ORAL CANCER: ETIOLOGY AND THERAPEUTIC ASPECTS. LITERATURE REVIEW

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ABSTRACT

Introduction The heterogeneity of head and neck cancers poses challenges in treatment planning, necessitating a nuanced approach.**Materials and methods** We have carried out a literature review that highlights the risk factors in the onset of oral and head and neck cancers. We also addressed the therapeutic aspects and the influence of epigenetics.**Results** In identifying risk factors, our literature research highlights systemic causes such as age, gender, heredity, race, socio-economic status, and immunodeficiency. Local causes, including tobacco and alcohol use, chronic traumas, chronic infections, and the role of viruses, underscore the multifactorial nature of oral cancer etiology. Addressing prevention strategies, our review underscores the potential of probiotics in suppressing oral cancer cell proliferation, with specific strains demonstrating efficacy in reducing mucositis caused by radiotherapy and chemotherapy. Additionally, the role of vitamins, omega-3 fatty acids, and compounds like curcumin in chemoprevention is explored. The Mediterranean diet emerges as a potential preventive measure, given its association with reduced cancer risk due to its rich content of monounsaturated fatty acids, antioxidants, and dietary fiber. **Conclusions** In conclusion, the intricate interplay of various risk factors underscores the multifactorial nature of oral cancer, with systemic and local influences contributing to its onset and progression. Age, gender, heredity, race, socio-economic status, immunodeficiency, and lifestyle choices such as tobacco, alcohol, and poor oral hygiene collectively elevate the risk. Specific chronic infections, the role of viruses, and even certain medications further contribute to the complexity of this disease.

Key words: oral cancer, HPV, epigenetics, probiotics

INTRODUCTION

Oral cancer accounts for 48% of head and neck cancer cases, making head and neck cancer the sixth most frequent cancer in humans [1-3] oral squamous cell carcinomas (OSCCs) are the histologically determined cause of 90% of mouth cancer cases [4]. In most countries, the 5-year survival rate for oral cancer remains below 50%, even with the use of innovative management regimens [5]. Because head and neck cancers are heterogeneous tumors, devising a treatment plan becomes difficult [6]. Prevention is essential for oral cancer because the disease has a bad prognosis [7].

For individuals with oral cancer, therapy and prognosis are greatly impacted by distant metastases [8]. The hypopharynx is

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the region with the most frequent primary site (60%) for distant metastases from oral cancer, followed by the base of the tongue (53%) and anterior tongue (50%) [9].

RISC FACTORS:

Systemic causes:

1. Age and gender

There is a progressively increasing incidence between 40-70 years, after which it significantly decreases, being more common in males [10, 11].

2. Heredity

Certain gene mutations that control the cell cycle can be found in all organism cells and can be inherited over two to three generations. In recent years, genes that favor the development of colon, ovarian, or osteosarcoma cancers have been described [12-15].

3. Race and socio-economic status

Recent studies have shown that the black race is more susceptible to oral carcinoma compared to Caucasians when exposed to the same carcinogens, such as smoking and alcohol. The population with a low socio-economic status presents a higher oncologic risk due to improper nutrition, chronic diseases, and poor medical control [16, 17].

4. Immunodeficiency

Lack of immune control makes tumors more likely to occur in individuals with congenital or acquired immune deficiencies (e.g., HIV-positive patients [18, 19] or patients with bone marrow or renal transplants) [11, 20].

5. Nutritional factors

- A diet rich in fresh fruits and vegetables, with vitamin A and C content, reduces the risk of oral carcinoma [21, 22].
- Chronic iron deficiency is associated with an increased risk of oral, pharyngeal, and esophageal carcinoma. Excessive consumption of salted and smoked meat and fish, without sufficient intake of fresh fruits and vegetables, constitutes an iron and vitamin-deficient diet [23, 24]. The association of chronic anemia with candidiasis is currently considered a risk factor for the development of oral carcinoma. It occurs more frequently in elderly individuals with certain underlying health conditions that hinder iron assimilation [25].
- Chronic liver dysfunctions such as liver cirrhosis can be accompanied by oral carcinomas [26].
- Chronic alcoholism is often associated with severe nutritional deficiencies, leading to a simultaneous deficiency in the absorption of vitamins and other micronutrients [11].

