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Dietary Iron Intake and Supplementation in Head and Neck Cancer Patients: Implications for Disease Progression and Management

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INTRODUCTION

Head and neck cancer is a general term encompassing multiple cancers that can develop in the head and neck region. These include cancers of the mouth, tongue, gums and lips (oral cancer), voice box (laryngeal), throat (nasopharyngeal, oropharyngeal, hypopharyngeal),salivary glands, nose and sinuses.[1] Head and neck cancer can present a wide range of symptoms depending on where the cancer developed. These can include an ulcer in the mouth that does not heal, changes in the voice, difficulty swallowing, red or white patches in the mouth, and a neck lump.[2][3]The majority of head and neck cancer is caused by the use of alcohol or tobacco (including smokeless tobacco). An increasing number of cases are caused by the human papillomavirus (HPV).[4] Other risk factors include the Epstein–Barr virus, chewing betel quid (paan), radiation exposure, poor nutrition and workplace exposure to certain toxic substances.[4] About 90% are pathologically classified as squamous cell cancers.[5] The diagnosis is confirmed by a tissue biopsy.[4] The degree of surrounding tissue invasion and distant spread may be determined by medical imaging and blood tests.[4]Not using tobacco or alcohol can reduce the risk of head and neck cancer.[6] Regular dental examinations may help to identify signs before the cancer develops.[7] The HPV vaccine helps to prevent HPV-related oropharyngeal cancer.[8] Treatment may include a combination of surgery, radiation therapy, chemotherapy, and targeted therapy. In the early stage head and neck cancers are often curable but 50% of people see their doctor when they already have an advanced disease.[9]

Overview of HNC & its Global Impact

Globally, head and neck cancer accounts for 650,000 new cases of cancer and 330,000 deaths annually on average. In 2018, it was the seventh most common cancer worldwide, with 890,000 new cases documented and 450,000 people dying from the disease.[10] The usual age at diagnosis is between 55 and 65 years old.[11] The average 5-year survival following diagnosis in the developed world is 42–64%.Head and neck cancer was the seventh most common cancer worldwide in 2018 (890,000 new cases and 450,000 deaths),1 accounting for 3% of all cancers (51,540 new cases) and just over 1.5% of all cancer deaths (10,030 deaths) in the United States.2 Cancers that are known collectively as head and neck cancers usually begin in the squamous cells that line the mucosal surfaces of the head and neck (for example, those inside the mouth, throat, and voice box). These cancers are referred to as squamous cell carcinomas of the head and neck. Head and neck cancers can also begin in the salivary glands, sinuses, or muscles or nerves in the head and neck, but these types of cancer are much less common than squamous cell carcinomas[12, 13].

Classification of Head and Neck Cancers by Anatomical Site

The anatomical sites of head and neck cancer were presented in Table 1 .

Oral cavity: Includes the lips, the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor (bottom) of the mouth under the tongue, the hard palate (bony top of the mouth), and the small area of the gum behind the wisdom teeth.
Throat (pharynx): The pharynx is a hollow tube about 5 inches long that starts behind the nose and leads to the esophagus. It has three parts: the nasopharynx (the upper part of the pharynx, behind the nose); the oropharynx (the middle part of the pharynx, including the soft palate [the back of the mouth], the base of the tongue, and the tonsils); the hypopharynx (the lower part of the pharynx).
Voice box (larynx): The voice box is a short passageway formed by cartilage just below the pharynx in the neck. The voice box contains the vocal cords. It also has a small piece of tissue, called the epiglottis, which moves to cover the voice box to prevent food from entering the air passages.
Paranasal sinuses and nasal cavity: The paranasal sinuses are small hollow spaces in the bones of the head surrounding the nose. The nasal cavity is the hollow space inside the nose.
Salivary glands: The major salivary glands are in the floor of the mouth and near the jawbone. The salivary glands produce saliva. Minor salivary glands are located throughout the mucous membranes of the mouth and throat.Cancers of the brain, the eye, the esophagus, the thyroid gland, and the skin of the head and neck are not usually classified as head and neck cancers.If a squamous cell carcinoma of the head and neck is going to spread, it almost always does so locally and/or to the lymph nodes in the neck. Sometimes, cancerous squamous cells can be found in the lymph nodes of the upper neck when there is no evidence of cancer in other parts of the head and neck, possibly because the original primary tumor is too small.

Table 1: Classification of Head and Neck Cancers by Anatomical Site

Site	**ICD-10 Code**	**Description**	**Common Symptoms**
Oral Cavity	C00–C06	Lips, tongue, gums, cheeks, palate, floor	Ulcer, bleeding, pain, swelling
Oropharynx	C09–C10	Base of tongue, tonsils, soft palate	Sore throat, pain, earache
Nasopharynx	C11	Upper part of throat behind the nose	Nasal obstruction, hearing loss
Hypopharynx	C12–C13	Lower pharynx (throat)	Difficulty swallowing, hoarseness
Larynx	C32	Voice box	Hoarseness, breathing trouble
Paranasal Sinuses/Nasal	C30–C31	Sinus & nasal cavity	Headache, bleeding, sinus congestion
Salivary Glands	C07–C08	Major and minor glands	Swelling, facial weakness, pain

