

# Incidence, prevalence, and mortality associated with head and neck cancer in India: Protocol for a systematic review

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## Abstract

**BACKGROUND:** Head and neck cancer (HNC) is a heterogeneous tumor at various anatomic sites and one of the most common cancers in India. Published and existing reports and studies highlight an alarming increase in the incidence, prevalence, and mortality of HNC. Despite its high incidence, there is a dearth of more precise estimates of reliable epidemiological data pertaining to HNC in India.

**AIM:** This protocol aims to conduct a full-scale systematic review and meta-analysis on the HNC epidemiology (incidence, prevalence, and mortality) in 29 states and 7 union territories of India.

**METHODS AND ANALYSIS:** We will search for eligible published studies through PubMed, Scopus, Science Direct, MEDLINE, Web of Science, and Cochrane Review. Cancer registries such as (but not limited to) World Health Organization, International Agency for Research on Cancer, and the National Centre for Disease Informatics and Research-National Cancer Registry Program, which is maintained by the Indian Council of Medical Research, will be used for extracting relevant data using a standardized data collection form. The random-effects model of meta-analysis will be employed to aggregate the pooled estimates of relative ratios with 95% confidence intervals. Publication bias will be assessed using a funnel plot, and Egger's regression will be applied to test the symmetry of the funnel plot.

**DISCUSSION:** This review will provide updated evidence of the current burden of HNC in India. This will guide future studies and cancer registry reports to provide holistically representative epidemiological data.

**SYSTEMATIC REVIEW REGISTRATION:** In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews and was assigned the registration number, CRD42017077482.

**Key Words:** Epidemiology, head and neck cancer, incidence, India, mortality, prevalence, protocol, systematic review

## Study Questions

Our systematic review and meta-analysis protocol on the incidence, prevalence, and mortality rate of head and neck cancer (HNC) in India will address the following crucial questions:

1. To conduct the full-scale systematic review and meta-analysis on the incidence, prevalence, and mortality of HNC in 29 states and 7 union territories of India.
2. To study the prevalence, incidence, and mortality rate in age-wise HNC cancer trends and projection of the burden of HNC.
3. To study the diverse demographical, clinicoepidemiological, clinicopathological, and biological characteristics of Indian HNC patients.

## Background

Estimating the incidence, prevalence, and mortality of head and neck cancer (HNC) in India poses many challenges owing to the complexity associated with it.<sup>[1]</sup> It is widely accepted that the lack of resources, such as funding and infrastructure, has led to weak and inadequate epidemiological data about the burden of HNC in India.<sup>[1]</sup> There is a scarcity of epidemiological reviews associated with HNC in India.<sup>[2]</sup> Furthermore, the few available studies suffer from unreliable findings due to insufficient geographic coverage, short study period, and small sample size.<sup>[2]</sup> The critical HNC risk factors such as alcohol consumption and tobacco chewing are strongly ingrained in the cultural diversity of India.<sup>[3,4]</sup> These issues control the incidence

and prevalence of HNC.<sup>[3,4]</sup> The available statistics show increased trends of HNC incidence and prevalence.<sup>[5,6]</sup> The interplay between risk factors, such as HPV, tobacco smoking, alcohol consumption, and betel quid chewing, is significantly affected by varying demographic profiles and lifestyle habits across the country.<sup>[7]</sup> Hence, the assessment and comparison of the obtained HNC epidemiology data on available national resources become a strenuous task due to its complexity and data setting.

Almost all the risk factors involved with HNC entail a substantial economic burden on the country, from drinking to smoking and even to the extent of betel quid and tobacco chewing.<sup>[8-10]</sup> The relevant risk factors not only incur a cost to the state regarding health expenses but also in terms of prevention and rehabilitation programmes.<sup>[8-10]</sup>

## Rationale

Most of the publicly available data extracted from published reports and cancer registry databases were only sourced from a few representative cities and their corresponding hospitals.<sup>[11,12]</sup> This proposed comprehensive and up-to-date protocol for a systematic review will identify all published relevant studies from several electronic bibliographical databases. This study may assist in developing essential elements of international cancer registry databases with emerging epidemiological changes in regions beyond the scope of such databases.

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The investigated data will help in covering crucial gaps in our current knowledge of the epidemiology of HNC in India. The findings from systematic reviews following this protocol will allow future researchers to focus better on their study and remove inherent drawbacks in their study design and settings. A comparison with a statistical account of risk factor prevalence will further help in understanding the pattern of HNC growth in India.

