GRADUATION PROJECT

Degree in Dentistry

Correlation between oral cancer and exercise

Madrid, academic year 2025/2026

Identification number: 185

RESUMEN

Introducción: El cáncer oral representa una carga sanitaria creciente, con una incidencia proyectada a aumentar un 60% para 2050. Aunque los principales factores de riesgo, tabaco, alcohol y nuez de betel (factores ABC), están bien establecidos, el papel del ejercicio físico como factor protector ha sido poco estudiado. Objetivos: Analizar la correlación entre la práctica regular de ejercicio físico y la incidencia de cáncer oral en adultos, desde una perspectiva epidemiológica y mecanística. Metodología: Se realizó una revisión narrativa siguiendo las directrices PRISMA. Se consultaron MEDLINE, Academic Search Ultimate y Dentistry & Oral Sciences Source. Tras el cribado de 595 registros, se incluyeron 32 artículos. Resultados: La inactividad física forma parte del perfil de alto riesgo para el cáncer oral y constituye un factor de riesgo independiente. El efecto protector del ejercicio se atenuó en algunos estudios tras el ajuste por factores ABC, pero persistió en otros análisis de gran tamaño. La intensidad, frecuencia, duración y tipo de ejercicio modulan la magnitud de la protección. El síndrome metabólico fue identificado como un factor de confusión frecuentemente omitido. A nivel biológico, el ejercicio regula la inflamación sistémica, mejora la función inmunitaria y activa vías anticarcinogénicas, aunque la evidencia mecanística procede principalmente de modelos animales. Conclusiones: El ejercicio físico regular parece reducir el riesgo de cáncer oral mediante mecanismos indirectos y directos, pero su efecto está moderado por variables de confusión, el estado metabólico y factores demográficos. Se necesitan estudios prospectivos con medidas estandarizadas de actividad física para confirmar estos hallazgos.

PALABRAS CLAVE: cáncer oral, ejercicio físico, actividad física, factores de riesgo, inflamación, síndrome metabólico, prevención primaria.

ABSTRACT

Introduction: Oral cancer represents a growing global health burden, with incidence projected to increase by 60% by 2050. While the primary risk factors, tobacco, alcohol, and betel nut (the ABC factors), are well established, the protective role of physical exercise remains underexplored. Objectives: To analyze the correlation between regular physical exercise and oral cancer incidence in adults, from both an epidemiological and mechanistic perspective. Methods: A narrative literature review was conducted following PRISMA guidelines. MEDLINE, Academic Search Ultimate, and Dentistry & Oral Sciences Source were searched. After screening 595 records, 32 articles were included. Results: Physical inactivity is part of the high-risk behavioral profile for oral cancer and constitutes an independent risk factor. The protective effect of exercise was attenuated in some studies after adjusting for ABC factors, but persisted in other large-scale analyses. Exercise intensity, frequency, duration, and type modulate the magnitude of protection. Metabolic syndrome was identified as a frequently overlooked confounder. Biologically, exercise regulates systemic inflammation, enhances immune function, and activates anti-carcinogenic pathways, though mechanistic evidence derives primarily from animal models. Conclusions: Regular physical exercise appears to reduce oral cancer risk through both indirect risk factor modification and direct biological mechanisms, but its effect is moderated by confounding variables, metabolic status, and demographic factors. Prospective studies with standardized physical activity measures are needed to confirm these findings.

KEYWORDS: oral cancer, physical exercise, physical activity, risk factors, inflammation, metabolic syndrome, primary prevention.

ÍNDICE

1.	**INTRODUCTION**	**5**
2.	**OBJETIVE**	**10**
3.	**MATERIAL AND METHODS**	**11**
4.	**RESULTS**	**14**
5.	**DISCUSION**	**14**
6.	**CONCLUSIONS**	**32**
7.	**SUSTAINABILITY**	**33**
8.	**REFERENCES**	**34**
9.	**ANNEXES**	**34**

1. INTRODUCTION

According to the GLOBOCAN 2022 projections, the incidence of oral cancer is growing steadily and is expected to rise by approximately 60 percent by 2050 (1). These concerning numbers can be attributed to an increasing exposure to risk factors and a late diagnosis due to the general population's lack of knowledge about the appearance and danger of the pathology. However, oral cancer is highly debilitating for the patients, affecting physiological functions, including difficulties in swallowing, speech, and eating, which significantly affect their quality of life and psychological well-being. Therefore, early detection and, above all, primary prevention of risk factors appear to be central in managing this rising global health concern.

1.1. Oral cancer: current clinical and epidemiological landscape

1.1.1. Definition and classification

Oral cancer is defined as "a malignancy that forms in tissues of the oral cavity or the oropharynx." Thus, in 2022, the WHO classified oral cancer into two categories: "oral cavity and mobile tongue tumors" and "oropharyngeal tumors." These pathologies are part of the broader classification of head and neck cancers, which encompasses malignancies of the larynx, pharynx, lips, mouth, nasal cavity, and salivary glands (2).

Several classification systems aim to categorize oral cancer into different groups. One common approach is to divide the oral cavity into seven subsites (the lip, tongue, floor of the mouth, buccal mucosa, hard palate, alveolar retromolar trigone, and soft palate), with tongue malignancies associated with the most unfavorable prognosis (3).

Otherwise, from a histological perspective, oral squamous cell carcinoma (OSCC) has the highest incidence, accounting for about 90% of all oral malignancies (3,4). Finally, a classification system grades cancer into stages by measuring tumor size and spread: the TNM system (Tumor size and local spread (T), regional lymph Node involvement (N), and Metastasis to distant sites (M)) (5-7).

1.1.2. Epidemiology and survival rate

According to the 2022 report from the Global Cancer Observatory (GCO), oral cavity and lip cancers rank as the 16th most common cancer worldwide, with 389,846 new cases annually. Based on SEER 2015-2021 statistical estimates, the relative survival rate for oral and pharyngeal cancers is 69.5%. Although the prognosis appears favorable, disparities exist

among populations, with mortality highly concentrated in Asia (66.3%) (8). Regarding the 5-year survival rate, staging is a key predictor of successful treatment, with prognosis worsening as the stage increases (20% for stage IV compared to an 80% survival rate for those diagnosed at stage I) (4,7). However, 50% of oral cancers are diagnosed at an advanced stage (4,7). Despite the recent advances in treatment, such as targeted therapy or immunotherapy, the combination of surgery with radiotherapy and chemotherapy remains the first-line treatment (9). Nevertheless, a late diagnosis at an advanced stage presents significant physiological impairments for patients, underscoring the importance of early detection and primary prevention to improve patient outcomes.

1.2. Risk factors

Oral cancer is a multifactorial disease, with its incidence arising mainly from exposure to several modifiable risk factors. Across studies, the most common are the group level 1 carcinogens, including tobacco (smoking or smokeless forms), excessive alcohol consumption, and areca nut with betel quid. Cofactors include human papillomavirus (HPV) infection, as well as age, sex, socioeconomic status, and genetics (10).

1.2.1. Alcohol and tobacco

Alcohol consumption and tobacco have long been recognized as the main etiological factors for the development of oral cancer (11). The use of both acts synergistically in significantly increasing the risk of oral cancer (11). Indeed, both present carcinogenic properties: tobacco smoke contains several chemicals such as polycyclic aromatic hydrocarbons and nitrosamines, which can provoke genetic mutations; alcohol acts by enhancing the penetration of carcinogens into the mucosa, causing cellular damage. Moreover, the alcohol metabolite acetaldehyde has been identified recently as a tumor promoter (12).

1.2.2. Smokeless tobacco and betel quid

Tobacco accounts for 85% of all oral cancers, with tobacco use being significantly widespread among populations: about 40% of all adult men and 30% of adults consume tobacco in some form. Notably, smokeless tobacco is used in 121 countries, particularly in India, other Asian countries, and the Western Pacific islands (13). The term encompasses several substances such as naswar, snuff, gutkha, which are a variety of “tobacco products that are not consumed by combustion but are chewed, spitted, dipped, or snuffed”. Their carcinogenic effect should be

underscored since they contain more than 30 carcinogens, making their consumption a key indicator to define individuals at high-risk of developing oral cancer (14).
Betel quid typically consists of a mixture of areca nut (also called betel nut), slaked lime, and flavoring ingredients, which are packed in a betel leaf. It constitutes an essential risk factor for the development of oral premalignant lesions, with 13 times more risk for oral cancer development when it is associated with tobacco chewing (14). This is even more concerning since smokeless tobacco consumption has increased by almost 50% in low and middle-income countries (15).

1.2.3. Socioeconomic status

Notable differences in oral cancer incidence are observed between low- and high-income countries, with survival rates in developing countries substantially lower (16). Other differences have been observed concerning the habits of consumption: in high-income regions, smoking, alcohol intake, and infection by HPV are identified as the principal risk factors for oral cancer, whereas in low-income regions, smoking, betel nut chewing, and insufficient oral hygiene remain the primary determinants (17). Notably, among high-income countries such as the United States, disparities have also been associated with the socioeconomic status since patients of black race, low income, low education, unmarried status, public insurance, and no insurance often have increased OSCC incidence (18). Consequently, along with tobacco, alcohol and betel quid consumption, socioeconomic status is a key cofactor for oral cancer development, which can be explained by the limited access to healthcare and education on the pathology.