Major Risk Factors for Head and Neck Cancer
Alcohol and tobacco use (including second hand smoke and smokeless tobacco, sometimes called "chewing tobacco" or "snuff") are the two most important risk factors for head and neck cancers, especially cancers of the oral cavity, hypopharynx, and voice box [14–18]. People who use both tobacco and alcohol are at greater risk of developing these cancers than people who use either tobacco or alcohol alone [19, 20]. Most head and neck squamous cell carcinomas of the mouth and voice box are caused by tobacco and alcohol use [19].Infection with cancer-causing types of human papillomavirus (HPV), especially HPV type 16, is a risk factor for oropharyngeal cancers that involve the tonsils or the base of the tongue [21–23]. In the United States, the incidence of oropharyngeal cancers caused by HPV infection is increasing, while the incidence of oropharyngeal cancers related to other causes is falling [21]. About three-quarters of all oropharyngeal cancers are caused by chronic HPV infection [24, 25]. Although HPV can be detected in other head and neck cancers, it appears to be the cause of cancer formation only in the oropharynx. The reasons for this are poorly understood. Other known risk factors for specific cancers of the head and neck were presented in Table 2 and include the following-Paan (betel quid): The use of paan (betel quid) in the

mouth, a common custom in Southeast Asia, is strongly associated with an increased risk of mouth cancers [26, 27]. Occupational exposure: Occupational exposure to wood dust is a risk factor for nasopharyngeal cancer [28, 29]. Certain industrial exposures, including exposures to asbestos and synthetic fibers, have been associated with cancer of the voice box, but the increase in risk remains controversial [30]. People working in certain jobs in the construction, metal, textile, ceramic, logging, and food industries may have an increased risk of cancer of the voice box [31]. Industrial exposure to wood dust, nickel dust, or formaldehyde is a risk factor for cancers of the paranasal sinuses and nasal cavity [32–34].Radiation exposure: Radiation to the head and neck, for noncancerous conditions or cancer, is a risk factor for cancer of the salivary glands [35–37].Epstein-Barr virus infection: Infection with the Epstein-Barr virus is a risk factor for nasopharyngeal cancer [38] and cancer of the salivary glands [39, 40].Ancestry: Asian ancestry, particularly Chinese ancestry, is a risk factor for nasopharyngeal cancer [28, 29].

Table 2: Major Risk Factors for Head and Neck Cancer

Risk Factor	**Affected Site(s)**	**Mechanism of Action**	**Regionally Prevalent (India)**
Tobacco Smoking	Oral cavity, larynx	DNA damage, chronic inflammation	High
Alcohol Consumption	Pharynx, oral cavity	Synergistic with tobacco, acetaldehyde toxicity	Moderate
HPV Infection	Oropharynx	Oncoproteins E6/E7 inactivate tumor suppressors	Increasing
Betel Quid (Paan)	Oral cavity	Mechanical trauma, carcinogens in areca nut	Very High
EBV Infection	Nasopharynx	Viral latency and transformation	Low to Moderate
Occupational Dust	Nasal cavity, sinuses	Inhaled carcinogens (wood, asbestos, formaldehyde)	Region-dependent

UNDERLYING GENETIC DISORDERS

Some genetic disorders, such as Fanconi anemia, can increase the risk of developing precancerous lesions and cancers early in life [41].Head and neck cancer symptoms may include a lump in the neck or a sore in the mouth or the throat that does not heal and may be painful, a sore throat that does not go away, difficulty in swallowing, and a change or hoarseness in the voice. These symptoms may also be caused by other, less serious conditions. It is important to check with a doctor or dentist about any of these symptoms.

POTENTIAL IMPACT OF DIETARY IRON ON CANCER RISK & PROGRESSION

Oral cavity: A white or red patch on the gums, the tongue, or the lining of the mouth; a growth or swelling of the jaw that causes dentures to fit poorly or become uncomfortable; and unusual bleeding or pain in the mouth.

Throat (pharynx): Pain when swallowing; pain in the neck or the throat that does not go away; pain or ringing in the ears; or trouble hearing.

Voice box (larynx): Trouble breathing or speaking, pain when swallowing or ear pain.

Paranasal sinuses and nasal cavity: Sinuses that are blocked and do not clear; chronic sinus infections that do not respond to treatment with antibiotics; bleeding through the nose; frequent headaches, swelling or other trouble with the eyes; pain in the upper teeth; or problems with dentures.

Salivary glands: Swelling under the chin or around the jawbone, numbness or paralysis of the muscles in the face, or pain in the face, the chin, or the neck that does not go away. Head and neck cancers account for nearly 4% of all cancers in the United States [42]. These cancers are more than twice as common among men as they are among women [42]. Head and neck cancers are also diagnosed more often among people over age 50 than they are among younger people. Researchers estimated that more than 68,000 men and women in the United States would be diagnosed with head and neck cancers in 2021 [42]. Most will be

diagnosed with mouth, throat, or voice box cancer. Para-nasal sinus and nasal cavity cancer and salivary gland cancer are much less common.