The systematic review can further be expanded into a time-trends analysis of HNC epidemiology, which will help us to identify geographical locations of high importance. This will further go on to allow implementation of early screening and treatment research at high cancer incidence locations.

### Objectives

The main objective of this protocol is to describe the qualitative and quantitative data syntheses of incidence, prevalence, and mortality of HNC in India.

The primary objective of this proposed study is to identify the age-standardized incidence; 1-year, 3-year, and 5-year prevalence; and age-standardized mortality of HNC in the 29 states and 7 union territories of India for the last 20 years.

The secondary objective is to correlate primary outcome data with geographical regions in India, addition to characteristics of the study, study participants, study methods, and results.

### Methods

This systematic review and meta-analysis research protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines.<sup>[13]</sup>

#### Study designs and participants

The authors will include all studies that have a clearly defined incidence, prevalence, and mortality of HNC in India that is further defined as a confirmative diagnosis of cancer by clinical examinations as well as any other conclusive clinical tests other than self-reporting. Authors will include studies examining the general human population with HNC. There will be no limits on study participants in terms of age, gender, ethnicity, morbidities (for patients and the general population), staff role, and occupation (for healthcare professionals such as nurses, surgeons, or physiotherapists).

The studies should have been carried out independently and should not be based on any global or national cancer registry for the statistical data of incidence, prevalence, and mortality. No publication date or publication status restrictions will be imposed. However, the language of the paper will be restricted to English only. The outcome measures that will be taken into account include age, gender, and city-wise distribution of incidence, prevalence, and mortality in a specific and standardised (both national and global) manner. A number of cases for HNC and each anatomical site will be taken for studies which fail to provide the aforementioned outcome measures distinctly. Studies will be selected according to the criteria outlined in the following sections.

### Selection criteria for studies

#### Inclusion criteria

Study has carried out independent data collection and has not relied on any cancer registries. Study provides statistical data regarding the epidemiology of HNC in India. Study describes a proper geographically specified region within India as the site of study. Language: English.

#### Exclusion criteria

Study has clearly stated that the data being commented upon are not of its own origin and have been taken from a cancer registry (either of national or global origin). Study does not provide statistical data regarding the epidemiology of HNC in India and has merely carried out a narrative or a descriptive review. Study does not mention any proper geographic demarcation.

### Selection criteria for participants

#### Inclusion criteria

Participants of all ages with age or age range clearly mentioned. All study participants have received clear test-based confirmation of HNC. All study participants should be residing in India.

#### Exclusion criteria

Participants' age or age range has not been clearly mentioned. Study participants' confirmative diagnosis of HNC has not been clearly identified. Self-reporting of the disease and questionable survey and screening methods of deduction have been employed.

### Setting

There will be no restrictions by type of clinical setting. Authors will include studies at all levels of healthcare setting (such as primary, secondary, and tertiary healthcare) and those conducted in the community for maximum representation.

### Language

Authors will include articles reported in the English language.

### Information sources

Authors will develop a comprehensively encompassing literature search strategy using medical subject headings and text words related to the epidemiology of HNC in India. The search will be carried out through Scopus, PubMed, Science Direct, MEDLINE, Web of Science, EMBASE, and Cochrane Library. This extensive search across multiple electronic bibliographic databases will ensure greater coverage of the topic by accounting for variability between indexing in each database. The literature search will be limited to the English language and human subjects.

In addition, epidemiological data (incidence, prevalence, and mortality pertaining to HNC in India) from credible reports by cancer registries will be incorporated, such as (but not limited to): clinicoepidemiological, clinicopathological, and biological characteristics of HNC participants (if sufficient study information and data are identified and available). The age-standardised method by Segi standard population,<sup>[14]</sup> Modified by Doll and colleagues,<sup>[15]</sup> will be used for comparing incidence rates across the various registries.

### Searching other resources

1. GLOBOCAN 2012 by World Health Organization (WHO): International Agency for Research on Cancer (IARC)
2. Cancer Incidence in 5 Continents by WHO: IARC
3. Global Cancer Observatory by WHO: IARC
4. Global Health Estimate 2012 by WHO: Department of Health Statistics and Information Systems
5. Three-Year Report of Population-Based Cancer Registries 2001–2014 by National Centre for Disease Informatics and Research-National Cancer Registry Programme maintained by Indian Council of Medical Research.

