

Changing landscape of oral squamous cell carcinoma: A scoping review of the pathogenesis, clinical profiles and prognosis of young, non-smoking patients

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Abstract. Oral squamous cell carcinoma (OSCC) is traditionally associated with long-term exposure to tobacco and alcohol in older populations. However, a global epidemiological shift has revealed an increasing incidence among adults aged ≤ 45 years, many of whom lack canonical risk factors. The present scoping review aimed to evaluate the distinct clinicopathological, etiological and molecular landscape of young-onset OSCC, with a focus on emerging non-canonical drivers. For this purpose, a comprehensive synthesis of recent high-volume meta-analyses (encompassing $>50,000$ patients), genomic sequencing data and regional epidemiological reports from Central Asia and the Asia-Pacific was performed. The interplay between traditional carcinogens and novel factors, such as chronic mechanical irritation (CMI) and occupational hazards was analyzed. The analysis revealed a 'prognostic

paradox': While younger patients faced a higher risk of local recurrence, their 5-year overall survival rate was superior or equivalent to that of older cohorts (hazard ratio, 0.97), likely due to greater physiological reserve and fewer comorbidities. Molecularly, young-onset OSCC in never-smokers and never-drinkers represents a distinct entity characterized by CDKN2A mutations, EGFR amplifications and a robust IFN- γ immune response, rather than human papillomavirus-driven oncogenesis. Furthermore, CMI functions as a potent 'effect modifier', lowering the threshold for malignant transformation through the TGF- β and NF- κ B pathways. On the whole, the present scoping review indicates that the 'rejuvenation' of OSCC profiles mandates a shift from age-based to biology-driven risk stratification. Addressing non-canonical factors, such as dental trauma and occupational exposures is essential for early detection and functional preservation in this growing demographic.

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Abbreviations: aHR, adjusted hazard ratio; CDKN2A, cyclin-dependent kinase inhibitor 2A; CI, confidence interval; CMI, chronic mechanical irritation; DFS, disease-free survival; DSS, disease-specific survival; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; HPV, human papillomavirus; HR, hazard ratio; IFN- γ , interferon- γ ; LR, local recurrence; MeSH, medical subject headings; NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; NSND, never-smokers and never-drinkers; OPSCC, oropharyngeal squamous cell carcinoma; OR, odds ratio; OS, overall survival; OSCC, oral squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; TGF- β , transforming growth factor β ; TP53, tumor protein p53

Key words: oral squamous cell carcinoma, oral tongue squamous cell carcinoma, oral cavity cancer, tongue cancer, risk factor

Introduction

Oral squamous cell carcinoma (OSCC) represents a heterogeneous group of malignancies arising from the mucosal lining of the tongue, floor of the mouth, gingiva and buccal mucosa (1). Originating from the stratified squamous epithelium, these lesions exhibit a high propensity for local invasion and lymphatic metastasis if not intercepted in the early stages. While clinical hallmarks include persistent ulcerative lesions, dysphagia, localized induration and cervical lymphadenopathy, the symptomatic overlap with benign inflammatory conditions necessitates a rigorous diagnostic framework to ensure timely intervention and improve survival outcomes (1,2).

Global statistics indicate that OSCC accounts for $>350,000$ new diagnoses annually, with a substantial mortality rate (3,4). A concerning trend is the increasing incidence among young adults (≤ 40 -45 years of age), many of whom present without traditional environmental exposures (5,6). This demographic shift has sparked a critical debate: Whether early-onset OSCC constitutes a distinct disease entity with unique molecular drivers or simply a chronological variant of the traditional malignancy (3). Understanding these biological nuances is

essential for tailoring precision interventions for this vulnerable patient population.

The global concerns regarding oral oncogenesis are mirrored in regional epidemiological data. In the Republic of Kazakhstan, recent statistics reveal a distressing upward trend in the incidence of orofacial malignancies. According to national registry data, the combined incidence of cancers of the tongue, oral cavity and oropharynx (including Kaposi's sarcoma of the palate) increased from 483 cases in 2022 to 547 cases in 2023, representing a significant 11.0% growth rate in only 1 year (<https://onco.kz/oncohelp/pokazateli-en.html>). This surge exceeds the overall 3.5% growth rate for all malignant neoplasms in the country, highlighting the escalating burden of oral cavity cancers. While certain anatomical sites, such as the lips and nasopharynx, exhibit a slight decline in crude rates (-9.5 and -6.5% respectively), the marked increase in intraoral malignancies emphasizes the urgent need for enhanced diagnostic vigilance and targeted screening programs within the region (7).

The pathogenesis of OSCC is linked to a multifactorial synergistic interaction of risk factors, most notably chronic tobacco use (both combustible and smokeless), heavy alcohol consumption, and high-risk human papillomavirus (HPV) infection (8). For lip-specific malignancies, cumulative ultraviolet radiation remains a primary oncogenic driver. Given the aggressive nature of these lesions, early detection via standardized screening protocols and comprehensive clinical examinations is the most significant prognostic determinant for long-term survival.

Accumulating evidence suggests that OSCC in younger cohorts may exhibit a more aggressive biological phenotype, often resulting in suboptimal oncologic outcomes compared to late-onset disease. Despite presenting at comparable or even earlier clinical stages, several retrospective studies have identified elevated rates of local recurrence and inferior disease-specific survival (DSS) in younger patients (3,9). These findings challenge the conventional paradigm that youth confers a physiological advantage and suggest that early-onset OSCC may represent a molecularly distinct, high-risk entity. However, the prognostic weight of age remains highly contentious. While some data indicate equivalent or superior survival (9), a significant body of literature reports increased cancer-specific mortality and locoregional failure (10,11). Such discrepancies are reflected in existing systematic reviews, which fail to reach a consensus on whether age serves as an independent adverse prognosticator (5,6). This lack of definitive evidence necessitates a more granular characterization of the young-onset OSCC phenotype.

Despite the clinical significance of the aforementioned trends, the lack of consensus regarding the prognostic impact of age in oral squamous cell carcinoma continues to hinder the development of standardized, age-specific treatment protocols. Existing studies often suffer from small sample sizes, heterogeneous inclusion criteria, and inconsistent adjustments for confounding risk factors, such as HPV status and depth of invasion. Consequently, there is an urgent need to synthesize the current evidence to determine whether young patients indeed harbor a more aggressive disease phenotype. Therefore, the present scoping review aimed to evaluate and compare the oncologic outcomes specifically overall survival

(OS), DSS and local recurrence (LR) rates between younger adults (≤ 45 years) and their older counterparts. By providing a comprehensive assessment of the available literature, the present scoping review aimed to clarify the prognostic significance of age and provide insight into whether early-onset OSCC necessitates more intensified therapeutic strategies.

Data and methods

Literature search methods

Study selection and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow. The study selection process followed the PRISMA 2020 guidelines (12). An initial comprehensive search was conducted across major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library, supplemented by regional statistical reports from the Kazakh Institute of Oncology and Radiology. As illustrated in Fig. 1, the systematic workflow transitioned through four phases: i) Identification: Records were identified through database searching and manual citation mining; ii) screening: Duplicate records were removed and titles/abstracts were screened against the inclusion criteria; iii) Eligibility: full-text articles were assessed for methodological rigor and relevance to the 'young-onset' and 'never-smokers and never-drinkers' (NSND) phenotypes; iv) inclusion: A final library of 56 studies was selected for qualitative and quantitative synthesis.

The search strategy utilized a combination of medical subject headings (MeSH) and free-text terms tailored to each database's syntax. The primary Boolean search query was structured as follows: ('oral squamous cell carcinoma' OR 'OSCC' OR 'oral tongue squamous cell carcinoma' OR 'oral tongue squamous cell carcinoma' ('OTSCC')) AND ('young adult' OR 'early-onset' OR 'under 45' OR 'never-smokers and never-drinkers' OR 'NSND') AND ('risk factors' OR 'prognosis' OR 'genomic profiling' OR 'mechanical irritation' OR 'tumor microenvironment' OR 'immunotherapy') NOT ('oropharyngeal'). As illustrated in the PRISMA 2020 flow diagram (Fig. 1), the systematic selection process resulted in a final library of 56 high-quality sources.

Literature search strategy. A systematic and comprehensive search of the literature was conducted to identify studies characterizing the clinicopathological and molecular landscape of OSCC, with a specific focus on young-onset and NSND phenotypes. The search encompassed major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library, covering the period from 2000 to early 2026. To ensure the inclusion of regional epidemiological trends and public health data relevant to Central Asia, specialized searches were performed in regional databases (G-Science) and official statistical repositories, such as the Kazakh Institute of Oncology and Radiology.

The search strategy utilized a combination of MeSH terms and free-text key words tailored to the specific syntax of each database. The primary search strings integrated three core thematic blocks: i) Anatomical and pathological focus: 'Oral squamous cell carcinoma', 'mouth neoplasms', 'tongue neoplasms', 'oral tongue squamous cell carcinoma (OTSCC)'. ii) Demographic and phenotypic focus: 'Young adult', 'early-onset', 'under 45', 'never-smokers', 'NSND'.

