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Oncogenic Viruses and Lifestyle Factors in the Rising Incidence of Head and Neck Cancers

Ioana Dumitrescu

University of Medicine and Pharmacy of Târgu Mureș

ioana.dumitrescu@umftgm.ro

Andrei Popescu

Department of Microbiology, University of Medicine and Pharmacy of Craiova

Abstract

Head and neck cancers (HNCs) encompass a diverse group of malignancies affecting various anatomical sites within the head and neck region. Despite advances in early detection and treatment strategies, the global burden of HNCs remains substantial, with an alarming rise in incidence rates observed in recent decades. This comprehensive review delves into the intricate interplay between oncogenic viruses, particularly human papillomavirus (HPV) and Epstein-Barr virus (EBV), and lifestyle factors, such as tobacco and alcohol consumption, that contribute to the development and progression of HNCs. By unraveling the complex molecular mechanisms underlying viral oncogenesis and the modulating effects of lifestyle exposures, this article aims to shed light on the multifaceted etiology of HNCs and inform strategies for prevention, early detection, and targeted therapeutic interventions.

Keywords: Head and Neck Cancers (HNCs), Human Papillomavirus (HPV), Epstein-Barr Virus (EBV), Lifestyle Factors, Targeted Therapies

Introduction

Head and neck cancers (HNCs) encompass a diverse array of malignancies arising from multiple anatomical sites within the head and neck region, comprising the oral cavity, pharynx, larynx, nasal cavity, and paranasal sinuses. These cancers collectively contribute to a substantial global health challenge, with staggering

statistics revealing an estimated 888,000 new cases and 463,000 deaths reported worldwide in 2020 alone Despite strides in early detection techniques and therapeutic interventions, the prognosis for HNCs remains notably unsatisfactory, especially in cases of advanced-stage diseases. This persistent challenge underscores the urgent need for further research and innovation to enhance both the prevention strategies and treatment outcomes for individuals afflicted with these malignancies [1].

Moreover, addressing this complex landscape demands interdisciplinary collaboration, leveraging insights from oncology, genetics, immunology, and other relevant disciplines to devise more effective approaches towards combating HNCs and ultimately improving patient survival rates and quality of life. Efforts should not only focus on refining existing treatment modalities but also on exploring novel therapeutic avenues, such as targeted therapies and immunotherapies, which hold promise in overcoming the resistance mechanisms often encountered in conventional treatments. Furthermore, public health initiatives aimed at raising awareness about the risk factors associated with HNCs and promoting early screening programs can play a pivotal role in reducing the burden of these diseases [2]. By fostering a comprehensive and multidisciplinary approach, healthcare professionals and researchers can strive towards achieving better outcomes for patients affected by HNCs, thereby addressing a significant unmet need in global oncology.

Head and neck cancers (HNCs) are influenced by a myriad of factors, showcasing a multifactorial etiology characterized by intricate interactions among environmental exposures, lifestyle choices, and viral infections [3]. Traditionally, tobacco and alcohol consumption have stood out as major contributors to the development of HNCs, constituting a significant proportion of cases globally as evidenced by epidemiological studies These substances, through direct carcinogenic effects and synergistic interactions, have long been implicated in the pathogenesis of HNCs, underscoring the importance of preventive measures aimed at curbing their consumption [4], [5]. However, in recent decades, a notable shift in the landscape of HNC epidemiology has emerged, marked by a rising incidence of oropharyngeal cancers associated with human papillomavirus (HPV), particularly among younger individuals with limited or no history of traditional risk factor exposure. This phenomenon has prompted a reevaluation of the risk profile for HNCs, emphasizing

the need for comprehensive screening strategies and tailored prevention efforts targeting both traditional and emerging risk factors [6].

