Early Detection and Treatment of Head & Neck Cancers

Theoretical Background and Newly Emerging Research

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Editors
Rami El Assal
Canary Center at Stanford for Cancer Early Detection
Stanford University School of Medicine
Palo Alto, CA
USA

Dyani Gaudilliere
Division of Plastic & Reconstructive Surgery, Department of Surgery
Stanford University School of Medicine
Palo Alto, CA
USA

Stephen Thaddeus Connelly
Department of Oral and Maxillofacial Surgery
University of California, San Francisco
San Francisco, CA
USA

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This book is dedicated to the late Professor Sam Gambhir of Stanford.

Sam was the pioneer in the foundation of cancer early detection. He dedicated his life to developing methods of early disease detection, ushering in a new era of molecular imaging and nanotechnologies to flag signals of disease in its nascent stages. Dr. Gambhir was the Virginia and D.K. Ludwig professor of cancer research and chair of radiology at Stanford University School of Medicine. He was the founding director of the Canary Center at Stanford for Cancer Early Detection, Precision Health and Integrated Diagnostics Center at Stanford, and the director of the molecular imaging program at Stanford.

The editor-in-chief, Dr. Rami El Assal, would like to express his gratitude for the selfless devotion of Dr. Gambhir, a kind and honest man. Dr. El Assal commented, "In our last meeting while I was transitioning out of Stanford, Dr. Gambhir demonstrated the care and support to me at multi-level including stating that 'if you wanted to come back to Stanford, just let me know.'"

Dr. El Assal added, "I still remember that in the 2015 Department of Radiology Retreat, Sam stated, 'I want to make an impact on human health even if it is not recognized in my lifetime.'" *"And I believe he did," Dr. El Assal said.*

Foreword

It is with great pleasure that I write this foreword for the first edition of *Early Detection and Treatment of Head and Neck Cancer* (HNC). The fields of early detection and early treatment in cancer biology are advancing rapidly as both the concept and practical applications have entered clinical practice.

The recent release of the most comprehensive genomic HNC data to date (Nature, 2015) from The Cancer Genome Atlas, a project funded by the National Institute of Health to characterize cancer genomes, is enabling scientists to refine their list of candidate biomarkers and to identify new ones for early detection of HNCs. Such an expanding body of knowledge is essential given that roughly two-thirds of HNCs present at advanced stages, and the prognosis remains poor. Therefore, new approaches are urgently needed for early HNC detection to improve treatment outcomes. For example, circulating DNA has shown great promise as a non-invasively obtained biomarker in a number of HNC cohorts. Using the known mutational signatures of HNC to identify tumor DNA in body fluids has demonstrated the potential for detecting tumors at early stages and for monitoring tumor relapse and response to treatment.

In the era of precision health and medicine, there are opportunities to select treatment plans that are most likely to succeed based on an individual's personal data. HNC can be monitored and treated more efficiently by taking multiple forms of medical data into consideration and by implementing more effective methodologies that are currently being validated, including liquid biopsy, salivary biomarkers, imaging, and treatments, including gene therapy, immunotherapy, surgery, radiotherapy, and many others.

Early detection is an evidence-based field in which we have come a long way, but it is still in its infancy. We have discovered many of the fundamental principles but still need to develop, translate, and improve detection and diagnostics as well as treatment standards to, hopefully, prevent cancer, including HNC.

Here, I would like to invite readers to enjoy the carefully and expertly prepared material by the authors of this book series (Volumes I and II), which are based on solid scientific evidence and diverse clinical experience achieved through many years of professional practice.

R. Bruce Donoff, DMD, MD
Dean of Harvard School of Dental Medicine (1991–2019)
Boston, MA, USA

Dean Emeritus R. Bruce Donoff in Few Words

Dr. R. Bruce Donoff served as dean of Harvard School of Dental Medicine (HSDM) from 1991 to 2019. He was born in New York City and attended Brooklyn College as an undergraduate. He received his DMD from HSDM in 1967 and his MD from Harvard Medical School in 1973. Dr. Donoff's professional career has centered on Harvard's Faculty of Medicine and the Massachusetts General Hospital's Department of Oral and Maxillofacial Surgery. He began as an intern in 1967, served as chairman and chief of service from 1982 through 1993, and continues to see patients today.

In addition to leading HSDM as its dean, Dr. Donoff has made major contributions in research to the specialty of oral and maxillofacial surgery with interest in oral and head and neck cancers. He has published over one hundred papers, authored textbooks, and lectured worldwide. He recently helped launch the HSDM Initiative – Integrating Oral Health and Medicine, a project of great importance to him.

Dr. Donoff served 12 years on the board of the Oral and Maxillofacial Surgery Foundation and is former president of the Friends of the National Institute of Dental and Craniofacial Research. He is editor of the *MGH Manual of Oral and Maxillofacial Surgery* and a member of the editorial board of the *Journal of Oral and Maxillofacial Surgery* and the *Massachusetts Dental Society Journal*.

Dr. Donoff has received numerous honors during his academic career, including the American Association of Oral and Maxillofacial Surgeons Research Recognition Award, the William J. Gies Foundation Award for Oral and Maxillofacial Surgery, Fellow of the American Association for the Advancement of Science, the Alpha Omega Achievement Award, and the Distinguished Alumni and Faculty Awards from HSDM. In 2014, he was a Shils-Meskin awardee for leadership in the dental profession.