Local causes:

1. Tobacco and alcohol

Over 90% of men and over 60% of women with oral and pharyngeal carcinomas are smokers. The combination of tobacco and alcohol has a carcinogenic action through the mediation of cyclic nitrosamines. They generate endocellular oxidant products with mutagenic effects on DNA [11, 27, 28].

Reverse smoking, practiced in India, produces a typical lesion on the hard palate called nicotinic stomatitis. The use of tobacco in other forms such as chewing or snuffing produces specific localized forms of oral carcinoma related to these habits [29].

2. Chronic traumas

These are mechanical microtraumas caused by incorrectly adapted prosthetic work, sharp edges of teeth or fillings, root

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remnants, malpositioned teeth, oral galvanism [30, 31].

3. Specific chronic infections

The presence of Candida on the surface of oral dysplastic lesions is considered to be due to superinfection, as a consequence of weakened immunity [11, 32, 33].

a. Chronic hyperplastic candidiasis itself produces leukoplakic lesions, which can be considered lesions with potential for malignancy.

b. Clinically, candidal leukoplakias often have a spotted appearance, frequently demonstrating a moderate to high degree of dysplasia progressing towards carcinoma.

c. Carcinoma is more frequently observed on candidal leukoplakias than on other types of leukoplakias.

d. Chronic Candida infections disrupt the metabolism of epithelial cells, leading to dysplasia and carcinomas [11].

4. Role of Viruses

Herpes simplex virus - Numerous studies have suggested the involvement of the herpes simplex virus in oral neoplasms, but the results are not fully conclusive. The virus could act synergistically with chemical mutagenic factors or with papillomaviruses [34, 35].

Human Papillomavirus (HPV) - Studies have highlighted the presence of HPV type 16 in cases of malignant lesions of the oral mucosa [26, 35, 36]. Individuals with circulating antibodies against HPV 16 seem to be part of the oncogenic risk group for the occurrence of oral carcinoma, especially when associated with other facilitating factors [11, 26].

5. Marijuana

Global consumption has increased, and it could have consequences on the occurrence of oral carcinoma. The risk of developing lesions is 2.5 times higher than in non-users, especially when combined with concurrent use of tobacco and alcohol [37].

6. Poor oral hygiene and dental factors

Although the results of some studies have often been contradictory, the lack of hygiene is still considered a facilitating factor in the occurrence of oral malignant tumors [11, 15].

7. Medications

Recent data suggest that mouthwashes with a high alcohol content have a high oncogenic potential, especially after periods of heavy smoking [11]. Tooth-whitening products are suspected to have an oncogenic effect on the oral mucosa due to the use of oxygen peroxide [38].

8. Ultraviolet Radiation and Sunlight expose

It is proven that prolonged exposure to radiation plays a role in the onset of neoplasms. In the oro-maxillo-facial area, radiation causes a modification of the lip color known as actinic cheilitis [39]. This constitutes a highly favorable environment for the occurrence of lip carcinoma, especially when associated with smoking. It occurs more frequently in individuals who spend more time outdoors, especially in rural environments [40].

PREVENTION STRATEGIES FOR ORAL CANCER

Several studies have revealed that probiotics can suppress the proliferation of oral cancerous cells [41-43]. Probiotics are live microorganisms that provide health benefits to the host. The majority of probiotic supplements contain lactic acid bacteria, which help the host maintain intestinal microbial equilibrium. Recent

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studies on probiotic supplements demonstrate that they protect from the carcinogenic activity of bacterial mediators. Lactobacillus acidophilus and Lactobacillus casei are known to reduce bacterial cytokines and mediators. Furthermore, the consumption of probiotics greatly reduces Streptococcus mutans counts, which minimizes tooth decay, improves periodontitis, and helps in the treatment of oral candida [42]. In a double-blind RCT-controlled study, Lactobacillus brevis CD2 was helpful in decreasing mucositis caused by radiotherapy and chemotherapy for individuals with head and neck cancer [44].

Probiotics have the ability to reduce tumor growth and metastasis. A daily probiotic supplement for six months improves the elimination of HPV as well as cervical premalignant lesions [45].

