HHS Public Access

Author manuscript

Oral Oncol. Author manuscript; available in PMC 2020 February 24.

Published in final edited form as:

Oral Oncol. 2018 December ; 87: 1–7. doi:10.1016/j.oraloncology.2018.10.009.

Early onset oral tongue cancer in the United States: a literature review

Benjamin R. Campbell, BS[a], **James L. Netterville, MD**[b], **Robert J. Sinard, MD**[b], **Kyle Mannion, MD**[b], **Sarah L. Rohde, MD**[b], **Alexander Langerman, MD, SM**[b], **Young J. Kim, MD, PhD**[b], **James S. Lewis Jr., MD**[b,c], **Krystle A. Lang Kuhs, PhD, MPH**[b,d]

[a]Vanderbilt University School of Medicine, 1161 21st Ave S #D3300, Nashville, TN 37232, USA

[b]Vanderbilt University Medical Center, Department of Otolaryngology, 1215 21st Ave S, Nashville, TN 37232, USA

[c]Vanderbilt University Medical Center, Department of Pathology, Microbiology, and Immunology, 1211 Medical Center Dr, Nashville, TN, 37232

[d]Vanderbilt University Medical Center, Department of Medicine, 1211 Medical Center Dr, Nashville, TN, 37232

Abstract

The incidence of early onset oral tongue squamous cell carcinoma (OTC) has been increasing in the United States, and no clear etiology has been identified. Studies on this topic have generally been small and presented varied results. The goal of this review is to analyze and synthesize the literature regarding early onset OTC risk factors, outcomes, and molecular analyses within the US. To date, studies suggest that early onset OTC patients tend to have less heavy cigarette use than typical onset patients, but there may be an association between early onset OTC and smokeless tobacco (chewing tobacco and snuff) use. Early onset OTC is associated with similar or possibly improved survival compared to typical onset OTC. There has been no evidence to support a significant role for human papillomavirus in development of early onset OTC. Further research with larger cohorts of these patients is needed to better characterize this disease entity.

Keywords

oral tongue; squamous cell carcinoma; United States; young; early onset; tobacco; survival; recurrence; molecular; human papillomavirus

INTRODUCTION

Tobacco use in the US has been declining over the last few decades, and with it, the incidence of many types of head and neck cancer (HNC).[1, 2] However, the incidence of two head and neck cancers, oropharyngeal squamous cell carcinoma (OPC) and oral tongue squamous cell carcinoma (OTC), are rising.[3] These increases are primarily occurring

Corresponding author: Krystle A. Lang Kuhs PhD, MPH, Vanderbilt University Medical Center, 2525 West End Ave, Suite 300, Nashville, TN 37203, USA, (615) 875-2512, krystle.kuhs@vumc.org.

within younger birth cohorts – those less than 50 years of age.[3] The rise in incidence of OPC among young individuals has been attributed to human papillomavirus (HPV) infection, yet for OTC, no single cause has been identified.[4]

Anatomically, OTC is defined as cancer occurring in the anterior two-thirds of the tongue, which is located in the oral cavity and extends from the apex of the tongue anteriorly to the circumvallate papillae posteriorly. This is in contrast to base of tongue cancer, which occurs in the posterior one-third of the tongue and is located within the oropharynx. OTC may spread secondarily to the base of tongue or other contiguous oral cavity subsites (such as the floor of mouth, gingiva, mandible, and beyond), but it is defined by its origination from the oral tongue. Like most head and neck cancers, OTC is overwhelmingly squamous cell carcinoma (SCC).

Despite the rapid increase in incidence of early onset OTC in the US, few studies have investigated possible risk factors, patient outcomes, and tumor somatic mutations, and many studies have reported conflicting findings. The objective of this review is to synthesize the existing literature on early onset OTC within the US, attempt to reconcile some the conflicting findings within the field, and suggest areas for future research. Only US-based studies with specific early onset OTC analyses for either risk factors, outcomes (survival and/or recurrence), or tumor molecular analyses were included.*

RISK FACTORS

Tobacco

Multiple studies have investigated tobacco use as a risk factor for early onset OTC (Table 1).[5–14] However, the majority of studies were published before the year 2000 and included only small numbers of early onset patients (range: 6 to 68).[5–11] As a whole, the literature suggests that early onset OTC patients may have less heavy cigarette use when compared to older patients. Some studies indicate a possible association between smokeless tobacco products and early onset OTC.