1.2.4. Sex and age

An incidence difference between men and women has been observed, with a higher burden in men, suggesting greater exposure to risk factors. According to the WHO, in developing countries, it is the sixth most common cancer, while in females, it is the tenth (19). Concerning the age determinant, between 1990 and 2021, the highest mortality rate was observed in the 65-69 age group (20). However, lip and oral cavity cancer cases have risen among younger individuals, particularly among individuals under 44 years old. The increase can be explained by the role of HPV infection, particularly HPV-16, which appears to be more predominant among younger patients without traditional risk factors. HPV 16-18 is associated with both benign and malignant lesions; diagnosis is made by detecting condylomas, focal epithelial hyperplasia, squamous cell papilloma, and malignant oral lesions. However, only a small

proportion develops malignant neoplasms, suggesting that carcinogenesis requires concomitant risk factors (21).

1.2.5. Genetics

Family history constitutes a risk factor for oral cancer, since genetic alterations have been observed among patients with head and neck cancers. Indeed, studies have shown that the ability to repair DNA damage induced by carcinogens is impaired in these patients, resulting in increased susceptibility to chromosome damage (22). Moreover, other genetic alterations are observed such as the genes p16 and p53. The latter serves several functions in the genome, including cell cycle progression (both the G1/S and G2/M checkpoints), cellular differentiation, DNA repair, and induction of apoptosis. In OSCC, the p53 gene appears to be inactivated by several mechanisms, including genetic alterations such as point mutations and deletions, as well as functional inactivation through interactions with cellular or viral proteins (23).

1.2.6. Diet

The connection between diet and oral cancer is multifaceted, with evidence demonstrating that dietary habits may significantly reduce the risk through both pro-inflammatory and protective mechanisms. Although tobacco and alcohol are the primary etiological factors, diet has been recognized as a significant modifiable component in oral carcinogenesis (24). High consumption of red meat, fried foods, and refined carbohydrates such as white bread is linked to systemic inflammation and a microenvironment that favors tumor development (24,25). Indeed, this is demonstrated by evidence that a high Dietary Inflammatory Index (DII) score is associated with elevated inflammatory biomarkers such as C-reactive protein (CRP) and interleukins (24). Compounds such as the saturated fats present in full-cream milk and the carcinogens generated in processed meats exacerbate DNA damage and elevate the risk of oral cancer (25,26). Conversely, a substantial body of evidence underscores the protective role of dietary components. In fact, a high intake of fruits and vegetables is consistently associated with a dose-dependent reduction in the risk of oral cancer due to the antioxidant, anti-inflammatory, and anti-proliferative properties of phytochemicals such as polyphenols, carotenoids, and vitamins (24,27). Certain foods, such as green salads, are associated with a decreased risk, increased survival, and diminished levels of the prognostic salivary biomarker soluble CD44 in patients (28).

Mendelian randomization analysis enhances causal inference, indicating that the consumption of whole grains, oats, and oily fish (rich in omega-3 fatty acids) is protective, whereas alcohol consumption elevates risk, which is diminished when alcohol is ingested with meals (29).

Holistic dietary patterns, especially the Mediterranean Diet (MD), which focuses on plant-based foods, olive oil, and fish, demonstrate a significant adverse correlation to the risk of head and neck cancer. Meta-analyses indicate that individuals who follow the diet closely have a 44% lower risk of developing oral cancer (30). Bioactive compounds in foods such as green tea (catechins), turmeric (curcumin), and berries (anthocyanins) exhibit chemopreventive effects by modulating epigenetic pathways, inhibiting cellular proliferation, and inducing apoptosis (31,32). However, current studies face limitations, including reliance on observational studies with recall bias, insufficient specificity for oral cancer within head and neck classifications, and variability in individual responses influenced by factors such as the oral microbiome (24,27). In conclusion, the equilibrium between pro-inflammatory and protective dietary components significantly influences the etiology and prognosis of oral cancer, highlighting the importance of nutritional strategies for public health prevention.

1.3. Physical exercise as a potential tool for primary prevention

Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure.” In daily life, it can be classified into occupational, sports, conditioning, household, or other activities. Exercise is defined as a “subset of physical activity that is planned, structured, and repetitive and has as a final or intermediate objective the improvement or maintenance of physical fitness” (33).

Physical activity and exercise have been shown to prevent several cancers, including breast, liver, lung, and colorectal cancers (34). However, there is limited evidence for head and neck cancer and particularly oral cancer (35,36). Despite the limited evidence, it can be supposed that similar mechanisms are applicable for oral cancer, which include processes involving hormonal balance, weight reduction, adiposity, inflammation, immunity, sunlight exposure and vitamin D levels and insulin resistance (34,37). Since the incidence of oral cancer is mainly associated with lifestyle factors, studying the correlation between the practice of exercise to prevent oral cancer incidence is particularly relevant. Indeed, adopting a proactive strategy shifts the standard approach of managing only known, established risk factors to practicing protective behaviors that may counteract carcinogenesis (38).

2. OBJECTIVE

Question: In the general adult population, does engaging in regular physical exercise, compared with low or no physical activity, reduce the incidence of oral cancer?

Hypothesis: The practice of exercise reduces the risk of oral cancer.

Objective: To analyze the potential correlation between regular physical exercise and the incidence of oral cancer.

1) Epidemiological Analysis: To assess the association between physical exercise and reduced oral cancer risk, examining both direct effects and indirect pathways through modification of key risk factors.

2) Mechanistic Analysis: To identify the biological mechanisms through which exercise may suppress oral cancer development, focusing on pathways such as inflammation regulation and immune function.

3. MATERIAL AND METHODS

Eligibility Criteria

Inclusion Criteria

Studies were included if they: (1) targeted individuals over 16 with or at risk of head and neck cancer (including oral cavity and oropharynx); (2) examined physical activity, exercise, or sedentary behavior as exposures or interventions; (3) reported outcomes on cancer incidence, mortality, survival, recurrence, or related biomarkers; and (4) used observational, interventional, or mechanistic studies.

Exclusion Criteria

Studies were excluded if they: (1) only addressed other cancer types without separate analysis for HNC; (2) did not consider physical activity; (3) were animal or in vitro studies lacking direct human clinical relevance; (4) consisted of editorials, commentaries, or conference abstracts without full data; or (5) were not published in English or French or Spanish; (6) were published more than 20 years ago.

Information Sources and Search Strategy

A literature search was performed using MEDLINE (via EBSCO), Academic Search Ultimate, and Dentistry & Oral Sciences Source, targeting terms for physical activity and head and neck cancer.

The main research was: (exercise or physical fitness or physical activity or recreational activity or moderate intensity exercise or aerobic exercise or physical inactivity or sedentary or athlete or physical behavior) AND (oral cancer or oral squamous cell carcinoma or head and neck cancers or head neck cell carcinoma or head and neck neoplasms or pan cancer) AND ("risk" OR "incidence" OR "prevention" OR "mortality" or occurrence or frequency or prevalence or epidemiology or risk factors or survival or prognosis and odds ratio or pathophysiology or lifestyle) NOT ((radiotherapy or radiation therapy or cancer radiotherapy or chemotherapy or rehabilitation or swallowing or trismus or quality of life))

Study Selection Process

The study selection process adhered to PRISMA guidelines.

- Identification: 850 records were found (MEDLINE: 489; Academic Search Ultimate: 260; Dentistry & Oral Sciences Source: 101). After removing duplicates, 595 unique records remained.
- Screening: Titles and abstracts were reviewed, excluding 562 as irrelevant.
- Eligibility: Of 33 full-text articles assessed, one was excluded for having the wrong patient population.
- Inclusion: 32 articles (14 MEDLINE, 17 Academic Search Ultimate, 1 Dentistry & Oral Sciences Source) were included in the final review.