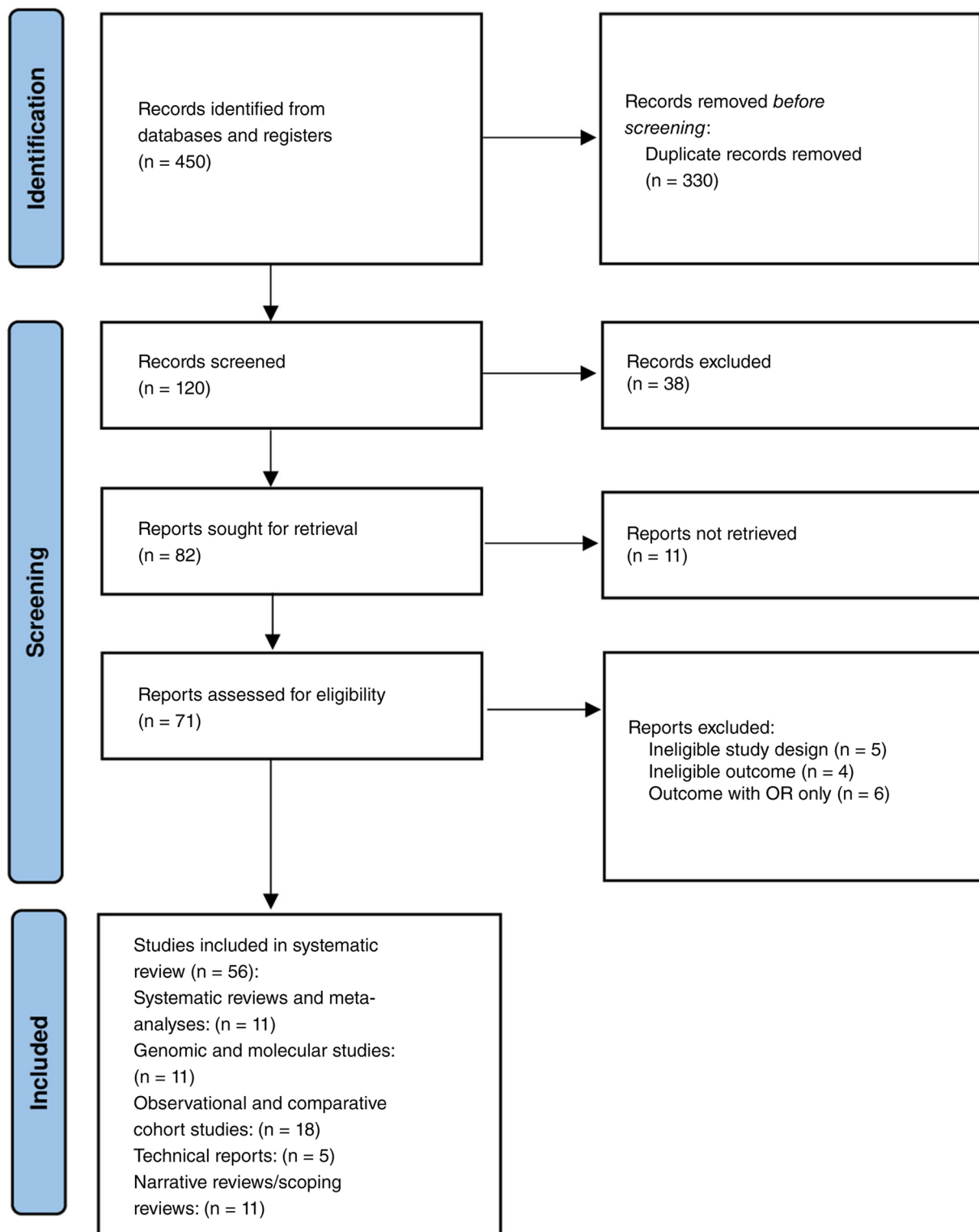


Figure 1. PRISMA 2020 flow diagram of the study selection process and evaluation outcomes.

iii) Etiological and prognostic focus: ‘Risk factors’, ‘prognosis’, ‘genomic profiling’, ‘mechanical irritation’, ‘survival’.

Specific filters and limits were applied to maintain high evidentiary standards, as detailed in Table I. These included restricting results to human studies, peer-reviewed articles (meta-analyses, systematic reviews and clinical trials), and documents published in English or Russian. To isolate oral cavity cancers from the distinct HPV-driven oropharyngeal

group, Boolean operators (e.g., AND NOT ‘oropharyngeal’) were employed where necessary.

Inclusion and exclusion criteria. To ensure the methodological rigor and thematic focus of the present scoping review, a set of predefined eligibility criteria was established based on the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework.

Table I. Detailed literature search strategy.

Database	Search query (search strings)	Filters/limits
PubMed/MEDLINE	(‘oral squamous cell carcinoma’[MeSH] OR ‘mouth neoplasms’[MeSH] OR ‘tongue neoplasms’[MeSH]) AND (‘young adult’[MeSH] OR ‘early-onset’ OR ‘under 45’) AND (‘risk factors’ OR ‘prognosis’ OR ‘genomic profiling’ OR ‘mechanical irritation’)	Language: English; Species: Humans; Timeframe: 2000-2026; Article types: Meta-Analysis, Systematic Review, Clinical Trial.
Scopus	TITLE-ABS-KEY [‘oral cancer’ AND ‘young patients’ AND (‘smoking’ OR ‘non-smoker’) AND (‘survival’ OR ‘mortality’) AND NOT ‘oropharyngeal’]	Document Type: Article, Review; Subject Area: Medicine, Dentistry, Biochemistry/Genetics.
Web of Science	TS=(‘oral cavity cancer’ OR ‘OTSCC’) AND TS=(‘molecular biomarkers’ OR ‘NGS’ OR ‘somatic mutations’) AND TS=(‘never-smokers’ OR ‘NSND’)	Timespan: All years; Language: English; Category: Oncology, Surgery, Otorhinolaryngology.
Cochrane Library	[mesh ‘Mouth Neoplasms’] AND [mesh ‘Age Factors’] AND ‘prognostic indicators’	Review Type: Intervention, Diagnostic; Date: Last 10 years.
Regional Databases (G-Science/Kazakhstan)	(‘oral cancer’ OR ‘oncology service’) AND ‘Kazakhstan’ AND ‘epidemiology’	Focus: Statistical and analytical materials (2023-2027); Language: English/Russian.

Inclusion criteria. Studies were considered eligible for inclusion if they met the following requirements: i) Population: Patients diagnosed with primary OSCC, with a specific emphasis on young adults (typically defined as ≤ 45 years) and NSND. ii) Study design: High-level secondary evidence (systematic reviews and meta-analyses), genomic and molecular profiling studies (next-generation sequencing, targeted sequencing), observational cohort studies (prospective and retrospective) and official technical or regional health reports. iii) Outcomes: Studies reporting on survival rates [OS and disease-free survival (DFS)], recurrence patterns, mutational landscapes [cyclin-dependent kinase inhibitor 2A (CDKN2A), tumor protein p53 (TP53) and epidermal growth factor receptor (EGFR)], or the impact of non-canonical risk factors (e.g., chronic mechanical irritation). iv) Language and timeline: Peer-reviewed articles published in English or Russian between January, 2000 and early 2026. v) Geographic scope: Global studies with additional inclusion of regional data from Central Asia (Kazakhstan) to provide epidemiological context.

Exclusion criteria. Studies were excluded from the final synthesis based on the following parameters: i) Anatomical misalignment: Research focusing exclusively on oropharyngeal squamous cell carcinoma (OPSCC), particularly HPV-positive cases involving the tonsils or base of tongue, to avoid confounding with the distinct OSCC phenotype. ii) Insufficient data: Case reports with limited follow-up or studies lacking a comparative control group (e.g., studies that did not compare young vs. aged or NSND vs. smokers). iii) Publication type: Conference abstracts, editorials, pre-prints and non-peer-reviewed articles (with the exception of official government statistical materials). iv) Redundancy: Duplicate publications or updated versions of the same study where only the most recent or comprehensive data were retained. v) *In vitro*/animal models: Studies conducted solely on cell lines or animal models that did not provide direct clinical or genomic correlates to human OSCC.

Data selection and analysis process. The data selection and extraction process was conducted in a standardized manner to ensure the reproducibility and internal validity of the systematic review findings.

Study selection and screening. The selection process was performed in two successive stages. In the first stage, two independent reviewers (NK and AS) screened the titles and abstracts of all identified records against the predefined inclusion and exclusion criteria. In the second stage, the full texts of potentially eligible studies were retrieved and independently reviewed for final inclusion. Any discrepancies between reviewers (NK and AS) regarding study eligibility were resolved through consensus or, if necessary, by consultation with a senior oncologist/researcher (NK) to maintain thematic consistency.

Data extraction and management. Data from the final 56 included studies were extracted using a standardized data collection form. The following variables were systematically recorded: i) Study characteristics: Author, year of publication, geographic region and study design (e.g., meta-analysis, cohort or genomic study); ii) patient demographics: Age cohorts (focusing on ≤ 45 years), sex distribution and risk factor profiles (smoking/drinking vs. NSND); iii) clinicopathological data: Anatomical subsite (specifically the mobile tongue), TNM stage and histological grade; iv) molecular data: Mutational frequency (CDKN2A, TP53, EGFR and PIK3CA), epigenetic modifications, and microRNA expression patterns; v) outcome measures: 5-year OS, DFS and LR.