Vitamin A, 13-cis retinoic acid, green tea extract, and various medicinal plants have all been utilized as chemopreventives [46]. Omega-3 fatty acids inhibit the synthesis of cytokines [47] such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) [48-53]. Clinical trials have shown that omega-3 can help epithelial cells recover. In cutaneous wound healing, free fatty acids has been shown to minimize edema and pain without tissue necrosis debridement [54, 55].

Curcumin, the active component of turmeric, is a polyphenol utilized as a spice or medicinal in India [56, 57]. Curcumin reduces inflammation and promotes apoptosis in HNSCC by down-regulating NF-κB. It also activates p53 and p21 [57].

The Mediterranean diet contains monounsaturated fatty acids coming from olive oil, fruits, vegetables, fish, low red meat consumption and low-fat dairy. It minimizes the risk of getting illnesses such as head and neck cancer because it contains phenol oils and α-tocopherol, as well as being high in antioxidants and dietary fiber [58, 59].

A modest consumption of milk and dairy products combined with a high intake of high-fiber foods (such as whole grains) may help lower the incidence of many cancers [60-65]. In contrast, meat and animal products, which are high in animal oils and fats and frequently cooked at elevated temperatures, could raise cancer incidence, particularly stomach cancer, colorectal cancer, and prostate cancer [65-71].

ORAL CANCER TYPES AND LOCATIONS

Oral cavity malignancies are divided into six subsites: buccal mucosa, upper alveolus and gingival, lower alveolus and gingival, tongue, hard palate, and floor of mouth [72].

Oral and tongue cancer has been classified into various categories. Sarcomas, melanomas, adenocarcinomas (affecting the salivary glands), verrucous carcinoma, and lymphomas (affecting lymphoid tissues) are possible additional forms of mouth cancer. On the other hand, squamous cell carcinoma is the most common type of cancer. These tumors impact a range of oral and dental cavity-related problems [72, 73].

EPIGENETIC INFLUENCE

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In the complexity of studies on cancer have shown that tumor and normal cells have distinct epigenetic landscapes, which affects the course of the disease and is implicated in all phases of malignant growth[74, 75].

Epigenetic regulation consists of heritable and persistent changes in gene expression which do not affect the DNA sequence but are responsible for the development and progression of OSCC neoplasms through gene expression control [76-79]. Epigenetic alterations include DNA methylation, histone covalent alteration, chromatin transformation, and the effect of ncRNAs on the expression of genes [80].

Epigenetic changes also influence cellular plasticity during the development of tumors and the onset of tumor-initiating cells or tumor stem cells [81-85].

PRECANCEROUS LESIONS

Precancerous lesions comprise homogeneous and nonhomogeneous leukoplakia, verrucous leukoplakia, lichen planus, erythroplakia, and chronic trauma ulcers. The predicted annual rate of cancerous transformations of oral precancerous lesions varies between 0.13 percent and 2.2% [86, 87].

Early preclinical invasive malignancies (early-stage tumors with no symptoms) manifest as painless, tiny ulcers, nodular lesions, or growths. These alterations are plainly visible and clinically observable with careful visual examination and touch of the oral mucosa. In the beginning, localized oral malignancies that have not progressed to regional lymph nodes are often efficiently treated and cured with surgery or radiotherapy alone, without any functional or cosmetic abnormalities, leading to a five-year survival rate of more than 80% [88, 89].

BIOLOGY OF METASTASIS

The process of metastatic cancer begins with the cancer cells separating from their original site, then they move throughout the tissue, travel through the extracellular matrix (ECM), invade blood vessels, settle in the microvasculature, and ultimately extravasate through the vessel wall and multiply in the recipient tissue [90]. Because of the breakdown of the extracellular matrix by matrix metalloproteinases (MMPs) [91-93] and the lack of cell-cell adhesion, the epithelial-mesenchymal transition (EMT) accelerates metastasis [91-94].

OPTIONS FOR TREATMENT

Even though there are several methods for treating OSCC, including surgery, radiation therapy (external beam radiation and/or brachytherapy), and adjuvant therapy (chemotherapy using drugs like carboplatin, cisplatin, paclitaxel, 5-fluorouracil, and docetaxel) [95], it is still a very expensive and harmful treatment [72].