Acknowledgments

A Historic Perspective

> I shall be telling this with a sigh somewhere ages and ages hence;
> Two roads diverged in a wood, and I took the road less traveled by,
> And that has made all the difference.
>
> *– The Road Not Taken by Robert Frost, 1916*

I would like to acknowledge first and foremost my family:

To my mother who endured this long process with me, always offering support and for whom grace is all in her steps, heaven in her eye, in every gesture dignity and love. Everything I am or ever hope to be, I owe to my angel mother.

To my wife, Somayeh, and my son, Adam, you all are my world and reason for being. My gratitude for your understanding that my career being of service to others often entails long hours. Thank you for your patience and compassion.

To my sister, Lina, who always supported and guided me all the way, and my devoted brother-in-law, Ghiath, and my elegant nieces, Sana, Maria, Naya, and Zeina.

To my brother, Shadi, who was always there for me.

I can never forget my father, who was a blend of strength (may he rest in peace).

To my cousin, Hussein, whose friendship and support I treasure.

To my wife's family: my father- and mother-in-law; brother-in-law, Wahid; and my sisters-in-law, Susan, Samira, Sudaba, and Saeeda.

To my close friends whom I consider part of my family. They helped shape my education and supported me throughout my academic and professional journey.

Additionally, I would like to thank my friends and co-editors, Dyani and Thaddeus; without their help, this book would not have come to fruition. I am so proud of you and wish to let you know that your friendship touches me deeply. I know we will continue to work closely in the future and support one another's ideas and projects.

I would like to express my sincere gratitude to all authors who contributed to these two volumes; this project would not be possible without their contribution.

I feel a deep sense of gratitude to Emeritus Dean R. Bruce Donoff, who kindly wrote the foreword to this book series.

To all of my past teachers, mentors, and fellow students, I hope this book is worthy of the many contributions you have given me.

I am very grateful to all my colleagues and friends around the world.

Lastly, to head and neck cancer (HNC) patients, my respectful and gentle gratitude goes to you all. As a part of our commitment to service HNC patients, I recently co-founded with Thaddeus an "Early Disease Detection & Treatment Fund" to translate innovations from research labs, bringing them close to patients. We are proud to have partnered and invested with visionary entrepreneurs who are tackling head and neck cancers.

Palo Alto, CA, USA Rami El Assal

Preface

Volume II of this book series provides an up-to-date overview of the theoretical background in the field of head and neck cancer (HNC) as well as of the emerging research that is impacting our understanding of this disease.

Volume II begins with a comprehensive review of the epidemiology, etiology, symptoms, diagnosis, and staging of HNC. Next, it covers the essentials of potentially malignant disorders of the oral cavity, an important variety of HNC.

Subsequently, Volume II covers the newly emerging research in the field of HNC. For example, the advances in genomics research during the past few decades allowed us to better understand the mutational landscape of HNC. In addition, a comprehensive understanding of the pro-inflammatory signaling pathways in HNC could lead to the identification of novel biomarkers for early detection and the development of new therapeutic strategies. Furthermore, an increasing number of studies demonstrate that circulating biomarkers, such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomal miRNAs, can open up new avenues to comprehensively study, early detect, and precisely treat HNC. The overall goal is to shift towards precision medicine (discussed in detail in Volume I), which will bring individualized clinical benefit to patients with HNC.

We conclude this volume with the topic of chronic pain associated with HNC, including both the mechanisms of pain and the management strategies, and the emerging oral mucoadhesive drug delivery approach for HNC. All HNC surgeons, scientists, residents, and individuals, whose lives have been touched by this disease, will recognize the impact pain has upon a patient's health and his or her recovery trajectory.

The editors and the authors of the chapters herein hope that the valuable information presented will help you grow your knowledge base and improve your ability to successfully treat a wide variety of HNCs.

Palo Alto, CA, USA — Rami El Assal
Palo Alto, CA, USA — Dyani Gaudilliere
San Francisco, CA, USA — Stephen Thaddeus Connelly

Contents

Contributors

Hamzah Alkofahi Division of Plastic & Reconstructive Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, CA, USA

Department of Oral and Maxillofacial Surgery, Jordanian Royal Medical Services, Irbid, Jordan

Zhong Chen Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA

Stephen Thaddeus Connelly Department of Oral and Maxillofacial Surgery, University of California San Francisco (UCSF) School of Dentistry, San Francisco, CA, USA

San Francisco VA Health Care System, San Francisco, CA, USA

Mehdi Ebrahimi Prince Philip Dental Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong, China

Lisa M. Evangelista Department of Otolaryngology/Head & Neck Surgery, University of California at Davis Medical Center, Sacramento, CA, USA

Ayman Fouad Department of Otolaryngology, Head & Neck Surgery, Stanford University, Stanford, CA, USA

Department of Otolaryngology, Head & Neck Surgery, Tanta University, Tanta, Egypt

Jennifer R. Grandis Department of Otolaryngology – Head and Neck Surgery, University of California at San Francisco, San Francisco, CA, USA

Jun Jeon Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA

Daniel E. Johnson Department of Otolaryngology – Head and Neck Surgery, University of California at San Francisco, San Francisco, CA, USA

Nagarjun Konduru Department of Cellular and Molecular Biology, University of Texas Health Science Center at Tyler, Tyler, TX, USA

Shilpa Kusampudi Department of Cellular and Molecular Biology, University of Texas Health Science Center at Tyler, Tyler, TX, USA