HEAD and NECK CANCER DIAGNOSIS

If a patient has symptoms suggestive of a head and neck cancer then the doctor will first of all take a detailed history, and ask other relevant questions. After this the patient will undergo a detailed physical examination. In addition to this the following tests may be required to diagnose head and neck cancer:

- Endoscopy
- Biopsy
- Molecular testing of the tumour
- X-ray/barium swallows
- Panoramic radiograph
- Ultrasound
- Computed Tomography Scan (CT scan)
- Magnetic Resonance Imaging Scan (MRI Scan)
- Positron Emission Tomography–Computed Tomography Scan (PET-CT scan)

IRON SUPPLEMENTATION IN CLINICAL PRACTICE

Common indications for iron supplementation in cancer patients

- **Surgery** - Surgery is the typical treatment for head and neck cancer. Minimally invasive procedures, such as laser microsurgery, robotic approaches, and Mohs surgery, are enough to remove some tumors. But others need complex head and neck cancer operations. Careful preparation and planning are a must, and MSK's surgeons use specialized techniques to preserve the key functions (speech and swallowing) and appearance. This is the benefit of getting head and neck surgery done by surgeons who are board-certified in head and neck surgery and have years of experience treating such types of cancer.
- **Radiation Therapy** - Radiation therapy for head and neck cancer can cure many patients. Radiation oncologists at MSK use advanced technologies to treat these cancers. Intensity-modulated radiation therapy and proton therapy are the most effective treatments for head and neck cancer. These techniques do not affect the patient's ability to eat or swallow and other such side effects.
- **Immunotherapy** - It is the most promising cancer therapy available today for people with advanced head and neck cancer. Immunotherapy uses the patient's immune system to fight off cancer. MSK scientists and doctors work closely to help develop new treatment modalities for patients who come to MSK for immunotherapy treatment.Not everyone can benefit from immunotherapy, especially if cancer has recurred after standard treatment. Such patients can get more options with clinical trials. Such trials give you the opportunity to try a new treatment option that is not available elsewhere.
- **Genomic Testing for Head and Neck Cancer** - In personalized medicine, the cells from a biopsy are screened for any genetic mutations. These gene mutations are linked to the type of cancer the patient has. Specific cancer drugs are more effective than others against cancer with specific gene mutations. This genomic testing can help determine the most effective therapy for a particular patient. Patients with advanced cancers (stage III or stage IV) and recurrent head and neck cancer have new treatment options with such advancements.Memorial Sloan Kettering also offers a genomic-sequencing test called MSK-IMPACT™. This test identifies genetic mutations and other abnormalities associated with specific cancer. MSK-IMPACT can help the doctors rule out treatments that might not work and also recommend clinical trials designed to target those mutations.
- **HPV-Associated Head and Neck Cancer** - The majority of cases of head or neck cancers are linked to alcohol and tobacco use, but infection with the human papillomavirus (HPV) is becoming a leading cause. HPV-associated head and neck cancers usually affect the tonsils and other areas of the throat. The only positive to this is patients with HPV-positive tumors typically respond well to treatment and have a better prognosis. They might also require a less-intensive course of treatment, reducing side effects. (Table 3)
- In case diagnosed with head and neck cancer related to HPV, it is best to find out the benefit from a less-intensive treatment plan at MSK.

Table 3: Role of Iron in Head and Neck Cancer Progression

Aspect	Role of Iron	Implications
Iron Deficiency	May impair immune surveillance	Increased infection risk
Iron Overload	Generates ROS and DNA damage	Promotes tumorigenesis
Ferritin and Transferrin Levels	Elevated in malignancy	Possible prognostic biomarkers
Supplementation (Oral/IV)	Corrects anemia, supports therapy tolerance	Requires careful monitoring due to cancer risks

MECHANISMS LINKING IRON TO CANCER PROGRESSION

Oxidative stress happens when there is too much reactive oxygen species (ROS) and not enough antioxidants in the body. Ionizing and UV radiation, particulate matter (PM), xenobiotics, smoking, and pollution are all environmental variables that might cause too much ROS to be made. Intracellular sources, like the mitochondria, electron transport chain, cytochrome P450 enzymes, and NADPH oxidase, make ROS production even worse. Superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) are the main ROS that cause oxidative stress in cells. This higher ROS environment causes oxidative damage to DNA, proteins, and lipids, which shows up as mutagenesis, enzyme inactivation, and membrane rupture, respectively. ROS also increase the activity of ribonucleotide reductase, which makes cells grow faster. ROS also stabilize hypoxia-inducible factor 1-alpha (HIF-1α), which helps blood vessels grow. At the same time, oxidative stress can lower immunological responses by changing the polarization of macrophages to an anti-inflammatory M2 phenotype. This helps tumors grow and avoid the immune system. Cells use antioxidant defenses to fight these effects. These include intracellular antioxidant molecules including vitamins C and E, glutathione, ubiquinone, and bilirubin, as well as enzymatic antioxidants like glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and catalase. But if these defenses fail, long-term oxidative stress can cause cells to die by apoptosis, autophagy, or necrosis The diagram below (Figure 1) illustrates about the mechanism of iron linking to cancer progression.[83]

