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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

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ABSTRACT

Introduction

Demographic, behavioural and environmental factors have been associated with increased risk of Head and Neck Cancer (HNC). We will review the published reports and explore connections between risk factors and HNC incidence. This protocol aims to provide guidelines for Head and Neck Cancer (HNC) risk factor analysis in India. It also informs about methods to visualise obtained HNC risk factor data in the form of a heat-map highlighting the variations across gender, age and geographic location.

Methods and analysis

We will identify well-established HNC risk factors and perform a comprehensive systematic review and meta-analysis to quantify each risk factor's impact on HNC incidence. A systematic search will be performed to identify the studies and published reports of HNC risk factors in India. Meta-analysis will be conducted to estimate the proportional contribution of the most prevalent risk factor in HNC on a city-wise basis in Indian States and Territories.

Ethics and dissemination

The review protocol draws on publically available anonymized data without directly involving human participants and therefore does not require formal human ethical review nor approval by a human research ethics committee. We will publish an outline of the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) in 2017. The results will provide updated analysis of HNC risk factor prevalence in India, and we will discuss the applicability of rehabilitation care. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings.

Review registration number

PROSPERO registration number CRD42017077758.

Strengths and limitations of this study

- The study attempts to calculate odds ratio of HNC occurrence due to risk factor prevalence while following geographical demarcation on the basis of cultural adaptation.
- The study can be further expanded into a time-trends analysis to analyse variations in odds ratio of HNC occurrence.
- Given the lack of infrastructure and funding in India, there is a possibility that the study participant population will be not representative of the overall population.
- The study largely focusses on published papers as no such national or state-wide cancer registry exists which provides information on risk factor prevalence and associated HNC incidence.

INTRODUCTION

The systematic review will generate up-to-date information on the combinatorial role of different risk factors of 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 highly affected areas.

The worldwide HNC trends for risk factor patterns have drastically changed in the past 15 years [1]. 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 [2]. HNC is the third-most common in India with 52,067 deaths and 77,003 cases diagnosed in 2012 [3]. Numerous reports highlight that risk factors are not only etiological determinants of HNC but also connected with increased risk of HNC prevalence [4-6]. The previously published studies have demonstrated that alcohol consumptions and tobacco use are the most significant risk factors of HNC in addition to HPV [7-9].

The most significant risk factor associations towards HNC disease establishment have already been elucidated [10]. However, the likelihood chances of an individual developing HNC, has not been studied completely. This is because of the scarcity of published review papers in this context. This study will give guidelines to help clinicians and scientists better understand the link between HNC and the risk factors, mainly smoking, alcohol consumption, HPV and betel quid chewing in Indian HNC patients.

The most significant risk factors are strongly associated with the sociocultural diversity and customs of India [11, 12], and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking, and tobacco chewing, significantly varies due to diverse demographic and lifestyle habits of people in India [13, 14].

Rationale

There is a scarcity of quantitative analysis and data synthesis of the casual relationships between HNC and their risk factors in the Indian demography. This could be due to the lack of data linkage and data reporting of HNC incidence in addition to absence of integrated state-wide and nation-wide functional cancer registry. This proposed systematic review and meta-analysis protocol will provide comprehensive and up-to-date information on the different combinations of risk factor relationship with HNC. This will also identify most appropriate HNC risk factor reports and studies published in this context. This extracted data will aid in filling the knowledge gaps of HNC risk factors and will provide most appropriate information to future cancer researchers and epidemiologists.

The aim of this study is to systematically review and meta-analyse the HNC risk factors in the Indian demography. The main objective of this study is to quantify HNC incidence in association with risk factor prevalence in different Indian cities. The subgroup analysis with different combinations of risk factors would further aid in figuring out the likelihood of developing HNC on a city-specific scale and also predict the endemic high-risk zones.

METHODS

Study designs and participants

The authors will consider reports and also all published studies as well as unpublished studies from conference proceedings. Only the articles published in English, will be eligible for inclusion. The study will include all studies that have clearly defined HNC risk factors expressed both individually as well as in combinations. Authors will also include studies describing the general human population in different geographic regions of India diagnosed with laboratory and clinically confirmed HNC from all ethnicities and socioeconomic backgrounds.

There will be no limits on study participants in terms of:

(a) demographic parameters; such as age, gender, ethnicity, and employment;
(b) clinco-pathological parameters such as anatomical sites, tumour stage, nodal status, nodal stage, post-operative radiotherapy, histological grade; and
(c) clinical outcomes such as recurrence (local and regional) and patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Authors will include risk factor studies pertaining to incidence, prevalence, and mortality of HNC in India. These studies will be independently carried out and will not be based on any global or national cancer registry for the statistical data of incidence, prevalence, and mortality. Studies will be selected according to the criteria outlined below.

Study selection criteria

Inclusion criteria

- The HNC risk factor study has performed independent data extraction and has not relied on any state, national and global cancer registries
- Study provides statistical data regarding the risk factor association with HNC incidence in India
- Study talks about the city-wise risk factor prevalence within India
- The inclusion of the factor based on the strength of the factor and the availability of at least three levels of interactions such as dose, exposure and level of associated risk.
- Language: English

Exclusion criteria

- The study has stated HNC screening.
- Study uses different HNC *in-vitro* analysis and evaluations.
- Review articles and studies comparing the different genetic profiles in HNC

Selection criteria for participants

Inclusion criteria

1. Participants of any age with HNC or receiving HNC treatment will be considered
2. Participants with a clearly confirmed diagnosis of HNC
3. Participants based in India

Exclusion criteria

1. Participants age or age range not clearly mentioned
2. Study participants' confirmative diagnosis of HNC has not been clearly identified
3. 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 and authors will include studies at all levels of healthcare setting (such as primary, secondary, and tertiary healthcare) and those conducted in the community.

Language
Authors will include articles reported in the English language.

Information sources
The authors will develop a comprehensive literature search strategy using medical subject headings (MeSh) and text words related to Prevalence of Head and Neck Cancer Risk Factors in India. The authors will scan the reference list through EMBASE, PubMed, Science Direct, Scopus, MEDLINE, Web of Science, and Cochrane Library. The authors will also search multiple electronic bibliographic databases to identify the grey literature and unpublished studies from conference proceedings. The authors will circulate the bibliography of the included articles to the systematic review team.

Search strategy
The systematic review and meta-analysis team will consider both qualitative as well as quantitative HNC risk factor studies primarily focusing on the Indian demography. All authors will provide their inputs for the draft Scopus search strategy to ensure that it retrieves high proportion of eligible studies. After the Scopus strategy is finalized, it will be adapted to the syntax and subject headings of the other electronic bibliographical databases to be searched. The specific search strategies will be created by all authors after consultation with the review team

Draft Scopus Search

1. "Head and Neck Cancer" [Topic] AND "India" [Topic]
2. "Head and Neck Cancer" [Topic] AND "Risk Factors" [Topic] AND "India" [Topic]
3. "Head and Neck Cancer" [Topic] AND "Alcohol" [Topic] AND "India" [Topic]
4. "Head and Neck Cancer" [Topic] AND "Smoking" [Topic] AND "India" [Topic]
5. "Head and Neck Cancer" [Topic] AND "Betel" [Topic] AND "India" [Topic]
6. "Head and Neck Cancer" [Topic] AND "HPV" [Topic] AND "India" [Topic]

Study records
Data management
The HNC risk factor literature will be fed into a reference management software EndNote™. This will contribute to a strong working relationship among the review team during the study selection process. The reviewers will select the studies based on selection criteria and will upload relevant studies into EndNote™. This will yield a PRIMSA flow diagram after the screening process by the HNC risk factor review team. HNC reviewers will also be using the traditional forms of data management in this process. Authors will avoid duplications when compiling together from multiple reports of the same study by including study design, HNC participants' characteristics and risk factor associations.