Peter Luke Santa Maria Department of Oral Rehabilitation, Prince Philip Dental Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong, USA

Solange Massa Department of Otolaryngology, Head & Neck Surgery, Stanford University, Stanford, CA, USA

Ethan L. Morgan Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA

Taichiro Nonaka Center for Oral/Head and Neck Oncology Research, School of Dentistry, University of California, Los Angeles, Los Angeles, CA, USA

Division of Oral Biology and Medicine, School of Dentistry, University of California, Los Angeles, Los Angeles, CA, USA

Kelechi Nwachuku School of Medicine, University of California at San Francisco, San Francisco, CA, USA

M. Anthony Pogrel Department of Oral and Maxillofacial Surgery, University of California, San Francisco, San Francisco, CA, USA

Carter Van Waes Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA

Ramya Viswanathan Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA

David T. W. Wong Center for Oral/Head and Neck Oncology Research, School of Dentistry, University of California, Los Angeles, Los Angeles, CA, USA

Division of Oral Biology and Medicine, School of Dentistry, University of California, Los Angeles, Los Angeles, CA, USA

Justin M. Young Private Practice, San Francisco, CA, USA

Department of Oral & Maxillofacial Surgery, University of the Pacific, Arthur A. Dugoni School of Dentistry, San Francisco, CA, USA

Chapter 1
General Introduction to Head and Neck Cancer: Etiology, Symptoms, Diagnosis, Staging, Prevention, and Treatment

Shilpa Kusampudi and Nagarjun Konduru

Introduction

Head and neck cancer (HNC) is a terminology used for a group of cancers originating in the lips, oral cavity, oropharynx, salivary glands, larynx, pharynx, hypopharynx, nasopharynx, and sinuses (Fig. 1.1). These cancers most commonly affect squamous cells, accounting for about 90% of all HNC [1–4]. In the 1950s, tumors of the facial bones, as well as primary and metastatic tumors of the neck and thyroid neoplasms were also termed head and neck tumors [5]. However, presently these tumors fall under different categories of malignancies such as thyroid and parathyroid malignancies under endocrine neoplasms and lymph nodes under hematological malignancies.

Neoplasms in various regions of the body are assigned codes, with C00–C14, C30, and C32 coding for head and neck cancers (Table 1.1).

Epidemiology

HNC is the sixth most common type of cancers, based on the estimated number of new cases (Fig. 1.2). In 2018, 710,237 out of 18 million new cases of all cancers recorded worldwide were HNC.

Based on Globocan world cancer data for 2018, the global incidence of HNC is 4.9% of all cancers (Fig. 1.3). Among the various HNCs, lip and oral cavity cancers together accounted for the highest percentage of the global HNC cases (40%),

S. Kusampudi · N. Konduru (✉)
Department of Cellular and Molecular Biology, University of Texas Health Science Center at Tyler, Tyler, TX, USA
e-mail: nagarjun.konduruvenkata@uthct.edu

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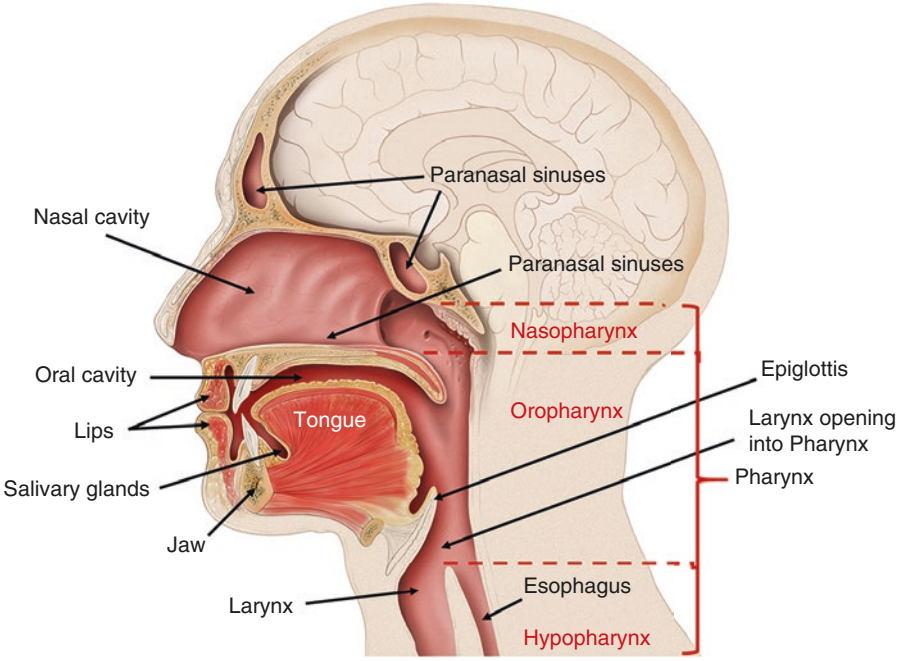


Fig. 1.1 Regions of head and neck cancer. (Edited from [6])