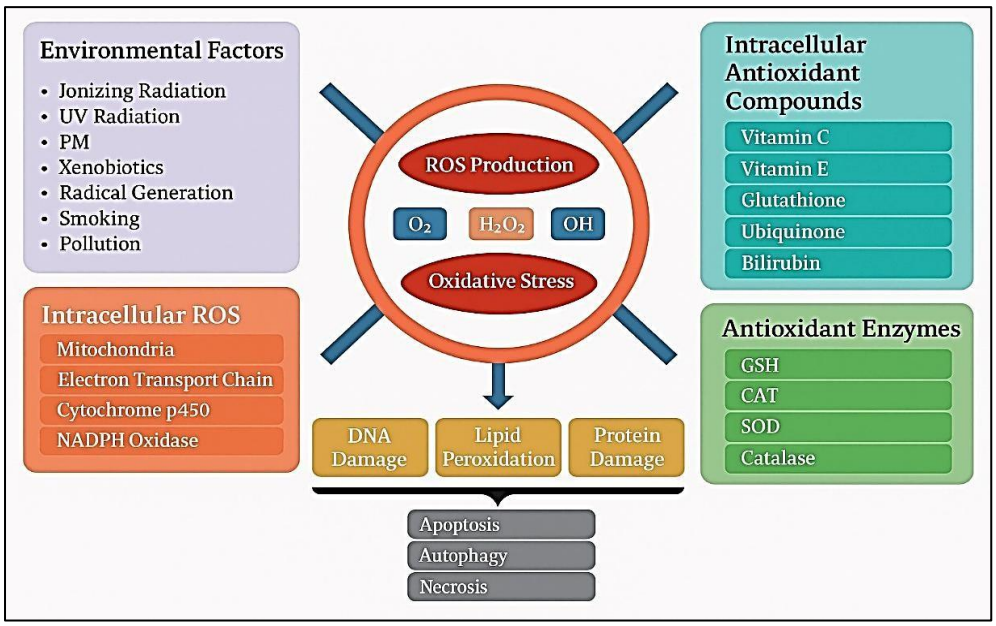

Figure 1: Mechanisms Linking Iron to Cancer Progression

HEAD AND NECK CANCER RISK FACTOR IN THE INDIA

Risks & benefits associated with supplementation

The systematic review will generate up-to-date information on the role of different risk factors of head and neck cancer (HNC) incidence in India. This study will provide the city-specific prevalence of HNC

risk factors which may have implications on health policies for management of HNC and for establishing cancer care in profoundly affected areas.The worldwide HNC trends for risk factor patterns have drastically changed in the past 15 years [43]. It is considered as a lethal disease for approximately half of all diagnosed cases, owing to low awareness and late detection at advanced stages of cancer [44]. HNC is the third most common in India with 52 067 deaths and 77 003 cases diagnosed in 2012 [45]. The real incidence is much more than the actual estimates as many cases of HNC go undiagnosed or unreported. Numerous reports highlight that risk factors are not only etiological determinants of HNC but are also connected with increased risk of HNC prevalence [46-48]. Previously published studies have demonstrated that alcohol consumption and tobacco use are the most significant risk factors of HNC in addition to HPV [49-51].

Guidelines & recommendations specific to HNC patients

The significant risk factors for HNC have already been elucidated [52]. However, the likelihood chances of an individual developing HNC have not been studied thoroughly. This is due to the scarcity of published review papers in this context. This study will provide guidelines to help clinicians and scientists better understand the link between HNC and its risk factors, mainly smoking, alcohol consumption, HPV and betel-quid chewing in Indian patients with HNC.The most significant risk factors are strongly associated with the sociocultural diversity and customs of India, [53-54] and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking and tobacco chewing, significantly vary due to diverse demographic and lifestyle habits of people in India [55-56].

CURRENT EVIDENCE & RESEARCH GAPS

Summary of existing studies on dietary iron & supplementation in HNC

In India, the number of cancer cases is rising. According to GLOBOCAN 2020, there will be 2.1 million new cancer cases in India by 2040, an increase of 57.5% from the year 2020 [57–59]. Moreover, one in nine Indians has a lifetime risk of developing cancer [59]. Head and neck cancer (HNC), in particular, accounts for 30% of the all-cancer cases [60]. Furthermore, a significant rise in the incidence of HNC was noted in the Indian population-based cancer registries (PBCRs) of Aurangabad, Delhi, Chennai, and Bhopal for males, and Nagpur for females [61]. HNC includes the cancers of the oral cavity, pharynx, and larynx – primarily originating from the mucosal epithelium, but also from less common sites like salivary glands, and nose, sinuses, muscles and nerves [62]. Squamous cell carcinoma makes up most cases of HNC [63].

Identification of gaps in Knowledge & Areas requiring further Research

In India, more than 65% of patients with HNC attend the hospital with locally advanced disease [64–66]. Late-stage presentation, lack of access to cancer care and failure to complete treatment led to poor survival in HNC patients [67, 68]. High-quality data from PBCRs are required to address this public health issue as well as to make better infrastructure and policy-related decisions about disease prevention. However, in India, PBCRs cover less than 15% of the population [69, 70]. Several challenges have been reported in establishing PBCRs in resource-constrained countries like India [71, 72].