We will consider additional reports from NCRP, national mortality data from Civil Registration System, Medical Certification of Cause of Death, and the Sample Registration System and Global Burden of Disease specifically Local Burden of Disease as well as state-level disease burden initiative in India if sufficient data are unavailable.

To ensure literature saturation, authors will scan the reference lists of included studies or relevant reviews identified through the search. They will also search the authors' personal publications to make sure that all relevant materials have been obtained. Finally, they will circulate a bibliography of the included articles to cancer statisticians or epidemiologists identified by them.

### Search strategy

Both qualitative and quantitative studies will be considered for this protocol. No study design or date limits will be set on the search, although only studies in the English language will be included, due to resource limitations. A Web of Science search strategy will be developed with inputs from all authors [Table 1]. A draft Web of Science search strategy will be created. After the Web of Science strategy is finalised, it will be adapted to the syntax and subject headings of the other databases to be searched. The specific search strategies will be created by all authors after consultation with an associate with expertise in systematic review searching, preferably a Chief Librarian.

The Web of Science search strategy will be updated towards the end of the review, after being validated to

ensure that the strategy retrieved a high proportion of eligible studies found through any means but indexed in Web of Science.

### Study records

#### Data extraction and management

Literature search results will be uploaded to EndNote V.8.0 software, internet-based software that facilitates collaboration among reviewers during the study selection process. The team will screen the results based on the inclusion and exclusion criteria. Citation abstracts and full-text articles will be uploaded into EndNote. The screening questions will be refined and piloted before the study selection process. EndNote will also aid in the creation of the PRISMA flowchart [Figure 1].

All authors will aim to avoid double counting of outcome measures when collating data from multiple reports of the same study by reviewing author names, sample size, epidemiological data, and outcomes. Authors will indicate whether all reports on a study will be considered, as inconsistencies may reveal study limitations.

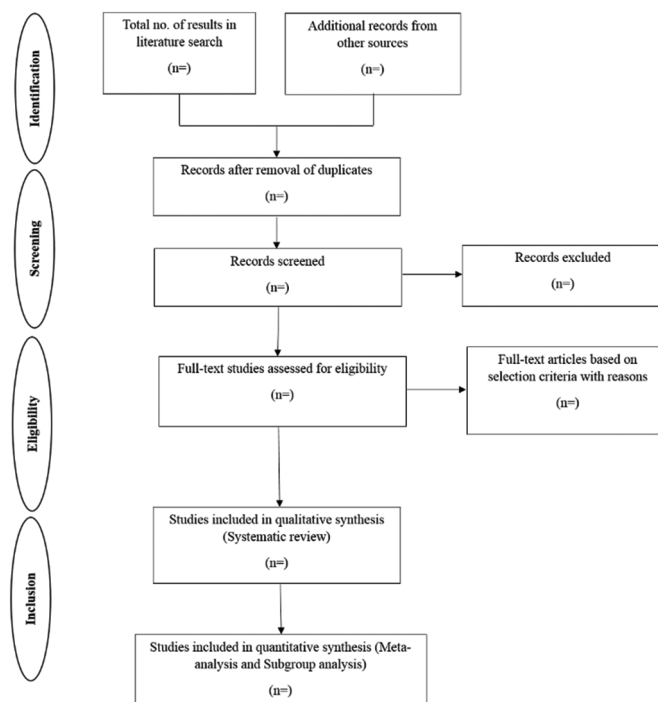
### Selection process

Authors will independently screen the titles and abstracts obtained by the search strategy against the selection criteria. They will obtain full reports for all titles that appear to meet the study selection criteria or where there is any uncertainty. The pairs of authors will then screen the full-text reports and decide whether these meet the participants' selection criteria. They will seek additional information from other authors where necessary to resolve questions about eligibility. Any disagreement will be resolved through discussion. Authors must record the reasons for excluding trials. Neither of the review authors will blind to the journal titles nor the study authors or institutions.