Selection process
The author team will review the titles and abstracts related to HNC risk factors in India. They will obtain full-length of all titles that meet the selection criteria. Authors will screen the full-length articles and confirm whether the screened articles meet the selection criteria. Any

disagreements during the screening and selection process will be resolved through team deliberation.

Data collection process

The selected HNC risk factor studies will be imported into EndNote™. The references extracted from the full-length articles will be reviewed to identify other publications of interest. References cited in the retrieved as well as selected publications will be reviewed to find additional articles in this context. The HNC risk factor data extraction form will be created and used by the review team during the data collection process. This particular form will be piloted on randomly selected eligible studies of HNC risk factors. Any discrepancies between the two groups will be sorted out via mutual discussion.

Data items

Authors will extract the various parameters using the HNC risk factor data extraction form. The key data items include:

(a) characteristics of studies (including author, year of publication, geographic region within India that the study talks about, year when the study took place, and type of study such as cross-sectional studies, observational studies and longitudinal studies);

(b) characteristics of the study participants consists of three classifications: HNC participants' demographic characteristics (such as age, gender, ethnicity, and employment);

(c) clinic-pathological characteristics (such as anatomical sites, tumour stage, nodal status, nodal stage, post-operative radiotherapy, histological grade);

(d) clinical outcomes (such as recurrence (local and regional)

(e) patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS));

(f) characteristics of individual HNC risk factors (such as alcohol consumption, tobacco smoking, HPV, and betel-quid chewing) and their combinations (such as alcohol and HPV, and tobacco smoking and HPV, and tobacco chewing and HPV);

(g) prevalence of HNC risk factors in different cities in India and its associations with HNC incidence

Outcomes

Primary outcomes

The primary outcome is to evaluate the risk factor prevalence and its associations with HNC in India.

Secondary outcomes

The secondary outcome is to link the variations in HNC risk factors with different geographic location of India in addition to other demographic clinico-pathological and clinical parameters.

Risk of bias in individual studies

The authors will collect the risk factor information from individual studies during their data synthesis phase using defined procedures for possible risk of bias. The defined procedure will include study validity based on specific parameters such as number of HNC patients, year of publication, mention of ICD code, disease diagnosis and confirmation, study locations and study period. The review team will take the decision on possible risk of bias within the extracted information from the included studies, either high-risk or low-risk. These decisions will be made independently by two authors and disagreements will be resolved by team decision and consultation with the third author.

Data synthesis

Authors will describe the risk factor prevalence with reference to ICD code for HNC (Lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32). The authors will also include different clinical studies with different combination of risk factors and different age ranges and studies with different follow-up times. This process will be performed in two phases. The first phase consists of identification and dissemination of risk factor resources collected followed by key study and participant data items extracted. The second phase will focus on utilisation of extracted data items to estimate the survival trends among the HNC participants using Comprehensive Meta-Analysis Software™. The software analysis will yield the information about heterogeneity of Odds Ratio (OR) using Cochran's Q test and Higgins' (I^2) statistic. Heterogeneity between the HNC risk factor studies will be assessed using the I^2 statistic, wherein substantial heterogeneity would be indicated by obtaining an I^2 value greater than 50%. Fixed or random effects model will be applied depending upon the heterogeneity. Q test statistical significance will be considered at a P-value of <0.01.

Subgroup analysis

Subgroup analysis will be performed on primary outcomes with subgroups defined by different study locations throughout India of reported incidence. Different combinations of the HNC risk factors and its associations with HNC incidence and prevalence will be measured.

Ethics and dissemination

The study does not require a formal ethics approval by human research ethics committee because this review protocol collects risk factor data from publicly published reports and studies. We plan to publish the results of this systematic review and meta-analysis in a peer-reviewed journal and present at relevant conference proceedings.

DISCUSSION

The precise risk factor analysis with respect to HNC incidence cannot be sufficiently explained in the published studies. Most published clinical studies focus on major referral centre, or city-wise or state-wise HNC incidence and prevalence [15, 16]. Estimation of nationwide risk factor prevalence is an urgently needed agenda from the perspective of epidemiologists to identify low-risk and high-risk endemic zones [17]. Further evaluations apart from our defined scope of this study is not advisable. Structuring a systematic review and meta-analysis around the framework of a registered protocol will offer a more consistent strategy [18]. Furthermore, a reviewed protocol will allow more in-depth analysis [18]. Contrary to popular belief, HNC incidence is on a staggering rise [19-22]. A large portion of this increase

is attributed to adults who indulge in the multifarious HNC risk factors widely prevalent in India [17, 23]. Immediate introduction of control measures would be a proactive step in order to curb the rising HNC incidence [24, 25].

Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived of this study, and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design, wrote the first draft of the protocol, and coordinated and integrated comments from all co-authors. RJ, RA, AP, KMG and RN critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ provided methodological guidance on the overall development of the protocol. RJ and rest of the author team read and approved the final version of the manuscript.

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Competing Interests The authors declare that they have no competing interests.

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 therein are those of the authors and not those of their institutions.

Provenance and peer-review Not commissioned; externally peer reviewed.

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

ABSTRACT

Introduction

Demographic, behavioural and environmental factors have been associated with increased risk of Head and Neck Cancer (HNC). We will review the published reports and explore connections between risk factors and HNC incidence. This protocol aims to provide strategies for a systematic review and meta-analysis of Head and Neck Cancer (HNC) risk factor analysis in India. It also provides guidelines in order to visualise HNC risk factor data in the form of a heat-map highlighting variations across gender, age, and geographic location.

Methods and analysis

We will identify well-established HNC risk factors and perform a comprehensive systematic review and meta-analysis to quantify each risk factor's impact on HNC incidence. A systematic search will be performed to identify the studies and published reports of HNC risk factors in India. Meta-analysis will be conducted to estimate the proportional contribution of the most prevalent risk factor in HNC on a city-wide basis in Indian States and Territories.

Ethics and dissemination

The review protocol draws on publically available anonymised data without directly involving human participants and therefore does not require formal human research ethical review nor approval by a human research ethics committee. We published an outline of the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) in 2017. The results will provide an updated analysis of HNC risk factor prevalence in India, and we will discuss the applicability of rehabilitation care. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings.

Review registration number

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Strengths and limitations of this study

- The study attempts to calculate the odds ratio of HNC occurrence due to risk factor prevalence while following geographical demarcation based on cultural adaptation.
- The study can be expanded into a time-trends analysis to analyse variations in odds ratio of HNC occurrence.
- Given the lack of infrastructure and funding in India, there is a possibility that the study participant population will not be representative of the overall population.
- The study primarily focuses on published papers as no such national or state-wide cancer registry exists which provides information on risk factor prevalence and associated HNC incidence.

INTRODUCTION

The worldwide HNC trends for risk factor patterns have drastically changed in the past 15 years.[1] 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.[2] HNC is the third-most common in India with 52,067 deaths and 77,003 cases diagnosed in 2012.[3] 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 also connected with increased risk of HNC prevalence.[4-6] Previously published studies have demonstrated that alcohol consumption and tobacco use are the most significant risk factors for HNC in addition to HPV. [7-9]

The significant risk factors for HNC have already been elucidated.[10] However, the likelihood or chance of an individual developing HNC has 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 HNC patients. The most significant risk factors are strongly associated with the sociocultural diversity and customs of India [11, 12], and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking, and tobacco chewing, significantly varies due to different demographic and lifestyle habits of people in India. [13, 14]

Rationale

The importance of the issue

There is a scarcity of quantitative analysis and data synthesis of the causal relationships between HNC and their risk factors in the Indian demography. This could be due to the lack of data linkage and data reporting of HNC incidence in addition to the absence of an integrated national and state-wide functional cancer registry. The prevalence of HNC is frequently dissimilar in different States and communities of the Indian population. It differs significantly from one community to another, and varies across various cities within the same geographic location, majorly depending upon the practices and lifestyles of the people in that location.[15]

Furthermore, there are several factors associated with an increased risk of HNC such as diverse demographical, socio-economical, clinicoepidemiological, clinicopathological, and biological characteristics of Indian HNC patients that will benefit the study in understanding the precise difference between these factors.