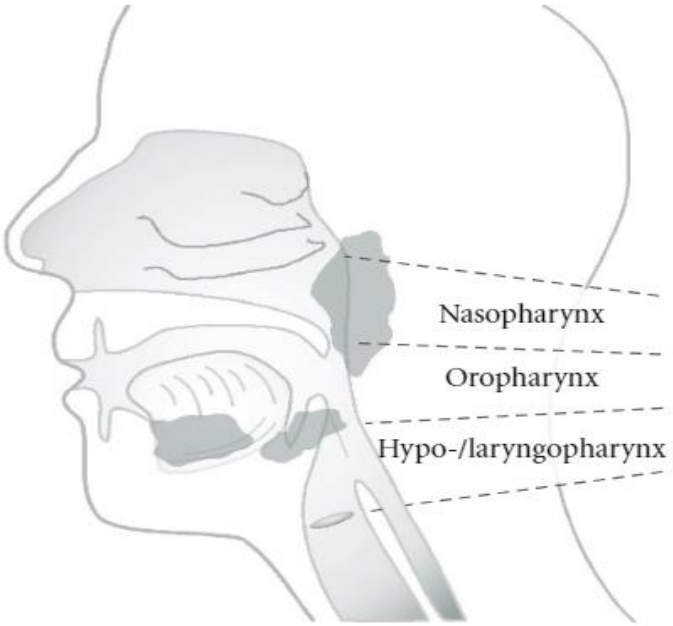

Figure 1. [7]

The escalating prevalence of HPV-associated oropharyngeal cancers underscores the dynamic nature of HNC etiology and highlights the evolving role of viral infections in disease pathogenesis. While tobacco and alcohol remain pivotal risk factors, the increasing recognition of HPV as a significant contributor to HNC incidence necessitates a nuanced understanding of the interplay between viral infections and other environmental/lifestyle determinants [8]. Factors such as changes in sexual behaviors, HPV vaccination status, and genetic susceptibility may further modulate individual susceptibility to HPV-associated HNCs, warranting comprehensive risk stratification approaches for optimal disease management. Consequently, elucidating the complex etiological framework of HNCs requires a multidisciplinary perspective that integrates epidemiological, molecular, and clinical insights to

inform targeted prevention, early detection, and therapeutic strategies tailored to the evolving landscape of HNC epidemiology [9].

This review aims to provide a comprehensive understanding of the enigmatic interplay between oncogenic viruses, primarily HPV and EBV, and lifestyle factors in the development and progression of HNCs [10]. By unraveling the molecular mechanisms underlying viral oncogenesis and the modulating effects of lifestyle exposures, this article seeks to inform strategies for prevention, early detection, and targeted therapeutic interventions tailored to the unique etiological profiles of HNC subtypes.

Oncogenic Viruses in Head and Neck Cancers:

Human papillomavirus (HPV) is a small, double-stranded DNA virus that can infect epithelial cells, including those of the head and neck region. Over 200 HPV types have been identified, with a subset classified as high-risk or oncogenic types due to their ability to promote cellular transformation and carcinogenesis [11]. The most well-established cancer-associated HPV types are HPV-16 and HPV-18, which are responsible for a significant proportion of HPV-related HNCs, particularly oropharyngeal cancers. The molecular mechanisms underlying HPV-induced carcinogenesis are complex and involve several key steps. First, viral DNA integrates into the host cell genome, leading to the disruption of viral regulatory genes and the persistent expression of viral oncoproteins, primarily E6 and E7. These oncoproteins interact with and inactivate critical tumor suppressor pathways, including those mediated by p53 and retinoblastoma (Rb) proteins, respectively. Additionally, HPV oncoproteins contribute to genomic instability, dysregulation of cellular signaling pathways, and the evasion of immune surveillance, ultimately driving cellular transformation and malignant progression [12].

The epidemiology of HPV-associated HNCs varies across anatomical subsites. Oropharyngeal cancers, particularly those arising in the tonsils and base of tongue, have the highest prevalence of HPV positivity, ranging from 40% to 80% In contrast, the prevalence of HPV in oral cavity cancers is lower, ranging from 10% to 30%, while laryngeal and nasopharyngeal cancers are rarely associated with HPV infection Several risk factors have been identified for HPV-associated HNCs, including sexual behavior (e.g., increased number of oral sex partners), immunosuppression, and potential genetic predisposition [13]. HSV enhances the development of oral cancer in conjunction with risk factors such as tobacco, alcohol,

and HPV viral infection, as well as co-infections. These factors could potentially serve as targets for diagnostic tests and therapeutic interventions, aiding in the comprehension of tumor development mechanisms [14].

Epstein-Barr virus (EBV) is a ubiquitous human herpesvirus that primarily targets B lymphocytes but can also infect epithelial cells and other cell types. EBV has been implicated in the pathogenesis of various malignancies, including several types of HNCs. Particularly notable is the strong association between EBV and nasopharyngeal carcinoma (NPC), a highly prevalent cancer in certain geographic regions such as Southeast Asia and North Africa. EBV-associated NPC is characterized by the presence of viral DNA and gene expression in tumor cells, suggesting a direct role for the virus in promoting carcinogenesis.