The earliest studies looking at tobacco and early onset OTC investigated cigarette use only. Small case series showed that less than 10% of early onset OTC patients had a history of heavy smoking.[5–7] Mild to moderate (< 5 pack-years) cigarette smoking was seen in roughly half of patients.[6, 7] In a more comprehensive study, Friedlander et al. reported no significant difference in cigarette use between younger and older patients with OTC (40% vs. 58%, respectively).[10]

Over the recent decades, cigarette use has become less common and smokeless tobacco products are increasing in popularity.[2, 15] This trend is most apparent among younger male birth cohorts, and the prevalence of male users of smokeless tobacco under age 35 has risen from 2% to nearly 7% since 1970.[15, 16] Yet, only four studies have included

*Abbreviations: HNC – head and neck cancer; OPC – oropharyngeal squamous cell carcinoma; OTC – oral tongue squamous cell carcinoma; HPV – human papillomavirus; SCC – squamous cell carcinoma; aOR – adjusted odds ratio; OS – overall survival; DSS – disease-specific survival; DFS – disease-free survival; PCR – polymerase chain reaction; IHC – immunohistochemistry; LOH – loss of heterozygosity; MSI – microsatellite instability; NA – not available; CP – conformation polymorphism; WES – whole exome sequencing; ISH – in situ hybridization

smokeless tobacco products in their analyses of early onset OTC risk factors.[8, 9, 11, 14] In a review of MD Anderson patients in 1988, Schantz et al. found that the proportion of early onset OTC patients that had a tobacco (cigarette or chewing tobacco) use history decreased from 64% to 35% between 1944 and 1984.[8] Sarkaria & Harari also looked at chewing tobacco use in early onset OTC patients, but their findings were limited by small sample size as 4 of 6 patients had either a history of cigarette or chewing tobacco use.[9]

We recently conducted the largest study to date to look at early onset OTC risk factors in the US (N = 395 [113 early onset]) and were able to identify specific use histories for the different available tobacco products through the use of a comprehensive head and neck clinic intake form. This form is completed by all new clinic patients and asked for the amount and duration of use of alcohol and tobacco (cigarette, cigar, pipe, snuff, chewing tobacco) products. For early onset patients, 54% had a tobacco use history versus 68% of typical onset patients. Early onset OTC patients were significantly more likely to report snuff use than patients with typical onset OTC (12.4 vs. 2.8%; adjusted odds ratio [aOR]: 5.4) and significantly less likely to be former cigarette smokers (20.4% vs. 33.7%; aOR: 0.5). No other associations between specific tobacco products (pipe, cigar, chewing tobacco) and early onset OTC were identified.[14]

Alcohol

Several studies have also looked at alcohol use in early onset OTC (Table 1).[5–7, 10–14, 17] These studies also tended to have small (range: 8 to 36) early onset OTC cohorts and were primarily performed before the year 2000. There is also a lack of consistent and reliable categorization of alcohol use, which does not adequately capture the wide spectrum of alcohol use in the US. Some studies grouped patients with any history of alcohol use, regardless of consumption per week, into one group for analyses.[10, 12, 17] Others used heavy and/or social alcohol use categories for further subset analyses, but most failed to define these terms.[5–7, 11, 13] This heterogeneity precludes any strong conclusions regarding alcohol use and early onset OTC. Friedlander et al. found no significant difference in alcohol use between young and old patients with OTC, but alcohol use was also not clearly defined in this study.[10] A recent study by our group stratified alcohol use by drinks per week using CDC guidelines both at the time of diagnosis and in the years prior. We identified a trend towards less heavy alcohol use (15+ drinks/week for males, 8+ drinks/week for females) among patients with early onset OTC, but this did not reach statistical significance.[14]

Two studies grouped their risk factor analyses. Siegelmann-Danieli et al. looked at combined tobacco (cigarette, cigar, and chewing tobacco) and alcohol use in patients with OTC and demonstrated that there was significantly less tobacco and alcohol use among younger patients (40% vs. 82%, respectively).[11] Another study, which compared young never-smokers/never-drinkers and young smoker-drinkers with HNC, found that young never-smokers/never-drinkers were significantly more likely to have OTC than their smoker-drinker counterparts.[13]