Qualitative and quantitative synthesis. Given the heterogeneity of the study designs ranging from high-level meta-analyses to technical regional reports, a narrative synthesis approach was primarily employed. i) Comparative analysis: Data were stratified to compare the clinical and biological behavior of OSCC in young vs. older patients and NSND vs. traditional cohorts;

ii) genomic mapping: Molecular findings were synthesized to identify distinct ‘biological signatures’ of young-onset OSCC, utilizing data from bioinformatic platforms (e.g., cBioPortal) cited in the included technology reports; iii) epidemiological trends: Regional data from Kazakhstan were integrated with global epidemiological trends to contextualize the ‘rejuvenation’ of OSCC within the Central Asian healthcare landscape.

Quality assessment (risk of bias). The methodological quality of the included studies was appraised using validated tools appropriate for each study design. Systematic reviews and meta-analyses were evaluated using the AMSTAR 2 tool (<https://researchgold.org/resources/amstar-2-tool>), while observational cohort studies were assessed using the Newcastle-Ottawa Scale (NOS). This ensured that the synthesis prioritized high-quality evidence, particularly in the evaluation of survival outcomes and prognostic factors.

Results

Data synthesis approach. A multi-step synthesis approach was employed to integrate the clinical, epidemiological and molecular findings from the 56 included studies (1-5,7-11,13-58). The main characteristics, study designs, sample sizes, and primary focuses of the 56 key included studies are systematically summarized in Table II. Due to the methodological heterogeneity of the source material ranging from large-scale meta-analyses to specialized genomic reports a narrative and thematic synthesis was prioritized, supplemented by comparative data mapping (Table III).

Thematic stratification. Data were synthesized across four primary thematic pillars to characterize the OSCC landscape: i) Epidemiological trends: Synthesis of global and regional (Kazakhstan) incidence data to map the ‘rejuvenation’ of OTSCC, specifically in the female and NSND populations (7,13,14). ii) Etiological clustering: Evaluation of canonical (tobacco, alcohol) vs. non-canonical risk factors, with a focused synthesis on the ‘oncogenic parallelogram’ involving chronic mechanical irritation (CMI), oral dysbiosis and chronic inflammation (15-17). iii) Molecular signatures: Integration of genomic data to identify distinct mutational profiles (e.g., CDKN2A and TP53 frequency) that differentiate young-onset OSCC from traditional tobacco-related cases (18,59). iv) Prognostic outcomes: Comparison of 5-year OS and DFS across different age cohorts and habit-related phenotypes (3,19,20).

Qualitative and quantitative integration. To ensure a robust synthesis, the following analytical techniques were applied: i) Weighting of evidence: Findings from high-level secondary evidence (meta-analyses) were used as the ‘gold standard’ to validate observations reported in smaller cohort studies and case reports. ii) Comparative mapping: Data were tabulated to highlight discrepancies and commonalities in the clinical behavior of OSCC in young vs. older patients, emphasizing subsite predilections and nodal metastasis risk. iii) Pathogenetic synthesis: A conceptual framework was developed to link molecular drivers with clinical manifestations and therapeutic resistance patterns reported in the literature (21,22).

Discrepancy analysis. Conflicting findings regarding the prognosis of young patients with OSCC where some studies suggest superior outcomes (23) and others report increased biological aggression (3,24) were synthesized by accounting for stage-matching, anatomical subsite variations, and the presence or absence of traditional risk factors.

Discussion

The epidemiological shift and prognostic paradox of early-onset OSCC: Demographic, racial and sex perspectives. While the classical demographic profile of OSCC is centered on the sixth and seventh decades of life (Fig. 2), a compelling epidemiological shift is manifesting globally, with an increasing incidence among adults aged ≤ 40 -45 years (4-6). A notable methodological consideration across the head and neck oncology literature is the inconsistency in defining ‘young’ or ‘early-onset’ OSCC, with thresholds ranging between ≤ 40 and ≤ 45 years. To reconcile these variations during data synthesis, studies were stratified based on habit exposure (NSND status) and genomic profiles. High-volume meta-analyses and TCGA subgroup analyses indicate that the molecular landscape [e.g., CDKN2A alterations, low tumor mutational burden (TMB), EGFR amplifications] and survival metrics remain highly consistent across the 18-45 age spectrum in NSND cohorts. Thus, applying a ≤ 45 -year threshold captures the full demographic transition without introducing statistical bias or obscuring prognostic outcomes (13). This transition is particularly noteworthy as younger cohorts frequently lack the cumulative exposure to traditional carcinogens, such as tobacco and alcohol, which historically defined the risk profile of the disease (4). The absence of these ‘canonical’ triggers has led to a growing consensus that early-onset OSCC may represent a biologically and molecularly distinct clinical entity. Identifying the unique oncogenic drivers in these patients is now a critical mandate, as their disease appears to follow a different pathogenetic trajectory than the age-related malignancies seen in older populations (3).

A comprehensive meta-analysis of 31 independent cohorts, encompassing >28,000 patients, revealed a complex prognostic landscape for early-onset OTSCC (6). That study highlighted a notable paradox: While younger patients (aged ≤ 45 years) demonstrate superior OS compared to their older counterparts after adjusting for confounders, they concurrently face a significantly higher risk of local recurrence. This divergence suggests that the biological aggressiveness of the tumor in the young may be offset by a lack of age-related comorbidities and a greater physiological reserve. Furthermore, the significant discrepancy between adjusted and unadjusted risk estimates ($P < 0.01$) underscores the critical necessity of accounting for confounding variables when evaluating age as an independent prognosticator (6). Recent multi-center epidemiological registries from the Asia-Pacific region (2023-2025), including updated data from Singapore, Taiwan, Australia and Korea, demonstrate a continued, statistically significant annual increase in mobile tongue SCC among non-smoking women <45 years of age ($P < 0.001$), reinforcing the global nature of this epidemiological paradigm shift (6).

A recent large-scale meta-analysis encompassing 6,965 young patients further clarifies the multifactorial nature of

Table II. Summary of primary studies included in the synthesis (n=56).

Author(s)	Year of publication	Study type/design	Cohort size (n)	Main clinical/biological focus	(Refs.)
Saini <i>et al</i>	2025	Systematic review and meta-analysis	Meta-analysis	Efficacy of oral rehabilitation techniques post-oral cancer treatment	(1)
Da Conceição <i>et al</i>	2021	Narrative literature review	Review	Acute oral radiation-induced manifestations in head and neck cancer	(2)
Saade <i>et al</i>	2026	Systematic review and meta-analysis	24 studies	Prognostic factors and survival in young oral cavity cancer cohorts	(3)
Kumar	2025	Comprehensive review	Review	Comprehensive evaluation of risk factors, diagnosis, and treatment in OSCC	(4)
Kaminagakura <i>et al</i>	2022	Systematic review and meta-analysis	Meta-analysis	Oncologic outcomes in adolescents and young adults with OSCC	(5)
KazIOR Repository	2024	National Cancer Registry/Report	Population-based	Epidemiological trends and oncology metrics in Kazakhstan (2023)	(7)
Aghiorghiesei <i>et al</i>	2022	Narrative review	Review	MicroRNA expression patterns and oral cancer risk factor interaction	(8)
Bello <i>et al</i>	2020	Multicenter matched-pair analysis	Matched cohort	Histopathological features of early-stage OTSCC in young vs. old	(9)
Lenoci <i>et al</i>	2024	Review and biomarker synthesis	Review	Molecular biomarkers, incidence, and prognosis in young OSCC	(10)
Panda <i>et al</i>	2022	Systematic review and meta-analysis	Meta-analysis	Survival outcomes comparison between young and older patients in OSCC/OPSCC	(11)
Koo <i>et al</i>	2021	Genomic profiling study	NGS Cohort	Genomic signature and mutation spectrum in non-smoking non-drinking OSCC	(13)
Xie and Li	2021	Letter/Scientific commentary	Commentary	Critical evaluation of chronic mechanical irritation meta-analyses	(14)
Mello <i>et al</i>	2019	Systematic review and meta-analysis	Meta-analysis	Synergistic effect of tobacco and alcohol consumption on OSCC risk	(15)
Gupta <i>et al</i>	2021	Systematic review and meta-analysis	Meta-analysis	Chronic mechanical irritation as an independent risk factor for OSCC	(16)
Piemonte and Lazos	2018	Critical review (Bradford Hill)	Review	Causal evaluation of chronic mechanical irritation (CMI) in OSCC	(17)
Mroueh <i>et al</i>	2017	Population-based nationwide study	Finnish registry	Longitudinal survival trends and outcomes in OTSCC in Finland	(18)
Mohideen <i>et al</i>	2019	Meta-analysis	Meta-analysis	Risk factors associated with tongue SCC in young adults	(19)
Zhao <i>et al</i>	2017	Tissue engineering/ <i>in vitro</i>	Bio-models	Decellularized tongue tissue models for studying tumor invasion	(20)
Gao <i>et al</i>	2013	Bioinformatics platform article	Framework	Integrative analysis of complex cancer genomics using cBioPortal	(21)
Mansour <i>et al</i>	2013	Experimental mechanistic study	Cell lines	miR-421 overexpression, ATM downregulation, and DSB repair defects	(22)
Paderno <i>et al</i>	2018	Narrative literature review	Review	Comprehensive literature review on tongue carcinoma in young adults	(23)
Satgunaseelan <i>et al</i>	2020	International multi-center cohort	Multi-institutional	Rising incidence of OTSCC in young non-smoking women	(24)
Hussein <i>et al</i>	2017	Systematic review	Global database	Global age-stratified incidence trends in young (<45 years) OSCC	(25)
Lin <i>et al</i>	2020	Retrospective single-center cohort	Clinical cohort	Sex-based clinicopathological differences in OSCC in Taiwan	(26)
Kourelis <i>et al</i>	2013	Retrospective clinical study	Clinical cohort	Negative prognostic indicators in young head and neck cancer patients	(27)
Kawecki <i>et al</i>	2019	Population cross-sectional survey	Survey cohort	Public mouth cancer awareness and symptom recognition in Scotland	(28)
Pang <i>et al</i>	2018	Narrative review	Review	Microbiota, mucosal inflammation, and TGF- β signaling in oncogenesis	(29)
Almasri <i>et al</i>	2007	<i>In vitro</i> experimental study	Cell line	Effects of nicotine and LPS on cytokine expression in gingival fibroblasts	(30)

Table II. Continued.