The location of the primary tumor, the patient, and the team of specialists treating the disease have an impact on the initial therapy decision [96]. Lip cancer has a good prognosis. Cancer of the hard palate and maxillary gingiva has a low chance of metastasis, whereas tumors of the floor of

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the mouth, the tongue, and the lower gum have a higher risk of metastasis and a worse prognosis [96].

CONCLUSIONS

Oral cavity cancer is a complex disease with a high death rate; dentists are essential at all phases of patient care. Prevention via education about quitting smoking and prudent alcohol consumption is essential, as is the early discovery and management of premalignant lesions.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin, 2005, 55(2):74-108.
2. Irani S. Metastasis to head and neck area: a 16-year retrospective study. Am J Otolaryngol, 2011, 32(1):24-27.
3. Nakashima T, Tomita H, Hirata A, Ishida K, Hisamatsu K, Hatano Y, Kanayama T, Niwa A, Noguchi K, Kato K, Miyazaki T, Tanaka T, Shibata T, Hara A. Promotion of cell proliferation by the proto-oncogene DEK enhances oral squamous cell carcinogenesis through field cancerization. Cancer Med, 2017, 6(10):2424-2439.
4. Irani S. Distant metastasis from oral cancer: A review and molecular biologic aspects. J Int Soc Prev Community Dent, 2016, 6(4):265-271.
5. Sathiasekar AC, Mathew DG, Jaish Lal MS, Arul Prakash AA, Goma Kumar KU. Oral Field Cancerization and Its Clinical Implications in the Management in Potentially Malignant Disorders. J Pharm Bioallied Sci, 2017, 9(Suppl 1):S23-S25.
6. Irani S. miRNAs Signature in Head and Neck Squamous Cell Carcinoma Metastasis: A Literature Review. J Dent (Shiraz), 2016, 17(2):71-83.
7. Irani S. Pre-Cancerous Lesions in the Oral and Maxillofacial Region: A Literature Review with Special Focus on Etiopathogenesis. Iran J Pathol, 2016, 11(4):303-322.
8. Takes RP, Rinaldo A, Silver CE, Haigentz M, Jr., Woolgar JA, Triantafyllou A, Mondin V, Paccagnella D, de Bree R, Shaha AR, Hartl DM, Ferlito A. Distant metastases from head and neck squamous cell carcinoma. Part I. Basic aspects. Oral Oncol, 2012, 48(9):775-779.
9. Kotwall C, Sako K, Razack MS, Rao U, Bakamjian V, Shedd DP. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg, 1987, 154(4):439-442.
10. Montero PH, Patel SG. Cancer of the oral cavity. Surg Oncol Clin N Am, 2015, 24(3):491-508.
11. Kumar M, Nanavati R, Modi TG, Dobariya C. Oral cancer: Etiology and risk factors: A review. J Cancer Res Ther, 2016, 12(2):458-463.
12. Scully C, Field JK, Tanzawa H. Genetic aberrations in oral or head and neck squamous cell carcinoma (SCCHN): 1. Carcinogen metabolism, DNA repair and cell cycle control. Oral Oncol, 2000, 36(3):256-263.
13. Fan CY. Genetic alterations in head and neck cancer: interactions among environmental carcinogens, cell cycle control, and host DNA repair. Curr Oncol Rep, 2001, 3(1):66-71.
14. Biolchini F, Pollastri G, Figurelli S, Chiarini L. Carcinogen metabolism, DNA damage repair and oral head and neck squamocellular carcinoma (HNSCC). A review. Minerva Stomatol, 2005, 54(7-8):405-414.
15. Irani S. New Insights into Oral Cancer-Risk Factors and Prevention: A Review of Literature. Int J Prev Med, 2020, 11:202.
16. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol, 2009, 45(4-5):309-316.
17. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol, 2015, 8(9):11884-11894.
18. Li S, Su B, He QS, Wu H, Zhang T. Alterations in the oral microbiome in HIV infection: causes, effects and potential interventions. Chin Med J (Engl), 2021, 134(23):2788-2798.