Table 1.1 Head and neck cancer codes

Cancer code	Cancer
C00–C06	Lip, oral cavity
C000	Malignant neoplasm of external upper lip
C001	Malignant neoplasm of external lower lip
C002	Malignant neoplasm of external lip, unspecified
C003	Malignant neoplasm of upper lip, inner aspect
C004	Malignant neoplasm of lower lip, inner aspect
C005	Malignant neoplasm of lip, unspecified, inner aspect
C006	Malignant neoplasm of commissure of lip, unspecified
C008	Malignant neoplasm of overlapping sites of lip
C009	Malignant neoplasm of lip, unspecified
C010	Malignant neoplasm of base of tongue
C020	Malignant neoplasm of dorsal surface of tongue
C021	Malignant neoplasm of border of tongue
C022	Malignant neoplasm of ventral surface of tongue
C023	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C024	Malignant neoplasm of lingual tonsil
C028	Malignant neoplasm of overlapping sites of tongue
C029	Malignant neoplasm of tongue, unspecified
C030	Malignant neoplasm of upper gum

Table 1.1 (continued)

Cancer code	Cancer
C031	Malignant neoplasm of lower gum
C039	Malignant neoplasm of gum, unspecified
C040	Malignant neoplasm of anterior floor of mouth
C041	Malignant neoplasm of lateral floor of mouth
C048	Malignant neoplasm of overlapping sites of floor of mouth
C049	Malignant neoplasm of floor of mouth, unspecified
C050	Malignant neoplasm of hard palate
C051	Malignant neoplasm of soft palate
C052	Malignant neoplasm of uvula
C058	Malignant neoplasm of overlapping sites of palate
C059	Malignant neoplasm of palate, unspecified
C060	Malignant neoplasm of cheek mucosa
C061	Malignant neoplasm of vestibule of mouth
C062	Malignant neoplasm of retromolar area
C0680	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C0689	Malignant neoplasm of overlapping sites of other parts of mouth
C069	Malignant neoplasm of mouth, unspecified
C07–08	Salivary glands
C07	Malignant neoplasm of parotid gland
C080	Malignant neoplasm of submandibular gland
C081	Malignant neoplasm of sublingual gland
C089	Malignant neoplasm of major salivary gland, unspecified
C09–10	Oropharynx
C090	Malignant neoplasm of tonsillar fossa
C091	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C098	Malignant neoplasm of overlapping sites of tonsil
C099	Malignant neoplasm of tonsil, unspecified
C100	Malignant neoplasm of vallecula
C101	Malignant neoplasm of anterior surface of epiglottis
C102	Malignant neoplasm of lateral wall of oropharynx
C103	Malignant neoplasm of posterior wall of oropharynx
C104	Malignant neoplasm of branchial cleft
C108	Malignant neoplasm of overlapping sites of oropharynx
C109	Malignant neoplasm of oropharynx, unspecified
C11	Nasopharynx
C110	Malignant neoplasm of superior wall of nasopharynx
C111	Malignant neoplasm of posterior wall of nasopharynx
C112	Malignant neoplasm of lateral wall of nasopharynx
C113	Malignant neoplasm of anterior wall of nasopharynx
C118	Malignant neoplasm of overlapping sites of nasopharynx
C119	Malignant neoplasm of nasopharynx, unspecified
C12–13	Hypopharynx
C12	Malignant neoplasm of pyriform sinus

(continued)

Table 1.1 (continued)

Cancer code	Cancer
C130	Malignant neoplasm of postcricoid region
C131	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C132	Malignant neoplasm of posterior wall of hypopharynx
C138	Malignant neoplasm of overlapping sites of hypopharynx
C139	Malignant neoplasm of hypopharynx, unspecified
C14	Unspecified
C140	Malignant neoplasm of pharynx, unspecified
C142	Malignant neoplasm of Waldeyer's ring
C148	Malignant neoplasm of overlapping sites of lip, oral cavity, and pharynx
C30–31	Sinus cancer
C30	Malignant neoplasm of nasal cavity
C301	Malignant neoplasm of middle ear
C310	Malignant neoplasm of maxillary sinus
C311	Malignant neoplasm of ethmoidal sinus
C312	Malignant neoplasm of frontal sinus
C313	Malignant neoplasm of sphenoid sinus
C318	Malignant neoplasm of overlapping sites of accessory sinuses
C319	Malignant neoplasm of accessory sinus, unspecified
C32	Malignant neoplasm of glottis
C321	Malignant neoplasm of supraglottis
C322	Malignant neoplasm of subglottis
C323	Malignant neoplasm of laryngeal cartilage
C328	Malignant neoplasm of overlapping sites of larynx
C329	Malignant neoplasm of larynx, unspecified