Clinical Evidence for Iron Supplementation in HNC

This paper aims to summaries the region-wise incidence of HNC based on the published data of the registries of that region. The study utilized the published and publicly available Indian PBCRs data. Data from 28 PBCRs available in public domain of the National Cancer Registry Programme (NCRP), Bengaluru [73] and 9 PBCRs established by the Tata Memorial Centre (TMC), Mumbai (for the states of Maharashtra, Punjab, Uttar Pradesh, Bihar, and Andhra Pradesh as well as the Chandigarh-Union Territory) were included [74–76]. The Barshi registry was the country's first rural cancer registry, established by TMC, Mumbai in 1987 and regularly submitted data to NCRP[T1] [77].

Risks of Iron Overload in Oncology

There is a variation in the definition of HNC by the National Cancer Institute and the International Agency for Research on Cancer (IARC) [82]. Therefore, there is a need to specify the anatomical subsites covered in this study. Here, we have defined HNC based on the International Classification of Diseases (ICD-10) topography codes which include lip (C00), tongue (C01-02), mouth (C03-06), tonsil (C09), another oropharynx (C10), nasopharynx (C11), hypopharynx (C12-13), pharynx unspecified (C14) and

larynx (C32) [78-81]. The cancers of salivary gland, maxillary sinus and nasal cavity are not included in the present data due to the different etiology of the disease.

RECOMMENDATIONS FOR FUTURE STUDIES & CLINICAL TRIALS

Current role of artificial intelligence in head & neck cancer surgery

Artificial intelligence (AI) is a new field of science in which computers will provide decision-supporting tools to help doctors make difficult clinical choices [83]. The achievement of a large number of health data and the desire to be able to make predictions about such data has generated considerable interest in machine learning (ML). ML represents a subset of AI that enables computers to learn from data and experiences and to act without being specifically programmed [85].

CONCLUSION

Iron works in two different ways when it comes to cancer. Cell division and oxygen transport depend on iron, yet an overload causes reactive oxygen species (ROS), damaged DNA and more tumor blood vessels and it is often present in HNC patients due to chronic redness, ongoing bleeding and nutrition issues. This frequently leads to anemia caused by cancer which interferes with how well patients react to treatment and their general wellbeing. High doses of iron without proper monitoring might help cancer cells grow, so watching iron levels is important for people with HNC.

Emphasis on the need for Comprehensive research in this area

Iron-related biomarkers and judicious iron supplementation can help boost the energy level and make surgeries or cancer treatments less stressful for Individualized testing is important to prevent too much iron, mainly in people with chronic illnesses or inflammation. Emerging researchers are analyzing possible uses of iron chelators to attack cancer metabolic processes, but they need more testing in people.

Future Perspectives

Only well-organized studies can determine if iron supplementation (given orally or by injection) is both safe and effective for HNC patients based on their anemia and cancer stage. It is necessary to determine if iron metabolism biomarkers influence treatment outcome and survival in HNC. Guidelines for HNC patients should recommend the right amount of iron by taking into account what patients in each region typically eat and any other medical problems they have. Additional studies ought to explain how the dysregulation of iron in the body is linked to HNC tumors, weaker immune defense, and difficulty overcoming treatment. In personalized medicine for cancer, it's important to check iron metabolism genes to identify and use specific medications for iron-related issues.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in relation to this article.

AUTHOR CONTRIBUTIONS

Writing—original draft preparation: **Megha Tiwari**; writing—review and editing: **Mayur Porwal** and **Jitendra Kumar Verma.**

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REFERENCES

1. Board PA. Oropharyngeal Cancer Treatment (Adult)(PDQ®). InPDQ Cancer Information Summaries [Internet] 2019 Nov 21. National Cancer Institute (US).
2. Wild C. World cancer report 2014. Wild CP, Stewart BW, editors. Geneva, Switzerland: World Health Organization; 2014.
3. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, Carter A, Casey DC, Charlson FJ, Chen AZ, Coggeshall M. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016 Oct 8;388(10053):1545-602.
4. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, Coggeshall M. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015 The Lancet. 2016 Oct 8;388(10053):1459-544.
5. Aupérin A. Epidemiology of head and neck cancers: an update. Current opinion in oncology. 2020 May 1;32(3):178-86.
6. Mathew A, Tirkey AJ, Li H, Steffen A, Lockwood MB, Patil CL, Doorenbos AZ. Symptom clusters in head and neck cancer: a systematic review and conceptual model. In Seminars in oncology nursing 2021 Oct 1 (Vol. 37, No. 5, p. 151215). WB Saunders.

