

New Insights into Oral Cancer Without Traditional Risk Factors

Genomic analysis reveals endogenous mutational processes and possible microbial involvement in oral cancers lacking traditional risk factors

CHINA, June 8, 2026 /EINPresswire.com/ -- A new study reveals that many oral cancers are no longer driven by traditional risk factors like smoking or Human papillomavirus infection. Instead, they arise from internal DNA damage and possible microbial influences. By analyzing tumor mutation patterns, researchers identified a distinct subtype of oral squamous cell carcinoma marked by immune evasion and antibacterial responses. These findings reshape our understanding of oral cancer and open the door to more precise, targeted treatments in the future.

Head and neck cancers, particularly those originating in the oral cavity, have historically been attributed to well-defined etiological factors like tobacco exposure, alcohol consumption, and infection with oncogenic strains of Human papillomavirus. These factors are known to drive majority of oral cavity squamous cell carcinomas (OCSCC), a major subtype of head and neck cancers.

However, an increasing proportion of OCSCC cases are being diagnosed in individuals who lack exposure to these established risk factors, particularly among younger individuals and women. Despite these changing patterns, the causes of OCSCC in this group are still not well understood, highlighting the need for further research.

Researchers conducted this study to better understand this subgroup of oral cancers, referred to as NIRF (No Identified Risk Factor) OCSCC. The study was led by Dr. Jiri Zavadil from the International Agency for Research on Cancer (IARC), World Health Organization, Epigenomics and Mechanisms Branch, France, and Prof. François Virard from the Cancer Research Center of Lyon. Dr. Zavadil explains the motivation behind this study, "We aimed to uncover the molecular mechanisms driving these cancers and to determine whether they represent a distinct subtype



Genomic analysis highlights divergent carcinogenic pathways in oral tumors.

with unique biological characteristics. Given that traditional carcinogenic exposures could not explain these cases, we sought to explore whether internal processes or alternative external influences might be responsible.” The study was published in the International Journal of Oral Science journal on 24 April 2026.

The study utilized large-scale public cancer datasets from The Cancer Genome Atlas. After rigorous quality filtering, the researchers analyzed 347 head and neck cancer samples, including 253 oral cavity cancers and 94 laryngeal cancers used as smoking-related controls. Advanced genomic techniques and multi-omics analysis were employed to examine DNA mutations, gene expression, and epigenetic changes. A key methodological approach involved the identification of mutational signatures, which are characteristic patterns of mutations that reflect the underlying processes causing DNA damage. By clustering tumors based on these signatures, researchers were able to stratify patients into biologically meaningful groups.

The analysis revealed four distinct mutational clusters. Two were strongly linked to known risk factors such as smoking and alcohol use, characterized by signatures like SBS4 and SBS16. Tobacco-related mutations varied by anatomical site, with laryngeal cancers showing a higher mutation burden than oral cancers, highlighting tissue-specific responses to carcinogens. “We identified two clusters enriched with NIRF cases. They were dominated by endogenous processes, particularly the aging-related SBS1 signature and APOBEC-associated signatures (SBS2 and SBS13) suggesting that internal biological mechanisms, rather than external exposures, play a key role in NIRF OCSCC,” shares Prof. Virard.

Importantly, no mutational signatures linked to known environmental carcinogens were identified in the NIRF tumor clusters, even though they showed biological heterogeneity, with one primarily driven by age-related mutations and the other by APOBEC-mediated mutagenesis. Further analyses revealed that NIRF tumors possess distinct molecular features, including unique driver gene mutations linked to immune function and cell signaling. Gene expression analysis indicated activation of antimicrobial and keratinization pathways, and the presence of bacterial components, histopathologically confirmed by the researchers, suggested a potential role of the oral microbiome in tumor development.

Clinically, these findings have important implications. NIRF tumors exhibited features of immune evasion, including alterations in antigen presentation pathways, which could potentially affect responses to immune checkpoint therapies. At the same time, APOBEC-driven mutagenesis points to potential sensitivity to therapies targeting DNA damage response pathways, suggesting possible future opportunities for precision medicine approaches. Overall, this study significantly refines our understanding of oral cancer by establishing NIRF OCSCC as a distinct molecular subtype. It highlights the importance of endogenous mutational processes, demonstrates site-specific effects of traditional risk factors, and suggests a possible contribution of microbial influences.

In conclusion, oral cancers arising in the absence of known risk factors represent a unique

disease entity with distinct biological drivers. These findings pave the way for future research into their etiology, improve diagnostic classification, and open new avenues for targeted and more effective therapeutic strategies.

Reference

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About the International Agency for Research on Cancer (IARC), WHO, France

The International Agency for Research on Cancer (IARC) is the specialized cancer research agency of the World Health Organization (WHO), headquartered in Lyon, France. Established in 1965, IARC coordinates and conducts international research on the causes of human cancer, mechanisms of carcinogenesis, cancer prevention, and global cancer surveillance. The agency brings together multidisciplinary researchers from around the world to advance understanding of cancer biology, environmental risk factors, genomics, and public health strategies. IARC is internationally recognized for its contributions to cancer epidemiology, molecular research, and evidence-based cancer prevention policies.

Website: <https://www.iarc.who.int/>

About the Cancer Research Center of Lyon (CRCL)

The Cancer Research Center of Lyon (CRCL) is a joint research unit affiliated with INSERM, CNRS, Claude Bernard Lyon 1 University, and the Léon Bérard Cancer Center. Located in Lyon, France, the CRCL brings together researchers and clinicians to investigate the molecular and cellular mechanisms underlying cancer development and progression. Its multidisciplinary approach bridges fundamental research and clinical applications, with the aim of developing more effective diagnostic tools and therapeutic strategies.

Website: <https://www.crcl.fr/>

About Dr. Jiri Zavadil from the International Agency for Research on Cancer (IARC), WHO

Dr. Jiri Zavadil is a molecular biologist and cancer researcher affiliated with the International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO), in Lyon, France, where he serves as senior Scientist and as Deputy Head of the Epigenomics and Mechanisms Branch during the time of the study. His research focuses on cancer prevention-oriented genomics, epigenetics, mutational processes, and molecular mechanisms underlying tumor development. Dr. Zavadil has authored numerous peer-reviewed scientific publications and is widely recognized for his contributions to molecular cancer research and biomarker discovery.

About Prof. François Virard from Cancer Research Center of Lyon (CRCL)

Prof. François Virard heads the Department of Oral Biology at the Faculty of Dentistry, Lyon 1 University, Lyon, France, and conducts his research at the Cancer Research Center of Lyon

(CRCL). He has long focused on oral and head and neck cancers in patients with no identified risk factors, investigating the genomic and molecular mechanisms underlying this emerging clinical entity.

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