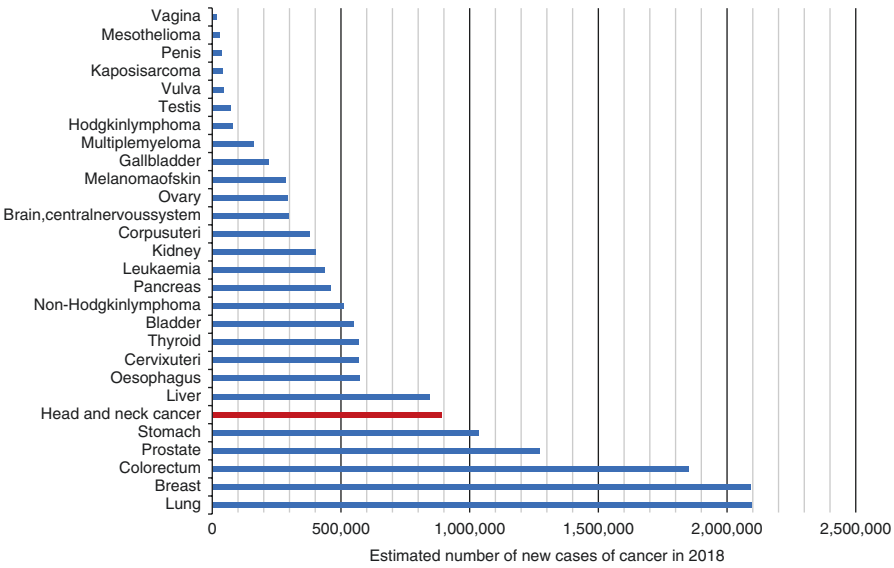


Fig. 1.2 The number of new cases of cancer estimated worldwide in 2018

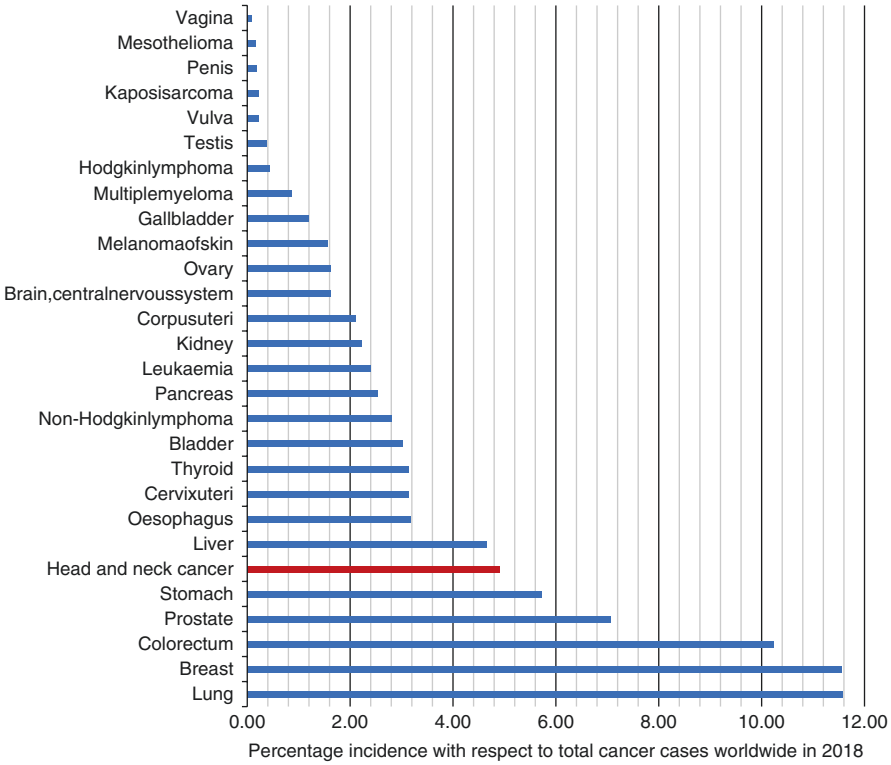


Fig. 1.3 Percentage incidence of different cancers to the total number of cancer cases estimated worldwide

followed by larynx 4 (20%), nasopharynx (15%), oropharynx (10%), hypopharynx (9%), and salivary glands (6%) (Fig. 1.4).

Based on 2018 Globocan data, the highest number of new cases of HNC was recorded in Asia, followed by Europe, North America, Latin America and the Caribbean, Africa, and Oceania. HNC in southeast Asia is actually ranked #1 among all other cancers, and in the US ranking #6. The percentage incidence of HNC to other cancers in the respective continent was highest in the Asian continent (6.3%) followed by Africa, Latin America and the Caribbean, Europe, Oceania, and North America (Fig. 1.5). In Asia, lip and oral cavity cancer accounted for the highest incidence (41%) of HNC cases, followed by nasopharynx, larynx, hypopharynx, oropharynx, and salivary glands.

As the Asian continent had the highest percentage incidence of HNC compared to other continents, the incidence of HNC was focused in various countries of Asia. Based on the year 2018 cancer statistics the top 10 countries with increased new incidences of HNC were India, China, Bangladesh, Indonesia, Pakistan, Japan, Thailand, Myanmar, Turkey, and the Philippines. In India, lip and oral cavity

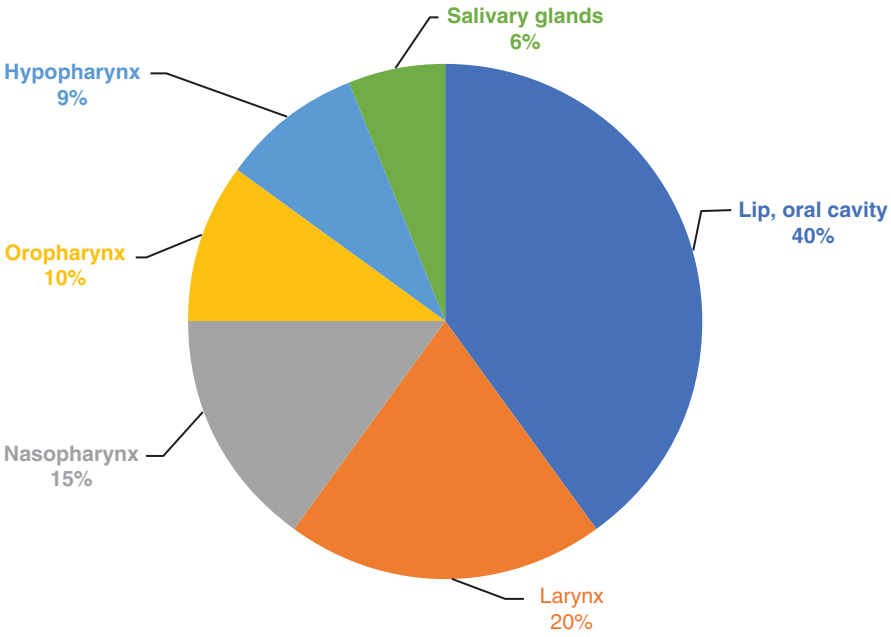


Fig. 1.4 The percentage incidence of various types of HNC (C00–14, 32) in the world