Other

Other factors have been hypothesized to play a role in the development of early onset OTC, such as poor dental hygiene, denture use, presence of precursor tongue lesions (glossitis, leukoplakia, lichen planus), prior radiation exposure, and chronic immunosuppression, but these studies have been purely observational.[5–7, 11] Byers noted that all 11 patients in his initial case series had good to excellent dental hygiene.[5] In another case series by Amsterdam & Strawitz, 3 out of the 8 (37.5%) early onset OTC patients had a potential chemical exposure.[6] One patient in the case series by Newman et al. had a history of head and neck radiation, but there was no history of leukoplakia, glossitis, poor oral hygiene, or denture use in any of the other cases.[7] In the most comprehensive assessment of other risk factors to date, Siegelmann-Danieli et al. assessed six other factors besides alcohol and tobacco use. They identified one early onset OTC patient with chronic immunosuppression and two with a history of oral lichen planus. Interestingly, in this study, two patients had a possible genetic predisposition and 13 patients had no identifiable risk factors for OTC.[11]

OUTCOMES

Survival

Over time, the reported survival rates for patients with early onset OTC has roughly transitioned from worse, to similar, and most recently, to better than typical onset OTC (Table 2).[5–7, 9–12, 14, 18–25] In early studies of early onset OTC patients, it was suggested that these patients had worse overall survival (OS) than their typical onset counterparts. These reports were small case series ranging from 8 to 13 patients and reported 2-year survival rates for early onset OTC ranged from 27% to 57%.[5–7, 19] These measured rates were compared to reported rates for OTC survival since each of these studies lacked a typical onset OTC control group. It is worth noting, however, that one early combined study from Norway and the US demonstrated improved OS and disease-specific survival (DSS) of patients with early onset OTC. Survival decreased as a function of age with 5-year OS rates of around 65%, 40%, and 20% for under 40, 40–59, over 60 years of age respectively.[18]

Larger studies evaluating survival of patients with early onset OTC have been since been performed.[9–12, 14, 18, 20–25] Within these, the report by Sarkaria & Harari was similar to the prior small case series and reported that there is worse survival for patients with early onset OTC. Only 2 out of 6 (33%) of the original early onset OTC patients from this study survived. However, the authors also calculated a higher OS rate of 53%, similar to typical OTC survival, through a literature review of early onset OTC cases to date.[7]

The next cluster of studies demonstrated that there was no difference in both disease-free survival (DFS) and OS for OTC patients by age of diagnosis. Reported survival for OTC patients varied by study (3-year DFS of 53% to 55%, 5-year DFS of 47% to 69%, 5-year OS of 49% to 76%), but no study found a significant difference in survival rate between early onset and typical onset OTC patients.[10–12, 20, 21] In 2011, Patel et al. found no significant differences in DSS among males and females with early onset OTC (69.7% and 74.1% respectively) and patients with typical onset OTC (64.1%).[25]

Since the year 2000, early onset OTC patients have mostly been shown to have improved survival when compared to typical onset OTC.[14, 22–24] Most of these studies utilized SEER data to compile large cohorts of OTC patients and stratify by age group. Davidson et al. showed that OTC patients diagnosed after age 60 had significantly worse DSS than OTC patients diagnosed before age 40.[12] Schantz & Yu confirmed these findings one year later in a study of over 12,000 OTC patients where early onset OTC patients (< 40 years) had 5-year OS rates of 70.6% compared to 49.8% and 45.8% for patients aged 40–65 and older than 65 respectively.[23] Joseph et al. conducted a SEER data study and showed that age greater than 50 was associated with significantly increased risk of death in an all-female OTC population.[24] Finally, a large institution based study performed by our group, also showed that early onset patients had a significantly improved OS.[14]

Despite this recent consistency, the body of literature is difficult to interpret completely due to the use of differing survival endpoints, such as OS, DFS, and DSS, and the lack of correction for age-related mortality and comorbidities. The earlier studies, which reported worse survival, also trend towards a younger age cutoff for early onset OTC (<30 and <35 years).[5–7] Therefore, it is possible that these studies are capturing a distinct subset of early onset OTC, which continues to have worse survival but is diluted with younger (35–45 years) patients in more recent studies. Most of the more recent studies that have reported better early onset OTC survival use OS as the primary endpoint. In these studies, early onset OTC patients may simply have better OS because they are younger and have less underlying health issues. Finally, general improvements in surgical technique and radiation/chemotherapy regimens could play a role in the changing reports of survival for early onset patients.