DOI : 10.62610/RJOR.2024.2.16.20

19. Lomeli-Martinez SM, Gonzalez-Hernandez LA, Ruiz-Anaya AJ, Lomeli-Martinez MA, Martinez-Salazar SY, Mercado Gonzalez AE, Andrade-Villanueva JF, Varela-Hernandez JJ. Oral Manifestations Associated with HIV/AIDS Patients. Medicina (Kaunas), 2022, 58(9)
20. Patini R, Cordaro M, Marchesini D, Scilla F, Gioco G, Rupe C, D'Agostino MA, Lajolo C. Is Systemic Immunosuppression a Risk Factor for Oral Cancer? A Systematic Review and Meta-Analysis. Cancers (Basel), 2023, 15(12)
21. Moynihan P, Petersen PE. Diet, nutrition and the prevention of dental diseases. Public Health Nutr, 2004, 7(1A):201-226.
22. Rodriguez-Molinero J, Miguelanez-Medran BDC, Puente-Gutierrez C, Delgado-Somolinos E, Martin Carreras-Presas C, Fernandez-Farhall J, Lopez-Sanchez AF. Association between Oral Cancer and Diet: An Update. Nutrients, 2021, 13(4)
23. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician, 2007, 75(5):671-678.
24. Murata M. Inflammation and cancer. Environ Health Prev Med, 2018, 23(1):50.
25. Elstrott B, Khan L, Olson S, Raghunathan V, DeLoughery T, Shatzel JJ. The role of iron repletion in adult iron deficiency anemia and other diseases. Eur J Haematol, 2020, 104(3):153-161.
26. Kumari P, Debta P, Dixit A. Oral Potentially Malignant Disorders: Etiology, Pathogenesis, and Transformation Into Oral Cancer. Front Pharmacol, 2022, 13:825266.
27. Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ. Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. Oral Dis, 1995, 1(1):54-58.
28. Dissanayaka WL, Pitiyage G, Kumarasiri PV, Liyanage RL, Dias KD, Tilakaratne WM. Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol, 2012, 113(4):518-525.
29. Zhang W, Lin H, Zou M, Yuan Q, Huang Z, Pan X, Zhang W. Nicotine in Inflammatory Diseases: Anti-Inflammatory and Pro-Inflammatory Effects. Front Immunol, 2022, 13:826889.
30. Talamini R, Vaccarella S, Barbone F, Tavani A, La Vecchia C, Herrero R, Munoz N, Franceschi S. Oral hygiene, dentition, sexual habits and risk of oral cancer. Br J Cancer, 2000, 83(9):1238-1242.
31. Lauritano D, Lucchese A, Contaldo M, Serpico R, Lo Muzio L, Biolcati F, Carinci F. Oral squamous cell carcinoma: diagnostic markers and prognostic indicators. J Biol Regul Homeost Agents, 2016, 30(2 Suppl 1):169-176.
32. Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. Am J Epidemiol, 1988, 127(2):283-296.
33. Muzio LL, Ballini A, Cantore S, Bottalico L, Charitos IA, Ambrosino M, Nocini R, Malcangi A, Dioguardi M, Cazzolla AP, Brauner E, Santacroce L, Cosola MD. Overview of Candida albicans and Human Papillomavirus (HPV) Infection Agents and their Biomolecular Mechanisms in Promoting Oral Cancer in Pediatric Patients. Biomed Res Int, 2021, 2021:7312611.
34. Gupta S, Kumar P, Das BC. HPV(+ve/-ve) oral-tongue cancer stem cells: A potential target for relapse-free therapy. Transl Oncol, 2021, 14(1):100919.
35. Di Spirito F, Pantaleo G, Di Palo MP, Amato A, Raimondo A, Amato M. Oral Human Papillomavirus Benign Lesions and HPV-Related Cancer in Healthy Children: A Systematic Review. Cancers (Basel), 2023, 15(4)
36. Martin-Hernan F, Sanchez-Hernandez JG, Cano J, Campo J, del Romero J. Oral cancer, HPV infection and evidence of sexual transmission. Med Oral Patol Oral Cir Bucal, 2013, 18(3):e439-444.
37. Ghasemiesfe M, Barrow B, Leonard S, Keyhani S, Korenstein D. Association Between Marijuana Use and Risk of Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open, 2019, 2(11):e1916318.
38. Epple M, Meyer F, Enax J. A Critical Review of Modern Concepts for Teeth Whitening. Dent J (Basel), 2019, 7(3)