How will the study address this issue?

This study will be the first of its kind to use meta-analysis on the evaluation of HNC risk factors in 29 Indian States and seven union Territories . The meta-analysis offers an accurate degree of consistency by quantifying the extent of the variation compared to narrative synthesis. This analysis will allow enumerating the diverse roles of the published risk factors of HNC to develop an HNC risk prediction model for future clinical research in India. The pooled effect size of HNC risk factors and the relative weight to the overall meta-analysis of the published studies from diverse India States and Territories can contribute to achieving the precision model to assess the specific dose-response association between multi-level risk factors and risk of HNC.

How will it help?

Since India is cosmopolitan in culture, while being quite economically and socio-demographically distinct from Western countries, our findings will also be useful in further

research for developing risk prediction models of HNC. This protocol provides in-depth information on HNC with the study objectives and design, search strategies, eligibility criteria, data extraction, and synthesis that is most appropriate to cancer researchers, clinicians and epidemiologists. This will also help to identify more appropriate HNC risk factor reports and studies published in this context. This extracted data will aid in filling the knowledge gaps of HNC risk factor distribution in 29 States and seven union Territories of India. This protocol outlines the strategies for a systematic review and meta-analysis that could be helpful to Indian oral health and care, public health, and political actions leading to personalising interventions for individuals at risk of HNC. The effect size estimates of risk factor distribution will help to address the research priorities identified by World Health Organisation (WHO) and National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR). This systematic review and meta-analysis based this protocol will prospectively help in improving early detection by addressing the percentage of prevalence and geographical distribution of risk factors in addition to early screening and treatment facilities thereby creating awareness among the Indian high-risk population. These public health measures will have an impact on reducing HNC mortality in India.

The aim of this protocol is to describe the methodological approach for conducting systematic review and meta-analysis on risk factor distribution of HNC in the Indian demography. Given the potential importance of this study, the systematic review and meta-analysis are to quantify HNC incidence in association with risk factor prevalence in different Indian cities. Furthermore, the subgroup analysis with varying combinations of risk factors would further aid in figuring out the likelihood of developing HNC on a city-specific scale and predicting the endemic high-risk zones.

METHODS

Study design

The authors will consider reports and also all published studies as well as unpublished studies from conference proceedings. The anticipated date of commencement of literature search for identifying studies is on 15 June 2018 and anticipate date of completion is on 15 December 2018. The study will include all studies that have clearly defined HNC risk factors expressed both individually as well as in combinations. Authors will also include studies describing the general human population in different geographic regions of India diagnosed with laboratory and clinically confirmed HNC from all ethnicities and socioeconomic backgrounds.

There will be no limits on study participants from published studies in terms of:

(a) demographic and clinicoepidemiological parameters such as age, gender, ethnicity, employment and location;
(b) clinicopathological parameters such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, histological grade; and
(c) clinical outcomes such as recurrence (local and regional) and patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Authors will include risk factor studies pertaining to incidence, prevalence, and mortality of HNC in India. Studies will be selected according to the criteria outlined below.

Patient and Public Involvement'

Patients and or public were not involved in the study.

Study selection criteria

Inclusion criteria

- The HNC risk factor study has performed independent data extraction and has not relied on any state, national or global cancer registries.
- Study provides statistical data regarding the risk factor association with HNC incidence in India.
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- The inclusion of the factor based on the strength of the factor and the availability of at least three levels of interactions such as dose, exposure and level of associated risk.

Exclusion criteria

- The study has stated HNC screening.
- The study uses different HNC *in-vitro* analysis and evaluations.
- Review articles and studies comparing the different genetic profiles in HNC.

Selection criteria for participants (from published studies)

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1. Participants of any age with HNC or receiving HNC treatment will be considered.
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3. Participants based in India.

Exclusion criteria

1. Participants' age or age range not clearly mentioned.
2. Study participants' confirmative diagnoses of HNC have not been clearly identified.
3. 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 and authors will include studies at all levels of healthcare setting (such as primary, secondary, and tertiary health care) and those conducted in the community.

Language

Authors will include articles reported in the English language.

Information sources

The authors will develop a comprehensive literature search strategy using Medical Subject Headings (MeSH) and text words related to the prevalence of Head and Neck Cancer risk factors in India. The authors will scan the reference list through Cochrane Library, EMBASE, MEDLINE, PubMed, Science Direct, Scopus and Web of Science. The authors will also search multiple electronic bibliographic databases to identify the grey literature and unpublished studies from conference proceedings. The authors will circulate the bibliography of the included articles to the systematic review team.

Searching other resources

The major metropolitan city and hospital-based cancer registries in India will be integrated with the following reports by national and international cancer registries:

- Cancer Incidence in Five Continents (CI5) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)

- Global Cancer Observatory (GCO) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- GLOBOCAN 2012 by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- Global Heath Estimate (GHE) 2012 by WHO: Department of Health Statistics and Information Systems (DHSIS)
- Three-Year Report of Population-Based Cancer Registries 2012-2014 by National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR)

Search strategy

The systematic review and meta-analysis team will consider both qualitative as well as quantitative HNC risk factor studies primarily focusing on the Indian demography. All authors will provide their inputs for the draft Scopus search strategy to ensure that it retrieves a high proportion of eligible studies. After the Scopus strategy is finalised, it will be adapted to the syntax and subject headings of the other electronic bibliographical databases to be searched. The specific search strategies will be created by all authors after consultation with the review team

Draft Scopus Search

1. "Head and Neck Cancer" [Topic] AND "India" [Topic]
2. "Head and Neck Cancer" [Topic] AND "Risk Factors" [Topic] AND "India" [Topic]
3. "Head and Neck Cancer" [Topic] AND "Risk Factors" [Topic] AND "India" [Topic]] AND "Geographical incidence" [Topic]
4. "Alcohol" [Topic] AND "India" [Topic]
5. "Head and Neck Cancer" [Topic] AND "Alcohol" [Topic] AND "India" [Topic]
6. "Smoking" [Topic] AND "India" [Topic]
7. "Head and Neck Cancer" [Topic] AND "Smoking" [Topic] AND "India" [Topic]
8. "Betel" [Topic] AND "India" [Topic]
9. "Head and Neck Cancer" [Topic] AND "Betel" [Topic] AND "India" [Topic]
10. "HPV" [Topic] AND "India" [Topic]
11. "Head and Neck Cancer" [Topic] AND "HPV" [Topic] AND "India" [Topic]

Study records

Data management

The HNC risk factor literature will be fed into a reference management software EndNote™. This will contribute to a strong working relationship among the review team during the study selection process. The reviewers will select the studies based on selection criteria and will upload relevant studies into EndNote™. This will yield a PRISMA flow diagram after the screening process by the HNC risk factor review team. HNC reviewers will also be using the traditional forms of data management in this process. Authors will avoid duplications when compiling together from multiple reports of the same study by including study design, HNC participants' characteristics and risk factor associations. The corresponding authors will be contacted for missing information in the studies.

Selection process

The author team will review the titles and abstracts related to HNC risk factors in India. They will obtain the full-length of all titles that meet the selection criteria. Authors will screen the full-length articles and confirm whether the screened articles meet the selection criteria.

Data collection process

The references extracted from the full-length articles will be reviewed to identify other publications of interest. References cited in the retrieved, as well as selected publications, will be considered to find additional articles in this context. The HNC risk factor data extraction form will be created and used by the review team during the data collection process. This particular form will be piloted on randomly selected eligible studies of HNC risk factors. Any discrepancies between the two authors will be sorted out via mutual discussion, consultation with the third author and team decision.