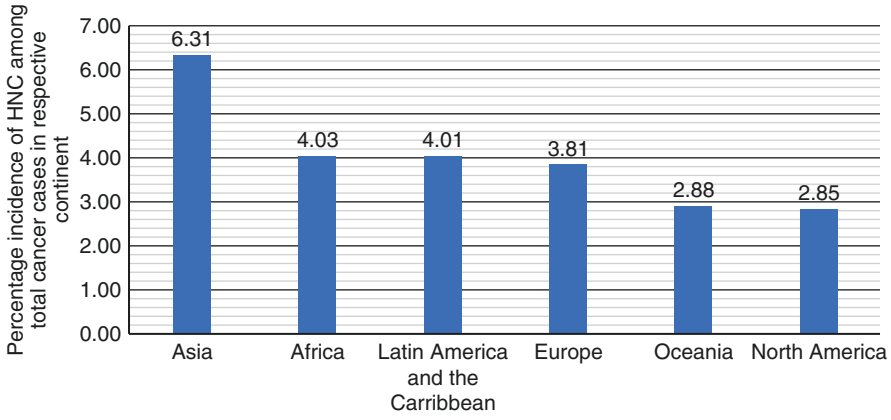


Fig. 1.5 Percentage incidence of HNC (C00–14, 32) by continent

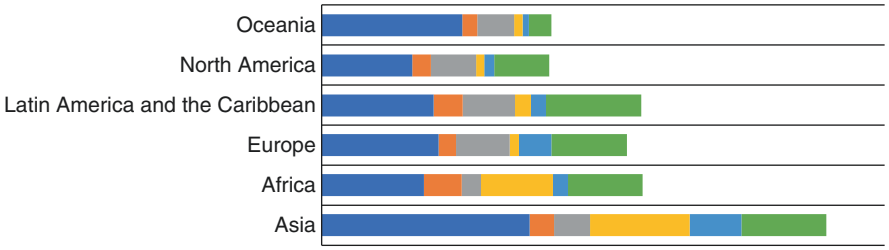
cancers were recorded to be 58% of HNC followed by larynx (14%), hypopharynx (13%), oropharynx (9%), salivary glands (4%), and nasopharynx (2%).

The number of new incidences of HNC was highest in India and China; the reason could be their billion-plus population. However, Bangladesh is the Asian country recorded with the highest percentage (20.5%) of HNC incidence to all cancers reported in the respective country, and Armenia (1%) is recorded with the least

percentage incidence of HNC. The top 10 countries with highest percentage incidence of HNC among other cancer incidences in their respective countries are Bangladesh, India, Pakistan, Sri Lanka, Bhutan, Myanmar, Afghanistan, Nepal, Indonesia, and Malaysia.

In Bangladesh among the various HNC, 43% incidence of the lip and oral cavity cancer was observed, followed by hypopharynx (23%), larynx (16%), oropharynx (12%), salivary gland (3%), and nasopharyngeal carcinoma (3%), respectively.

The percentage incidence of different types of head and neck cancer vary by continent and are summarized in Fig. 1.6. Based on 2018 Globocan world cancer data, HNC is among the top 10 cancers in North America with its place being in the ninth place with 2.9% (Fig. 1.7). Among the various HNCs, lip and oral cavity



	Asia	Africa	Europe	Latin America and the Caribbean	North America	Oceania
Lip,oralcavity	2.60	1.29	1.46	1.41	1.14	1.77
Salivaryglands	0.31	0.46	0.22	0.36	0.23	0.18
Oropharynx	0.44	0.24	0.66	0.65	0.56	0.46
Nasopharynx	1.25	0.90	0.12	0.19	0.10	0.10
Hypopharynx	0.64	0.18	0.40	0.20	0.13	0.09
Larynx	1.07	0.95	0.94	1.21	0.69	0.29

Percentage incidence compared to all cancer incidences in respective continent

Fig. 1.6 Percentage incidence of each type of HNC (C00–14, 32) in comparison to total cancers occurring in the respective continents

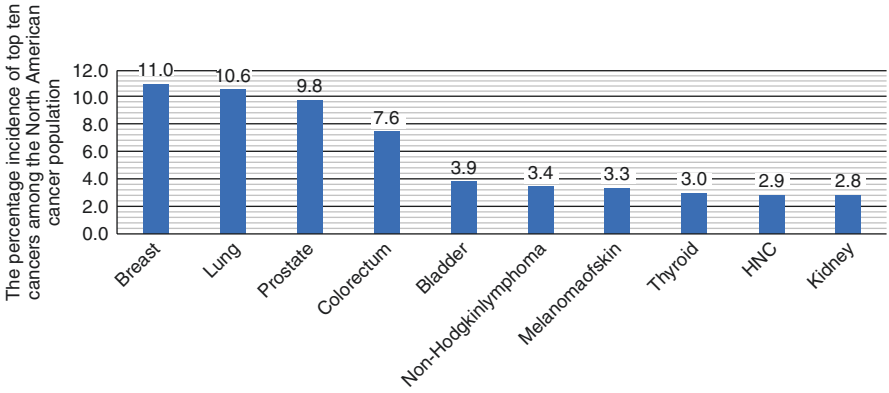


Fig. 1.7 The percentage incidence of the top 10 cancers among the North American cancer population in 2018

cancers together accounted for the highest percentage of the global HNC cases (40%), followed by larynx (24%), oropharynx (20%), salivary glands (8%), hypopharynx (5%), and nasopharynx (3%).