7. Mendez LM, Posey RR, Pandolfi PP. The interplay between the genetic and immune landscapes of AML: mechanisms and implications for risk stratification and therapy. Frontiers in Oncology. 2019 Nov 7; 9:1162.
8. Liu JC, Egleston BL, Blackman E, Ragin C. Racial survival disparities in head and neck cancer clinical trials. JNCI: Journal of the National Cancer Institute. 2023 Mar 1;115(3):288-94.
9. Vigneswaran N, Williams MD. Epidemiological trends in head and neck cancer and aids in diagnosis. Oral and maxillofacial surgery clinics of North America. 2014 May;26(2):123.
10. Macilwraith P, Malsem E, Dushyanthen S. The effectiveness of HPV vaccination on the incidence of oropharyngeal cancers in men: a review. Infectious Agents and Cancer. 2023 Apr 24;18(1):24.
11. Johnson DE, Burtness B, Leemans CR, Lui VW, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nature reviews Disease primers. 2020 Nov 26;6(1):92.
12. Chow LQ. Head and neck cancer. New England Journal of Medicine. 2020 Jan 2;382(1):60-72.
13. Kumar S, Ghosh P, Ghosh SK, Biswas S, Basak B, Biswas KD, Roy S, Choudhary A, Banerjee S. A Prospective Study of Auditory Alterations Following Radiotherapy in Patients with Head and Neck Malignancy. Journal of Medical Sciences & Clinical Research.2019 June;7(6)203-209.
14. Chow LQ. Head and neck cancer. New England Journal of Medicine. 2020 Jan 2;382(1):60-72.
15. Son E, Panwar A, Mosher CH, Lydiatt D. Cancers of the major salivary gland. Journal of Oncology Practice. 2018 Feb;14(2):99-108.
16. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P. Tobacco smoking and cancer: a meta-analysis. International journal of cancer. 2008 Jan 1;122(1):155-64.
17. Hashibe M, Boffetta P, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D, Janout V, Fabiánová E, Bencko V, Moullan N, Chabrier A. Evidence for an important role of alcohol-and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. Cancer Epidemiology Biomarkers & Prevention. 2006 Apr 1;15(4):696-703.
18. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Maso LD, Daudt AW, Fabianova E, Wünsch-Filho V, Franceschi S. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Journal of the National Cancer Institute. 2007 May 16;99(10):777-89.
19. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. The lancet oncology. 2008 Jul 1;9(7):667-75.
20. Mariano LC, Warnakulasuriya S, Straif K, Monteiro L. Secondhand smoke exposure and oral cancer risk: a systematic review and meta-analysis. Tobacco Control. 2022 Sep 1;31(5):597-607.
21. Hashim D, Genden E, Posner M, Hashibe M, Boffetta P. Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden. Annals of Oncology. 2019 May 1;30(5):744-56.
22. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiology Biomarkers & Prevention. 2009 Feb 1;18(2):541-50.
23. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of clinical oncology. 2011 Nov 10;29(32):4294-301.
24. Adelstein DJ, Ridge JA, Gillison ML, Chaturvedi AK, D'Souza G, Gravitt PE, Westra W, Psyrri A, Kast WM, Koutsky LA, Giuliano A. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9–10, 2008, Washington, DC. Head & neck. 2009 Nov 1;31(11).
25. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillomavirus type 16–positive and human papillomavirus type 16–negative head and neck cancers. Journal of the National Cancer Institute. 2008 Mar 19;100(6):407-20.
26. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, Steinau M, Watson M, Wilkinson EJ, Hopenhayn C, Copeland G. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. Journal of the National Cancer Institute. 2015 Jun 1;107(6): djv086.
27. Senkomago V. Human papillomavirus–attributable cancers—United States, 2012–2016. MMWR. Morbidity and mortality weekly report. 2019;68.
28. Ho PS, Ko YC, Yang YH, Shieh TY, Tsai CC. The incidence of oropharyngeal cancer in Taiwan: an endemic betel quid chewing area. Journal of oral pathology & medicine. 2002 Apr;31(4):213-9.
29. Goldenberg D, Lee J, Koch WM, Kim MM, Trink B, Sidransky D, Moon CS. Habitual risk factors for head and neck cancer. Otolaryngology—Head and Neck Surgery. 2004 Dec;131(6):986-93.
30. Yu MC, YUAN JM. Nasopharyngeal cancer. Cancer epidemiology and prevention. 2006 Oct 12:620-6.
31. Mimi CY, Yuan JM. Epidemiology of nasopharyngeal carcinoma. InSeminars in cancer biology 2002 Dec 1 (Vol. 12, No. 6, pp. 421-429). Academic Press.
32. Kaste LM, Dolecek TA, Zavras AI. Head and neck cancer epidemiology and health services research. Head & Neck Cancer: Current Perspectives, Advances, and Challenges. 2013:37-71.
33. Boffetta P, Richiardi L, Berrino F, Estéve J, Pisani P, Crosignani P, Raymond L, Zubiri L, Del Moral A, Lehmann W, Donato F. Occupation and larynx and hypopharynx cancer: an international case–control study in France, Italy, Spain, and Switzerland. Cancer Causes & Control. 2003 Apr; 14:203-12.
34. Littman AJ, Vaughan TL. Cancers of the nasal cavity and paranasal sinuses. Cancer epidemiology and prevention. 2006.