Recurrence

While survival is a critical endpoint, OS is not necessarily a reflection of inherent tumor biology. Disease recurrence and DSS speak more directly to the inherent prognostic differences in younger versus older patients. Few studies have assessed the risk of recurrence in patients with early onset OTC, and only one study has been performed since the year 2000. Early case series suggested that early onset OTC had high recurrence rates of 50 to 70%, primarily at regional sites.[6, 9] Larger studies comparing early onset and typical onset OTC recurrence rates have found mixed results. Both Friedlander et al. and Vargas et al. showed that younger patients had significantly higher rates of recurrence than older patients.[10, 21] In the study by Friedlander et al., younger patients had significantly higher rates of locoregional recurrence (44% vs 22%).[10] Among female patients, Vargas et al. reported that those with early onset OTC patients recurred earlier (mean time to recurrence: 14 vs. 40 months) and more frequently (65% vs 41%).[21] On the other hand, studies by Siegelmann-Danieli et al. and Campbell et al. found no difference in recurrence rates between early onset and typical onset patients.[11, 14] In these studies, 5-year recurrence rates ranged between 44% and 53%.[11, 14]

MOLECULAR ANALYSES

Molecular testing of early onset OTC has been the focus of more recent research. These analyses have primarily focused on cell cycle markers, mainly p53, and HPV. Much like the research of early onset OTC risk factors and outcomes, the study of cell cycle markers in OTC pathogenesis has produced widely variable results and few strong conclusions (Table 3).[17, 26–32] On the other hand, there is a general consensus that HPV infection is not a primary etiology of early onset OTC or OTC in general (Table 3).[30, 32–35]

Cell cycle markers

Molecularly, “traditional” head and neck SCC patients are thought to have overexpression of EGFR and p53 mutations, whereas younger patients are thought to express wild-type p53.[30] Sorenson et al. performed polymerase chain reaction (PCR) and immunohistochemical (IHC) staining for p53 in 11 patients with early onset OTC. Only 2 of 11 (18%) tumors had p53 mutations, and of these, one had strong p53 staining. Both of these patients had a history of alcohol and tobacco use, and from this, the authors concluded that p53 was not a driver of early onset OTC in non-smokers and non-drinkers.[17] These findings were supported by a study by Li et al., which used whole exome sequencing on 89 early onset OTCs. When grouped by smoking status, non-smokers were significantly younger (50.4 vs. 61.9 years) and less likely to have p53 mutations (12.5 vs. 70%).[32]

Two studies concluded that the role of p53 in OTC did not vary by patient age. Regezi et al. identified similar proportions (50 vs. 67%) of lateral tongue cancers with p53 overexpression in young (<35 years) and elderly (>75 years) patients respectively.[27] Jin et al. looked for loss of heterozygosity (LOH) and microsatellite instability (MSI) at the TP53 (17p13) locus and found that 42% of early onset OTC patients had mutations. These mutation rates were not significantly different from rates reported for typical onset OTC in the literature.[26]

More recent studies have shown that p53 may play more of a role in early onset OTC. In a study of early onset OTC patients with no tobacco exposure, 81% of tumors had p53 overexpression without any detectable mutations in p53 exons 5–9. This suggests that p53 plays some role in early onset OTC pathogenesis, but mutations occur outside the typical mutation patterns.[28] Other studies have identified increased p53 mutation and expression in early onset tumors (59–93%) when compared to typical onset tumors, however, these trends have failed to reach statistical significance.[29–31] While some recent studies have established gain of function mutations in p53 as having clinical importance for tumor biology in head and neck SCC, we are not aware of any specific research on the type of p53 mutations in early versus typical onset OTC.[36]