DOI : 10.62610/RJOR.2024.2.16.20

39. Vasilovici A, Ungureanu L, Grigore L, Cojocaru E, Senila S. Actinic Cheilitis - From Risk Factors to Therapy. Front Med (Lausanne), 2022, 9:805425.
40. Toprani SM, Kelkar Mane V. A short review on DNA damage and repair effects in lip cancer. Hematol Oncol Stem Cell Ther, 2021, 14(4):267-274.
41. Zhang M, Wang F, Jiang L, Liu R, Zhang L, Lei X, Li J, Jiang J, Guo H, Fang B, Zhao L, Ren F. Lactobacillus salivarius REN inhibits rat oral cancer induced by 4-nitroquioline 1-oxide. Cancer Prev Res (Phila), 2013, 6(7):686-694.
42. Aghazadeh Z, Pouralibaba F, Yari Khosroushahi A. The prophylactic effect of Acetobacter syzygii probiotic species against squamous cell carcinoma. J Dent Res Dent Clin Dent Prospects, 2017, 11(4):208-214.
43. Kaur K, Topchyan P, Kozlowska AK, Ohanian N, Chiang J, Maung PO, Park SH, Ko MW, Fang C, Nishimura I, Jewett A. Super-charged NK cells inhibit growth and progression of stem-like/poorly differentiated oral tumors in vivo in humanized BLT mice; effect on tumor differentiation and response to chemotherapeutic drugs. Oncoimmunology, 2018, 7(5):e1426518.
44. Sharma A, Rath GK, Chaudhary SP, Thakar A, Mohanti BK, Bahadur S. Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: a randomized double-blind placebo-controlled study. Eur J Cancer, 2012, 48(6):875-881.
45. Verhoeven V, Renard N, Makar A, Van Royen P, Bogers JP, Lardon F, Peeters M, Baay M. Probiotics enhance the clearance of human papillomavirus-related cervical lesions: a prospective controlled pilot study. Eur J Cancer Prev, 2013, 22(1):46-51.
46. Xie A, Liu J. Chemoprevention of oral cancer in leukoplakia patients: A systematic review and meta-analysis. J Pak Med Assoc, 2017, 67(9):1415-1419.
47. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol, 2013, 75(3):645-662.
48. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem, 2001, 276(20):16683-16689.
49. Calder PC. Immunonutrition. BMJ, 2003, 327(7407):117-118.
50. Vanden Berghe W, Vermeulen L, Delerive P, De Bosscher K, Staels B, Haegeman G. A paradigm for gene regulation: inflammation, NF-kappaB and PPAR. Adv Exp Med Biol, 2003, 544:181-196.
51. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients, 2010, 2(3):355-374.
52. Liang P, Henning SM, Schokrpur S, Wu L, Doan N, Said J, Grogan T, Elashoff D, Cohen P, Aronson WJ. Effect of Dietary Omega-3 Fatty Acids on Tumor-Associated Macrophages and Prostate Cancer Progression. Prostate, 2016, 76(14):1293-1302.
53. Gutierrez S, Svahn SL, Johansson ME. Effects of Omega-3 Fatty Acids on Immune Cells. Int J Mol Sci, 2019, 20(20)
54. McDaniel JC, Belury M, Ahijevych K, Blakely W. Omega-3 fatty acids effect on wound healing. Wound Repair Regen, 2008, 16(3):337-345.
55. McDaniel JC, Massey K, Nicolaou A. Fish oil supplementation alters levels of lipid mediators of inflammation in microenvironment of acute human wounds. Wound Repair Regen, 2011, 19(2):189-200.
56. Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer, 2003, 3(10):768-780.
57. Surh YJ, Chun KS. Cancer chemopreventive effects of curcumin. Adv Exp Med Biol, 2007, 595:149-172.
58. Giraldi L, Panic N, Cadoni G, Boccia S, Leoncini E. Association between Mediterranean diet and head and neck cancer: results of a large case-control study in Italy. Eur J Cancer Prev, 2017, 26(5):418-423.
59. Mentella MC, Scaldaferri F, Ricci C, Gasbarrini A, Miggiano GAD. Cancer and Mediterranean Diet: A Review. Nutrients, 2019, 11(9)
60. Magalhaes B, Bastos J, Lunet N. Dietary patterns and colorectal cancer: a case-control study from Portugal. Eur J Cancer Prev, 2011, 20(5):389-395.