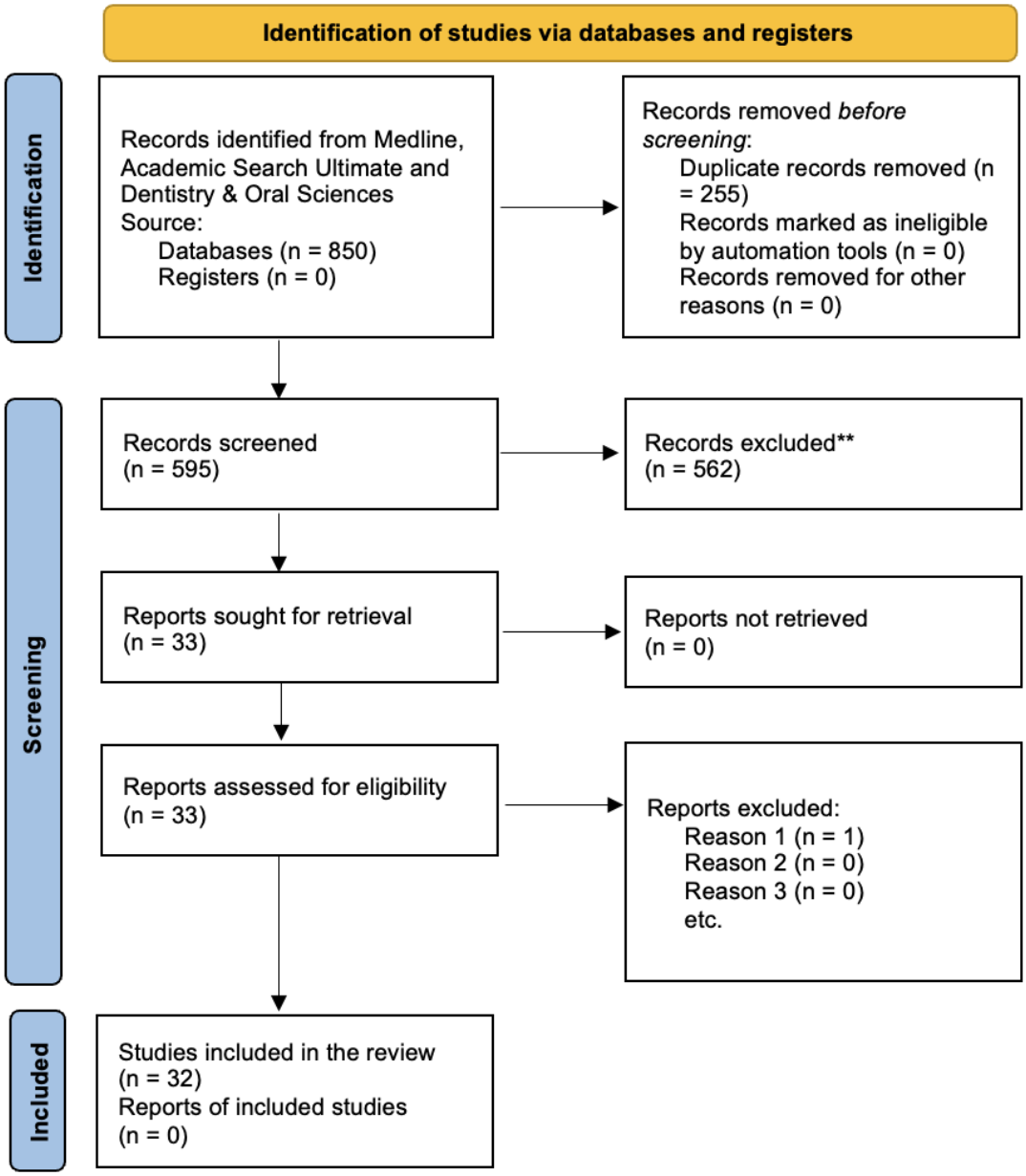


Figure 1: Flowchart PRISMA

4. RESULTS

4.1. Epidemiology

Study (Year)	Design	Population	Exposure	Key Finding for HNC/Oral Cancer
Moore et al. (2016)	Pooled Cohorts	1.44 million (U.S./Europe)	High vs. low leisure-time PA (90th vs. 10th percentile)	HR = 0.85 (0.78-0.93) for HNC
Lavery et al. (2024)	Prospective cohort (PLCO)	60,045 (U.S.)	Vigorous exercise ≥2 h/wk vs. 0-1 h/wk	HR = 0.74 (0.59-0.94) for HNC
Ballin et al. (2025)	Cohort + sibling	1.12 million men (Sweden)	High vs. low cardiorespiratory fitness (quartiles) at age 18	HR = 0.85 (0.78-0.93) for HNC (cohort)
Leitzmann et al. (2008)	Prospective cohort (NIH-AARP)	487,732 (U.S.)	Vigorous activity ≥5x/wk vs. <1x/month	RR = 0.89 (0.74-1.06) (null after smoking adjustment)
Hashibe et al. (2013)	Prospective cohort (PLCO)	101,182 (U.S.)	Vigorous activity ≥3 h/wk vs. <1 h/wk	RR = 0.58 (0.35-0.96) for HNC
Kim et al. (2019)	Prospective cohort (NHIS-HEALS)	257,854 (South Korea)	Sweat-inducing exercise 1-2x/wk vs. none	HR = 0.76 (0.63-0.93) for HNC
Nicolotti et al. (2011)	Pooled case-control (INHANCE)	2,289 cases, 5,580 controls	Moderate recreational PA vs. none/low	OR = 0.78 (0.66-0.91) for HNC Oral cavity: OR = 0.74 (0.56-0.97) Pharynx: OR = 0.67 (0.53-0.85) Larynx (high PA): OR = 1.73 (1.04-2.88)

Lin et al. (2017)	Case-control	623 cases, 731 controls (Taiwan)	Regular recreational PA (≥3 days/wk)	OR = 0.97 (0.73-1.28) (null after full adjustment)
Platek et al. (2017)	Case-control	246 cases, 504 controls (U.S.)	Lifetime physical inactivity vs. any activity	OR = 2.73 (1.87-3.99) for HNSCC
Tabatabaei-Zadeh et al. (2024)	Case-control	100 cases, 200 controls (Iran)	High vs. low lifetime time spent in PA	OR = 0.44 (0.24-0.68) for OSCC
Shabir et al. (2025)	Case-control	277 cases, 411 controls (Pakistan)	Physical activity (yes vs. no)	AOR = 0.41 (0.23-0.75) for OC

4.2. FACTORS (Behavioral, metabolic and socioeconomic)

Clustering of risk factors and interactions with physical activity

Study (Year)	Design	Population	Risk Factor	Key Finding
Guo et al. (2013)	Cross-sectional	6,203 adults (Taiwan)	Behavioral clustering (ABC: Alcohol, Betel, Cigarettes)	Only 14.5% of betel nut and cigarette users exercised regularly. ABC users had poorer diet and oral hygiene.
Leitzmann et al. (2008)	Prospective cohort	487,732 adults (U.S.)	Smoking intensity	Age-sex adjusted RR for exercise and HNC = 0.62. After adjusting for detailed smoking intensity, RR attenuated to 0.89 (non-significant).
Lin et al. (2017)	Case-control	623 cases, 731 controls (Taiwan)	Betel quid, smoking, alcohol, diet	Minimally adjusted OR for exercise = 0.65. After full adjustment for betel quid, smoking, alcohol, and diet, OR = 0.97 (null).
Feng et al. (2020)	Pooled cohorts	54,686 adults (UK)	Alcohol × PA interaction	Hazardous/harmful drinkers who were inactive had higher alcohol-related cancer mortality (HR = 1.47-1.64). This excess risk was eliminated in those who were active (>7.5 MET-h/wk).
Lo et al. (2016)	Prospective cohort	419,378 adults (Taiwan)	Betel quid × PA interaction	Inactive chewers lost 6.3 years of life expectancy vs. non-chewers. Active chewers gained back 2.5 years and had a 19% reduction in all-cause mortality.
Chang et al. (2015)	Cross-sectional	5,161 adults (Taiwan)	Metabolic syndrome (MetS)	MetS associated with 39% higher risk of pre-oral cancerous lesions (OR = 1.39), independent of betel nut and smoking. Irregular physical activity also associated with POC lesions (OR = 1.41).

Kim et al. (2023)	Prospective cohort	9.6 million adults (South Korea)	Metabolic syndrome (MetS)	MetS associated with increased risk of oral cavity cancer (HR = 1.12) and laryngeal cancer (HR = 1.18). Association persisted in never-smokers/drinkers (HR = 1.09).
Seo et al. (2020)	Prospective cohort	9.7 million adults (South Korea)	Hypertension	Hypertension (especially untreated) associated with oral cancer (HR = 1.15), laryngeal cancer (HR = 1.25), and esophageal cancer (HR = 1.47), independent of age, smoking, and alcohol.
Lin et al. (2025)	Prospective cohort	289,557 adults (UK Biobank)	MetS × Lifestyle interaction	Without MetS: Favorable lifestyle (including PA) strongly protective for lip/oral cavity/pharynx cancers in men (HR = 0.46). With MetS: Protective association completely neutralized (non-significant).
Tran et al. (2023)	Prospective cohort	8.35 million adults (South Korea)	Socioeconomic status (SES)	Lower income groups had higher odds of multiple unhealthy behaviors (smoking, heavy drinking, physical inactivity). Poorest + unhealthiest men had 2.1-fold higher risk of cancer-related death.
Morais et al. (2020)	Cross-sectional	90,846 adults (Brazil)	Socioeconomic status (SES)	High-risk group for oral cancer: low education, rural residence, no regular dental check-ups, no regular physical exercise.
Shabir et al. (2025)	Case-control	277 cases, 411 controls (Pakistan)	Socioeconomic status (SES)	Low SES and limited education were key drivers of oral cancer. Physical activity was protective (AOR = 0.41), but its distribution was skewed by SES.

4.3. BIOLOGICAL MECHANISMS

Mechanistic studies relevant to oral/head and neck cancer

Study (Year)	Design	Subject / Model	Mechanism Investigated	Key Finding
Yoshimura et al. (2024)	In vivo + in vitro	Mouse xenograft model (HSC-3-M3 tongue cancer cells); human HNSCC cell lines	Myokine (Oncostatin M - OSM)	Exercise increased blood OSM levels in mice. OSM directly inhibited HNSCC cell proliferation in a concentration-dependent manner by increasing p21/p27 expression, causing G0/G1 cell cycle arrest.
Caballero-Borrego et al. (2024)	Clinical cohort	64 patients with R/M SCCHN (Spain)	Physical activity + immune biomarker (dNLR)	Walking ≥1 h/day was independently associated with better PFS (HR = 2.45) and OS (HR = 3.43). Low baseline dNLR (<3.5) was independently associated with better OS (HR = 2.19).
Duffy et al. (2013)	Clinical cross-sectional	407 newly diagnosed HNSCC patients (U.S.)	Health behaviors and IL-6 levels	Smoking (current/former) and decreased sleep were independent predictors of higher IL-6 levels. IL-6 is a known predictor of recurrence and survival in HNSCC.
Irmawati et al. (2018)	Animal experimental	18 mice (Mus musculus) induced with benzopyrene	Apoptosis (Bax/Bcl-2 ratio)	Moderate exercise significantly increased the Bax/Bcl-2 ratio in oral squamous epithelial cells (p = 0.000), promoting apoptosis of damaged cells.