Aside from p53, several studies have looked into the role of other cell cycle markers in early onset OTC pathogenesis. No differences in expression of p21, Rb, and MDM2 between early and typical onset tumors have been found.[27, 28] Harris et al. identified high levels of EGFR expression, but unlike what has been seen with other forms of HNC, this was not associated with poor clinical outcomes.[30] Lastly, Pickering et al. found a trend towards decreased *FAT1* mutations in early onset tumors, but the role of this gene in tumor pathogenesis is still largely unknown.[31]

Oncogenic viruses

HPV has been identified as a cause of OPC, especially in younger patients without alcohol or tobacco use. Given the similar trends in incidence and general proximity of the two anatomic sites, HPV (or another oncogenic virus) has been hypothesized as a cause of early onset OTC. However, there is extensive literature on HPV in oral cavity SCC. One of the largest and most thorough studies on this subject is by Lingen et al. They analyzed 409 oral cavity SCC patients from four institutions and found 24 (5.9%) to have transcriptionally-active high-risk HPV by reverse transcription PCR. This included 6 of 162 (3.7%) of OTCs. There was no specific sub-analysis by patient age, but median age of HPV-positive cases was similar to HPV-negative cases (61 vs. 64 years).[37]

Regarding early onset OTC patients, studies have not found any convincing evidence for a virus in its pathogenesis and certainly no enrichment for HPV in younger versus older patients. Liang et al. only detected HPV-16 DNA in 1 of 8 early onset OTC specimens and detected non in the 43 typical onset specimens.[33] Using RNA-Seq, Bragelmann et al. did not detect any presence of HPV in 7 tumors from young non-tobacco users.[34] Harris et al. found that 44% of early onset OTC were p16 positive (a cell cycle regulator and surrogate marker of HPV infection frequently seen in OPC). However, none of these tumors were HPV positive by ISH or PCR. Although p16 positivity was associated with improved survival in this study, its expression was not associated with HPV positivity.[30] In a study of 78 patients with OTC, only 1 patient, a 62-year-old male with a history of alcohol and tobacco use, had detectable levels of E6 or E7 mRNA within the tumor. No HPV mRNA was detected in the tumors of patients less than 40, light or former smokers, or light drinkers. p16 was again a poor surrogate of HPV infection in this study with a positive predictive value of 0.12.[35]

Studies searching for other viral causes besides HPV have been unsuccessful. Using a newly developed digital subtraction method with viral screening and discovery algorithms, Bragelmann et al. searched the RNA-Seq data from 7 early onset oral tongue tumors for the presence of EBV or other viruses. No transcripts from any known or related novel viruses were found.[34] In the most recent molecular study of early onset OTC, no HPV or EBV was detected in 6 tumors analyzed by exome sequencing, and no viral transcripts were detected in 20 early onset tumors analyzed by massively parallel RNA sequencing.[32]

Overall mutational landscape

Some studies have attempted to characterize the mutational landscape of early onset OTC as a whole. Jin et al. looked for LOH and MSI at 13 frequently mutated sites in HNC. Each of the 19 tumors had LOH at one or more sites, with the highest incidence of mutations occurring at D9S168 (9p23–22) and TP53 (17p13). Twenty-six percent had MSI occurring on chromosomes 3 and 9p. There was no observed correlation between mutations at these sites and patient age was seen.[26] Pickering et al. showed that early and typical onset OTC was similar in regards to gene-specific mutations and copy-number alteration frequencies. These authors also identified a “smoking signature” by examining the mutational profile of HNC as a whole. Both early and typical onset OTC lacked this smoking signature, with a

higher C to T mutational frequency. According to the authors, this indicates that tobacco use may play a different role in OTC pathogenesis than other forms of HNC.[31]

CONCLUSION

Despite the limitations of the current literature, some trends regarding early onset OTC have emerged. Heavy cigarette use may play less of role in early onset OTC development. Instead, smokeless tobacco products may be involved in the pathogenesis of some patients with early onset OTC. In contrast to early reports, early onset OTC patients likely have similar or even better survival than patients with typical onset OTC. HPV infection is not a driving factor for the occurrence or increasing rates of early onset OTC.