Data items

Authors will extract the various parameters using the HNC risk factor data extraction form. The critical data items include:

(a) characteristics of studies (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 studies such as cross-sectional studies, observational studies and longitudinal studies);

(b) clinicoepidemiological characteristics of the study participants consist of three classifications: HNC participants' demographic components (such as age, gender, ethnicity, employment and location);

(c) clinicopathological characteristics (such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, and histological grade);

(d) clinical outcomes (such as recurrence (local and regional)

(e) patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS));

(f) characteristics of individual HNC risk factors (such as alcohol consumption, tobacco smoking, HPV, and betel-quid chewing etc.) and their combinations (such as alcohol and HPV, and tobacco smoking and HPV, and tobacco chewing and HPV);

(g) prevalence of HNC risk factors in different cities in India and its associations with HNC incidence

Outcomes

Primary outcomes

The primary outcome is to evaluate the risk factor prevalence and its associations with HNC in India.

Secondary outcomes

The secondary outcome is to link the variations in HNC risk factors with different geographic locations in India in addition to other demographic, clinicoepidemiological, clinicopathological and clinical parameters.

Risk of bias in individual studies

A checklist from Dutch Cochrane using the MOOSE guidelines will be used to perform the quality assessment of the studies.[16] The authors will collect the risk factor information from individual studies during their data synthesis phase using defined procedures for possible risk of bias. The defined procedures will include study validity based on specific parameters such

as year of publication, mention of ICD code, disease diagnosis and confirmation, study locations, and study period. The review team will decide on possible risk of bias within the extracted information from the included studies, either high-risk or low-risk. .
Publication bias will be assessed using Harbord-Egger's bias indicator test,[17] Orwin's classic fail-safe N test,[18] Begg and Mazumdar's rank correlation test,[19] Duval and Tweedie's trim and fill calculation,[20] and inverted funnel plot.

Data synthesis

Authors will describe the risk factor prevalence with reference to ICD code for HNC (Lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32)). The authors will also include different clinical studies with different combinations of risk factors and different age ranges and studies with varying times of follow-up. This process will be performed in two phases. The first phase consists of identification and dissemination of risk factor resources collected followed by crucial study and participant data items extracted. The second phase will focus on utilisation of retrieved data items to estimate the survival trends among the HNC participants using Comprehensive Meta-Analysis Software™. The software analysis will yield the information about the heterogeneity of Odds Ratio (OR) using Cochran's Q test and Higgins' (I^2) statistic. Heterogeneity between the HNC risk factor studies will be assessed using the I^2 statistic, wherein substantial heterogeneity would be indicated by obtaining an I^2 value greater than 50%. Fixed or random effects model will be applied depending upon the heterogeneity. Q test statistical significance will be considered at a *P*-value of <0.01.

Subgroup analysis and meta-regression model

Subgroup analysis will be performed on primary outcomes with subgroups defined by different study locations throughout India of reported incidence. Different combinations of the HNC risk factors and its associations with HNC incidence and prevalence will be measured. The source of heterogeneity will be assessed using meta-regression analysis of fitting co-variables.[21] Heterogeneity will be considered significant if *P*-value is <0.05. The heterogeneity of proportional contributions of risk factor associations with one or more study variable will be assessed using meta-regression analysis. The impact of proportional contributions of risk factor and combination of risk factors on fitting co-variables including gender distribution, methods of data collection, sample size, research quality, and sampling procedure will be calculated using meta-regression model. It needs a large ratio of studies for assessing the impact of combinations of risk factors to calculate true regression.

Ethics and dissemination

The study does not require formal ethics approval by a human research ethics committee because this review protocol collects risk factor data from publicly published reports and studies. We plan to publish the results of this systematic review and meta-analysis in a peer-reviewed journal and present at relevant conference proceedings.

DISCUSSION

The precise risk factor analysis with respect to HNC incidence cannot be sufficiently explained in the published studies. Most published clinical studies focus on major referral centre, or city-wise, or state-wide HNC incidence and prevalence.[22, 23] Estimation of a national risk factor prevalence is an urgently needed agenda from the perspective of epidemiologists to identify low-risk and high-risk endemic zones.[24] Further evaluations apart from our defined scope of this study are not advisable. Structuring a systematic review and meta-analysis around the framework of a registered protocol will offer a more consistent

strategy.[25] Furthermore, a reviewed protocol will allow more in-depth analysis.[25] The systematic review will generate up-to-date information on the combinatorial role of different risk factors of HNC incidence in India and 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. HNC incidence is on a staggering rise.[26-29] A large portion of this increase is attributed to adults who indulge in the multifarious HNC risk factors widely prevalent in India.[24, 30] Immediate introduction of control measures would be a proactive step to curb the rising HNC incidence.[31, 32]

Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived this study and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design, wrote the first draft of the protocol, and coordinated and integrated comments from co-authors. RJ, AP and RA critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ, GKM and RN provided methodological guidance on the overall development of the protocol. RJ, AP, RA, GKM and RN read and approved the final version of the manuscript.

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Competing Interests None declared

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.

Provenance and peer review Not commissioned; externally peer reviewed.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page no
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3,4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	-

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

ABSTRACT

Introduction

Demographic, behavioural, and environmental factors have been associated with increased risk of Head and Neck Cancer (HNC). We will review published reports and explore connections between risk factors and HNC incidence. This protocol aims to provide strategies for a systematic review and meta-analysis of Head and Neck Cancer (HNC) risk factor analysis in India. It also provides guidelines in order to visualise obtained HNC risk factor data in the form of a heat-map highlighting variations across gender, age, and geographic location.

Methods and analysis

We will identify well-established HNC risk factors and perform a comprehensive systematic review and meta-analysis to quantify each risk factor's impact on HNC incidence. A systematic search will be performed to identify the studies and published reports of HNC risk factors in India. Meta-analysis will be conducted to estimate the proportional contribution of the most prevalent risk factor in HNC on a city-wide basis in Indian States and Territories.

Ethics and dissemination

The review protocol draws on publically available anonymised data without directly involving human participants and therefore requires neither formal human ethical review nor approval by a human research ethics committee. We published an outline of the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) in 2017. The results will provide an updated analysis of HNC risk factor prevalence in India, and we will discuss the applicability of rehabilitation care. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings.

Review registration number

PROSPERO registration number CRD42017077758.

Strengths and limitations of this study

- The study attempts to calculate the odds ratio of HNC occurrence due to risk factor prevalence while following geographical demarcation based on cultural adaptation.
- The study can be expanded into a time-trends analysis to analyse variations in an odds ratio of HNC occurrence.
- Given the lack of infrastructure and funding in India, there is a possibility that the study participant population will not be representative of the overall population.
- The study primarily focuses on published papers as no such national or state-wide cancer registry exists which provides information on risk factor prevalence and associated HNC incidence.

INTRODUCTION

The systematic review will generate up-to-date information on the combinatorial role of different risk factors of 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.[1] 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.[2] HNC is the third-most common in India with 52,067 deaths and 77,003 cases diagnosed in 2012.[3] 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 also connected with increased risk of HNC prevalence.[4-6] Previously published studies have demonstrated that alcohol consumption and tobacco use are the most significant risk factors of HNC in addition to HPV. [7-9]

The significant risk factors for HNC have already been elucidated.[10] However, the likelihood chances of an individual developing HNC has 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 HNC patients.

The most significant risk factors are strongly associated with the sociocultural diversity and customs of India [11, 12], and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking, and tobacco chewing, significantly varies due to diverse demographic and lifestyle habits of people in India. [13, 14]

Rationale

What is the issue?