Irmawati et al. (2018)	Animal experimental	18 mice (Mus musculus) induced with benzopyrene	Apoptosis (Caspase-3 expression)	Moderate exercise significantly increased Caspase-3 expression (p = 0.000), the key executioner caspase in apoptosis, promoting elimination of transformed cells.
Irmawati et al. (2020)	Animal experimental	18 mice (Mus musculus) induced with benzopyrene	Tumor suppressor (p53 mutant expression)	Moderate exercise significantly decreased p53 mutant expression (p = 0.000), suggesting preservation of wild-type p53 function and genomic integrity.
Bai et al. (2024)	Prospective cohort + mediation analysis	96,687 UK Biobank participants (with accelerometer data)	Circadian PA patterns + inflammation (SII/SIRI)	Four PA trajectories identified. Vigorous and double-peak patterns were associated with lower risk of oral & pharynx cancer (HR = 0.51). The protective effect was partially mediated by lower inflammation levels (SII/SIRI).
Luo et al. (2022)	Pan-cancer bioinformatics + in vitro	TCGA, GTEx, HPA databases; breast cancer cell lines	Myokine (IL-15)	Exercise-induced IL-15 is downregulated in 12 cancer types. High IL-15 expression predicts better survival in several cancers. IL-15 correlates with immune cell infiltration and ferroptosis/cuproptosis-related genes (ACSL4, LIPT1).
Luo et al. (2024)	Animal + in vitro + bioinformatics	Mouse breast cancer model (voluntary running); TCGA pan-cancer analysis	Exercise-augmented gene (THSD7B)	Exercise upregulated THSD7B expression in tumors. THSD7B overexpression suppressed breast cancer cell proliferation, migration, and invasion. THSD7B expression correlates with better prognosis in multiple cancers.

Luo et al. (2024)	Animal + in vitro + bioinformatics	Mouse breast cancer model (voluntary running); TCGA pan-cancer analysis	Exercise-downregulated gene (CD300E)	Exercise downregulated CD300E expression in tumors. CD300E overexpression promoted cancer cell proliferation and migration. High CD300E expression correlates with poorer prognosis and immunosuppressive microenvironment.
Shi et al. (2024)	Bioinformatics + in vitro	TCGA-HNSCC data; HNSCC cell lines	Exercise-related genes + PIGF (Placental Growth Factor)	Identified exercise-related prognostic genes in HNSCC. PIGF was upregulated in advanced HNSCC and associated with poor prognosis. PIGF knockdown significantly reduced HNSCC cell proliferation and colony formation.
Irmawati et al. (2022)	Narrative review	Literature review	Exercise as a method to reduce oral cancer risk	Summarizes mechanisms: moderate exercise increases Bax/Bcl-2 ratio, Caspase-3 expression, and reduces p53 mutant expression, promoting apoptosis of carcinogen-damaged cells.

5. DISCUSSION

5.1. An apparent protective association in line with the pan-cancer epidemiological landscape

5.1.1. Physical inactivity as a cluster of risk factors in the oral cancer patient profile

Oral cancer, one of the leading causes of death worldwide, has been the subject of several long-standing epidemiological studies aimed at pinpointing its causes and risk factors. Ultimately, epidemiological evidence shows that the risk factors are not isolated or sporadic but rather a cluster of unhealthy behaviors that synergistically contribute to carcinogenesis (39-41). Among them, the most important remain the “ABC” factors, standing for Alcohol, Betelnut, and Cigarettes (39,41,42). Nonetheless, recent studies have identified additional risk factors, progressively clarifying the high-risk oral cancer patient profile (39,40,41).
Indeed, epidemiological studies have revealed a distinct demographic pattern: high-risk individuals are more likely to be male, middle-aged, less educated, and of low socioeconomic status (39,40,42).
Regarding lifestyle factors, in addition to the high rate of ABC consumption, poor diet and inadequate oral hygiene were identified as confounding risk factors (39,40,41). Among these, physical inactivity has received particular attention as both a central component of the high-risk behavior cluster and a distinct predictor of oral cancer. In a study examining the association between lifetime physical inactivity and head and neck squamous cell carcinoma (HNSCC), the results indicate a 2.73-fold higher risk of HNSCC (43). The study controlled for confounding risk factors such as smoking status and alcohol consumption and found a positive association between physical inactivity and HNSCC (43). This association remained consistent across subgroups, including BMI and smoking status, supporting the hypothesis that physical inactivity is an independent, modifiable risk factor for HNSCC (43). Thus, physical inactivity remains a significant risk factor even among never smokers (OR = 2.71, 95% CI: 1.21-6.05), suggesting that inactivity may have a greater impact than initially suggested (43).

These findings were supported by a study on the prevalence of inactivity among the Brazilian population, in which 56.6% did not engage in physical activity over the past three months (44). These individuals were more likely to belong to the high-risk group for oral cancer development, with an odds ratio of 1.7 (44). Beyond identifying physical inactivity as an independent risk factor, this research underscores the importance of education and diet as concomitant modifiable variables, implying that exercise can indirectly serve as a protective factor and that access to healthcare services and education can help address the burden of oral cancer in this population (44).

In several studies, physical inactivity has often been associated with ABC factors and poor health behaviors, providing statistical evidence of an association between physical activity and ABC consumption, indicating that those who are less physically active are more likely to engage in these habits (39,40). Indeed, ABC consumers were more likely to have poor health-promoting behaviors, including inadequate exercise, poor diet, and poor oral hygiene (39). This study also identified several confounders associated with ABC consumption, including demographic factors such as sex, age, education level, and socioeconomic status (39). Indeed, middle-aged males with secondary education were significantly more likely to engage in ABC consumption and to exercise less (14.5%) than the general population (39). Therefore, the paper aligns with studies that acknowledge physical inactivity as a modifiable risk factor.

In another pooled analysis, 73.9% of cases were in the none/low recreational physical activity category, which is correlated with oral cancer, and the preventable fraction for oral cancer with moderate recreational physical activity was estimated at 26% (45). Building on evidence that physical inactivity is a risk factor, epidemiological studies have explored whether physical exercise might protect against oral cancer, although results are contradictory and need thorough analysis (18,19,20,41-3,45-48).

5.1.2. Exercise as a risk-buffering exposure: conditions for protection (duration, intensity, timing)

In the ongoing effort to identify risk factors, particularly in demographic and lifestyle areas, a study conducted on Pakistani patients with oral cancer found similar results, highlighting inactivity as a significant risk factor (42). The study underscores the need for targeted prevention strategies to lessen the burden of oral cancer, observing that physical activity seems to offer protective benefits against oral cancer, with an adjusted odds ratio of 0.41 (95% CI: 0.23-0.75; p = 0.004) (42). These results were confirmed by other epidemiological studies, but the latter emphasize that the protective effect, in order to be effective, seems to be subject to specific conditions of practice, especially the parameters of duration, intensity, frequency, and timing patterns, which play crucial roles in determining cancer risk reduction (18,19,21,22,24,43,45-49).

5.1.2.1. Intensity

Other studies focus exclusively on a single intensity parameter, such as those that analyze only the impact of vigorous exercise (46), those that study only moderate-to-vigorous exercise (47), or the indicator of “sweat-inducing” physical activity (48).

5.1.2.2. Frequency

Kim et al. focused on measuring the impact of physical activity frequency on several systemic conditions, including head and neck cancer (48). To assess the impact, they specifically asked how often the participant engages in sweat-inducing exercise (none, 1-2 times/week, 3-4 times/week, 5-6 times/week, or almost every day) (48). The authors observed that moderate levels of exercise (3-4 or 5-6 times/week) were consistently associated with a lower overall risk of disease, whereas for head and neck cancer specifically, a J-shaped association was observed, with exercising 1-2 times a week as the optimal frequency (48). This shows that even the frequency parameter can be a modifiable variable that affects the magnitude of the protective effect of exercise against head and neck cancer (48).

5.1.2.3. Type of exercise: from recreational to "trajectory pattern"

Studies have examined different types of exercise. Indeed, while early studies focused on recreational and leisure-time activity (19,41,45,47) or simple movement such as occupational and household physical activity (49), more recent research has adopted complex paradigms. Bai et al., building on the postulate that physical activity is associated with cancer incidence, based their study on a physical activity "trajectory model" that included information on both exercise intensity and circadian rhythm (55). They identified four distinct patterns: persistent low, single-peak, double-peak, and vigorous (55). They concluded that the vigorous physical activity pattern reduced the risk of oral and pharyngeal cancer, with a hazard ratio of 0.51 (95% CI: 0.26-0.98), and that this effect was mediated through regulation of inflammation (55).