More recent research is needed studying early onset OTC, especially studies with larger early onset cohorts. Given the low incidence of early onset OTC, multicenter studies or the use of national cancer registries should be pursued. These studies should aim to gather more comprehensive risk factor information from patients, including tobacco (smoking and smokeless products) and alcohol (drinks per week) use histories. Information regarding other possible environmental risk factors, such as dental hygiene product use and radiation exposure, may be informative. Outcomes research should be sure to include information on OTC recurrence. Finally, cohorts complete with risk factor, outcomes, and molecular information will allow for better characterization of the disease entity as a whole.

ACKNOWLEDGEMENTS

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

[1]. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26:612–9. [PubMed: 18235120]

[2]. Jamal A KB, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current Cigarette Smoking Among Adults — United States, 2005–2015. MMWR Morb Mortal Wkly Rep2016. p. 1205–11.

[3]. Tota JE, Anderson WF, Coffey C, Califano J, Cozen W, Ferris RL, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. Oral Oncol. 2017;67:146–52. [PubMed: 28351569]

[4]. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015;33:3235–42. [PubMed: 26351338]

[5]. Byers RM. Squamous cell carcinoma of the oral tongue in patients less than thirty years of age. Am J Surg. 1975;130:475–8. [PubMed: 1166939]

[6]. Amsterdam JT, Strawitz JG. Squamous cell carcinoma of the oral cavity in young adults. J Surg Oncol. 1982;19:65–8. [PubMed: 7057649]

[7]. Newman AN, Rice DH, Ossoff RH, Sisson GA. Carcinoma of the tongue in persons younger than 30 years of age. Arch Otolaryngol. 1983;109:302–4. [PubMed: 6847480]

[8]. Schantz SP, Byers RM, Goepfert H. Tobacco and cancer of the tongue in young adults. JAMA. 1988;259:1943–4.

[9]. Sarkaria JN, Harari PM. Oral tongue cancer in young adults less than 40 years of age: rationale for aggressive therapy. Head Neck. 1994;16:107–11. [PubMed: 8021128]

[10]. Friedlander PL, Schantz SP, Shaha AR, Yu G, Shah JP. Squamous cell carcinoma of the tongue in young patients: a matched-pair analysis. Head Neck. 1998;20:363–8. [PubMed: 9663661]

[11]. Siegelmann-Danieli N, Hanlon A, Ridge JA, Padmore R, Fein DA, Langer CJ. Oral tongue cancer in patients less than 45 years old: institutional experience and comparison with older patients. J Clin Oncol. 1998;16:745–53. [PubMed: 9469366]

[12]. 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;122:44–51. [PubMed: 10629481]

[13]. 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. [PubMed: 19691028]

[14]. Campbell BR, Sanders CB, Netterville JL, Sinard RJ, Rohde SL, Langerman A, et al. Early onset oral tongue squamous cell carcinoma: associated factors and patient outcomes Under review. 2018.

[15]. Smokeless Tobacco Use in the United States. In: Prevention CfDCa, editor.: Centers for Disease Control and Prevention.

[16]. Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: World Health Organization: International Agency for Research on Cancer; 2007.

[17]. 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;123:503–6. [PubMed: 9158397]

[18]. Vermund H, Brennhovd IO, Harvei S, Kaalhus O, Poppe E, Wiley AL Jr. Carcinoma of the tongue in Norway and Wisconsin. I. Incidence and prognosis related to sex and age. Acta Radiol Oncol. 1982;21:155–68. [PubMed: 6293256]

[19]. 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. [PubMed: 3965099]

[20]. Pitman KT, Johnson JT, Wagner RL, Myers EN. Cancer of the tongue in patients less than forty. Head Neck. 2000;22:297–302. [PubMed: 10748455]

[21]. Vargas H, Pitman KT, Johnson JT, Galati LT. More aggressive behavior of squamous cell carcinoma of the anterior tongue in young women. Laryngoscope. 2000;110:1623–6. [PubMed: 11037814]

[22]. Davidson BJ, Root WA, Trock BJ. Age and survival from squamous cell carcinoma of the oral tongue. Head Neck. 2001;23:273–9. [PubMed: 11400227]

[23]. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973–1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg. 2002;128:268–74. [PubMed: 11886342]