There is a scarcity of quantitative analysis and data synthesis of the causal relationships between HNC and their risk factors in the Indian demography. This could be due to the lack of data linkage and data reporting of HNC incidence in addition to the absence of integrated national and state-wide functional cancer registry. The prevalence of HNC is frequently dissimilar in different states and communities of the Indian population. It differs significantly from one community to another, and varies across various cities within the same geographic location, majorly depending upon the practices and lifestyles of the people in that location.[15] Furthermore, there are several factors associated with an increased risk of HNC such as diverse demographical, socio-economical, clinicoepidemiological, clinicopathological, and biological characteristics of Indian HNC patients that will benefit the study in understanding the precise difference between these factors.

How our study address this?

This study will be the first of its kind to use meta-analysis in the evaluation of HNC risk factors in 29 Indian states and seven union territories. The meta-analysis offers an accurate degree of consistency by quantifying the extent of the variation compared to narrative synthesis. Quantitative synthesis will allow enumerating the diverse roles of the published risk factors of HNC to develop an HNC risk prediction model for future clinical research in India. The pooled effect size of HNC risk factors and the relative weight to the overall meta-analysis of the published studies from diverse Indian states and territories can contribute to

achieving the precision model to assess the specific dose-response association between multi-level risk factors and risk of HNC.

How will it help?

Since, India is cosmopolitan in culture, while being quite economically and socio-demographically distinct from other western countries, our findings will also be useful in further research for developing risk prediction models of HNC. This proposed systematic review and meta-analysis protocol will provide comprehensive and up-to-date information on the different combinations of risk factor relationship with HNC. This will also identify more appropriate HNC risk factor reports and studies published in this context. This extracted data will aid in filling the knowledge gaps of HNC risk factor distribution in 29 states and seven union territories of India. The effect size estimates of risk factor distribution will help to address the research priorities identified by World Health Organisation (WHO) and National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR). This protocol outlines the strategies for a systematic review and meta-analysis that could be helpful to Indian oral health and care, public health and political actions leading to personalising interventions for individuals at risk of HNC. This protocol provides in-depth information on HNC with the study objectives and design, search strategies, eligibility criteria, data extraction and synthesis, that is most appropriate to cancer researchers, clinicians and epidemiologists. This systematic review and meta-analysis will prospectively help in improving the early detection by addressing the percentage of prevalence and geographical distribution of risk factors in addition to early screening and treatment facilities thereby creating awareness among the high-risk Indian population. These public health measures will have an impact on reducing HNC mortality in India.

This protocol aims to describe the methodological approach for conducting systematic review and meta-analysis on risk factor distribution of HNC in the Indian demography. Given the potential importance of this study, the systematic review and meta-analysis are to quantify HNC incidence in association with risk factor prevalence in different Indian cities. The subgroup analysis with varying combinations of risk factors would further aid in figuring out the likelihood of developing HNC on a city-specific scale and predicting the endemic high-risk zones.

METHODS

Study designs and participants

The authors will consider reports and also all published studies as well as unpublished studies from conference proceedings. The anticipated date of commencement of literature search for identifying studies is on 15 July 2018 and anticipate date of completion is on 15 December 2018. The study will include all studies that have clearly defined HNC risk factors expressed both individually as well as in combinations. Authors will also include studies describing the general human population in different geographic regions of India diagnosed with laboratory and clinically confirmed HNC from all ethnicities and socioeconomic backgrounds.

There will be no limits on study participants in terms of:

(a) demographic parameters such as age, gender, ethnicity, and employment;
(b) clinicopathological parameters such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, histological grade; and
(c) clinical outcomes such as recurrence (local and regional) and patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Authors will include risk factor studies pertaining to incidence, prevalence, and mortality of HNC in India. These studies will be carried out independently and will not be based on any global or national cancer registry for the statistical data of HNC risk factor distribution. Studies will be selected according to the criteria outlined below.

Study selection criteria

Inclusion criteria

- The HNC risk factor study has performed independent data extraction and has not relied on any state, national or global cancer registries
- Study provides statistical data regarding the risk factor associated with HNC incidence in India
- Study talks about the city-wise risk factor prevalence within India
- The inclusion of the factor based on the strength of the factor and the availability of at least three levels of interactions such as dose, exposure, and level of associated risk.
- Language: English

Exclusion criteria

- The study has stated HNC screening.
- The study uses different HNC *in-vitro* analysis and evaluations.
- Review articles and studies comparing the different genetic profiles in HNC

Selection criteria for participants

Inclusion criteria

1. Participants of any age with HNC or receiving HNC treatment will be considered.
2. Participants with a clearly confirmed diagnosis of HNC.
3. Participants based in India.

Exclusion criteria

1. Participants' age or age range not clearly mentioned.
2. Study participants' confirmative diagnoses of HNC have not been clearly identified.
3. 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 and authors will include studies at all levels of healthcare setting (such as primary, secondary, and tertiary healthcare) and those conducted in the community.

Language

Authors will include articles reported in the English language.

Information sources

The authors will develop a comprehensive literature search strategy using Medical Subject Headings (MeSH) and text words related to the prevalence of Head and Neck Cancer risk factors in India. The authors will scan the reference list through Cochrane Library, EMBASE, MEDLINE, PubMed, Science Direct, Scopus and Web of Science. The authors will also search multiple electronic bibliographic databases to identify the grey literature and unpublished studies from conference proceedings. The authors will circulate the bibliography of the included articles to the systematic review team.

Searching other resources

The major metropolitan city and hospital-based cancer registries in 29 states and 7 union territories of India will be integrated with the following reports by national and international cancer registries:

- Cancer Incidence in Five Continents (CI5) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- Global Cancer Observatory (GCO) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- GLOBOCAN 2012 by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- Global Heath Estimate (GHE) 2012 by WHO: Department of Health Statistics and Information Systems (DHSIS)
- Three-Year Report of Population-Based Cancer Registries 2012-2014 by National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR)

Search strategy

The systematic review and meta-analysis team will consider both qualitative as well as quantitative HNC risk factor studies primarily focusing on the Indian demography. All authors will provide their inputs for the draft Scopus search strategy to ensure that it retrieves a high proportion of eligible studies. After the Scopus strategy is finalised, it will be adapted to the syntax and subject headings of the other electronic bibliographical databases to be searched. The specific search strategies will be created by all authors after consultation with the review team

Draft Scopus Search

1. “Head and Neck Cancer” [Topic] AND “India” [Topic]
2. “Head and Neck Cancer” [Topic] AND “Risk Factors” [Topic] AND “India” [Topic]
3. “Head and Neck Cancer” [Topic] AND “Risk Factors” [Topic] AND “India” [Topic]] AND “Geographical incidence” [Topic]
4. “Head and Neck Cancer” [Topic] AND “Alcohol” [Topic] AND “India” [Topic]
5. “Head and Neck Cancer” [Topic] AND “Smoking” [Topic] AND “India” [Topic]
6. “Head and Neck Cancer” [Topic] AND “Betel” [Topic] AND “India” [Topic]
7. “Head and Neck Cancer” [Topic] AND “HPV” [Topic] AND “India” [Topic]

Study records

Data management

The HNC risk factor literature will be fed into a reference management software EndNote™. This will contribute to a strong working relationship among the review team during the study selection process. The reviewers will select the studies based on selection criteria and will upload relevant studies into EndNote™. This will yield a PRISMA flow diagram after the screening process by the HNC risk factor review team. HNC reviewers will also be using the traditional forms of data management in this process. Authors will avoid duplications when compiling together from multiple reports of the same study by including study design, HNC participants’ characteristics and risk factor associations. The corresponding authors will be contacted for missing information in the studies.

Selection process
The author team will review the titles and abstracts related to HNC risk factors in India. They will obtain the full-length of all titles that meet the selection criteria. Authors will screen the full-length articles and confirm whether the screened articles meet the selection criteria.