Author(s)	Year of publication	Study type/design	Cohort size (n)	Main clinical/biological focus	(Refs.)
Gilligan <i>et al</i>	2017	Theoretical/narrative review	Review	Role of mechanical irritation in facilitating epithelial HPV entry	(31)
Lazos <i>et al</i>	2017	Observational clinical study	Clinical cohort	Clinical and histological characterization of CMI in oral mucosal lesions	(32)
Andersen <i>et al</i>	2022	Population-based retrospective	Population cohort	Impact of tobacco smoking on survival metrics in OSCC	(33)
Tran <i>et al</i>	2023	Contemporary review	Review	Oral cavity cancer in young, non-smoking and non-drinking patients	(34)
Gamez <i>et al</i>	2018	Retrospective cohort study	Young adult cohort	Treatment outcomes and patterns of recurrence in young OSCC patients	(35)
Hilly <i>et al</i>	2013	Matched retrospective cohort	<30 vs. >60 years	Comparative survival analysis of OTSCC in patients <30 vs. >60 years	(36)
Park <i>et al</i>	2010	Stage-matched comparative study	Stage-matched	Stage-matched clinical outcome analysis of young patients with OTSCC	(37)
Patel <i>et al</i>	2011	Population registry analysis (SEER)	SEER registry	Epidemiological analysis of rising OTSCC incidence in young women	(38)
Blanchard <i>et al</i>	2017	Case-matched single-center cohort	Case-matched	Outcomes and prognostic drivers in young adult OTSCC	(39)
Kandoth <i>et al</i>	2013	Pan-cancer genomic synthesis	TCGA cohort	Mutational landscape and driver identification across 12 cancer types	(40)
Cerami <i>et al</i>	2012	Bioinformatics platform paper	Framework	cBioPortal framework for multidimensional cancer genomics data	(41)
Pickering <i>et al</i>	2014	Whole-exome sequencing study	NGS cohort	Genomic comparison of OTSCC in young non-smokers vs. older smokers	(42)
Knopf <i>et al</i>	2015	Molecular alteration study	Clinical cohort	Oncogenes and tumor suppressor gene alterations in young OTSCC	(43)
Sankunny <i>et al</i>	2014	Experimental cell line/ <i>in vitro</i>	Cell lines	ATR/CHEK1 inhibition in reversing radioresistance with 11q loss	(44)
Joo <i>et al</i>	2013	Retrospective molecular study	Clinical cohort	Loss of FHIT gene expression and lymphatic metastasis in early OSCC	(45)
Lee <i>et al</i>	2014	Experimental/cancer stem cell	Functional assays	Wnt/ β -catenin signaling and Oct4 activation in HNSCC stem cells	(46)
Lee <i>et al</i>	2021	Systematic review and meta-analysis	Meta-analysis	Survival comparison between young and old patients with OSCC	(47)
Adeoye <i>et al</i>	2021	Retrospective cohort study	Clinical cohort	Prognostic implications of non-smoking, non-drinking status in OSCC	(48)
Dediol <i>et al</i>	2016	Clinical biomarker cohort	Clinical cohort	HPV prevalence and p16INK4a overexpression in NSND OSCC	(49)
Yang <i>et al</i>	2021	Comparative clinical cohort	NSND vs. Controls	Clinical and biological distinctiveness of NSND OSCC patients	(50)
Bao <i>et al</i>	2020	Propensity score-matched analysis	PSM cohort	Impact of smoking and alcohol consumption on OSCC prognosis	(51)
Thomson	2018	Expert commentary/review	Review	Prevention, proliferation, and progression paradigms in OSCC	(52)
Al-Jaber <i>et al</i>	2016	Epidemiological systematic review	Regional studies	Epidemiology and risk factor profile of oral cancer in Arab countries	(53)
Coelho	2012	Epidemiological review	Review	Health burden and unique risk factors of oral cancer in India	(54)
Ng <i>et al</i>	2017	Global multi-center registry study	Global dataset	Changing global epidemiology of oral tongue squamous cell carcinoma	(55)
Ayers <i>et al</i>	2017	Biomarker/clinical trial study	Clinical trial cohort	IFN- γ gene expression signature predicting response to PD-1 blockade	(56)
Vos <i>et al</i>	2021	Phase II clinical trial (IMCISION)	Clinical trial	Neoadjuvant nivolumab plus ipilimumab in resectable HNSCC	(57)
Schoenfeld <i>et al</i>	2020	Phase II randomized clinical trial	Clinical trial	Neoadjuvant nivolumab vs. nivolumab + ipilimumab in oral cavity SCC	(58)

OSCC, oral squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; NSND, non-smoker non-drinker; CMI, chronic mechanical irritation; DSB, double strand break; LPS, lipopolysaccharide; HNSCC, head and neck squamous cell carcinoma.

Table III. Summary of pathogenetic categories and evidence in OSCC.

Pathogenetic category	Study types	Primary findings and manifestations	(Refs.)
Classical toxicological axis	Meta-analyses and prospective cohorts	Dose-dependent synergy: ATE >60 PYs significantly elevates mortality risk (aHR 1.89). 98.5% male predominance in SD groups.	(16,26,51)
Young-onset and NSND phenotype	Multi-center matched-pair and systematic reviews	Epidemiological shift: Rising incidence in females ≤45 years. Predominant lingual involvement; superior OS (HR 0.47) despite higher recurrence.	(3,12,13, 27,47,50)
Oncogenic parallelogram (CMI)	Systematic reviews and biological synthesis	Mechanical promotion: Chronic irritation (dentures/sharp teeth) acts as a 'sufficient component cause' (RR, 2.56) via NF-κB and TGF-β pathways.	(18,20, 22,25)
Molecular and genomic drivers	Targeted NGS and genomic characterization	Distinct signatures: NSND tumors enriched with CDKN2A mutations and EGFR amplifications. Young patients show dysregulated WNT/STK11 axes.	(36,39, 45,48)
Environmental and occupational	Statistical materials and systematic reviews	Inhalation risks: Significant correlation with coal dust, formaldehyde, and asbestos. Critical for industrial regions (e.g., Central Asia).	(7,17)
Viral and microbiological	Systematic reviews and narrative synthesis	Low HPV prevalence: HPV (p16) plays a limited role in OSCC compared to OPC; dysbiosis modulates epithelial barrier permeability.	(22,24,49)

ATE, accumulated tobacco exposure; PYs, pack years; aHR, adjusted hazard ratio; CMI, chronic mechanical irritation; OS, overall survival; HR, hazard ratio; RR, relative risk; NSND, never-smokers and never-drinkers; HPV, human papillomavirus.

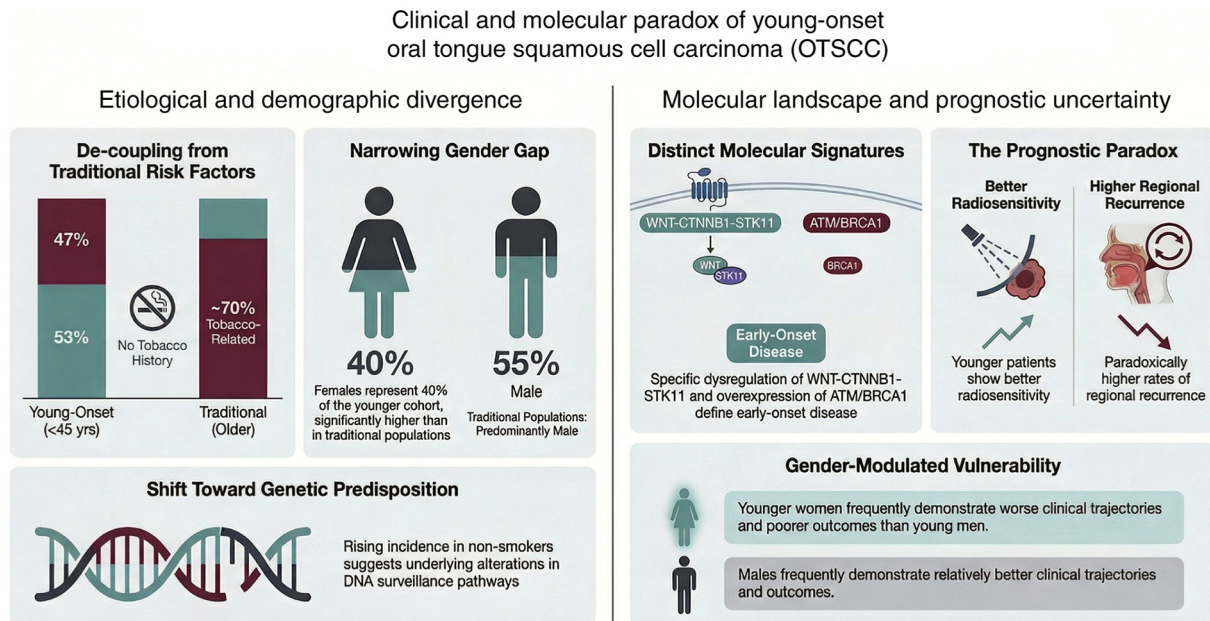


Figure 2. The clinical and molecular paradox of young-onset oral tongue squamous cell carcinoma (OTSCC). OTSCC, oral tongue squamous cell carcinoma; OSCC, oral squamous cell carcinoma; OR, odds ratio; CMI, chronic mechanical irritation; TGF-β, transforming growth factor-β.