Age-adjusted statistics of HNC in the United States for the years 2013–2017 are presented in Table 1.2. The rate of cancer-related deaths increased till 1991,

Table 1.2 Head and neck cancer statistics in the United States' Surveillance, Epidemiology, and End Results (SEER 21) 2013–2017, age-adjusted [9]

	Oral cavity and pharynx cancer	Lip cancer	Tongue cancer	Laryngeal cancer
Estimated new cases in 2020	53,260		17,660	12,370
Percentage of all new cancer cases	2.9%		1.0%	0.7%
Estimated deaths in 2020	10,750		2830	3750
Percentage of all cancer deaths	1.8%		0.5%	0.6%
5-year Relative Survival (2010–2016)	66.2%	92.0%	67.1%	60.6%
Rate of new cases per 100,000 men and women per year (2013–2017)	11.4	0.6	3.5%	2.9
Rate of deaths per 100,000 men and women per year (2013–2017)	2.5	0.02	0.7%	1
Percent of men and women with lifetime risk of developing cancer	1.2%	0.1%	0.4%	0.3%
Percentage of all new cancer cases in the US	2.9%		1.0%	0.7%
Prevalence of this cancer in US in the year 2017	383,415			96,231
Frequently diagnosed among people aged between	55–64	65–74	55–64	55–64
Laryngeal cancer deaths is highest among people aged between	65–74	85+	65–74	65–74
Race and gender exhibiting increased number of new cases	Non-Hispanic male	White male	White male	Black male
Race and gender exhibiting increased number of deaths	Black male	Non-Hispanic male and White male	Non-Hispanic and white	Black male
Age-adjusted death rates on average each year over 2008–2017	Raising by 0.5%	Stable	Raising on average 1.2%	Falling by 2.3%

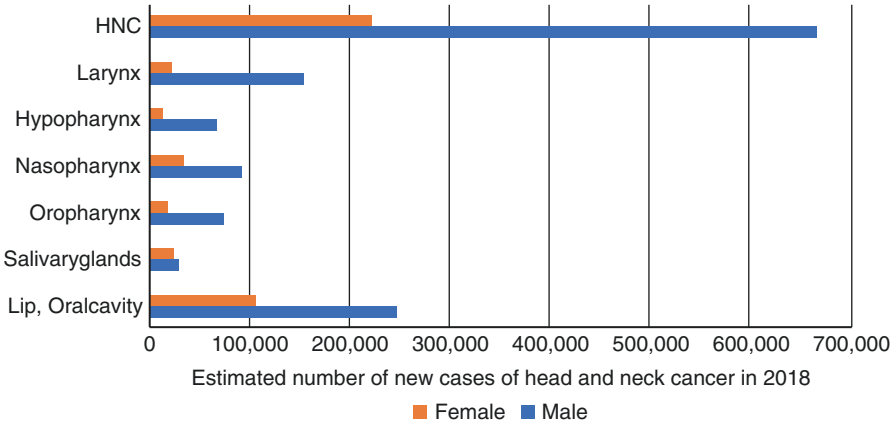


Fig. 1.8 The number of new cases of the male and female population with HNC (C00–14, 32) estimated worldwide in the year 2018

then decreased through 2017, thereby projecting 2.9 million less deaths due to cancer in comparison to the deaths estimated in case the rates persisted [8]. In 2018, North America stands in third position in the number of new incidences of head and neck cancer in the world. While this continent rank sixth in percentage incidence of HNC in comparison to total cancers by continent (Globocan 2018). American Cancer Society has projected 1,806,590 new cases of cancer and 606,520 deaths due to cancer in year 2020, in the United States [8].

Based on the Globocan 2018 data, the estimated number of new cases of HNC as well as the percentage incidence of each type of HNC was globally higher in the male population in comparison to the female population (Figs. 1.8 and 1.9). The discrepancy in the incidence of HNC in males and females is generally related to the population exposed to risk factors such as tobacco smoking or chewing, betel nut chewing, and alcohol consumption [10]. This was confirmed by a retrospective and hospital-based study conducted by Addala et al. (2012) focusing only on the histologically confirmed cases of HNC patients suggested a preponderance of cancer in males compared to females due to indulgence of males in the habits that increase risk for HNC (smoking and chewing tobacco, drinking alcohol, and using them in combination) [11]. Exposure to these risk factors for longer duration together with diet and occupation increased the incidence of HNC [11]. However, the incidence of lip, oral cavity cancers, salivary gland cancer, and nasopharyngeal carcinoma was higher in females than in males. Whereas the percentage incidence of oropharynx, hypopharynx, and larynx cancer were higher males than in females (Fig. 1.10).