Data collection process
The references extracted from the full-length articles will be reviewed to identify other publications of interest. References cited in the retrieved, as well as selected publications, will be considered to find additional articles in this context. The HNC risk factor data extraction form will be created and used by the review team during the data collection process. This particular form will be piloted on randomly selected eligible studies of HNC risk factors. Any discrepancies between the two groups will be sorted out via mutual discussion.

Data items
Authors will extract the various parameters using the HNC risk factor data extraction form. The key data items include:

(a) characteristics of studies (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 studies such as cross-sectional studies, observational studies and longitudinal studies);

(b) characteristics of the study participants consist of three classifications: HNC participants' demographic characteristics (such as age, gender, ethnicity, and employment);

(c) clinicopathological characteristics (such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, and histological grade);

(d) clinical outcomes (such as recurrence (local and regional);

(e) patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS));

(f) characteristics of individual HNC risk factors (such as alcohol consumption, tobacco smoking, HPV, and betel-quid chewing) and their combinations (such as alcohol and HPV, and tobacco smoking and HPV, and tobacco chewing and HPV);

(g) prevalence of HNC risk factors in different cities in India and its associations with HNC incidence

Outcomes
Primary outcomes
The primary outcome is to evaluate the risk factor prevalence and its associations with HNC in India.

Secondary outcomes
The secondary outcome is to link the variations in HNC risk factors with different geographic locations in India in addition to other demographical, clinico-pathological and clinical parameters.

Risk of bias in individual studies

STROBE tool will be used to perform the quality assessment of the studies.[16] This tool has 22 elements including abstracts, rationale, study design, setting, participants, outcome, limitations, variables and statistics.[16] The authors will collect the risk factor information from individual studies during their data synthesis phase using defined procedures for possible risk of bias. The defined procedures will include study validity based on specific parameters such as a number of HNC patients, year of publication, mention of ICD code, disease diagnosis and confirmation, study locations, and study period. The review team will decide on possible risk of bias within the extracted information from the included studies, either high-risk or low-risk. Two authors will independently make these decisions and disagreements will be resolved by team decision and consultation with the third author.

Data synthesis

Authors will describe the risk factor prevalence with reference to ICD code for HNC (Lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32)). The authors will also include different clinical studies with the different combination of risk factors and different age ranges and studies with varying times of follow-up. This process will be performed in two phases. The first phase consists of identification and dissemination of risk factor resources collected, followed by critical study and participant data items extracted. The second phase will focus on utilisation of retrieved data items to estimate the survival trends among the HNC participants using Comprehensive Meta-Analysis Software™. The software analysis will yield the information about the heterogeneity of Odds Ratio (OR) using Cochran's Q test and Higgins' (I^2) statistic. Heterogeneity between the HNC risk factor studies will be assessed using the I^2 statistic, wherein substantial heterogeneity would be indicated by obtaining an I^2 value greater than 50%. Fixed or random effects model will be applied depending upon the heterogeneity. Q test statistical significance will be considered at a P-value of <0.01. Publication bias will be assessed using Harbord-Egger's bias indicator test,[17] Orwin's classic fail-safe N test,[18] Begg and Mazumdar's rank correlation test,[19] Duval and Tweedie's trim and fill calculation,[20] and inverted funnel plot.

Subgroup analysis and meta-regression model

Subgroup analysis will be performed on primary outcomes with subgroups defined by different study locations throughout India of reported incidence. Different combinations of the HNC risk factors and its associations with HNC incidence and prevalence will be measured. The source of heterogeneity will be assessed using meta-regression analysis of fitting co-variables.[21] Heterogeneity will be considered significant if *P*-value is <0.05. The heterogeneity of proportional contributions of risk factor associations with one or more study variable will be assessed using meta-regression analysis. The impact of proportional contributions of risk factor and combination of risk factors on fitting co-variables including gender distribution, methods of data collection, sample size, research quality, and sampling procedure will be calculated using meta-regression model. It needs a large ratio of studies for assessing the impact of combinations of risk factors to calculate true regression.

Ethics and dissemination

The study does not require formal ethics approval by a human research ethics committee because this review protocol collects risk factor data from publicly published reports and studies. We plan to publish the results of this systematic review and meta-analysis in a peer-reviewed journal and present at relevant conference proceedings.

Patient and Public Involvement

The proposed study is literature-based systematic review and meta-analysis. Therefore, no patients and or public were involved in the proposed study.

DISCUSSION

The precise risk factor analysis with respect to HNC incidence cannot be sufficiently explained in the published studies. Most published clinical studies focus on major referral centre, or city-wise, or state-wise HNC incidence and prevalence.[22, 23] Estimation of a national risk factor prevalence is an urgently needed agenda from the perspective of epidemiologists to identify low-risk and high-risk endemic zones.[24] Further evaluations apart from our defined scope of this study are not advisable. Structuring a systematic review and meta-analysis around the framework of a registered protocol will offer a more consistent strategy.[25] Furthermore, a reviewed protocol will allow more in-depth analysis.[25] HNC incidence is on a staggering rise.[26-29] A large portion of this increase is attributed to adults who indulge in the multifarious HNC risk factors widely prevalent in India.[24, 30] Immediate introductions of control measures would be a proactive step in order to curb the rising HNC incidence.[31, 32]

Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived this study and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design, wrote the first draft of the protocol, and coordinated and integrated comments from co-authors. RJ and AP critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ provided methodological guidance on the overall development of the protocol. AP and RJ read and approved the final version of the manuscript.

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Competing Interests None declared

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 therein are those of the authors and not those of their institutions.

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

ABSTRACT

Introduction

Demographic, behavioural, and environmental factors have been associated with increased risk of Head and Neck Cancer (HNC). We will review ~~the~~ published reports and explore connections between risk factors and HNC incidence. This protocol aims to provide ~~the~~ strategies for a systematic review and meta-analysis of ~~-~~Head and Neck Cancer (HNC) risk factor analysis in India. It also provides guidelines in order~~informs about methods~~ to visualise obtained HNC risk factor data in the form of a heat-map highlighting ~~the~~ variations across gender, age, and geographic location.

Methods and analysis

We will identify well-established HNC risk factors and perform a comprehensive systematic review and meta-analysis to quantify each risk factor's impact on HNC incidence. A systematic search will be performed to identify the studies and published reports of HNC risk factors in India. Meta-analysis will be conducted to estimate the proportional contribution of the most prevalent risk factor in HNC on a city-wide basis in Indian States and Territories.

Ethics and dissemination

The review protocol draws on publically available anonymised data without directly involving human participants and therefore ~~does not~~ requires neither formal human ethical review nor approval by a human research ethics committee. We published an outline of the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) in 2017. The results will provide an updated analysis of HNC risk factor prevalence in India, and we will discuss the applicability of rehabilitation care. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings.

Review registration number

PROSPERO registration number CRD42017077758.

Strengths and limitations of this study

- The study attempts to calculate the odds ratio of HNC occurrence due to risk factor prevalence while following geographical demarcation ~~on the basis of~~based on cultural adaptation.
- The study can be ~~further~~ expanded into a time-trends analysis to analyse variations in an odds ratio of HNC occurrence.
- Given the lack of infrastructure and funding in India, there is a possibility that the study participant population will ~~-~~not be representative of the overall population.
- The study ~~largely~~ primarily focuses on published papers as no such national or state-wide cancer registry exists which provides information on risk factor prevalence and associated HNC incidence.

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INTRODUCTION

The systematic review will generate up-to-date information on the combinatorial role of different risk factors of 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~~.~~[1] 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.[2] HNC is the third-most common in India with 52,067 deaths and 77,003 cases diagnosed in 2012.[3] 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 also connected with increased risk of HNC prevalence.[4-6] ~~The p~~Previously published studies have demonstrated that alcohol consumption~~s~~ and tobacco use are the most significant risk factors of HNC in addition to HPV. [7-9]

The ~~major~~ significant risk factors for HNC ~~disease establishment~~ have already been elucidated.[10] However, the likelihood chances of an individual developing HNC~~,~~ has not been studied ~~completely~~thoroughly. This is ~~because of~~due to the scarcity of published review papers in this context. This study will ~~give~~ provide guidelines to help clinicians, and scientists better understand the link between HNC and ~~the~~ its risk factors, mainly smoking, alcohol consumption, HPV, and betel quid chewing in Indian HNC patients.