[24]. Joseph LJ, Goodman M, Higgins K, Pilai R, Ramalingam SS, Magliocca K, et al. Racial disparities in squamous cell carcinoma of the oral tongue among women: a SEER data analysis. Oral Oncol. 2015;51:586–92. [PubMed: 25865553]

[25]. 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. [PubMed: 21383286]

[26]. Jin YT, Myers J, Tsai ST, Goepfert H, Batsakis JG, el-Naggar AK. Genetic alterations in oral squamous cell carcinoma of young adults. Oral Oncol. 1999;35:251–6. [PubMed: 10621844]

[27]. Regezi JA, Dekker NP, McMillan A, Ramirez-Amador V, Meneses-Garcia A, Ruiz-Godoy Rivera LM, et al. p53, p21, Rb, and MDM2 proteins in tongue carcinoma from patients < 35 versus > 75 years. Oral Oncol. 1999;35:379–83. [PubMed: 10645402]

[28]. Lingen MW, Chang KW, McMurray SJ, Solt DB, Kies MS, Mittal BB, et al. Overexpression of p53 in squamous cell carcinoma of the tongue in young patients with no known risk factors is not associated with mutations in exons 5–9. Head Neck. 2000;22:328–35. [PubMed: 10862014]

[29]. Siegelmann-Danieli N, Ben-Izhack O, Hanlon A, Ridge JA, Stein ME, Khandelwal V, et al. P53 alteration in oral tongue cancer is not significantly associated with age at diagnosis or tobacco exposure. Tumori. 2005;91:346–50. [PubMed: 16277102]

[30]. Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. Head Neck. 2011;33:1622–7. [PubMed: 21990227]

[31]. 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. [PubMed: 24874835]

[32]. Li R, Faden DL, Fakhry C, Langelier C, Jiao Y, Wang Y, et al. Clinical, genomic, and metagenomic characterization of oral tongue squamous cell carcinoma in patients who do not smoke. Head Neck. 2015;37:1642–9. [PubMed: 24954188]

[33]. Liang XH, Lewis J, Foote R, Smith D, Kademani D. Prevalence and significance of human papillomavirus in oral tongue cancer: the Mayo Clinic experience. J Oral Maxillofac Surg. 2008;66:1875–80. [PubMed: 18718395]

[34]. Bragelmann J, Dagogo-Jack I, El Dinali M, Stricker T, Brown CD, Zuo Z, et al. Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA. Oral Oncol. 2013;49:525–33. [PubMed: 23490885]

[35]. Poling JS, Ma XJ, Bui S, Luo Y, Li R, Koch WM, et al. Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue. Oral Oncol. 2014;50:306–10. [PubMed: 24485566]

[36]. Zhou G, Liu Z, Myers JN. TP53 Mutations in Head and Neck Squamous Cell Carcinoma and Their Impact on Disease Progression and Treatment Response. J Cell Biochem. 2016;117:2682–92. [PubMed: 27166782]

[37]. Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49:1–8. [PubMed: 22841678]

Table 1.

Tobacco and Alcohol in Early Onset OTC.

Tobacco and Alcohol						
Authors	**Journal**	**Year**	**Early Onset Age**	**Early Onset Cases**	**Tobacco**	**Alcohol**
Byers et al.[a]	*Am J Surg*	1975	< 30	11	0% – heavy cigarette	0% - heavy
Amsterdam & Strawitz[a]	*J Surg Oncol*	1982	< 35	8	58% - cigarette history 0% - heavy cigarette	75% - social 0% - heavy
Newman et al.[a]	*Arch Otolaryngol*	1983	< 30	13	38% - cigarette history 8% - heavy cigarette	23% - occasional 8% - heavy
Schantz et al.[a]	*JAMA*	1988	≤ 40	68	Early onset OTC cigarette and chew use decreased between 1944–1984 (64 to 35%)	-
Sarkaria & Harari[a]	*Head Neck*	1994	< 40	6	66% - cigarette or chew history	-
Friedlander et al.	*Head Neck*	1998	< 40	36	Similar cigarette	Similar
Siegelmann-Danieli et al.	*J Clin Oncol*	1998	≤ 45	30	Less alcohol or cigarette/cigar/chew (40% early, 82% typical)	
Myers et al.[a]	*Otolaryngol Head Neck Surg*	2000	< 40	37	41% - tobacco use	55% - use
Harris et al.	*Head Neck*	2010	< 40	28[b]	Young never-smokers/never-drinkers with HNC more likely to have OTC than young smoker-drinkers with HNC (57 vs. 24%)	
Campbell et al.	*Head Neck*[c]	2018	< 50	113	More snuff (12% early, 3% typical) Less former cigarette (20% early, 34% typical) Similar pipe, cigar, chew	Similar