The molecular mechanisms underlying EBV-induced carcinogenesis involve both latent and lytic infection cycles. During latent infection, EBV expresses a subset of viral genes, including latent membrane proteins (LMPs) and Epstein-Barr nuclear antigens (EBNAs), which modulate various cellular signaling pathways involved in cell proliferation, survival, and immune evasion. For instance, LMP1 mimics activated cellular receptors and activates downstream pathways such as NF-κB, PI3K/Akt, and MAPK, promoting cell growth and survival Additionally, EBV employs intricate immune evasion strategies, including the downregulation of antigen presentation and the modulation of cytokine and chemokine responses, facilitating viral persistence and tumor progression [15].

The epidemiology of EBV-associated HNCs is largely centered around NPC, which exhibits a remarkable geographic variation in incidence rates, with high-risk regions including Southeast Asia, North Africa, and the Arctic region EBV is detected in virtually all cases of non-keratinizing and undifferentiated NPCs, underscoring its etiological role in these tumor types. Additionally, EBV has been associated with a subset of lymphoepithelioma-like carcinomas arising in various head and neck subsites, as well as other EBV-associated malignancies such as Burkitt's lymphoma and post-transplant lymphoproliferative disorders.

Several risk factors have been implicated in the development of EBV-associated HNCs, particularly NPC. Genetic susceptibility plays a crucial role, with certain human leukocyte antigen (HLA) haplotypes and polymorphisms in immune-related genes conferring increased risk Environmental exposures, such as consumption of certain preserved foods and exposure to chemical carcinogens, have also been

associated with an increased risk of NPC in endemic regions [15]. Dietary factors, including the intake of nitrosamines and other carcinogenic compounds, may contribute to the development of EBV-associated HNCs through their potential to induce chronic inflammation and modulate viral reactivation.

Table 1: Prevalence of HPV in Head and Neck Cancer Subsites

Cancer Subsite	HPV Prevalence (%)
Oropharyngeal	40-80%
Oral Cavity	10-30%
Larynx	3-7%
Nasopharynx	<5%

Source adapted from [16]

Lifestyle Factors in Head and Neck Cancers:

Tobacco and alcohol consumption have long been recognized as major risk factors for HNCs, with substantial epidemiological evidence supporting their causal roles. Numerous studies have consistently demonstrated a dose-response relationship between tobacco smoking and the risk of developing HNCs, with higher levels of exposure, longer duration, and earlier age of initiation associated with increased risks Similarly, alcohol consumption, particularly heavy and chronic intake, has been consistently linked to an elevated risk of HNCs, with a synergistic effect observed when combined with tobacco use [17].

The molecular mechanisms underlying the carcinogenic effects of tobacco and alcohol are multifaceted and involve various cellular processes. Tobacco smoke contains a complex mixture of carcinogenic compounds, including polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and reactive oxygen species (ROS). These compounds can directly induce DNA damage and form DNA adducts, leading to mutations and genomic instability Additionally, tobacco smoke and alcohol metabolites can generate oxidative stress and chronic inflammation, further promoting DNA damage, impaired DNA repair mechanisms, and the activation of cellular signaling pathways involved in cell proliferation and survival [18].

Notably, there is a dose-response relationship between tobacco and alcohol exposure and the risk of HNCs, with higher levels of consumption associated with increased risks. Furthermore, a synergistic effect has been observed when tobacco and alcohol

are used in combination, suggesting a potential interaction between their carcinogenic mechanisms .Serum lipid levels were significant across all three risk factors: smoking, chewing, and can serve as significant prognostic indicators in the diagnosis of oral cancer [19].

Diet and nutrition have also been implicated in the etiology of HNCs, with both protective and harmful effects observed. Numerous epidemiological studies have consistently demonstrated an inverse association between the consumption of fruits and vegetables and the risk of HNCs This protective effect has been attributed to the presence of various bioactive compounds, including antioxidants (e.g., vitamin C, carotenoids) and phytochemicals (e.g., flavonoids, isothiocyanates), which may modulate carcinogen metabolism, reduce oxidative stress, and exert anti-inflammatory and anti-proliferative effects.

