigarettes/week in lifetime Non-drinker = <3 standard drinks/ week in lifetime	Tongue = 51.2% Gingiva = 19.5% Floor of mouth = 9.8% Buccal = 7.0% Retromolar = 19.5% Hard palate = 3.9% Vestibule = 0.8%	Kaplan-Meier Log-rank test Multivariable Cox regression	- Worse DSS in elderly NSND females compared to elderly SD patients. Otherwise, similar DSS in NSND vs ESED - NSND have higher recurrence rates	5-year DSS HR (95% CI) Age-matched female ESED 1 (ref) Elderly female NSND 2.97 (1.47–10.1) 5-year recurrence NSND 42.9% ESED 27.6% (p = 0.005)
Dediol et al. (PMID: 26993152) 2016	NSND (n = 103) ESED (n = 971)	Non-smoker = <10 packs per year Non-drinker = not daily alcohol consumption	Tongue = 42% Gingiva = 25% Floor of mouth = 17% Buccal = 10% Retromolar = 4%	Kaplan- Meier Log-rank test Multivariable Cox regression	- No difference in DSS, recurrence and metastasis	Cumulative survival HR (95% CI) NSND 1 (ref) Smoking 1 (0.98011.0124) Alcohol 0.63(0.2213 – 1.7762)

Author	No. of Subjects	Definition of NSND	Anatomical Subsites in Non-Smokers	Analysis	Conclusions	Reported Data
			Hard palate = 3%			
Fang et al. (PMID: 24820715) 2014	Never smoker (n = 66) Ever smoker (n = 66) Current smoker (n = 66)	Non-smoker = 100 cigarettes in lifetime Non-drinker = never drank alcohol weekly for a year	Tongue = 48.5% Gingiva = 18.2% Floor of mouth = 15.2% Buccal = 6.1% Lip = 12.1%	Matched-pair Kaplan-Meier Log-rank test	- Better RFS and DSS in never smokers than ever smokers - Smoking increased risk for disease-related death by 5-fold	Significant RFS rates in ever smokers vs never smokers (P = 0.006) Significant DSS rates in ever smokers vs never smokers (P = 0.027)
Fan et al. (PMID: 25374224) 2014	NSND (n = 54) ESED (n = 46)	Non-smoker = negligible history of tobacco use Non-drinker = <1 alcohol consumption per day with no history alcohol abuse	Mobile tongue = 74.1% Other sites = 25.9%	Kaplan-Meier Log-rank test	- No difference in DFS or OS	5-year OS NSND 76.7% ESED 73.9% (p=0.823) 5-year DFS NSND 61.4% ESED 60.4% (p=0.482)
Bachar et al. (PMID: 21167767) 2010	NSND (n=116) ESED (n=175)	Non-smoker = less than daily smoking history Non-drinker = 3 drinks per day	Tongue = 100%	Kaplan-Meier Log-rank test Multivariable Cox regression	- No difference in DFS and OS - However, young(<40 years) NSND have worse OS and DFS than young ESED - ESED have greater tumor depth of invasion and higher tumor grade	5-year OS NSND 64% ESED 68% (p=0.53) 5-year DFS NSND 57% ESED 59% (p= 0.526) 5-year OS Young NSND 89% Young ESED 55% (p = 0.015)
						5-year DFS Young NSND 77% Young ESED 50% (p = 0.038)

Abbreviations: CI, confidence interval; HR, hazard ratio; NSND, non-smoking and nondrinking; ESED, ever-smoker and ever-drinker; OS, overall survival; DFS, disease-free survival; LRC, locoregional control; DSS, disease-specific survival; RFS, recurrence-free survival