The most significant risk factors are strongly associated with the sociocultural diversity and customs of India [11, 12], and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking, and tobacco chewing, significantly varies due to diverse demographic and lifestyle habits of people in India~~[13, 14]~~ [13, 14]

Rationale

What is the issue?

There is a scarcity of quantitative analysis and data synthesis of the ~~casual~~ causal relationships between HNC and their risk factors in the Indian demography. This could be due to the lack of data linkage and data reporting of HNC incidence in addition to the absence of integrated national and state-wide ~~and nation wide~~ functional cancer registry. The prevalence of HNC is ~~more~~ frequently dissimilar in different states and communities of the Indian population~~.~~. It differs ~~greatly~~ significantly from one community to another, and varies ~~in~~ across various cities within the same geographic location, majorly depending upon the practices and lifestyles of the people in that location.[15] Furthermore, there are several factors associated with an increased risk of HNC such as diverse demographical, socio-economical, clinicoepidemiological, clinicopathological, and biological characteristics of Indian HNC patients that will benefit the study in understanding the precise difference between these factors.

How our study address this?

This study will be the first of its kind to use meta-analysis ~~i~~on the evaluation of HNC risk factors in 29 Indian states and seven union territories~~.~~. The meta-analysis offers an accurate degree of consistency by quantifying the extent of the variation compared to narrative synthesis. Quantitative synthesis will allow enumerating the diverse roles of the published risk factors of HNC to develop an HNC risk prediction model for future clinical research in

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India. The pooled effect size of HNC risk factors and the relative weight to the overall meta-analysis of the published studies from diverse Indian states and territories can contribute to ~~achieve~~ achieving the precision model to assess the specific dose-response association between multi-level risk factors and risk of HNC.

How will it help?

Since, India is cosmopolitan in culture, while being quite economically~~,~~ and socio-demographically distinct from other western countries, our findings will also be useful in further research for developing risk prediction models of HNC. This proposed systematic review and meta-analysis protocol will provide comprehensive and up-to-date information on the different combinations of risk factor relationship with HNC. This will also identify ~~most~~ more appropriate HNC risk factor reports and studies published in this context. This extracted data will aid in filling the knowledge gaps of HNC risk factor distribution in 29 states and seven union territories of India. The effect size estimates of risk factor distribution will help to address the research priorities identified by World Health Organisation (WHO) and National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR). This protocol outlines the strategies for a systematic review and meta-analysis that could be helpful to Indian oral health and care, public health and political actions leading to personalising interventions for individuals at risk of HNC. This protocol provides in-depth ~~most appropriate information~~information on HNC with the study objectives and design, search strategies, eligibility criteria, data extraction and synthesis, that is most appropriate to ~~-~~cancer researchers, clinicians and epidemiologists. This systematic review and meta-analysis will prospectively help in improving the early detection by addressing the percentage of prevalence and geographical distribution of risk factors in addition to early screening~~,~~ and treatment facilities ~~and create~~thereby creating awareness among the high-risk Indian~~Indian high risk~~ population. These public health measures will have an impact on reducing HNC mortality in India.

This protocol aim~~e aim of this protocol i~~s to describe the methodological approach for conducting systematic review and meta-analysis on risk factor distribution of HNC ~~-~~in the Indian demography. Given the potential importance of this study, the systematic review and meta-analysis are~~is~~ to quantify HNC incidence in association with risk factor prevalence in different Indian cities. The subgroup analysis with varying combinations of risk factors would further aid in figuring out the likelihood of developing HNC on a city-specific scale ~~and also~~and predicting the endemic high-risk zones.

METHODS

Study designs and participants

The authors will consider reports and also all published studies as well as unpublished studies from conference proceedings. The anticipated date of commencement of literature search for identifying studies is on 15 ~~June~~ July 2018 and anticipate date of completion is on 15 December 2018. The study will include all studies that have clearly defined HNC risk factors expressed both individually as well as in combinations. Authors will also include studies describing the general human population in different geographic regions of India diagnosed with laboratory and clinically confirmed HNC from all ethnicities and socioeconomic backgrounds.

There will be no limits on study participants in terms of:

(a) demographic parameters~~,~~ such as age, gender, ethnicity, and employment;

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(b) clinico-pathological parameters such as anatomical sites, tumour stage, nodal status, nodal stage, post-operative radiotherapy, histological grade; and
(c) clinical outcomes such as recurrence (local and regional) and patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Authors will include risk factor studies pertaining to incidence, prevalence, and mortality of HNC in India. These studies will be ~~independently~~ carried out independently and will not be based on any global or national cancer registry for the statistical data of HNC risk factor ~~distribution~~ distribution. Studies will be selected according to the criteria outlined below.

Study selection criteria

Inclusion criteria

- The HNC risk factor study has performed independent data extraction and has not relied on any state, national ~~and~~ or global cancer registries
- Study provides statistical data regarding the risk factor associated~~ion~~ with HNC incidence in India
- Study talks about the city-wise risk factor prevalence within India
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Study records

Data management

The HNC risk factor literature will be fed into a reference management software EndNote™. This will contribute to a strong working relationship among the review team during the study selection process. The reviewers will select the studies based on selection criteria and will upload relevant studies into EndNote™. This will yield a PRISMSA flow diagram after the screening process by the HNC risk factor review team. HNC reviewers will also be using the traditional forms of data management in this process. Authors will avoid duplications when compiling together from multiple reports of the same study by including study design, HNC participants' characteristics and risk factor associations. The corresponding authors will be contacted for missing information in the studies.

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Selection process

The author team will review the titles and abstracts related to HNC risk factors in India. They will obtain the full-length of all titles that meet the selection criteria. Authors will screen the full-length articles and confirm whether the screened articles meet the selection criteria.

Data collection process

The references extracted from the full-length articles will be reviewed to identify other publications of interest. References cited in the retrieved, as well as selected publications, ~~as well as selected publications,~~ will be ~~reviewed~~ considered to find additional articles in this context. The HNC risk factor data extraction form will be created and used by the review team during the data collection process. This particular form will be piloted on randomly selected eligible studies of HNC risk factors. Any discrepancies between the two groups will be sorted out via mutual discussion.

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Data items

Authors will extract the various parameters using the HNC risk factor data extraction form. The key data items include:

(a) characteristics of studies (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 studies such as cross-sectional studies, observational studies and longitudinal studies);

(b) characteristics of the study participants consist~~s~~ of three classifications: HNC participants' demographic characteristics (such as age, gender, ethnicity, and employment);

(c) clinico-pathological characteristics (such as anatomical sites, tumour stage, nodal status, nodal stage, post-operative radiotherapy, and histological grade);

(d) clinical outcomes (such as recurrence (local and regional);

(e) patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS));

(f) characteristics of individual HNC risk factors (such as alcohol consumption, tobacco smoking, HPV, and betel-quid chewing) and their combinations (such as alcohol and HPV, and tobacco smoking and HPV, and tobacco chewing and HPV);

(g) prevalence of HNC risk factors in different cities in India and its associations with HNC incidence

Outcomes

Primary outcomes

The primary outcome is to evaluate the risk factor prevalence and its associations with HNC in India.

Secondary outcomes

The secondary outcome is to link the variations in HNC risk factors with different geographic locations ine~~f~~ India in addition to other demographical, clinico-pathological and clinical parameters.