prognosis in early-onset oral cancer (3). While demographic factors, such as age and sex exhibited no significant association with OS, racial disparities were evident, with patients of African origin demonstrating significantly poorer outcomes [adjusted hazard ratio (aHR), 2.79]. From a clinicopathological perspective, that study identified nodal involvement (aHR, 2.05), high-grade tumors (aHR, 2.15) and poorly differentiated histology (aHR, 7.75) as the most formidable adverse

prognosticators (3). These findings align with the observations of the present scoping review, suggesting that tumor biology and stage at presentation, rather than age-related physiological factors, remain the primary determinants of mortality in the younger cohort.

A notable sex-specific divergence is observed in OSCC, where younger females (aged ≤45 years) are increasingly represented, primarily presenting with lingual malignancies (24-26).

Shifting Paradigms in Oral Squamous Cell Carcinoma (OSCC) Etiology

While synergistic use of tobacco and alcohol remains the primary driver, recent evidence highlights a “non-canonical” trajectory involving chronic **mechanical irritation** (CMI) and industrial carcinogens, particularly in younger populations.

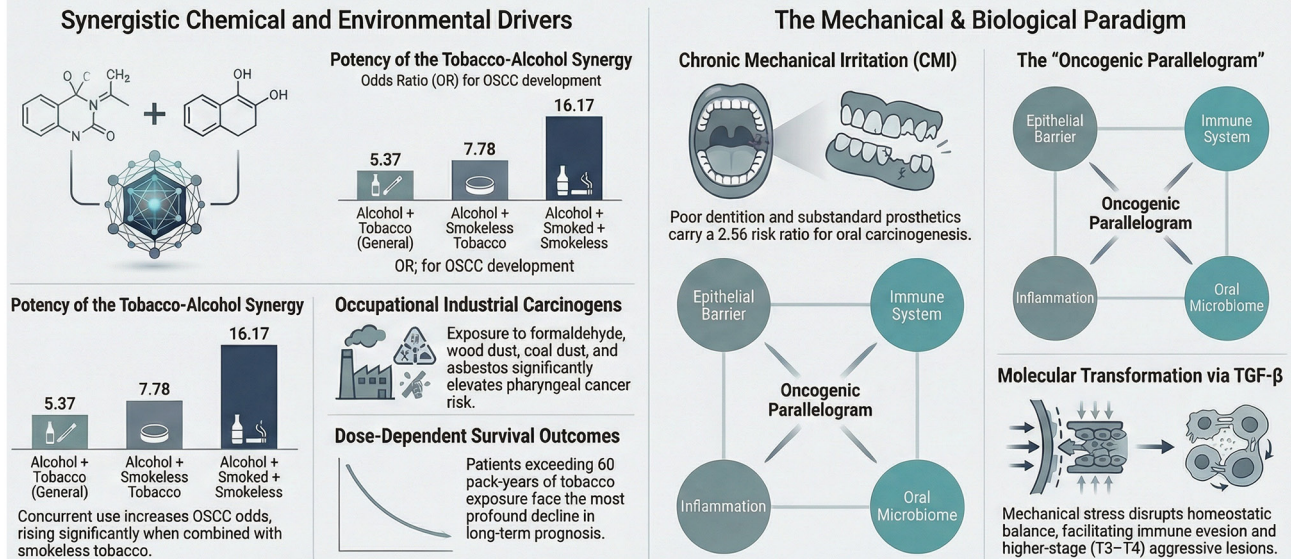


Figure 3. Shifting paradigms in oral squamous cell carcinoma (OSCC) etiology.

This is in contrast to the male population (ages 51–60 years), where buccal mucosa involvement remains more frequent (26). While the higher incidence in women >70 years of age suggests a classical cumulative etiological model, the rising trend in younger females points toward an alternative oncogenic pathway. Nevertheless, the lack of significant variance in OS between male and female cohorts suggests that while etiology and localization may differ, the ultimate oncologic outcome remains consistent across the sex spectrum, necessitating a standardized therapeutic approach despite varying clinical presentations.

Beyond the established role of tobacco and alcohol, the identification of novel oncogenic drivers in young adults is essential for redefining risk stratification and tailoring surveillance protocols (27). Younger patients often present a unique clinical paradox: While they may possess a greater physiological reserve for recovery, the anatomical and functional impairments following treatment can devastatingly affect their future personal and professional prospects. This necessitated a shift in the therapeutic paradigm toward ‘function-preserving’ interventions. Establishing specific prevention measures and post-operative follow-up programs for this vulnerable population remains a paramount challenge, as early intervention must be balanced with the preservation of social skills and long-term quality of life (27).

The higher documented rates of recurrence in younger patients with OSCC must be critically evaluated alongside the ‘competing risk’ of mortality in older populations. In elderly cohorts, non-cancer-related deaths driven by age-related frailty and preexisting comorbidities often occur before a clinical relapse can be detected or managed (6). Conversely, the relative absence of such competing mortalities in younger adults allows for a longer observation window, during which

local failures are more likely to manifest. Furthermore, the robust physical status of younger patients facilitates a more rapid recovery and a higher probability of successful rescue therapy, which ultimately contributes to their favorable OS profile notwithstanding the heightened risk of initial treatment failure (6).

Beyond the tobacco-alcohol axis: Chronic mechanical irritation, occupational hazards and the ‘oncogenic parallelogram’. As illustrated in Fig. 3, beyond traditional lifestyle-related triggers, poorly explored factors, such as chronic trauma and microbial dysbiosis are increasingly recognized in the pathogenesis of OSCC (15,16,60). While emerging evidence highlights non-canonical drivers in young-onset oral cancer, the synergistic consumption of alcohol and tobacco remains the most potent classical risk profile for OSCC, as also demonstrated in Table IV. A previous comprehensive systematic review of observational studies confirmed that the concurrent use of these substances dramatically elevates the odds of developing OSCC [odds ratio (OR), 5.37; 95% CI, 3.54–8.14] (15). This pathogenic synergy is even more pronounced when combining alcohol with smokeless tobacco (OR, 7.78) or a triple combination of alcohol, smoked and smokeless tobacco (OR, 16.17). These data serve as a critical baseline: While older cohorts are predominantly driven by this intense chemical synergy, the increasing incidence of OSCC in young, non-smoking females suggests a distinct biological trajectory that bypasses this traditional toxicological axis (15).

The geographical and demographic shifts in oral and pharyngeal cancers incidence mandate a broader evaluation of environmental and occupational risk factors. The systematic review by Awan *et al* (60) identified a significant association between exposure to industrial carcinogens

Table IV. Evidence-based synthesis of non-canonical risk factors.

Risk category	Specific trigger	Impact/risk ratio	Scientific evidence	(Refs.)
Mechanical	Sharp teeth, ill-fitting dentures (CMI)	RR 2.56	Induced chronic inflammation via NF- κ B	(18,20)
Occupational	Coal dust, asbestos, formaldehyde	High correlation	Significant in industrial and welding environments	(17)
Viral	Human Papillomavirus (HPV)	Rare in OSCC	p16 is a poor prognosticator in NSND OSCC	(48,49)
Biological	Oral Microbiota Dysbiosis	Barrier disruption	Interplay with TGF- β signaling in oncogenesis	(22)
Genetic	DNA repair pathway alterations	Predisposition	Widespread epigenetic alterations (CpG hypermethylation)	(27,45)

Categorization of emerging etiological drivers beyond the tobacco-alcohol axis. CMI, chronic mechanical irritation; HPV, human papilloma-virus; NSND, never-smokers and never-drinkers; OSCC, oral squamous cell carcinoma.

specifically formaldehyde, wood dust, coal dust and asbestos, and an increased risk of developing oral and pharyngeal cancers, highlighting the critical role of occupational hazards in non-canonical oncogenesis. The topographical distribution of OSCC is frequently associated with areas of high mechanical stress, such as the lateral borders of the tongue and the buccal mucosa. Recent systematic evidence involving high-quality studies (low risk of bias per JBI criteria) identifies edentulous subjects and those with substandard prosthetics as a high-risk group (16). With an estimated risk ratio of 2.56, chronic irritation emerges as a significant contributor to oral carcinogenesis. Given the increasing incidence of tongue SCC in younger cohorts, the role of CMI as a dependent risk factor necessitates a more comprehensive dental evaluation during routine screenings, moving beyond the traditional focus on chemical carcinogens alone (16).