DOI : 10.62610/RJOR.2024.2.16.20

61. Bamia C, Lagiou P, Buckland G, Grioni S, Agnoli C, Taylor AJ, Dahm CC, Overvad K, Olsen A, Tjonneland A, Cottet V, Boutron-Ruault MC, Morois S, Grote V, Teucher B, Boeing H, Buijsse B, Trichopoulos D, Adarakis G, Tumino R, Naccarati A, Panico S, Palli D, Bueno-de-Mesquita HB, van Duijnhoven FJ, Peeters PH, Engeset D, Skeie G, Lund E, Sanchez MJ, Barricarte A, Huerta JM, Quiros JR, Dorronsoro M, Ljuslinder I, Palmqvist R, Drake I, Key TJ, Khaw KT, Wareham N, Romieu I, Fedirko V, Jenab M, Romaguera D, Norat T, Trichopoulou A. Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemiol, 2013, 28(4):317-328.
62. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. Gastroenterology, 2015, 148(6):1244-1260 e1216.
63. Torres Stone RA, Waring ME, Cutrona SL, Kiefe CI, Allison J, Doubeni CA. The association of dietary quality with colorectal cancer among normal weight, overweight and obese men and women: a prospective longitudinal study in the USA. BMJ Open, 2017, 7(6):e015619.
64. Solans M, Castello A, Benavente Y, Marcos-Gragera R, Amiano P, Gracia-Lavedan E, Costas L, Robles C, Gonzalez-Barca E, de la Banda E, Alonso E, Aymerich M, Campo E, Dierssen-Sotos T, Fernandez-Tardon G, Olmedo-Requena R, Gimeno E, Castano-Vinyals G, Aragones N, Kogevinas M, de Sanjose S, Pollan M, Casabonne D. Adherence to the Western, Prudent, and Mediterranean dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study. Haematologica, 2018, 103(11):1881-1888.
65. Fliss-Isakov N, Kariv R, Webb M, Ivancovsky D, Margalit D, Zelber-Sagi S. Mediterranean dietary components are inversely associated with advanced colorectal polyps: A case-control study. World J Gastroenterol, 2018, 24(24):2617-2627.
66. Gann PH. Risk factors for prostate cancer. Rev Urol, 2002, 4 Suppl 5(Suppl 5):S3-S10.
67. Cheung E, Wadhera P, Dorff T, Pinski J. Diet and prostate cancer risk reduction. Expert Rev Anticancer Ther, 2008, 8(1):43-50.
68. Hardin J, Cheng I, Witte JS. Impact of consumption of vegetable, fruit, grain, and high glycemic index foods on aggressive prostate cancer risk. Nutr Cancer, 2011, 63(6):860-872.
69. Wei MY, Giovannucci EL. Lycopene, Tomato Products, and Prostate Cancer Incidence: A Review and Reassessment in the PSA Screening Era. J Oncol, 2012, 2012:271063.
70. Pelser C, Mondul AM, Hollenbeck AR, Park Y. Dietary fat, fatty acids, and risk of prostate cancer in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev, 2013, 22(4):697-707.
71. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, Vatten LJ, Norat T. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr, 2015, 101(1):87-117.
72. Chong V. Oral cavity cancer. Cancer Imaging, 2005, 5 Spec No A(Spec No A):S49-52.
73. Scully C, Porter S. Oral cancer. West J Med, 2001, 174(5):348-351.
74. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet, 2002, 3(6):415-428.
75. Jones PA, Baylin SB. The epigenomics of cancer. Cell, 2007, 128(4):683-692.
76. D'Souza W, Saranath D. Clinical implications of epigenetic regulation in oral cancer. Oral Oncol, 2015, 51(12):1061-1068.
77. Castilho RM, Squarize CH, Almeida LO. Epigenetic Modifications and Head and Neck Cancer: Implications for Tumor Progression and Resistance to Therapy. Int J Mol Sci, 2017, 18(7)
78. Irimie AI, Ciocan C, Gulei D, Mehterov N, Atanasov AG, Dudea D, Berindan-Neagoe I. Current Insights into Oral Cancer Epigenetics. Int J Mol Sci, 2018, 19(3)
79. Bais MV. Impact of Epigenetic Regulation on Head and Neck Squamous Cell Carcinoma. J Dent Res, 2019, 98(3):268-276.
80. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell, 2007, 128(4):635-638.
81. Flueckiger F, Fueger GF, Hausegger K, Nicoletti R. Results of quantification of frusemide response in 123I-hippuran renal studies of unilateral renal artery stenosis. Contrib Nephrol, 1990, 79:196-199.