5.1.2.4. Duration and lifetime exposure

Whereas intensity and frequency were commonly studied parameters, lifetime exposure was less examined, with only a few studies addressing this aspect of physical exercise. Thus, Tabatabaie-Zadeh et al. focused on lifetime physical activity, showing a statistically significant difference in total lifetime physical activity time ($p < 0.001$), with an adjusted OR for total lifetime physical activity of 0.367 (95% CI: 0.207-0.650) for above-median vs. below-median time spent (49). The existence of protective conditions raises the question of the opposite effect, with parameters that modify the apparent protective impact of physical exercise on oral cancer incidence (18,19,41-43,45-49).

5.2. The ABC Adjustment Debate: Independent Versus Attenuated Protection

Across epidemiological studies, although a protective effect was observed, adjusting for ABC confounding significantly altered the results, shifting the effect from clear protection to attenuation or even absence (18,19,21,24,41,50). The question then raised was the role of exercise: whether it is merely a marker of healthy lifestyle habits or elicits a true biological effect by modulating mechanistic processes (18,19,24,41,45,47,50).

5.2.1. Attenuated protective findings: exercise as a proxy for a healthy lifestyle?

Two studies by Lin et al. (41) and Leitzmann et al. (50) illustrate the complex relationship between confounding adjustment and the observed protective effect of physical activity on head and neck cancer. Lin et al. reported a strong protective effect as the primary outcome, observing an inverse association between exercise and head and neck cancer after adjusting for sex, age, and education (OR = 0.65, 95% CI: 0.51-0.82) (41). However, when controlling for ABC consumption and fruit and vegetable intake, the association became null, with an attenuated OR of 0.97 (95% CI: 0.73-1.28) (41).

These findings were similar to those observed by Leitzmann et al., in which the initial negative correlation was attenuated and became non-significant, with an RR = 0.89 (95% CI: 0.74-1.06; p for trend = 0.272) after adjustment for several risk factors, particularly smoking (50).

Therefore, both concluded that physical activity was unlikely to play a significant role in preventing head and neck cancer (41,50). Lin specifically argued that the primary focus of head and neck cancer prevention should be on lifestyle changes, such as smoking and alcohol cessation and a healthy diet, rather than on physical activity (41). Consequently, both attribute the protective effect to clustering of healthy lifestyle factors, rather than to a direct biological mechanism (18,19,41,50).

These inferences were indirectly supported by studies focused on oral cancer risk factors. Thus, Guo et al. showed that healthy behaviors tend to cluster, mirroring the pattern of co-occurrence of unhealthy habits in high-risk profiles (39). However, the attenuation observed was not replicated across studies, with several showing a persistent protective effect independent of ABC confounders (18,19,21-23,25,47,48,51).

However, these studies are limited by their dependence on self-reported physical activity measures, which may introduce recall bias and measurement error. Additionally, the cross-sectional and case-control methodologies are unable to determine temporal relationships between exercise routines and the development of cancer, consequently limiting causal inference.

5.2.2. Persistent protective findings: exercise as a true biological process?

Although adjusting for ABC confounding can significantly alter the association between cancer incidence and exercise, multiple studies demonstrate that a protective effect persists (18,19,21-23,25,47,48,51). This suggests an underlying biological mechanism, alongside the postulate that healthy individuals tend to engage in healthy behaviors. Moore et al., in one of the largest pooled analyses on cancer incidence involving 1.44 million participants, observed that leisure-time physical activity was associated with lower risks of 13 cancers, including head and neck cancer (HR 0.85; 95% CI: 0.78-0.93) (47). The authors included several parameters to identify the epidemiological profile and habits of high-risk patients: age, sex, smoking status, alcohol consumption, education, and race/ethnicity, thereby controlling for the two main risk factors, smoking and alcohol consumption (47).

Similarly, Hashibe et al. observed a persistent effect after adjusting for tobacco and alcohol (OR = 0.58, 95% CI: 0.35-0.96), underscoring the high prevalence of head and neck cancer cases attributed to tobacco and/or alcohol (51).

Finally, in Ballin et al. (2025), the authors conducted a Sibling-controlled cohort study and examined the cardiorespiratory fitness of young men, focusing on the relationship between cardiorespiratory fitness (influenced by physical activity) and cancer risk. High adolescent cardiorespiratory fitness is associated with lower overall cancer mortality (HR: 0.71, 95% CI: 0.67-0.76; $P < 0.001$), *with head and neck cancers among the protected sites*. These findings provide distinct information regarding the biological process hypotheses, since, unlike other epidemiological studies that could measure traditional confounders, this study controlled for unmeasured genetic factors by comparing brothers within the same family. Therefore, by isolating these unmeasured genetic and familial factors, Ballin et al.'s results support the hypothesis of genuine biological protection rather than a simple proxy for a healthy lifestyle.

Despite these important findings, some methodological limitations should be acknowledged. Since these studies are observational, they cannot definitively establish cause-and-effect relationships, and there may still be unmeasured lifestyle factors that confound the results.

Additionally, differences in how physical activity was measured across studies make it difficult to directly compare their effect sizes.

5.3. The Metabolic Syndrome Bridge

Metabolic syndrome (MetS), formerly called insulin resistance syndrome or Syndrome X, is now recognized as a cluster of related cardiovascular and diabetes risk factors, although specific diagnostic criteria may vary among organizations. Despite these differences, all definitions include the following core components: abdominal obesity, insulin resistance or hyperglycemia, high blood pressure, low HDL cholesterol, and high triglycerides (52,53). Consequently, MetS involves multiple metabolic disturbances and is linked to higher risks of type 2 diabetes, cardiovascular diseases, and overall mortality (52,53). Notably, cancers are among the conditions most frequently associated with MetS, and several studies have explored the link between MetS and oral cancer (40,52,53).

5.3.1. MetS as an illustration of inflammation-related confounding

MetS is widely acknowledged as a risk factor for several serious diseases and has been increasingly studied in oral oncology (40,52,53). In a 10-year follow-up study, Kim et al. observed a higher risk of head and neck cancer in patients with MetS, reporting a 1.06-fold increase (95% CI: 1.01-1.10) and an HR of 1.12 for oral cavity cancer (95% CI: 1.03-1.23) (52). Subgroup analysis indicates that the association between MetS and head and neck cancer risk remains consistent regardless of gender and smoking status (52).

Seo et al. found similar findings, focusing on the component of hypertension, showing that it is associated with an increased risk of oral cancer (HR 1.11), and this association remained after adjustment for several confounders, including age, gender, smoking status, alcohol intake, exercise, BMI, and diabetes (33). This shows that even individual components of MetS are associated with an increased risk of oral cancer (33,52).

A study by Chang-Cheng Chang et al. examined pre-oral cancerous lesions rather than oral cancer and found similar results, reporting a high prevalence of metabolic syndrome and pre-oral cancerous lesions, with 40% and 7.3% of participants affected, respectively (40). The study also found that participants with pre-oral cancerous lesions were more likely to engage in irregular physical activity (40). The authors conclude that reducing metabolic syndrome and inflammation-induced diseases is important for preventing oral cancer, highlighting the

mechanistic processes by which obesity and insulin resistance affect lipid signaling and inflammatory cytokine levels, thereby contributing to carcinogenesis (40).
This metabolic inflammatory process is further described by Hong et al., where results show that a healthy lifestyle, including regular physical exercise, is insufficient for oral cancer risk reduction in men with MetS (53).
The importance of MetS as a significant confounder sheds new light on the results from studies (Lin 2017, Leitzmann 2008) that observed an attenuated protective effect after adjusting for ABC confounding.

5.3.2. MetS as a revealer of methodological limitations and forgotten confounders

The case of MetS, observed as a distinct risk factor, revealed a major blind spot in epidemiological studies. In fact, multiple studies (Moore 2016, Hashibe 2012, Lin 2017, Leitzmann 2008) fail to account for MetS as a significant confounder, potentially biasing their findings. This omission also revealed other blind spots that could have been repeated, such as the omission of the socioeconomic environment. Indeed, as revealed in Chang et al., participants with pre-oral cancerous lesions were more likely to be male, with lower educational attainment, poor socioeconomic status, and metabolic syndrome. This clustering of factors suggests complex interactions among demographic, metabolic, and lifestyle factors that traditional study adjustments failed to capture (40). Geographic confounding is also often neglected, since Asian studies tend to show a distinct, attenuated protective effect when adjusting for lifestyle factors, whereas this remains in Western studies. Omitting this parameter fails to capture epidemiological disparities in metabolic burden, SES, and genetic profiles across populations. This is especially relevant given that the joint effect of SES and unhealthy lifestyle has been demonstrated in the study by Tran et al., highlighting its distinct contribution to cancer incidence, particularly among men. The failure to account for these "forgotten confounders" may explain why current epidemiological studies on exercise and oral cancer have generated such contradictory findings, suggesting that the metabolic and socioeconomic profiles of study populations can significantly affect the measured effect of exercise on oral cancer incidence (18,19,40,52-54). These methodological gaps indicate that upcoming exercise-cancer studies should consider metabolic status and population-specific factors to avoid biased population representation. These insights into methodology provide a perspective into the challenges of research, especially since they rely on analyzing past data to find confounding patterns. Moreover, different studies have used varying definitions of metabolic syndrome, which can complicate comparisons. Moreover, regional differences may

not stem solely from metabolic factors but could also be influenced by variations in healthcare systems, environmental factors, and genetic backgrounds, all of which are still under investigation.