CMI, resulting from poor dentition, parafunctional habits (e.g., cheek biting), or substandard prosthetics, represents a preventable yet under-researched etiological component (16,28). Although previous qualitative assessments utilizing the Bradford Hill criteria found existing studies to be limited by confounding variables, the potential for CMI to induce frictional keratosis and subsequent malignant transformation cannot be dismissed (17,61). In light of the rising incidence of orofacial malignancies in regions such as Kazakhstan, where dental hygiene standards vary, addressing CMI through regular examinations and the removal of traumatic dental factors could prove as effective as traditional de-addiction programs in preventing OSCC.

The role of CMI in oral oncogenesis is increasingly viewed through the lens of the ‘oncogenic parallelogram’, a complex interplay between the epithelial barrier, the immune system, chronic inflammation, and the oral microbiome (29). Recent evidence suggests that these three components are not isolated factors, but form a tightly interdependent network during carcinogenesis. Central to this reciprocal crosstalk is the transforming growth factor- β (TGF- β) signaling pathway, which appears to modulate every facet of this triangle. In younger patients, where traditional carcinogens may be absent, the disruption of this homeostatic balance, potentially triggered by

chronic mechanical irritation could serve as a primary driver for cellular transformation and immune evasion (29). While CMI alone may not possess independent mutagenic potential, it functions as a potent promoter that significantly lowers the threshold for malignant transformation. For instance, tobacco exposure on a chronically irritated mucosa aggravates the inflammatory cascade by upregulating pro-inflammatory cytokines, such as IL-1, IL-6 and TNF (30). Furthermore, CMI disrupts the epithelial barrier and increases the expression of syndecan-1, which facilitates HPV attachment and internalization a critical step for persistent viral infection and subsequent oncogenesis (31). These synergistic mechanisms explain why patients with long-standing dental trauma (mean duration of 49 months) exhibit a 1.7-fold increased risk of OSCC, often presenting with more aggressive, higher-stage (T3-T4) lesions (16,32).

Evidence from a large-scale longitudinal study of >1,700 patients with OSCC demonstrated a clear linear association between accumulated tobacco exposure and diminished survival outcomes (33). Multivariable Cox regression analyses revealed that current smokers face significantly higher hazard ratios for both OS and DFS compared to never-smokers (33). Notably, this detrimental effect is dose-dependent, with patients exceeding 60 pack-years exhibiting the most profound decline in long-term prognosis. Furthermore, the impact of tobacco on survival appears to be modulated by the specific tumor subsite and the presence of excessive alcohol consumption, suggesting that the chemical synergy between these carcinogens varies across the oral cavity (33).

The recent genomic characterization of OSCC in NSND highlights a molecular landscape that is distinctly divergent from traditional, habit-driven malignancies. While a definitive genetic etiology remains elusive, NSND tumors are frequently characterized by widespread epigenetic alterations, specifically CpG island hypermethylation and subsequent gene silencing (34). Furthermore, genomic profiling reveals unique mutational frequencies in genes, such as *CASP8*, suggesting a different pathogenetic trajectory. Notably, the presence of a robust interferon- γ (IFN- γ) response and the activation of immune checkpoint ligands in these patients point toward

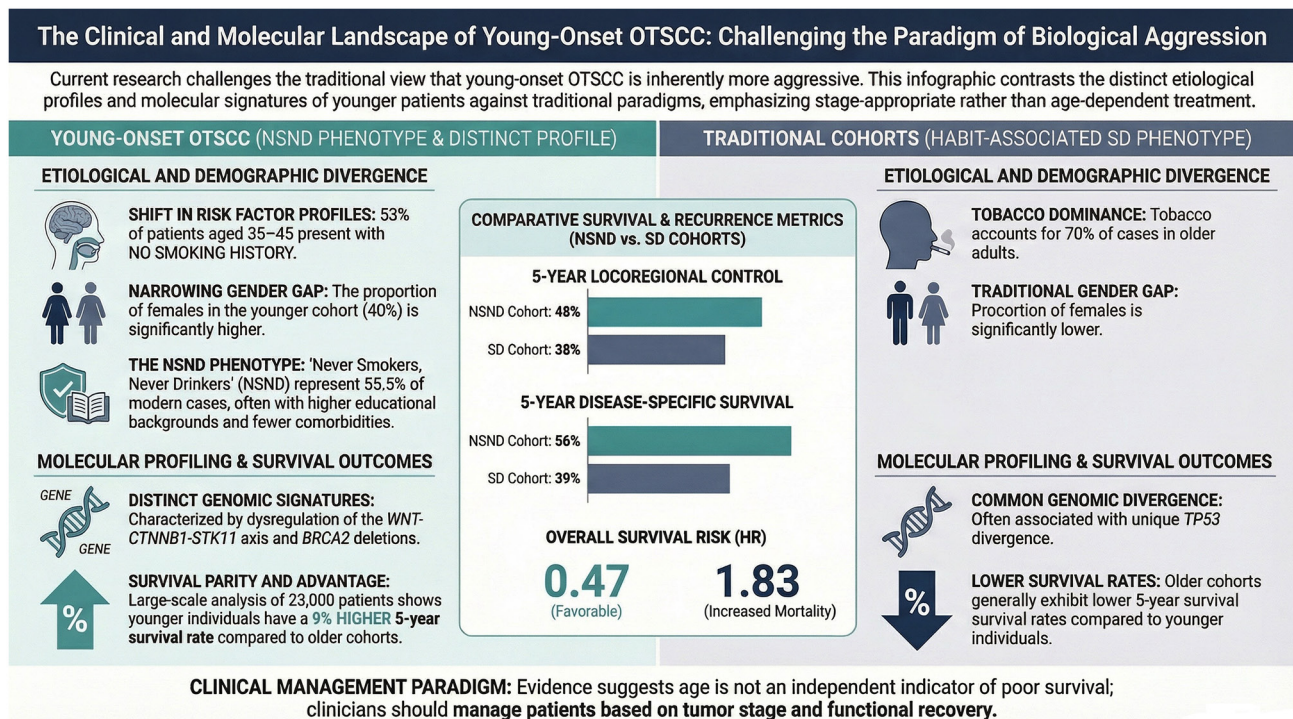


Figure 4. The clinical and molecular landscape of young-onset oral tongue squamous cell carcinoma (OTSCC): Challenging the paradigm of biological aggression.

a potential viral etiology or a distinct immune-mediated oncogenic pathway that warrants further investigation in younger, low-risk cohorts (34).

In the complex, multistep process of oral carcinogenesis, CMI functions as a critical 'effect modifier' or enhancer. Applying the Bradford Hill criteria to current clinical data reveals that while CMI may not function as an independent initiator, it serves as a 'sufficient component cause' a factor that, when eliminated, significantly diminishes the overall risk of malignancy (17). This is particularly relevant for high-risk populations where CMI interacts synergistically with sub-clinical triggers. By stimulating the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and cyclooxygenase-2 (COX-2) pathways, chronic mechanical trauma from dental or prosthetic factors provides the necessary promotional stimulus following an initial predisposed state. Thus, treating CMI is not merely a palliative measure but a primary preventive strategy that could reduce OSCC morbidity and mortality (17).

The clinical and molecular paradox of young-onset OTSCC: From etiological divergence to prognostic uncertainty. The prognostic significance of age in OTSCC remains one of the most contentious issues in head and neck oncology (6,35). While traditional paradigms suggest that younger patients may have a physiological advantage, several cohorts have reported paradoxically poorer outcomes in this demographic, particularly regarding regional recurrence and DFS (27,36,62) (Fig. 4). For instance, advanced-stage OTSCC in patients <45 years of age has been shown to be associated with significantly higher rates of locoregional failure compared to older counterparts (37). This prognostic vulnerability appears to be further modulated

by sex, with younger women frequently demonstrating worse clinical trajectories than men (27,38). Conversely, a substantial body of evidence maintains that survival rates in the young are comparable, if not superior, to those in the elderly (18,39). Such persistent inconsistencies mandate a deeper investigation into the molecular and histopathological alterations unique to 'young-onset' disease to optimize risk-stratified therapeutic interventions (20,59) (Table V).

From a molecular perspective, OTSCC in patients <45 years of age often presents a biological paradox. While traditional mutational signatures (e.g., *TP53*, *CDKN2A* and *NOTCH1*) appear largely comparable to those in elderly populations (21,40,41), recent evidence identifies specific pathway alterations predominant in the younger cohort (42). Notably, the dysregulation of the WNT-CTNNB1-STK11 and CDKN2A-HGF-MET axes, alongside the overexpression of ATM and BRCA1, suggests a distinct molecular landscape in early-onset disease (43). These biological signatures may translate into enhanced radiosensitivity, providing critical prognostic and therapeutic advantages for this patient demographic (22,44–46). However, the absence of age-related genomic divergence in large-scale databases such as The Cancer Genome Atlas (TCGA) underscores the necessity of accounting for population heterogeneity in molecular reporting (21,41).

A previous systematic analysis of 23 high-quality studies underscored a profound etiological divergence in tongue squamous cell carcinoma (TSCC) across different age cohorts. While traditional risk factors, primarily tobacco use, accounted for ~70% of cases in older adults, a striking 53% of younger patients (typically defined as those aged 35–45 years) present without any history of smoking (19). This demographic shift

Table V. Comparative clinicopathological and molecular profiles: NSND vs. SD patients.