35. Luce D, Leclerc A, Bégin D, Demers PA, Gérin M, Orlowski E, Kogevinas M, Belli S, Bugel I, Bolm-Audorff U, Brinton LA. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case–control studies. Cancer causes & control. 2002 Mar; 13:147-57.
36. Luce D, Gérin M, Leclerc A, Morcet JF, Brugère J, Goldberg M. Sinonasal cancer and occupational exposure to formaldehyde and other substances. International Journal of Cancer. 1993 Jan 21;53(2):224-31.
37. Mayne ST, Morse DE, Winn DM. Cancers of the oral cavity and pharynx. Cancer epidemiology and prevention. 2009 Sep 1.
38. Preston-Martin S, Thomas DC, White SC, Cohen D. Prior exposure to medical and dental x-rays related to tumors of the parotid gland1. JNCI: Journal of the National Cancer Institute. 1988 Aug 17;80(12):943-9.
39. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. Epidemiology. 1997 Jul 1;8(4):414-9.
40. Chien YC, Chen JY, Liu MY, Yang HI, Hsu MM, Chen CJ, Yang CS. Serologic markers of Epstein–Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. New England Journal of Medicine. 2001 Dec 27;345(26):1877-82.
41. Hamilton-Dutoit SJ, Therkildsen MH, Nielsen NH, Jensen H, Hansen JH, Pallesen G. Undifferentiated carcinoma of the salivary gland in Greenlandic Eskimos: demonstration of Epstein-Barr virus DNA by in situ nucleic acid hybridization. Human pathology. 1991 Aug 1;22(8):811-5.
42. Chan JK, Yip TT, Tsang WY, Poon YF, Wong CS, Ma VW. Specific association of Epstein-Barr virus with lymphoepithelial carcinoma among tumors and tumorlike lesions of the salivary gland. Archives of pathology & laboratory medicine. 1994 Oct 1;118(10):994-7.
43. Beddok A, Krieger S, Castera L, Stoppa-Lyonnet D, Thariat J. Management of Fanconi Anemia patients with head and neck carcinoma: Diagnosis and treatment adaptation. Oral Oncology. 2020 Sep 1;108:104816.
44. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA: a cancer journal for clinicians. 2021 Jan;71(1):7-33.
45. Johnson-Obaseki S, McDonald JT, Corsten M, Rourke R. Head and neck cancer in Canada: trends 1992 to 2007. Otolaryngology--Head and Neck Surgery. 2012 Jul;147(1):74-8.
46. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral oncology. 2009 Apr 1;45(4-5):309-16.
47. Khazaei Z, Jarrahi AM, Momenabadi V, Ghorat F, Adineh H, Sohrabivafa M, Goodarzi E. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide stomach cancers and their relationship with the human development index (HDI). World Cancer Res J. 2019;6(9):e1257.
48. Döbróssy L. Epidemiology of head and neck cancer: magnitude of the problem. Cancer and Metastasis Reviews. 2005 Jan; 24:9-17.
49. Ragin CC, Modugno F, Gollin SM. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. Journal of dental research. 2007 Feb;86(2):104-14.
50. Sturgis EM, Wei Q, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. InSeminars in oncology 2004 Dec 1 (Vol. 31, No. 6, pp. 726-733). WB Saunders.
51. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni Jr JF. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer research. 1988 Jun 1;48(11):3282-7.
52. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Maso LD, Daudt AW, Fabianova E, Wünsch-Filho V, Franceschi S. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Journal of the National Cancer Institute. 2007 May 16;99(10):777-89.
53. Franceschi S, Talamini R, Barra S, Barón AE, Negri E, Bidoli E, Serraino D, La Vecchia C. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer research. 1990 Oct 15;50(20):6502-7.
54. Singh J, Ramamoorthi R, Baxi S, Thomas M. The risk factors of head and neck cancer and their general patterns in Australia: a descriptive review and update. Journal of Environmental Pathology, Toxicology and Oncology. 2014;33(1).
55. Addala L, Pentapati CK, Thavanati PR, Anjaneyulu V, Sadhnani MD. Risk factor profiles of head and neck cancer patients of Andhra Pradesh, India. Indian journal of cancer. 2012 Apr 1;49(2):215-9.
56. Sharan RN, Mehrotra R, Choudhury Y, Asotra K. Association of betel nut with carcinogenesis: revisit with a clinical perspective.2012 Aug 13; PLoS ONE7(8): e42759.
57. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiology Biomarkers & Prevention. 2009 Feb 1;18(2):541-50.
58. Vargas-Ferreira F, Nedel F, Etges A, Gomes AP, Furuse C, Tarquinio SB. Etiologic factors associated with oral squamous cell carcinoma in non-smokers and non-alcoholic drinkers: a brief approach. Brazilian dental journal. 2012; 23:586-90.
59. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global cancer observatory: cancer today. Lyon: International agency for research on cancer. 2020 Nov 25;20182020.
60. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. World Health Organization; 2020 Apr 3.
61. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: result from National Cancer Registry Programme, India. Indian journal of medical research. 2022 Oct 1;156(4&5):598-607.
62. Kulkarni MR. Head and neck cancer burden in India. Int J Head Neck Surg. 2013 Jan;4(1):29-35.
63. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, Icmr-Ncdir-Ncrp Investigator Group. Cancer statistics, 2020: report from national cancer registry programme, India. JCO global oncology. 2020 Jul; 6:1063-75.