5.4. Biological Mediation: From Systemic to Cellular Mechanisms

The previously mentioned studies raised the hypothesis that exercise can modulate the systemic inflammatory and immunological environment, which could explain its protective effect.

5.4.1. Exercise as a modulator of systemic inflammation and immune responses

Bai et al (2023) represents a key study showing the modulating effect of exercise on inflammation. In fact, the study uses systemic immune-inflammation indices (SII and SIRI) to evaluate these effects, indicating that inflammation is a key pathway through which physical activity influences cancer risk. The study found that the vigorous physical activity pattern reduced the risk of oral and pharynx cancer, with a hazard ratio of 0.51 (95% CI: 0.26-0.98). The authors highlight that inflammation is a critical factor in cancer development and progression, suggesting that its regulation is a key mechanism by which physical activity influences cancer risk. The paper highlights that physical activity modulates circadian rhythms, which in turn affect inflammation levels. This modulation is a cellular mechanism as it involves changes in leukocyte counts and other inflammatory markers. The study's focus on inflammation as a mediator provides a cellular-level explanation for how physical activity patterns influence cancer risk.

Clinical evidence supports this mechanistic explanation. Duffy et al. describe the relationship between health behaviors (smoking, alcohol problems, BMI, physical activity, and sleep) and IL-6 levels in patients with head and neck cancer, including those with oral cancer. They also underscore that inactivity is part of the cluster of health behaviors associated with higher IL-6 levels, which are produced by tumor cells and endothelial cells in the tumor microenvironment, facilitating tumor invasion and metastasis.

Other studies propose the mechanisms by which exercise may protect against oral carcinogenesis. In particular, Caballero-Borrego et al. (2024) provide direct clinical evidence by examining the impact of walking 1 hour per day on survival outcomes in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) treated with immunotherapy. They found that walking 1 hour per day significantly improves

progression-free survival (PFS) and overall survival (OS) compared with those who do not walk. The study suggests that the derived neutrophil-to-lymphocyte ratio (dNLR) is a significant predictor of survival, with lower dNLR values associated with better OS. Finally, the study found that both physical activity and baseline dNLR are independent predictors of better OS in these patients.

5.4.2. Beyond metabolism: cellular and molecular pathways linking exercise and oral carcinogenesis

Besides systemic modulation, exercise has been shown to modify metastatic cellular biology by directly regulating apoptotic genes, tumor suppressors, and oncogenic epidermal growth factors. According to Yoshimura and Al, recent animal models demonstrate that exercise inhibits the progression of oral cancer, specifically head and neck squamous cell carcinoma (HNSCC), by reducing tumor formation and growth and increasing survival rates. Indeed, the results show that tumor formation was significantly lower in the exercise group than in the control group, indicating a reduced incidence risk. The authors identified Oncostatin M (OSM) as a myokine elevated by exercise that directly inhibits cancer cell proliferation, providing a potential mechanism for the observed effects.

At the cellular level, exercise triggers various anti-cancer pathways within oral epithelial cells. Irmawati et al. examine how moderate exercise influences the Bax/Bcl-2 ratio. Their experimental design includes groups that swim with a load, a form of physical activity, and groups that do not participate in such activity. The study suggests that moderate exercise can increase Bax expression, a pro-apoptotic protein, and suppress Bcl-2 expression, an anti-apoptotic protein, thereby promoting apoptosis and potentially reducing cancer risk. These findings are supported by previous research that shows similar effects of exercise on the Bax/Bcl-2 ratio in other tissues.

Exercise not only maintains tumor suppressor function but also actively targets oncogenic pathways. Irmawati et al. (2020) investigate the effect of moderate intensity exercise on p53 mutant expression in oral squamous cell epithelial cells of Mus musculus. The study finds that moderate-intensity exercise can decrease p53 mutant expression, a marker of malignancy. This suggests that exercise has a protective effect by reducing the expression of a protein associated with cancer development.

Shi et al. (2024) discuss the role of exercise-related genes in cancer biology, particularly in HNSCC, and their potential impact on tumor progression and patient prognosis. The study focuses on the tumor immune microenvironment. The study suggests a possible mechanism by

which exercise may influence cancer prognosis by improving overall health, enhancing immune function, and lowering chronic inflammation, factors known to reduce cancer risk.

Luo et al. (2024) demonstrate in two separate studies that exercise decreases CD300E, a pro-tumoral factor, and increases THSD7B, an anti-tumoral protein. The increase in THSD7B associated with exercise highlights its potential as a prognostic marker and therapeutic target. This indicates that physical activity may influence gene expression, thereby affecting cancer risk factors. The authors also note that CD300E plays a role in suppressing oxidative stress pathways while enhancing pathways like TNF-α signaling and EMT, which are cellular processes involved in tumor growth.

The mechanisms range from systemic factors, such as inflammation, NLR, and myokines, to cellular processes, including Bax/Bcl-2/caspase-3/p53-mediated apoptosis and direct suppression by OSM. Although data specific to oral cancer are limited, since they mostly come from small animal models and bioinformatics analyses. Collectively, these findings show that exercise influences biological pathways that fundamentally modify carcinogenic processes at the tissue level, where oral cancers originate.

Although data on oral cancer are limited, primarily from small animal studies and bioinformatics analyses with uncertain clinical relevance, these findings collectively indicate that exercise affects biological pathways that could significantly alter carcinogenic processes in the tissue where oral cancers develop. Nevertheless, the gap between mechanistic evidence and human clinical results is still large, emphasizing the need for translational research to connect laboratory discoveries with epidemiological data.

6. CONCLUSIONS

This literature review examined whether physical exercise lowers the risk of oral cancer in adults compared with low or no activity. The evidence suggests an association between exercise and a reduced incidence of oral cancer, but this relationship is complex and influenced by confounding variables, particularly ABC cluster, exercise practice, metabolic status, and population differences.

Physical inactivity often co-occurs with other oral cancer risk factors such as poor diet and low socioeconomic status, supporting an indirect protective role for exercise. Direct associations were found, with most studies reporting lower odds ratios and hazard ratios for oral cancer among those who exercise, though results varied based on how confounders were adjusted. In some cases, adjusting for lifestyle factors eliminated the protective effect, while other large analyses showed continued protection after accounting for tobacco and alcohol use. The impact of exercise depends on its intensity, frequency, duration, and lifetime exposure, indicating that broad recommendations may not be sufficient. Protective effects vary according to these parameters.

Biologically, exercise appears to reduce the risk of oral cancer through both systemic and cellular mechanisms. Systemically, exercise regulates inflammation and enhances immune function, lowering cancer risk even in high-risk groups. At the cellular level, exercise promotes anti-carcinogenic processes in oral tissues, including triggering apoptosis and maintaining tumor-suppressor functions.

Overall, regular physical exercise likely reduces the risk of oral cancer, acting through both indirect modification of risk factors and direct biological pathways. However, its effect is moderated by confounding, metabolic, and demographic factors. Further research should focus on prospective studies with standardized exercise measures and stratification by metabolic and population characteristics to clarify when exercise provides independent protection against oral cancer.

7. SUSTAINABILITY

By examining the role of physical exercise in oral cancer prevention, this review supports the promotion of accessible, low-cost preventive strategies to reduce the global burden of the disease. Unlike pharmacological interventions or advanced therapies, physical exercise requires minimal economic resources and generates no environmental waste, making it a sustainable public health tool applicable across diverse socioeconomic settings.

From a social sustainability perspective, the findings highlight that oral cancer disproportionately affects populations with lower socioeconomic status, limited education, and reduced access to healthcare. Promoting physical activity as a modifiable protective factor could help reduce these health inequalities, particularly in low and middle-income countries where the incidence of oral cancer is rising most rapidly. Furthermore, integrating exercise-based prevention into primary healthcare and dental practice represents an economically sustainable approach, as it may decrease the need for costly late-stage treatments such as surgery, radiotherapy, and chemotherapy, ultimately reducing the financial burden on healthcare systems and patients alike.