Parameter	Smoking and drinking (SD) group	Non-smoking/non-drinking (NSND) group	(Refs.)
Gender distribution	Predominantly male (up to 98%)	Predominantly female	(14,51)
Anatomical subsite	Floor of mouth, buccal mucosa	Mobile tongue, lateral borders	(13,27,50)
Molecular markers	High p53, p63 expression	CDKN2A mutations, EGFR amplifications	(48,50)
Tumor differentiation	More likely poorly differentiated	Well to moderately differentiated	(50)
Proliferation index	Higher Ki-67 index (~35.7%)	Lower Ki-67 index (~24.5%)	(50)
Survival outcome (OS)	Inferior survival (HR, ~1.8)	Superior overall survival (HR ~0.47)	(26,47,51)

Synthesized data comparing non-smokers/non-drinkers and smoking/drinking cohorts. NSND, never-smokers and never-drinkers; SD, smoking/drinking; HR, hazard ratio; OS, overall survival.

was further characterized by a narrowing sex gap; although a slight male predominance persists (55%), the proportion of affected females in the younger group (40%) was significantly higher than that observed in classical head and neck oncology populations. These findings support the emerging classification of young-onset TSCC as a distinct biological entity, necessitating the identification of novel, non-canonical risk factors to mitigate its rising incidence (19).

The progressive increase in OTSCC among young adults, a group frequently lacking traditional risk factors, suggests a complex etiopathogenesis that may involve an underlying genetic predisposition. Alterations in pathways governing genetic stability and DNA surveillance may render certain individuals more susceptible to head and neck cancers at an earlier age (23). However, current molecular evidence indicates that the mutational landscape of these tumors remains largely comparable across age groups, challenging the long-held belief that young-onset OTSCC is a distinct, highly aggressive biological subtype (23). Given the conflicting prognostic data in the recent literature, a specialized ‘aggressive’ treatment protocol based solely on age is currently unjustified; rather, the focus should shift toward identifying subtle markers of genetic susceptibility and optimizing functional recovery.

Diagnostic pitfalls of p16INK4a testing in young OSCC. A critical diagnostic nuance in evaluating young patients with OSCC involves the interpretation of p16INK4a immunohistochemistry (IHC). While p16 overexpression is a validated, robust surrogate marker for transcriptionally active high-risk HPV in OPSCC, its diagnostic utility in OSCC is significantly constrained. In young OSCC cohorts, p16 positivity frequently occurs via HPV-independent pathways, such as mutations or dysregulation in the Retinoblastoma protein or downstream *CDKN2A* alterations (59). Relying solely on p16 IHC without confirmatory HPV-DNA PCR or RNA *in situ* hybridization introduces a substantial risk of misclassifying HPV-negative OSCC as an HPV-driven lesion, which could lead to the inappropriate de-escalation of therapeutic protocols.

Molecular mechanisms of CMI-induced carcinogenesis. While CMI from substandard dental prosthetics or sharp malposed teeth is not a direct mutagen, it functions as a potent tissue-remodeling promoter within the ‘oncogenic parallelogram’. Chronic physical trauma continuously disrupts

the mucosal epithelial barrier, leading to the release of damage-associated molecular patterns and persistent activation of the NF- κ B and COX-2 pro-inflammatory signaling cascades. Sustained mechanical stress induces the local accumulation of reactive oxygen species, promoting oxidative DNA damage in keratinocytes (63). Concurrently, mechanical trauma causes the degradation of syndecan-1, downregulates epithelial cadherins, and activates TGF- β /SMAD signaling, which drives epithelial-mesenchymal transition. This chronically inflamed, hyperplastic microenvironment significantly lowers the activation energy threshold for malignant transformation in cells harbor non-canonical epigenetic or genomic alterations (20).

Survival outcomes and molecular profiling in the habit-free cohort: Challenging the paradigm of biological aggression. Contrary to earlier, smaller retrospective cohorts that reported mixed outcomes, a comprehensive meta-analysis of 22 studies encompassing >23,000 patients confirmed that a young age (≤ 40 years) is not an independent indicator of poor survival in OSCC (47). When pooling the available literature, the 5-year OS for younger patients revealed no significant disadvantage compared to older cohorts [hazard ratio (HR), 0.97; 95% CI, 0.66-1.41]. These findings are corroborated by large-scale database analyses, such as the pooled cohort of nearly 23,000 patients with OTSCC, where younger individuals actually demonstrated a 9% higher 5-year survival rate (HR, 0.59) (48). Consequently, the traditional perception of ‘biological aggression’ in early-onset oral cancer is not supported by high-volume data, suggesting that clinicians should manage these patients based on tumor stage rather than chronological age (47).

The prognostic landscape for OSCC in NSND remains a subject of intense debate, often confounded by the inconsistent use of age as a proxy for risk-free status. Emerging evidence suggests that when cohorts are strictly defined by habit history rather than chronological age, NSND patients frequently exhibit superior or equivalent survival outcomes compared to their counterparts with extensive smoking and drinking histories (13,33,48-50). Notably, large-scale adjusted analyses have demonstrated that cumulative tobacco exposure is associated with a poorer OS and DFS in a dose-dependent manner, with current smokers facing a significantly higher risk of mortality (HR, 1.83) (33). Targeted next-generation

sequencing of OSCC cohorts has revealed that NSND patients possess a distinct genomic profile compared to traditional high-risk groups. While TP53 (60%) and CDKN2A (24%) mutations remain prevalent across the entire spectrum, the NSND subgroup exhibits a significant enrichment of CDKN2A mutations, EGFR amplifications and BRCA2 deletions (13). Notably, a younger subset of these NSND patients exhibits a higher mutational burden, suggesting that in the absence of exogenous carcinogens, genomic instability may be driven by endogenous or hereditary factors. These molecular alterations are not merely incidental; CDKN2A mutations and EGFR amplifications are strongly associated with advanced tumor stage, perineural invasion, and extracapsular spread, providing a biological rationale for the aggressive clinical behavior sometimes observed in low-risk cohorts (13).

A longitudinal analysis of >300 OSCC patients suggests that the perceived aggressiveness of oral cancer does not significantly differ between NSND individuals and those with traditional risk factors (SD). While NSND patients predominantly elderly females exhibit a markedly superior overall survival (HR, 0.47; $P=0.002$), their DSS and relapse-free survival remain comparable to the SD group (48). This prognostic divergence indicates that the survival advantage in NSND cohorts is likely a reflection of a lower burden of chronic comorbidities rather than inherently less virulent tumor biology. Notably, advanced features, such as extracapsular extension remain potent negative predictors across both groups, reinforcing the need for stage-appropriate rather than habit-stratified treatment planning (48). The demographic and clinical profile of NSND patients significantly deviates from the traditional OSCC paradigm, with a higher prevalence among younger individuals (≤ 40 years), females and those with higher educational backgrounds (50). Anatomically, NSND tumors are less likely to involve the lower gingiva and floor of the mouth (15.1% vs. 35.6% in smokers), typically presenting at less advanced stages. These clinical characteristics translate into superior oncological outcomes: NSND patients demonstrate significantly higher 5-year locoregional control (LRC) (48% vs. 38%) and DSS (56% vs. 39%) rates. Cox proportional hazards models confirm that the absence of smoking and drinking is an independent predictor of favorable LRC and DSS, further distinguishing this cohort from habit-driven oral malignancies (50). The clinicopathological profile of oral cancer continues to exhibit a marked divergence between habit-associated and habit-free cases. While the SD cohort is overwhelmingly male (98.5%) and tends to present with more advanced clinical stages, the NSND group accounts for more than half (55.5%) of the modern oral cancer population (51). Even following rigorous statistical matching, the association between traditional risk factors and increased mortality remains potent, with SD patients exhibiting a nearly two-fold increase in the risk of death. This robust correlation underscores the necessity of aggressive primary prevention and highlights the inherently more favorable survival trajectory of the emerging NSND phenotype (51).

The emerging phenotype of young-onset OSCC: Geographical disparities and the shift toward non-canonical drivers. The global epidemiological landscape of oral malignancy remains heterogeneous, with ~300,000 new diagnoses and 145,000

related deaths reported annually (14,52). The findings of some researchers on the increasing incidence in Central Asia should be interpreted in the context of high-prevalence regions, particularly Southeast Asia, which continues to have the highest mortality rates globally (53).

The marked heterogeneity in the incidence of OTSCC ranging from endemic levels in South Asia to relatively low frequencies in the Middle East reflects a complex interplay of regional risk factors (54). In India, where OSCC accounts for almost one-third of the total oncological burden, the epidemiological profile is fundamentally shaped by widespread habit-driven carcinogens (54). Conversely, the significantly lower prevalence in Western and Middle Eastern populations (3 and <2%, respectively) highlights a distinct etiological landscape. These marked discrepancies in incidence and clinical presentation necessitate a shift toward region-specific diagnostic frameworks, as the 'global' paradigm of oral cancer may not adequately address the unique pathological drivers identified in high-incidence zones (54). Regional studies in Central Asia have noted a trend towards the 'rejuvenation' of cancer profiles, with an increasing proportion of patients being diagnosed in the 30-49 age group, particularly in ecologically sensitive zones (7). This aligns with the finding of an emerging younger cohort in Kazakhstan that deviates from the global mean age of onset. The escalating burden of oral cancer has been recognized as a public health priority in Kazakhstan's 'Comprehensive Plan for Combating Oncological Diseases (2023-2027)', which emphasizes the urgent need for early detection of visual-location tumors to mitigate the high proportion of advanced-stage (III-IV) presentations (7).