64. Li H, Torabi SJ, Yarbrough WG, Mehra S, Osborn HA, Judson B. Association of human papillomavirus status at head and neck carcinoma subsites with overall survival. JAMA Otolaryngology–Head & Neck Surgery. 2018 Jun 1;144(6):519-25.
65. JJ P. Histological typing of cancer and precancer of the oral mucosa. World Health Organization International histological classification of tumours. Journal of Japanese Society for Oral Mucous Membrane7(2),45-48,2001
66. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, Icmr-Ncdir-Ncrp Investigator Group. Cancer statistics, 2020: report from national cancer registry programme, India. JCO global oncology. 2020 Jul; 6:1063-75.
67. Parikh PM, Bhattacharyya GS, Biswas G, Krishnamurty A, Doval D, Heroor A, Sharma S, Deshpande R, Chaturvedi H, Somashekhar SP, Babu G. Practical consensus recommendations for optimizing risk versus benefit of chemotherapy in patients with HR positive Her2 negative early breast cancer in India. South Asian Journal of Cancer. 2021 Dec;10(04):213-9.
68. Bagal S, Budukh A, Thakur JS, Dora T, Qayyumi B, Khanna D, Fernandes D, Chakravarti P, Singh R, Patil S, Dikshit R. Head and neck cancer burden in India: an analysis from published data of 37 population-based cancer registries. ecancermedicalscience. 2023 Sep 21; 17:1603.
69. Lucas E. Cancer survival in Africa, asia, the caribbean and central America. Sankaranarayanan R, Swaminathan R, editors. Lyon, France: International Agency for Research on Cancer; 2011 Sep 21.
70. Budukh AM, Chaudhary D, Sancheti S, Dora T, Goel AK, Singla A, Sali A, Shinde S, Chauhan KS, Kadam P, Mohammad R. Determinants of completion of cancer directed treatment: an experience from a rural cancer centre, Sangrur, Punjab state, India. ecancermedicalscience. 2021 Nov 1; 15:1313.
71. Bhatia A, Victora CG, Beckfield J, Budukh A, Krieger N. "Registries are not only a tool for data collection, they are for action": Cancer registration and gaps in data for health equity in six population-based registries in India. International Journal of Cancer. 2021 May 1;148(9):2171-83.
72. Budukh AM, Bagal S, Thakur JS, Khanna D, Sancheti S, Banavali S. Pediatric cancer burden in different regions of India: analysis of published data from 33 population-based cancer registries. Indian Pediatrics. 2023 Jul;60(7):541-5.
73. Boyle P, Parkin DM. Cancer registration: principles and methods. Statistical methods for registries. IARC scientific publications. 1991 Jan 1(95):126-58.
74. Budukh AM, Pradhan S, Singh VB, Khanna D, Bagal SS, Chakravarti PS, Sharma AN, Vishwakarma RK, Shinde SS, Khargekar NC, Chaturvedi P. Cancer pattern in Varanasi district from Uttar Pradesh state of India, a foundation for cancer control based on the first report of the population-based cancer registry. Indian Journal of Cancer. 2024 Apr-Jun;61(2):383-389.
75. Budukh A, Dikshit R, Thakur JS, Kadam P, Dora T, Sancheti S, Chaudhary D, Badwe RA. Linkage of cancer registration with cancer treatment in predominantly rural district: a model form Sangrur district, Punjab state, India. International Journal of Noncommunicable Diseases. 2018 Apr 1;3(2):56-9.
76. Budukh A, Thakur JS, Dikshit R. Cancer Incidence and Mortality in Sangrur District, Punjab, India: 2017-2018 Tata Memorial Centre (TMC), Mumbai and Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India 2022.International Journal of Noncommunicable Diseases 2018 Apr-June;3(2):56-59.
77. Bagal S, Budukh A, Thakur JS, Dora T, Qayyumi B, Khanna D, Fernandes D, Chakravarti P, Singh R, Patil S, Dikshit R. Head and neck cancer burden in India: an analysis from published data of 37 population-based cancer registries. Ecancer medical science. 2023 Sep 21; 17:1603.
78. Khanna D, Sharma P, Budukh A, Vishwakarma R, Sharma AN, Bagal S, Tripathi V, Maurya VK, Chaturvedi P, Pradhan S. Rural-urban disparity in cancer burden and care: findings from an Indian cancer registry. BMC cancer. 2024 Mar 6;24(1):308.
79. Bulstra CA, Le Rutte EA, Malaviya P, Hasker EC, Coffeng LE, Picado A, Singh OP, Boelaert MC, de Vlas SJ, Sundar S. Visceral leishmaniasis: Spatiotemporal heterogeneity and drivers underlying the hotspots in Muzaffarpur, Bihar, India. PLoS Neglected Tropical Diseases. 2018 Dec 6;12(12): e0006888.
80. Balasubramaniam G, Cheulkar SA, Joshi PK, Patil AR, Badwe R, Dikshit R, Banavali S, Patil S. Incidence of cancer in a rural registry in India-Ratnagiri, Maharashtra. Indian Journal of Medical Sciences. 2023 Aug 19;75(2):47-52.
81. Yang YC, Zhu Y, Sun SJ, Zhao CJ, Bai Y, Wang J, Ma LT. ROS regulation in gliomas: implications for treatment strategies. Frontiers in Immunology. 2023 Dec 7; 14:1259797.
82. Menon VS, Padhy AS, Nittala R, Basani M, Arora SR. Short-Term Surgical Outcomes of Curative Colorectal Resections from an Evolving Low-Volume Cancer Center in a Tier-2 City in India. Indian Journal of Surgical Oncology. 2025 May 26:1-1.
83. Gormley M, Creaney G, Schache A, Ingarfield K, Conway DI. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. British Dental Journal. 2022 Nov 11;233(9):780-6.