8. REFERENCES

1. Bizuayehu HM, Dadi AF, Ahmed KY, Tegegne TK, Hassen TA, Kibret GD, et al. Burden of 30 cancers among men: Global statistics in 2022 and projections for 2050 using population-based estimates. Cancer. 2024;130(21):3708-23. doi: 10.1002/cncr.35458. https://pubmed.ncbi.nlm.nih.gov/39129420/
2. Montero PH, Patel SG. Cancer of the oral cavity. Surg Oncol Clin N Am. 2015;24(3):491-508. doi: 10.1016/j.soc.2015.03.006. https://pubmed.ncbi.nlm.nih.gov/25979396/
3. Kijowska J, Grzegorczyk J, Gliwa K, Jędras A, Sitarz M. Epidemiology, Diagnostics, and Therapy of Oral Cancer—Update Review. Cancers (Basel). 2024;16(18):3156. doi: 10.3390/cancers16183156. https://pubmed.ncbi.nlm.nih.gov/39335128/
4. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, et al. Oral squamous cell carcinomas: state of the field and emerging directions. Int J Oral Sci. 2023;15:44. doi: 10.1038/s41368-023-00249-w. https://pubmed.ncbi.nlm.nih.gov/37736748/
5. Markiewicz MR, Callahan N, Morlandt A. Oral Cancer: Classification, Diagnosis, and Staging. In: Peterson's Principles of Oral and Maxillofacial Surgery [Internet]. 2022:965-1008. doi: 10.1007/978-3-030-91920-7_33. Available from: https://doi.org/10.1007/978-3-030-91920-7_33
6. Nagesh M, Gowtham S, Bharadwaj B, Ali M, Goud AK, Siddiqua S. Evolution of TNM Classification for Clinical Staging of Oral Cancer: The Past, Present and the Future. J Maxillofac Oral Surg. 2023;22(3):710-9. doi: 10.1007/s12663-023-01915-6. https://pubmed.ncbi.nlm.nih.gov/37534341/
7. Zhou Y, Wang L, Liu M, Jiang H, Wu Y. Oral squamous cell carcinoma: Insights into cellular heterogeneity, drug resistance, and evolutionary trajectories. Cell Biol Toxicol. 2025;41(1):101. doi: 10.1007/s10565-025-10048-0. https://pubmed.ncbi.nlm.nih.gov/40504271/
8. Global Cancer Observatory (WHO/IARC). Lip and Oral Cavity Cancer Fact Sheet [Internet]. 2025. Available from: https://gco.iarc.who.int/media/globocan/factsheets/cancers/1-lip-oral-cavity-fact-sheet.pdf
9. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-16. doi: 10.1016/j.oraloncology.2008.06.002. https://pubmed.ncbi.nlm.nih.gov/18804401/
10. Liu Y, Han B. Global, regional, and national burden trends of lip and oral cavity cancer among individuals aged 60 and above from 1990 to 2021: a systematic analysis based

on the 2021 global burden of disease data. BMC Cancer. 2025;25(1):1322. doi: 10.1186/s12885-025-14768-8. https://pubmed.ncbi.nlm.nih.gov/40818979/

11. Jumparway D, Su CW, Yen AMF, Liu YT, Chen MK, Liu KJ, et al. Quantifying Genetic and Environmental Factors Accounting for Multistage Progression of Precancerous Lesions and Oral Cancer: Applications to Risk-Guided Prevention. Cancers. 2025;17(13):2114. doi: 10.3390/cancers17132114. https://pubmed.ncbi.nlm.nih.gov/40647413/
12. Dalirsani Z, Ghazi A, Pakfetrat A, Jamali J, Foroughi Z, Mirzaei M. The Relationship Between Smokeless Tobacco and the Incidence of Oral Cancer: A Systematic Review Study. Addict Health. 2025;17:1522. doi: 10.34172/ahj.1522. https://pubmed.ncbi.nlm.nih.gov/40666083/
13. Menon A, Mutalik VS, Chen Y, Ponamgi SP, Peela S, Schroth RJ, et al. Beyond Genetics: Exploring Lifestyle, Microbiome, and Social Determinants in Oral Cancer Development. Cancers. 2025;17(7):1094. doi: 10.3390/cancers17071094. https://pubmed.ncbi.nlm.nih.gov/40227635/
14. Schussel JL, Villarroel-Dorrego M, Niklander S. Editorial: Incidence, mortality, and risk factors for oral cancers. Front Oral Health. 2025;6:1636210. doi: 10.3389/froh.2025.1636210. https://pubmed.ncbi.nlm.nih.gov/40599684/
15. Chen S, Yang X, Huang L, Xie Y, Li Y, Lin Y. Increasing incidence, prevalence, and mortality of lip and oral cavity cancer in adults aged 70 and older globally: findings from GBD 2021. World J Surg Oncol. 2025;23(1):276. doi: 10.1186/s12957-025-03933-9. https://pubmed.ncbi.nlm.nih.gov/40652241/
16. Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. Med Sci (Basel). 2023;11(2):42. doi: 10.3390/medsci11020042. https://pubmed.ncbi.nlm.nih.gov/37367741/
17. Petti S. Lifestyle risk factors for oral cancer. Oral Oncol. 2009;45(4):340-50. doi: 10.1016/j.oraloncology.2008.05.018. https://pubmed.ncbi.nlm.nih.gov/18674956/
18. Morais TM, et al. Physical inactivity and oral cancer risk: Insight from a population-based study in Brazil. BMC Public Health. 2020;20:1452. doi: 10.1186/s12889-020-09529-1. Available from: https://doi.org/10.1186/s12889-020-09529-1
19. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA Intern Med. 2016;176(6):816-25. doi: 10.1001/jamainternmed.2016.1548. https://pubmed.ncbi.nlm.nih.gov/27183032/

20. Lavery JA, Boutros PC, Knight D, Tammela T, Moskowitz CS, Jones LW. Association of Exercise with Pan-cancer Incidence and Overall Survival. Cancer Cell. 2024;42(2):169-71. doi: 10.1016/j.ccell.2023.12.007. https://pubmed.ncbi.nlm.nih.gov/38181796/
21. Tabatabaie-Zadeh S, Mahdavi N, Mahdaviani B, Selk Ghaffari M. Evaluating the Association Between Lifetime Physical Activity and Oral Squamous Cell Carcinoma: A Case-Control Study. PLoS One. 2024;19:e0303929. doi: 10.1371/journal.pone.0303929. https://pubmed.ncbi.nlm.nih.gov/38768241/
22. Leitzmann MF, Koebnick C, Freedman ND, Park Y, Ballard-Barbash R, Hollenbeck AR, et al. Physical activity and head and neck cancer risk. Cancer Causes Control. 2008;19(10):1391-9. doi: 10.1007/s10552-008-9211-0. https://pubmed.ncbi.nlm.nih.gov/18704714/
23. Lin CL, Lee WT, Ou CY, Hsiao JR, Huang CC, Huang JS, et al. Regular recreational physical activity and risk of head and neck cancer. BMC Cancer. 2017;17(1):286. doi: 10.1186/s12885-017-3223-7. https://pubmed.ncbi.nlm.nih.gov/28431509/
24. Nicolotti N, Chuang SC, Cadoni G, Arzani D, Petrelli L, Bosetti C, et al. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) Consortium. Eur J Epidemiol. 2011;26(8):619-28. doi: 10.1007/s10654-011-9612-3. https://pubmed.ncbi.nlm.nih.gov/21842237/
25. Platek A, Cannioto R, Etter J, Kim J, Joseph J, Gulati N, et al. The association of lifetime physical inactivity with head and neck cancer: a hospital-based case-control analysis. Eur Arch Otorhinolaryngol. 2017;274(10):3773-80. doi: 10.1007/s00405-017-4688-3. https://pubmed.ncbi.nlm.nih.gov/28780667/
26. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort. Head Neck. 2013;35(7):914-22. doi: 10.1002/hed.23052. https://pubmed.ncbi.nlm.nih.gov/22711227/
27. Duffy SA, Teknos T, Taylor JMG, Fowler KE, Islam M, Wolf GT, et al. Health Behaviors Predict Higher Interleukin-6 Levels among Patients Newly Diagnosed with Head and Neck Squamous Cell Carcinoma. Cancer Epidemiol Biomarkers Prev. 2013;22(3):374-81. doi: 10.1158/1055-9965.EPI-12-0987. https://pubmed.ncbi.nlm.nih.gov/23300019/
28. Bai P, Ning X, Gao R, Shao X, Zhou S, Li J, et al. Association between circadian physical activity patterns and cancer incidence through regulation of inflammation: A UK Biobank study. Prev Med. 2024;179:107831. doi: 10.1016/j.ypmed.2023.107831. https://pubmed.ncbi.nlm.nih.gov/38145876/

29. Caballero-Borrego J, et al. Walking one hour per day and the derived neutrophil-to-lymphocyte ratio are associated with outcome in palliative second-line immunotherapy for patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Braz J Otorhinolaryngol. 2024;90(5):101462. doi: 10.1016/j.bjorl.2024.101462. https://pubmed.ncbi.nlm.nih.gov/39205362/
30. Shi Q, Ying H, Weng W. Targeting exercise-related genes and placental growth factor for therapeutic development in head and neck squamous cell carcinoma. Front Pharmacol. 2024;15:1476076. doi: 10.3389/fphar.2024.1476076. https://pubmed.ncbi.nlm.nih.gov/39431157/
31. Kim GJ, Han KD, Joo YH. Association of Metabolic Syndrome with the Risk of Head and Neck Cancer: A 10-Year Follow-Up Study of 10 Million Initially Healthy Individuals. Cancers. 2023;15(16):4118. doi: 10.3390/cancers15164118. https://pubmed.ncbi.nlm.nih.gov/37627146/
32. Seo JH, Kim YD, Park CS, Han KD, Joo YH. Hypertension is associated with oral, laryngeal, and esophageal cancer: a nationwide population-based study. Sci Rep. 2020;10(1):10291. doi: 10.1038/s41598-020-67329-3. https://pubmed.ncbi.nlm.nih.gov/32581314/
33. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31. https://pubmed.ncbi.nlm.nih.gov/3920711/
34. Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin. 2020;70(4):245-71. doi: 10.3322/caac.21591. https://pubmed.ncbi.nlm.nih.gov/32515498/
35. Lavery JA, et al. Physical activity and pancreatic cancer risk: Systematic review and meta-analysis. Cancer Causes Control. 2016;27:1187-97. doi: 10.1007/s10552-016-0794-1. Available from: https://doi.org/10.1007/s10552-016-0794-1
36. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015. https://pubmed.ncbi.nlm.nih.gov/29056514/
37. Beydoun H, et al. Vitamin D, sun exposure, and risk of head and neck cancers: a review. Nutr Cancer. 2011;63(7):1020-30. doi: 10.1080/01635581.2011.601847. Available from: https://doi.org/10.1080/01635581.2011.601847
38. Cormie P, Atkinson M, Buber N, Banerjee S, Dunstan D,"; Galvão DA. Exercise medicine in cancer care. Aust J Gen Pract. 2020;49(4):169-74. doi: 10.31128/AJGP-08-19-5027. https://pubmed.ncbi.nlm.nih.gov/32233341/