In contrast, certain dietary factors, such as the consumption of processed meats and high levels of saturated fats, have been associated with an increased risk of HNCs. These dietary components may contribute to carcinogenesis through the formation of carcinogenic compounds during cooking processes (e.g., heterocyclic amines, polycyclic aromatic hydrocarbons) and the promotion of chronic inflammation and oxidative stress [20].

Additionally, micronutrient deficiencies, particularly folate, vitamin B12, and antioxidant vitamins (A, C, and E), have been linked to an increased risk of HNCs. These micronutrients play crucial roles in various cellular processes, including DNA synthesis, repair, and antioxidant defense mechanisms Deficiencies in these micronutrients may disrupt these protective mechanisms and contribute to increased genomic instability and oxidative stress, ultimately promoting carcinogenesis.

Physical activity and obesity have also emerged as potential risk factors for HNCs, although the evidence is somewhat conflicting. Several studies have suggested that regular physical activity may confer a protective effect against HNCs, potentially through mechanisms involving reduced insulin resistance, decreased inflammation, and modulation of cellular signaling pathways Conversely, obesity and metabolic syndrome have been associated with an increased risk of HNCs, possibly due to the dysregulation of adipokines, chronic inflammation, and oxidative stress

Interplay between Oncogenic Viruses and Lifestyle Factors:

The interplay between oncogenic viruses and lifestyle factors in the development of HNCs is complex and multifaceted. Lifestyle factors, such as tobacco and alcohol consumption, can modulate viral oncogenesis through various mechanisms. In the context of HPV-associated HNCs, tobacco smoke and alcohol metabolites have been shown to facilitate viral entry and persistence by inducing cellular and tissue damage, as well as impairing antiviral immune responses Additionally, these lifestyle exposures may synergize with HPV oncoproteins in promoting cellular transformation and carcinogenesis through shared mechanisms, such as the induction of oxidative stress, DNA damage, and the dysregulation of cellular signaling pathways [21].

Conversely, dietary factors, particularly those with antioxidant and anti-inflammatory properties, may modulate the oncogenic potential of EBV in HNCs. Phytochemicals and antioxidants present in fruits and vegetables have been shown to exhibit antiviral activities and may influence EBV latency and reactivation Furthermore, these dietary components may counteract the oxidative stress and chronic inflammation induced by EBV, potentially mitigating its carcinogenic effects.

On the other hand, viral infections can also influence the carcinogenic effects of lifestyle factors. Viral oncoproteins, such as HPV E6 and E7, and EBV LMP1 and LMP2A, have been shown to modulate various cellular signaling pathways involved in carcinogen metabolism, DNA repair, and cell cycle regulation For instance, HPV E6 can enhance the metabolism of tobacco-derived carcinogens and impair DNA repair mechanisms, thereby potentiating the mutagenic effects of these environmental exposures.

Additionally, viral-mediated immune evasion and the induction of chronic inflammation may create a permissive microenvironment for carcinogen-induced mutagenesis and tumor progression. Both HPV and EBV employ strategies to evade immune surveillance, which can contribute to viral persistence and chronic inflammation, further exacerbating the carcinogenic effects of lifestyle exposures

Table 2: Molecular Mechanisms of Tobacco and Alcohol in Head and Neck Carcinogenesis

Mechanism	Tobacco	Alcohol
Formation of DNA adducts and mutations	✓	✓
Oxidative stress and inflammation	✓	✓

Impaired DNA repair mechanisms	✓	✓
Modulation of cellular signaling pathways	✓	✓
Suppression of immune surveillance	✓	✓

Source: Compiled from various sources, including [22], [23]

Clinical and Therapeutic Implications:

The intricate interplay between oncogenic viruses and lifestyle factors in the etiology of HNCs has significant implications for clinical practice, including screening, early detection, and therapeutic interventions.

Screening and Early Detection:

The identification of viral and lifestyle-associated risk factors has paved the way for the development of novel screening and early detection strategies. For HPV-associated HNCs, HPV DNA testing and p16 immunohistochemistry have emerged as valuable tools for risk stratification and treatment planning Additionally, the detection of EBV serological markers and molecular assays may aid in the early diagnosis of EBV-associated HNCs, particularly NPC [24]. By integrating information on viral status and lifestyle exposures, clinicians can develop personalized risk assessment models and tailor screening and prevention strategies accordingly.