However, while the mean age of onset in these high-prevalence areas remains ~55 years, the current synthesis highlights a concerning demographic shift toward younger cohorts (≤ 45 years). This suggests that while traditional risk factors drive the epidemic in South Asia, distinct etiological drivers may be emerging in other geographic regions, necessitating tailored screening strategies (14). Recent epidemiological shifts have prompted a reassessment of OSCC patterns globally, with increasing reports of early-onset disease across both Western and Eastern populations (24,25,55). This rising trend in Scotland, North America and Scandinavia, as well as in high-prevalence zones such as India and China, suggests a potential change in the etiopathogenesis of the disease. Despite this surge in 'young-onset' cases, the oncological community has yet to reach a definitive consensus on the exact age cutoff ranging in the literature from ≤ 40 to ≤ 45 years.

The rising incidence of orofacial malignancies observed in Kazakhstan indicates a striking parallel in developed Asia-Pacific nations. Multi-institutional analyses involving >1,800 patients in Australia and Singapore have demonstrated a statistically significant surge in tongue SCC among the cohort aged ≤ 45 years ($P<0.001$) (24). The fact that this trend is most pronounced in young females, often in the absence of a significant smoking history, suggests a global epidemiological shift. This 'emerging phenotype' young, female and non-smoking challenges existing screening protocols, which traditionally target older, high-risk males. Consequently, the integration of these international findings with regional Central Asian data underscores the necessity for a universal re-evaluation of OSCC etiology in the post-tobacco era (24).

A previous comprehensive systematic review covering four decades of global data confirmed a significant upward trajectory in the incidence of OSCC and oropharyngeal squamous cell carcinoma among patients <45 years of age (25). Notably, this rising trend is globally pervasive, with the exception of The Netherlands, and is characterized by a distinct demographic shift: A prominent increase in mobile tongue cancer among females and oropharyngeal malignancies in males. Furthermore, the relative burden of early-onset disease exhibits a profound geographical disparity, with the proportion of young patients in Africa (17.2%) and the Middle East (14.5%) significantly exceeding that in North America (5.5%). These findings reinforce the hypothesis that OSCC and oropharyngeal squamous cell carcinoma in the younger cohort may represent a biologically distinct clinical entity, potentially driven by non-canonical etiological factors beyond traditional tobacco and alcohol exposure (25).

Therapeutic implications and future directions: Tumor microenvironment, immune profiles, and targeted interventions. The distinct biological profile of young-onset and NSND OSCC mandates a transition toward personalized, microenvironment-driven therapeutic strategies. As regards the programmed death-ligand 1 (PD-L1) expression and the IFN- γ axis, although young NSND patients with OSCC typically exhibit a lower TMB due to the absence of tobacco-induced neoantigens, genomic profiling reveals a robust IFN- γ gene expression signature (56). IFN- γ is a pivotal cytokine that upregulates PD-L1 expression on tumor cells and tumor-infiltrating lymphocytes. Consequently, young NSND patients often present with elevated combined positive scores (≥ 1 or ≥ 20), rendering them highly responsive to immune checkpoint inhibitors (ICIs), such as anti-PD-1 monoclonal antibodies (e.g., pembrolizumab, nivolumab), despite low TMB (56).

As regards the immune microenvironment, 'hot' vs. 'cold' phenotypes and the recurrence stratification of early-onset OSCC by the tumor microenvironment (TME) provides critical insights into the 'prognostic paradox' of high local recurrence rates alongside favorable overall survival (34). Young OSCC tumors span a spectrum from 'hot' (inflamed, highly infiltrated by CD8⁺ T-cells) to 'cold' (immune-excluded or immunosuppressed) phenotypes. Immune-excluded tumors, characterized by dense stromal fibrosis driven by TGF- β signaling, prevent cytotoxic T-lymphocytes from reaching the tumor core. Recognizing these TME subtypes allows for the targeted application of TME-modulating agents (e.g., TGF- β inhibitors) to convert 'cold' non-responsive tumors into 'hot' immunogenic substrates (34).

Perioperative (neoadjuvant) immunotherapy is used for functional preservation. Given the long-life expectancy and functional demands of young adults, preserving speech, deglutition and facial esthetics is a top clinical priority (57). The emergence of neoadjuvant (preoperative) ICI regimens either as monotherapy or combined with short-course induction chemotherapy has demonstrated marked pathological complete response and major pathological response rates in locally advanced head and neck cancers. Achieving significant tumor downstaging prior to surgery enables function-sparing, minimal-resection surgical techniques,

drastically reducing long-term morbidity while maintaining oncologic safety (57).

Synergy between EGFR amplification and immune checkpoint inhibition molecular characterization indicates that young NSND OSCC is enriched with EGFR gene amplifications and over-expression. Elevated EGFR signaling not only drives proliferation, but also promotes immune evasion by upregulating PD-L1 and immunosuppressive cytokines (58). Combining anti-EGFR targeted therapy (e.g., cetuximab) with anti-PD-1 ICIs creates a potent dual mechanism: anti-EGFR therapy induces antibody-dependent cellular cytotoxicity and restores immune susceptibility, while ICIs relieve T-cell exhaustion, offering a promising chemo-sparing regimen for this demographic (58).

Strengths and limitations of the systematic synthesis. Despite the comprehensive nature of this synthesis, several limitations should be acknowledged: i) Heterogeneity of age cut-off values: A primary challenge in synthesizing data on 'young-onset' OSCC is the lack of a standardized age threshold. While the present scoping review primarily focuses on patients aged 40-45 years, variations in age categorization across the cited studies (ranging from 35 to 50 years) may introduce subtle inconsistencies in the reported prognostic and etiological trends. ii) Retrospective nature and confounding factors: A number of the analyzed cohorts, particularly those investigating non-canonical risk factors such as CMI, rely on retrospective data. This inherently limits the ability to control for all confounding variables, such as dietary habits, environmental pollutants beyond the workplace and silent viral co-factors. iii) Geographical data imbalance: While the present scoping review integrated regional data from Kazakhstan and Central Asia, the majority of large-scale genomic and database studies (e.g., TCGA, NCDB) originate from Western or East Asian populations. This geographical bias underscores the need for more localized molecular research in industrialized Central Asian regions to confirm the prevalence of the identified; young-onset' genomic signatures. iv) Methodological limitations in CMI assessment: The evaluation of mechanical trauma often lacks objective quantification (e.g., duration and intensity of irritation). The majority of studies utilize qualitative assessments, which may underestimate the synergistic potential of CMI when combined with sub-clinical chemical exposures. v) Evolution of the nomenclature: The recent shift in head and neck cancer classification and nomenclature (e.g., the distinction between OSCC and OPC regarding HPV status) suggests that older literature may not consistently separate these entities, potentially masking some subsite-specific trends.

Concluding remarks

Epidemiological transformation. There is a sustained global trend toward the 'rejuvenation' of OSCC. The increasing incidence among individuals <45 years of age, particularly non-smoking females, suggests the existence of alternative pathogenetic pathways that bypass classical cumulative chemical mutagenesis.

Biological uniqueness of the NSND phenotype. OSCC in NSND is a distinct biological entity. It is characterized by a specific genomic landscape enriched with CDKN2A mutations

and EGFR amplifications and widespread epigenetic silencing, distinguishing it from the traditional 'tobacco-type' OSCC.

Deconstructing prognostic myths. Data from large-scale cohorts (>23,000 patients) refute the long-held perception of increased biological aggression in the young. Age alone is not an independent predictor of poor survival; higher recurrence rates in younger patients are offset by a lack of comorbidities and a better response to rescue therapy, resulting in favorable overall survival.

The 'oncogenic parallelogram' concept. CMI from poor dentition or ill-fitting prosthetics acts as a critical 'effect modifier'. By disrupting the epithelial barrier and triggering chronic inflammation via NF- κ B and COX-2 pathways, CMI functions as a potent promoter that lowers the threshold for malignant transformation.

Regional public health priorities. The increasing burden of oral cancer in Central Asia, as highlighted in Kazakhstan's 'Comprehensive Plan for Combating Oncological Diseases (2023-2027)' (7), necessitates the integration of occupational and environmental risks into diagnostic frameworks. The early detection of visual-location tumors must be prioritized to reduce advanced-stage presentations.

Shift in therapeutic paradigm. Given the high life expectancy of younger patients, treatment should prioritize functional preservation. Aggressive escalation of therapy based solely on chronological age lacks high-quality evidentiary support and may unnecessarily diminish the long-term quality of life and social integration of survivors.

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The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NK, AS and AB were involved in the writing, reviewing and editing of the manuscript, as well as in the writing and preparation of the original draft of the manuscript, and the conceptualization of the study. NK, NU and MN supervised the study, and were also involved in project administration, in the literature search and in the conceptualization of the study. All authors have read and approved the final manuscript. NK and AS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (AMSTAR 2 tool and Gemini Notebook) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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