**Table 1: Search strategy**

#### Search terms (Medical Subject Headings)

"Cancer" [Topic] AND "India" [Topic]
"Cancer" [Topic] AND "Epidemiology" [Topic] AND "India" [Topic]
"Cancer" [Topic] AND "Incidence" [Topic] AND "India" [Topic]
"Cancer" [Topic] AND "Prevalence" [Topic] AND "India" [Topic]
"Cancer" [Topic] AND "Mortality" [Topic] AND "India" [Topic]
"Head and Neck Cancer" [Topic] AND "India" [Topic]
"Head and Neck Cancer" [Topic] AND "Epidemiology" [Topic] AND "India" [Topic]
"Head and Neck Cancer" [Topic] AND "Incidence" [Topic] AND "India" [Topic]
"Head and Neck Cancer" [Topic] AND "Prevalence" [Topic] AND "India" [Topic]
"Head and Neck Cancer" [Topic] AND "Mortality" [Topic] AND "India" [Topic]



**Figure 1: Flow diagram of the flow of data information on HNC incidence, prevalence and mortality through the different phases of this systematic review, meta-analysis, and subgroup analysis**



### Data collection process

Selected studies will have their records imported into EndNote. The full text of the selected studies' references will be retrieved and reviewed in a second phase to classify the studies based on the region (geographical city) in which they were carried out and to extract the relevant information. References cited in the retrieved publications will be reviewed to identify additional articles considered relevant, which will undergo the same selection process as described above. In order to standardise the data extraction process, a data extraction sheet will be created and used by all researchers involved in data extraction. The sheet will be pilot tested on randomly selected included studies and refined accordingly. One author can extract the following data from included studies, and another can check the extracted data. Disagreements will be resolved by discussion between the authors; if no agreement is reached, then the third author will hold the deciding vote.

### Data items

The information (if available) that would be extracted from each study:

- (1) Characteristics of study (including author, year of publication, a geographic region within India that the study talks about, the year when the study took place, and type of study);
- (2) Characteristics of study participants (including age, stage and severity of disease, and method of diagnosis), and the study's inclusion and exclusion criteria; and
- (3) Characteristics of study methods and results (including International Classification of Diseases (ICD) Code for the anatomical site of cancer under study, number of cases or patients, and a statistical measure of the epidemiology of HNC in India such as incidence, prevalence, and mortality).

### Outcomes and prioritisation

#### Primary outcomes

The primary outcome is to evaluate age-standardised incidence; 1-year, 3-year, and 5-year prevalence; and age-standardised mortality of HNC in India.

#### Secondary outcomes

The secondary outcome is to link the variations in primary outcomes with geographic location, age, and gender.

### Assessment of methodological quality

The independent reviewers will appraise the selected studies at the study level for methodological quality using quality assessment tool by the National Heart, Lung and Blood Institute for Observational cohort and cross-sectional studies.<sup>[16]</sup> The disagreements between the reviewers will be resolved by the involvement of a third reviewer. The eligibility of the articles will be evaluated by this assessment and will be considered eligible for systematic review based on rating such as good, fair, and poor. There are 14 elements to be analyzed and to be rated such as sample size, study period, follow-up period, survival outcome, evaluation of exposure, miRNA expression, and outcome variables; statistical adjustment and other factors will be recorded and assessed as quality appraisal elements.

### Assessment of risk of bias in individual studies

The reviewers will work independently and with adequate reliability to assert and determine the validity of these epidemiological studies based on parameters such as the number of patients considered, year of publication, ICD code, mode of disease diagnosis (whether histological or other type), relevant geographical demarcation for area under study, and period of study. Other factors can be included if the need to do so arises.

### Data synthesis

The HNC data synthesis will be reported as age-standardised incidence; 1-year, 3-year, and 5-year prevalence; and age-standardised mortality of HNC in India. The first step is an identification of the epidemiology data sources, while the second step is the application of the different models to enumerate trends by anatomical site of the HNC (lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32)), by age groups, and by gender. If the HNC data allow, we will proceed with trend analysis of age-standardised incidence; 1-year, 3-year, and 5-year prevalence; and age-standardised mortality of HNC in India. This analysis includes plotting of different figures and comparison of the results to see how they differ from the overall results. Studies that are considerably heterogeneous, such that pooling of data is not possible, will have their findings narratively explained. An independent reviewer will resolve any disagreements between the authors.

### Meta-analysis and subgroup analysis

Meta-analyses will be accomplished using the Comprehensive Meta-Analysis V.3.0 software for the obtained ORs and 95% CIs from the eligible studies. Heterogeneity will be calculated using the Cochran's Q test<sup>[17]</sup> and I<sup>2</sup> statistic.<sup>[18]</sup> Z statistic will be performed to assess heterogeneity. Publication bias will be quantified using Egger's bias indicator test, Orwin<sup>[19]</sup> and Classic fail-safe N test, Begg and Mazumdar rank collection test, Duval and Tweedie's trim and fill<sup>[20]</sup> calculation, and inverted funnel plot.