Targeted Therapies:

The identification of viral oncogenic drivers in HNCs has opened new avenues for targeted therapeutic interventions. For HPV-associated HNCs, several therapeutic strategies are being explored, including therapeutic vaccines aimed at inducing antigen-specific T-cell responses against viral oncoproteins Additionally, immunotherapies, such as checkpoint inhibitors, have shown promising results in HPV-positive HNCs by enhancing anti-tumor immune responses. Efforts are also underway to develop small molecule inhibitors that target and degrade HPV oncoproteins, thereby disrupting their oncogenic functions.

In the case of EBV-associated HNCs, particularly NPC, epigenetic modifiers, such as histone deacetylase inhibitors and DNA methyltransferase inhibitors, have shown potential in reactivating viral lytic cycles and enhancing immunogenicity Adoptive T-cell therapies, involving the ex vivo expansion and reinfusion of EBV-specific cytotoxic T cells, have also demonstrated promising results in clinical trials [25].

Moreover, the development of novel antiviral agents targeting EBV-specific proteins or processes may offer additional therapeutic opportunities for EBV-associated HNCs.

Prevention Strategies:

Implementing effective prevention strategies is crucial in reducing the global burden of HNCs. For HPV-associated cancers, widespread implementation of HPV vaccination programs, particularly in adolescents and young adults, represents a promising approach for primary prevention However, challenges remain in improving vaccine uptake and addressing disparities in access to vaccination programs.

Tobacco and alcohol control policies, including taxation, advertising restrictions, and public education campaigns, play a vital role in reducing the burden of lifestyle associated HNCs. Additionally, dietary interventions and lifestyle modifications, such as promoting the consumption of fruits and vegetables, maintaining a healthy body weight, and regular physical activity, may contribute to the prevention of HNCs by mitigating the impact of lifestyle risk factors [26].

Public awareness and education campaigns are essential for disseminating information about the various risk factors associated with HNCs, emphasizing the importance of primary prevention and early detection. These efforts should be tailored to specific populations and cultural contexts to maximize their effectiveness.

Table 3: Potential Therapeutic Strategies for HPV-Associated and EBV-Associated Head and Neck Cancers

Therapeutic Strategy	HPV-Associated HNCs	EBV-Associated HNCs
Therapeutic vaccines	✓	✓
Immunotherapies (checkpoint inhibitors)	✓	✓
Targeted degradation of viral oncoproteins	✓	
Epigenetic modifiers		✓
Adoptive T-cell therapies		✓

Therapeutic Strategy	HPV-Associated HNCs	EBV-Associated HNCs
Antiviral agents		✓

Source: Compiled from various sources, including [27], [28], [29]

Future Perspectives and Challenges:

Despite the significant progress made in understanding the intricate interplay between oncogenic viruses and lifestyle factors in the etiology of HNCs, several challenges and future perspectives remain.

Elucidating the complex interplay between viral, lifestyle, and host factors:

Furthering our understanding of the intricate interactions between viral infections, lifestyle exposures, and host genetic and environmental factors is crucial. Integrated multi-omics approaches, combining genomic, epigenomic, transcriptomic, and proteomic data in, OSCC tumorigenesis may provide valuable insights into the molecular mechanisms underlying these interactions [30], [13], [14]. Additionally, longitudinal cohort studies tracking viral exposure, lifestyle factors, and disease outcomes over time can elucidate the temporal relationships and identify potential biomarkers for risk stratification and early detection. Developing in vitro and in vivo modeling systems that accurately recapitulate the interplay between viral oncogenesis and lifestyle factors will also be essential for mechanistic investigations and preclinical testing of potential interventions [31].

Overcoming therapeutic resistance and tumor heterogeneity:

Despite the promising potential of targeted therapies for virus associated HNCs, challenges remain in addressing therapeutic resistance and tumor heterogeneity. Combination therapies targeting multiple pathways and exploiting synthetic lethality may be necessary to overcome compensatory mechanisms and prevent the development of resistance. Additionally, personalized medicine approaches that incorporate detailed molecular profiling of individual tumors may guide the selection of optimal targeted therapies or combination regimens. Furthermore, elucidating the mechanisms underlying immune evasion by oncogenic viruses and developing strategies to counteract these processes will be crucial for enhancing the efficacy of immunotherapies.