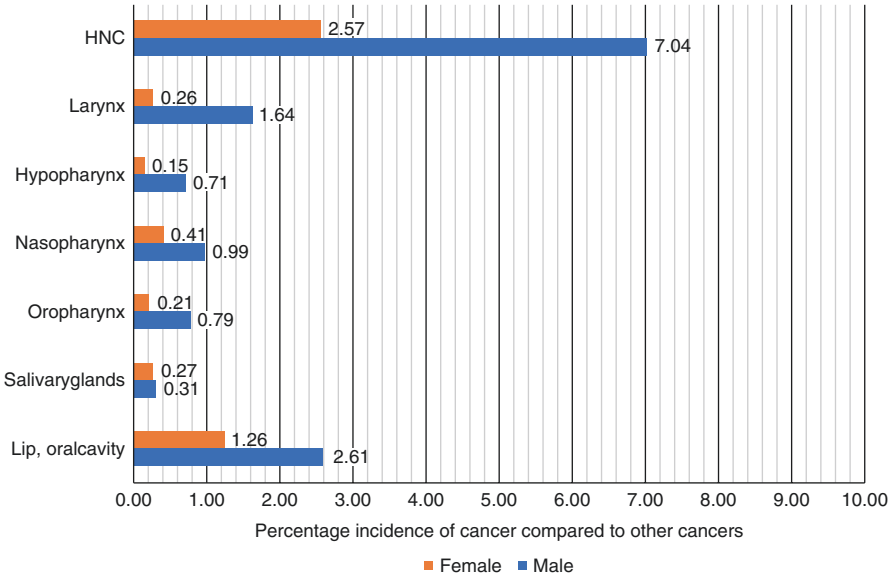


Fig. 1.9 Percentage incidence of HNC (C00–14, 32) in comparison to total cancers occurring worldwide

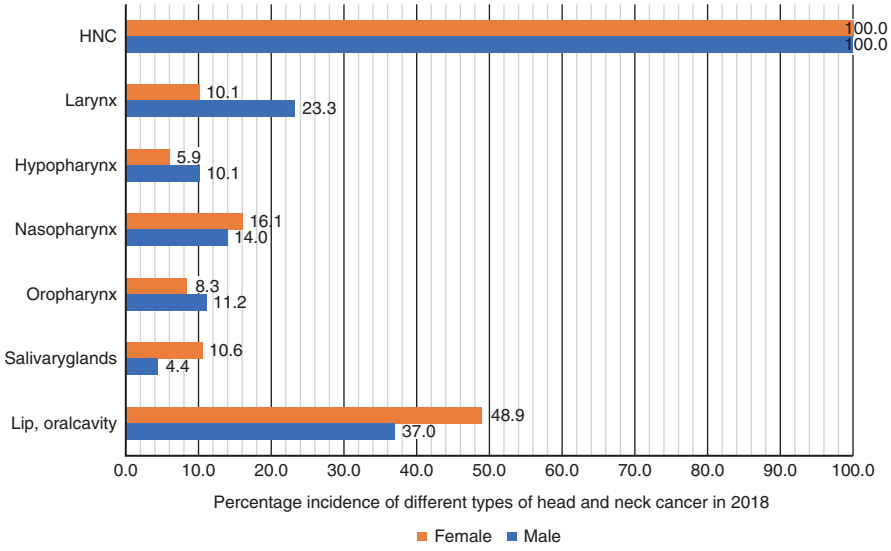


Fig. 1.10 Percentage incidence of different types of HNC (C00–14, 32) compared to total incidences of HNC in respective male and female populations

Etiology

"Exposome" is a term defined as the measure of all the internal and external exposure a person is introduced to in a lifetime and its effect on health [12]. People are exposed to various environmental and occupational sources before birth and throughout their life. Understanding the relationship between the exposomes and an individual's genetics and epigenetics impact our health. Assessment of internal exposome occurs at the level of the genes, proteins, lipids, and metabolites [12]. External exposure assessment relies on measuring environmental stressors, and these influence the occurrence of HNC. The various external agents causing HNC will be discussed in detail (Table 1.3).

Tobacco

Tobacco is used in several ways such as smoking cigarettes, cigars, pipes, chewing, and snuffing tobacco and is considered to be the prime risk factor for HNC [4, 10]. Exposure to tobacco and related products is a component of the external exposome, contributing to development of oral cavity cancer, pharyngeal cancer, oropharyngeal cancer, hypopharyngeal cancer, supraglottis cancer, and nasopharyngeal cancer.

In the Arabian peninsula, a traditional smokeless tobacco habit called "shammah" is associated with the incidence of leukoplakia in a dose-dependent manner [13]. Use of tobacco with products socially acceptable in Southeast Asia, the South Pacific Islands, and India, such as betel nuts, *paan*, *chaalia*, *gutka*, *naswar*, and areca also increase the risk for oral cavity cancer [13]. Smokeless tobacco contains carcinogenic substances such as nitrosamines and is considered to be a significant risk factor for oral cavity cancer. South Asia is known to be a hub for global smokeless tobacco use [14]. Khan et al. (2014) have reported that chewing *paan* with tobacco increases the risk of oral cavity cancer [14]. A large portion of the population of the Asia-Pacific region chews betel quid regularly [15, 16]. Areca nut alone is an age-old carcinogen and causes oral cavity cancer [17, 18].

Alcohol

Increased consumption of alcohol increases the risk of developing oral cavity, pharyngeal, and laryngeal cancer. Elwood et al. (1984) have reported increased risks with alcohol consumption in comparison to smoking [19].