Subgroup analyses will be conducted on primary outcomes with subgroups defined by the geographic location of the reported incidence (as referred in a heat map), anatomical site of reported HNC, variation in HNC epidemiology across age groups, and differential HNC epidemiology between genders. The anatomical site of reported HNC subgroup analysis will be carried out in accordance with ICD codes as different regions in India have different disease epidemiology profiles. We may conduct additional analysis based on time-trends over a significant period of years (such as 10–15 years) for instance, provided we have sufficient data.

### Reporting of this review and its findings

This systematic review and its findings will be reported as per the recommendations of the PRISMA 2015 guidelines. A flow diagram (or other suitable form of data visualisation) will be employed to outline the selection process of studies, the inclusion criteria, and the exclusion criteria detailed with the reasons for exclusion. In-text descriptions will be used to describe the qualitative data in the studies. Outputs of

data analysis may be represented as forest plots or Grading of Recommendations Assessment, Development, and Evaluation approach towards the findings, depending upon the adequacy and relevancy of obtained data. The search strategy and quality appraisal tool will also be published as supplementary documents.

### Ethics and dissemination

The review protocol draws on publically available anonymised data without directly involving human participants and therefore does not require formal ethical review nor approval by an ethics committee. We published an outline of the protocol in the International Prospective Register of Systematic Reviews in 2017 (registration number: CRD42017077482). The results will provide updated epidemiology of HNC in India, and we will discuss the applicability of the findings to the prevalence of risk factors across India. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings. In addition, we believe that the results of this systematic review will have implications for policy and practice. Thus, we will prepare a policy-maker friendly summary using a validated format and disseminate the same through social media and email discussion groups. To the best of our knowledge, there are no systematic reviews that have specifically looked at the burden of HNC in India.

### Patient and public involvement

No patients or public were involved in the proposed systematic review and meta-analysis study.

### Discussion

Precise HNC epidemiological data in India concerning its incidence, prevalence, and mortality cannot be adequately addressed from reviews of the recently published literature. Most clinical reports carry out an analysis of a small geographic subgroup for a short time. Any additional extrapolations unless specified in the protocol are not recommended. Most of the published papers usually garner attention solely when statistically significant differences have been observed, thereby creating a potential for introducing reporting and publication biases. Adopting a systematic review based on a registered protocol would be a more reliable approach.<sup>[13]</sup> Additionally, adopting a similar protocol between systematic reviews allows incisive analysis of data about different ages and different regions.<sup>[13]</sup>

However, current epidemiological data suggest that proactive and pre-emptive measures need to be brought into effect immediately for control of the diseases, especially in adults who show the greatest indulgence and exposure to the risk factors.<sup>[3]</sup> The growing prevalence of these manufactured risk factors during early adulthood would be the primary cause behind such an unprecedented increase in HNC epidemiology.<sup>[11]</sup> The lack of foresight into controlling manageable clinical diseases such as HNC will further encumber the frail and strenuous healthcare system in India, adding to its woes of limited resources and infrastructure.<sup>[21]</sup> The cost-to-state in terms of dealing with the disease and the subsequent loss in productivity

of the patient can be mitigated with vigilant risk factor awareness programmes.<sup>[22]</sup>

### Abbreviations

HNC = Head and Neck Cancer, WHO = World Health Organization, IARC = International Agency for Research on Cancer, NCDIR = National Centre for Disease Informatics and Research, NCRP = National Cancer Registry Programme, ICMR = Indian Council of Medical Research, PROSPERO = International Prospective Register of Systematic Reviews, MeSH = medical subject headings, CI5 = Cancer Incidence in 5 Continents, GCO = Global Cancer Observatory, GHE = Global Health Estimate, DHSIS = Department of Health Statistics and Information Systems, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, ICD = International Classification of Diseases, GRADE = Grading of Recommendations Assessment, Development, and Evaluation

### Disclaimer

Neither the authors' institutions nor any funder or sponsor played a role in developing the protocol. The authors wrote this protocol during their routine work in their respective institutions, but the views expressed herein are those of the authors and not those of their institutions.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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