[a] No typical onset OTC comparison group (shaded)

[b] Patients grouped by tobacco and alcohol use status (28 never-smokers/never-drinkers)

[c] In revision

Table 2.

Early Onset OTC Survival.

Survival						
Authors	**Journal**	**Year**	**Early Onset Age**	**Early Onset Cases**	**Survival Measure**	**Survival vs. Typical Onset**
Byers et al.	*Am J Surg*	1975	< 30	11	OS	Worse
Amsterdam & Strawitz	*J Surg Oncol*	1982	< 35	8	OS	Worse
Vermund et al.	*Acta Radiol Oncol*	1982	< 40	16	OS, DSS	Better
Newman et al.	*Arch Otolaryngol*	1983	< 30	13	OS	Similar
Son & Kapp	*Cancer*	1985	≤ 40	11	OS	Worse
Sarkaria & Harari	*Head Neck*	1994	< 40	6	OS	Worse
Friedlander et al.	*Head Neck*	1998	< 40	36	DFS	Similar
Siegelmann-Danieli et al.	*J Clin Oncol*	1998	≤ 45	30	DFS	Similar
Vargas et al.	*Laryngoscope*	2000	< 40	17[a]	OS, DFS	Similar
Pitman et al.	*Head Neck*	2000	< 40	28	DFS	Similar
Myers et al.	*Otolaryngol Head Neck Surg*	2000	< 40	37	DSS	Similar
Davidson et al.	*Head Neck*	2001	< 40	NA	DSS	Better
Schantz & Yu	*Arch Otolaryngol Head Neck Surg*	2002	< 40	617	OS	Better
Patel et al.	*J Clin Oncol*	2011	< 45	814	DSS	Similar
Joseph et al.	*Oral Oncol*	2015	< 50	688[a]	OS	Better
Campbell et al.	*Head Neck*[b]	2018	< 50	113	OS	Better

[a] All female patients

[b] In revision

Table 3.

Early Onset Molecular Analyses.

Molecular Analyses						
Authors	**Journal**	**Year**	**Early Onset Age**	**Early Onset Cases**	**Detection Method**	**Early Onset Finding**
p53 Studies						
Sorensen et al.	*Arch Otolaryngol Head Neck Surg*	1997	< 40	11	IHC, CP	Few p53 mutations
Regezi et al.	*Oral Oncol*	1999	< 35	36	IHC	Similar to typical onset
Jin et al.	*Oral Oncol*	1999	< 40	19	PCR for LOH & MSI	Similar to typical onset
Lingen et al.	*Head Neck*	2000	< 40	21	IHC, CP, DNASeq	p53 overexpression
Siegelmann-Danieli et al.	*Tumori*	2005	≤ 45	17	IHC	Similar to typical onset
Harris et al.	*Head Neck*	2011	< 40	25	IHC	Similar to typical onset
Pickering et al.	*Clin Cancer Res*	2014	< 45	29	WES	Similar to typical onset
Li et al.	*Head Neck*	2015	< 50	34[a]	WES	Nonsmokers were younger and had less p53 mutations
HPV Studies						
Liang et al.	*J Oral Maxillofac Surg*	2008	< 45	8	PCR	12.5% of tumors HPV+
Harris et al.	*Head Neck*	2011	< 40	25	ISH, PCR	0% of tumors HPV+
Bragelmann et al.	*Oral Oncol*	2013	< 45	7	RNASeq	0% of tumors HPV+
Poling et al.	*Oral Oncol*	2014	< 40	11	ISH	0% of tumors HPV+
Li et al.	*Head Neck*	2015	< 50	34[a]	Transcriptome analysis	0% of tumors HPV+

[a]Patients grouped by smoking status