Addressing health disparities and global implementation:

The global burden of HNCs is disproportionately distributed, with substantial disparities in incidence, mortality, and access to screening and prevention programs observed across different geographic regions and socioeconomic groups. Addressing these disparities is a critical challenge that requires concerted efforts from governments, healthcare organizations, and global health initiatives. Improving access to screening and prevention programs, such as HPV vaccination and tobacco control measures, is essential, particularly in low- and middle-income countries where the burden of HNCs is often highest. Additionally, culturally tailored interventions and health education campaigns that consider the unique sociocultural contexts and beliefs of diverse populations are crucial for effective implementation.

International collaborations and resource allocation:

Tackling the global challenge of HNCs demands international collaborations and coordinated efforts. Establishing global research networks and data-sharing platforms can facilitate the exchange of knowledge, resources, and best practices across different regions. Furthermore, strategic resource allocation and funding initiatives are essential to support research and development efforts, as well as the implementation of comprehensive prevention, screening, and treatment programs in regions with limited resources.

Conclusion:

In this comprehensive review, the intricate etiology of head and neck cancers (HNCs) is thoroughly examined, highlighting the complex interplay between oncogenic viruses, particularly human papillomavirus (HPV) and Epstein-Barr virus (EBV), and various lifestyle factors including tobacco and alcohol consumption, dietary habits, and levels of physical activity [32]. The multifaceted nature of HNC development underscores the imperative for a holistic approach that integrates molecular insights into viral oncogenesis with the influence of environmental exposures. Integration is pivotal in crafting targeted prevention, detection, and treatment strategies that account for the diversity of HNC subtypes and their underlying etiological mechanisms. By dissecting the molecular pathways through which viral infections and lifestyle factors contribute to HNC initiation and progression, researchers and clinicians can pinpoint novel therapeutic targets and biomarkers for early detection and personalized treatment modalities. Moreover, comprehending the synergistic or antagonistic effects of viral and lifestyle factors

holds promise for the development of preventive measures and interventions aimed at alleviating the global burden of HNCs [33].

By delving into the intricate web of factors contributing to the onset and progression of HNCs, this review underscores the imperative for a nuanced understanding that encompasses both viral oncogenesis and environmental influences. Such an approach is essential for devising comprehensive strategies that address the heterogeneity of HNC subtypes and their underlying etiological pathways. Through unraveling the molecular intricacies governing the interplay between viral infections and lifestyle factors, researchers and clinicians can identify promising avenues for therapeutic intervention and biomarker discovery, thereby enhancing early detection and personalized treatment strategies [34]. Furthermore, elucidating the complex dynamics between viral and lifestyle factors may pave the way for targeted preventive measures and interventions aimed at mitigating the global burden of HNCs. Ultimately, this holistic approach to understanding HNC etiology not only sheds light on the multifaceted nature of the disease but also offers hope for more effective management and control strategies that can significantly impact public health outcomes on a global scale.

The recognition of health disparities in head and neck cancer (HNC) incidence and outcomes emphasizes the critical need to address socio-economic and cultural factors that contribute to inequities in access to healthcare, screening programs, and treatment options [31]. These disparities underscore the necessity for tailored efforts aimed at promoting awareness of HNC risk factors, advocating for lifestyle modifications, and enhancing access to preventive services, particularly for populations facing limited healthcare resources or belonging to marginalized communities. Collaborative endeavors involving healthcare providers, public health agencies, policymakers, and community organizations are imperative for the implementation of comprehensive strategies that prioritize equity and inclusivity in HNC prevention and control endeavors.

Moreover, fostering international collaborations and facilitating the exchange of best practices play pivotal roles in disseminating evidence-based interventions and enhancing the efficacy of global initiatives targeting the reduction of the burden associated with HNCs [35]. By pooling resources, sharing knowledge, and aligning efforts across borders, the international community can address the multifaceted challenges posed by HNCs more effectively. Such collaborations not only enable the identification and implementation of culturally sensitive interventions but also

promote the development of sustainable solutions that can be adapted to diverse socio-cultural contexts. Thus, fostering collaboration at both local and global levels is paramount in advancing the collective goal of mitigating the impact of HNCs worldwide while ensuring equitable access to prevention and treatment services for all individuals, regardless of their background or geographical location [36].

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