39. Guo SE, et al. Behavioral clustering analysis of risk factors for oral cancer. J Epidemiol. 2013;23(4):227-33. Available from: https://doi.org/10.2188/jea.JE20120179
40. Chang CC, Lin MS, Chen YT, Tu LT, Jane SW, Chen MY. Metabolic syndrome and health-related behaviours associated with pre-oral cancerous lesions among adults aged 20-80 years in Yunlin County, Taiwan: a cross-sectional study. BMJ Open. 2015;5(12):e008788. doi: 10.1136/bmjopen-2015-008788. https://pubmed.ncbi.nlm.nih.gov/26685025/
41. Lin CL, Lee WT, Ou CY, Hsiao JR, Huang CC, Huang JS, et al. Regular recreational physical activity and risk of head and neck cancer. BMC Cancer. 2017;17(1):286. doi: 10.1186/s12885-017-3223-7. https://pubmed.ncbi.nlm.nih.gov/28431509/
42. Shabir A, et al. Unveiling Oral Cancer Epidemiology in Pakistan: Insights From a Case-Control Study. Glob Health Epidemiol Genomics. 2025:1-9. doi: 10.1155/ghe3/9982580. https://pubmed.ncbi.nlm.nih.gov/40519788/
43. Platek AE, Cannioto R, Etter JL, et al. The association of lifetime physical inactivity with head and neck cancer: a hospital-based case-control analysis. Eur Arch Otorhinolaryngol. 2017;274(10):3773-80. doi: 10.1007/s00405-017-4688-3. https://pubmed.ncbi.nlm.nih.gov/28780667/
44. Morais TM, et al. Determinants of physical inactivity in Brazil and links to oral cancer risk. BMC Public Health. 2020;20:1452. doi: 10.1186/s12889-020-09529-1. Available from: https://doi.org/10.1186/s12889-020-09529-1
45. Nicolotti N, Chuang SC, Cadoni G, Arzani D, Petrelli L, Bosetti C, et al. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the INHANCE Consortium. Eur J Epidemiol. 2011;26(8):619-28. doi: 10.1007/s10654-011-9612-3. https://pubmed.ncbi.nlm.nih.gov/21842237/
46. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the PLCO cohort. Head Neck. 2013;35(7):914-22. doi: 10.1002/hed.23052. https://pubmed.ncbi.nlm.nih.gov/22711227/
47. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA Intern Med. 2016;176(6):816-25. doi: 10.1001/jamainternmed.2016.1548. https://pubmed.ncbi.nlm.nih.gov/27183032/
48. Kim Y, Sharp S, Hwang S, Jee SH. Exercise frequency and site-specific cancer risk in 257 854 adults in South Korea. BMJ Open. 2019;9(3):e025590. doi: 10.1136/bmjopen-2018-025590. https://pubmed.ncbi.nlm.nih.gov/30872551/

49. Tabatabaie-Zadeh S, Mahdavi N, Mahdaviani B, Selk Ghaffari M. Lifetime physical activity and oral squamous cell carcinoma: Evidence from a case-control study. PLoS One. 2024;19:e0303929. doi: 10.1371/journal.pone.0303929. https://pubmed.ncbi.nlm.nih.gov/38768241/
50. Leitzmann MF, Koebnick C, Freedman ND, Park Y, Ballard-Barbash R, Hollenbeck AR, et al. Physical activity and head and neck cancer risk. Cancer Causes Control. 2008;19(10):1391-9. doi: 10.1007/s10552-008-9211-0. https://pubmed.ncbi.nlm.nih.gov/18704714/
51. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the PLCO cohort. Head Neck. 2013;35(7):914-22. doi: 10.1002/hed.23052. https://pubmed.ncbi.nlm.nih.gov/22711227/
52. Kim GJ, Han KD, Joo YH. Metabolic syndrome and head and neck cancer risk: a 10-year South Korean study. Cancers (Basel). 2023;15(16):4118. doi: 10.3390/cancers15164118. https://pubmed.ncbi.nlm.nih.gov/37627146/
53. Lin F, Li Y, Cao J, Fan S, Wen J, Zhu G, et al. Associations of combined lifestyle and metabolic risks with cancer incidence in the UK Biobank study. BMC Cancer. 2025;25(1):547. doi: 10.1186/s12885-025-13955-x. https://pubmed.ncbi.nlm.nih.gov/40140964/
54. Tran CL, Choi KS, Kim SY, Oh JK. Individual and joint effect of socioeconomic status and lifestyle factors on cancer in Korea. Cancer Med. 2023;12(16):17389-402. doi: 10.1002/cam4.6372. https://pubmed.ncbi.nlm.nih.gov/37489083/
55. Bai P, Ning X, Gao R, Shao X, Zhou S, Li J, et al. Association between circadian physical activity patterns and cancer incidence through regulation of inflammation: A UK Biobank study. Prev Med. 2024;179:107831. doi: 10.1016/j.ypmed.2023.107831. https://pubmed.ncbi.nlm.nih.gov/38145876/
56. Duffy SA, Teknos T, Taylor JMG, Fowler KE, Islam M, Wolf GT, et al. Health Behaviors Predict Higher Interleukin-6 Levels among Patients Newly Diagnosed with Head and Neck Squamous Cell Carcinoma. Cancer Epidemiol Biomarkers Prev. 2013;22(3):374-81. doi: 10.1158/1055-9965.EPI-12-0987. https://pubmed.ncbi.nlm.nih.gov/23300019/
57. Caballero-Borrego J, et al. Walking one hour per day and the derived neutrophil-to-lymphocyte ratio are associated with outcome in palliative second-line immunotherapy for patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Braz J Otorhinolaryngol. 2024;90(5):101462. doi: 10.1016/j.bjorl.2024.101462. https://pubmed.ncbi.nlm.nih.gov/39205362/

58. Luo S, et al. Exercise-induced IL-15 acted as a positive prognostic implication and tumor-suppressed role in pan-cancer. Front Pharmacol. 2022;13:1053137. doi: 10.3389/fphar.2022.1053137. https://pubmed.ncbi.nlm.nih.gov/36467072/
59. Yoshimura H, et al. Exercise Suppresses Head and Neck Squamous Cell Carcinoma Growth via Oncostatin M. Cancers (Basel). 2024;16(6):1187. doi: 10.3390/cancers16061187. https://pubmed.ncbi.nlm.nih.gov/38539521/
60. Irmawati A, Rachma LA, Sidarningsih, Hatta MN, Arundina I, Aljunaid M. Exercise as a method to reduce the risk of oral cancer: A narrative review. Dent J (Majalah Kedokteran Gigi). 2022;55(1):56-61. Available from: https://doi.org/10.20473/j.djmkg.v55.i1.p56-61
61. Irmawati A, Handayani ATW, Balqis NF, Surboyo MDC. The Decreased of p53 Mutant Expression on Squamous Cell Epithelial of Oral in Mus musculus by Moderate Intensity of Exercise. Malays J Med Health Sci. 2020;16(Supp 4):1-5. Available from: https://medic.upm.edu.my/upload/dokumen/2020070611150901_MJMHS_0106.pdf
62. Luo Z, Zhu X, Hu Y, Yan S, Chen L. Association between dietary inflammatory index and oral cancer risk: A systematic review and dose-response meta-analysis. Front Oncol. 2022;12:920452. doi: 10.3389/fonc.2022.920452. https://pubmed.ncbi.nlm.nih.gov/36226053/
63. 63a. Luo Z, Zhu J, Fang Z, Xu R, Wan R. Exercise-augmented THSD7B exhibited a positive prognostic implication and tumor-suppressed functionality in pan-cancer. Front Immunol. 2024;15:1440226. doi: 10.3389/fimmu.2024.1440226. https://pubmed.ncbi.nlm.nih.gov/39161765/
63b. Luo Z, Zhu J, Fang Z, Xu R, Wan R. Exercise-downregulated CD300E acted as a negative prognostic implication and tumor-promoted role in pan-cancer. Front Immunol. 2024;15:1437068. doi: 10.3389/fimmu.2024.1437068. https://pubmed.ncbi.nlm.nih.gov/39144140/
64. Shi Q, Ying H, Weng W. Targeting exercise-related genes and placental growth factor for therapeutic development in head and neck squamous cell carcinoma. Front Pharmacol. 2024;15:1476076. doi: 10.3389/fphar.2024.1476076. https://pubmed.ncbi.nlm.nih.gov/39431157/