DOI : 10.62610/RJOR.2024.2.16.20

82. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature, 2001, 414(6859):105-111.
83. Gupta PB, Fillmore CM, Jiang G, Shapira SD, Tao K, Kuperwasser C, Lander ES. Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. Cell, 2011, 146(4):633-644.
84. Easwaran H, Tsai HC, Baylin SB. Cancer epigenetics: tumor heterogeneity, plasticity of stem-like states, and drug resistance. Mol Cell, 2014, 54(5):716-727.
85. Toh TB, Lim JJ, Chow EK. Epigenetics in cancer stem cells. Mol Cancer, 2017, 16(1):29.
86. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med, 2008, 37(1):1-10.
87. Amagasa T, Yamashiro M, Uzawa N. Oral premalignant lesions: from a clinical perspective. Int J Clin Oncol, 2011, 16(1):5-14.
88. Chinn SB, Myers JN. Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions. J Clin Oncol, 2015, 33(29):3269-3276.
89. Sankaranarayanan R, Ramadas K, Amarasinghe H, Subramanian S, Johnson N. Oral Cancer: Prevention, Early Detection, and Treatment. In: Gelband H, Jha P, Sankaranarayanan R, Horton S (Eds): 2015, Washington (DC),
90. Spano D, Heck C, De Antonellis P, Christofori G, Zollo M. Molecular networks that regulate cancer metastasis. Semin Cancer Biol, 2012, 22(3):234-249.
91. Jechlinger M, Grunert S, Tamir IH, Janda E, Ludemann S, Waerner T, Seither P, Weith A, Beug H, Kraut N. Expression profiling of epithelial plasticity in tumor progression. Oncogene, 2003, 22(46):7155-7169.
92. Derksen PW, Liu X, Saridin F, van der Gulden H, Zevenhoven J, Evers B, van Beijnum JR, Griffioen AW, Vink J, Krimpenfort P, Peterse JL, Cardiff RD, Berns A, Jonkers J. Somatic inactivation of E-cadherin and p53 in mice leads to metastatic lobular mammary carcinoma through induction of anoikis resistance and angiogenesis. Cancer Cell, 2006, 10(5):437-449.
93. Irani S, Salajegheh A, Smith RA, Lam AK. A review of the profile of endothelin axis in cancer and its management. Crit Rev Oncol Hematol, 2014, 89(2):314-321.
94. Liliac IM, Ungureanu BS, Margaritescu C, Sacerdotianu VM, Saftoiu A, Mogoanta L, Moraru E, Pirici D. E-Cadherin Modulation and Inter-Cellular Trafficking in Tubular Gastric Adenocarcinoma: A High-Resolution Microscopy Pilot Study. Biomedicines, 2022, 10(2)
95. Huang SH, O'Sullivan B. Oral cancer: Current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal, 2013, 18(2):e233-240.
96. Nandini DB, Rao RS, Hosmani J, Khan S, Patil S, Awan KH. Novel therapies in the management of oral cancer: An update. Dis Mon, 2020, 66(12):101036.

DOI : 10.62610/RJOR.2024.2.16.20