Risk of bias in individual studies

STROBE tool will be used to perform the quality assessment of the studies.[16] This tool has 22 elements including abstracts, rationale, study design, setting, participants, outcome, limitations, variables and statistics.[16] ~~A checklist from Dutch Cochrane using the MOOSE guidelines will be used to perform the quality assessment of the studies.[16]~~ The authors will collect the risk factor information from individual studies during their data synthesis phase using defined procedures for possible risk of bias. The defined procedures will include study validity based on specific parameters such as a number of HNC patients, year of publication, mention of ICD code, disease diagnosis and confirmation, study locations, and study period. The review team will ~~take the decision~~decide on possible risk of bias within the extracted information from the included studies, either high-risk or low-risk. Two authors will ~~These decisions will~~independently make these decisions ~~be made independently by two authors~~ and disagreements will be resolved by team decision and consultation with the third author.

Data synthesis

Authors will describe the risk factor prevalence with reference to ICD code for HNC (Lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32)). The authors will also include different clinical studies with the ~~the~~ different combination of risk factors and different age ranges and studies with varying times of follow-up. This process will be performed in two phases. The first phase consists of identification and dissemination of risk factor resources collected, followed by ~~key~~ critic~~uci~~al study and participant data items extracted. The second phase will focus on utilisation of ~~extracted~~ retrieved data items to estimate the survival trends among the HNC participants using Comprehensive Meta-Analysis Software™. The software analysis will yield the information about the heterogeneity of Odds Ratio (OR) using Cochran's Q test and Higgins' (I^2) statistic. Heterogeneity between the HNC risk factor studies will be assessed using the I^2 statistic, wherein substantial heterogeneity would be indicated by obtaining an I^2 value greater than 50%. Fixed or random effects model will be applied depending upon the heterogeneity. Q test statistical significance will be considered at a P-value of <0.01. Publication bias will be assessed using Harbord-Egger's bias indicator test,[17] Orwin's classic fail-safe N test,[18] Begg and Mazumdar's rank correlation test,[19] Duval and Tweedie's trim and fill- calculation,[20] and inverted funnel plot.

Subgroup analysis and meta-regression model

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Subgroup analysis will be performed on primary outcomes with subgroups defined by different study locations throughout India of reported incidence. Different combinations of the HNC risk factors and its associations with HNC incidence and prevalence will be measured. The source of heterogeneity will be assessed using meta-regression analysis of fitting co-variables.[21] -Heterogeneity will be considered significant if ~~is~~ *P*-value is <0.05. The heterogeneity of proportional contributions of risk factor associations with one or more study variable will be assessed using meta-regression analysis. The impact of proportional contributions of risk factor and combination of risk factors on fitting co-variables including gender distribution, methods of data collection, sample size, research quality, and sampling procedure will be calculated using meta-regression model. It needs a large ratio of studies for assessing the impact of combinations of risk factors to calculate true regression.

Ethics and dissemination

The study does not require ~~a~~ formal ethics approval by a human research ethics committee because this review protocol collects risk factor data from publicly published reports and studies. We plan to publish the results of this systematic review and meta-analysis in a peer-reviewed journal and present at relevant conference proceedings.

Patient and Public Involvement

The proposed study is literature-based systematic review and meta-analysis. Therefore, no patients and or public were involved in the proposed study.

DISCUSSION

The precise risk factor analysis with respect to HNC incidence cannot be sufficiently explained in the published studies. Most published clinical studies focus on major referral centre, or city-wise, or state-wise HNC incidence and prevalence.[22, 23] Estimation of a national~~nationwide~~ risk factor prevalence is an urgently needed agenda from the perspective of epidemiologists to identify low-risk and high-risk endemic zones.[24] Further evaluations apart from our defined scope of this study are not advisable. Structuring a systematic review and meta-analysis around the framework of a registered protocol will offer a more consistent strategy.[25] Furthermore, a reviewed protocol will allow more in-depth analysis.[25] ~~Contrary to popular belief,~~ HNC incidence is on a staggering rise.[26-29] A large portion of this increase is attributed to adults who indulge in the multifarious HNC risk factors widely prevalent in India.[24, 30] Immediate introductions of control measures would be a proactive step in order to curb the rising HNC incidence.[31, 32]

Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived this study, and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design, wrote the first draft of the protocol, and coordinated and integrated comments from co-authors. RJ and AP critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ provided methodological guidance on the overall development of the protocol. AP and RJ read and approved the final version of the manuscript.

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Competing Interests None declared

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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 therein are those of the authors and not those of their institutions.

~~**Provenance and peer review** Not commissioned; externally peer reviewed.~~

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Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived of this study, and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design,

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wrote the first draft of the protocol, and coordinated and integrated comments from co-authors. RJ and AP critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ provided methodological guidance on the overall development of the protocol. AP and RJ read and approved the final version of the manuscript.

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Competing Interests The authors declare that they have no competing interests.

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 therein are those of the authors and not those of their institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page no
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3,4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	-

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

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Head and Neck Cancer Risk Factors in India: Protocol for Systematic Review and Meta-Analysis

ABSTRACT

Introduction

Demographic, behavioural, and environmental factors have been associated with increased risk of Head and Neck Cancer (HNC). We will review published reports and explore connections between risk factors and HNC incidence. This protocol aims to provide strategies for a systematic review and meta-analysis of Head and Neck Cancer (HNC) risk factor analysis in India. It also provides guidelines in order to visualise obtained HNC risk factor data in the form of a heat-map highlighting variations across gender, age, and geographic location.

Methods and analysis

We will identify well-established HNC risk factors and perform a comprehensive systematic review and meta-analysis to quantify each risk factor's impact on HNC incidence. A systematic search will be performed to identify the studies and published reports of HNC risk factors in India. Meta-analysis will be conducted to estimate the proportional contribution of the most prevalent risk factor in HNC on a city-wide basis in Indian States and Territories.

Ethics and dissemination

The review protocol draws on publically available anonymised data without directly involving human participants and therefore requires neither formal human ethical review nor approval by a human research ethics committee. We published an outline of the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) in 2017. The results will provide an updated analysis of HNC risk factor prevalence in India, and we will discuss the applicability of rehabilitation care. We plan to disseminate the findings of this systematic review through publication in a peer-reviewed journal and presentation at relevant conference proceedings.

Review registration number

PROSPERO registration number CRD42017077758.

Strengths and limitations of this study

- The study attempts to calculate the odds ratio of HNC occurrence due to risk factor prevalence while following geographical demarcation based on cultural adaptation.
- The study can be expanded into a time-trends analysis to analyse variations in an odds ratio of HNC occurrence.
- Given the lack of infrastructure and funding in India, there is a possibility that the study participant population will not be representative of the overall population.
- The study primarily focuses on published papers as no such national or state-wide cancer registry exists which provides information on risk factor prevalence and associated HNC incidence.

INTRODUCTION

The systematic review will generate up-to-date information on the combinatorial role of different risk factors of 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.[1] 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.[2] HNC is the third-most common in India with 52,067 deaths and 77,003 cases diagnosed in 2012.[3] 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 also connected with increased risk of HNC prevalence.[4-6] Previously published studies have demonstrated that alcohol consumption and tobacco use are the most significant risk factors of HNC in addition to HPV.[7-9]

The significant risk factors for HNC have already been elucidated.[10] However, the likelihood chances of an individual developing HNC has 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 HNC patients.

The most significant risk factors are strongly associated with the sociocultural diversity and customs of India[11 12], and this obstacle leads to poor clinical outcomes. The connections between diverse risk factors including alcohol, HPV, tobacco smoking, and tobacco chewing, significantly varies due to diverse demographic and lifestyle habits of people in India.[13 14]

Rationale

What is the issue?

There is a scarcity of quantitative analysis and data synthesis of the causal relationships between HNC and their risk factors in the Indian demography. This could be due to the lack of data linkage and data reporting of HNC incidence in addition to the absence of integrated national and state-wide functional cancer registry. The prevalence of HNC is frequently dissimilar in different states and communities of the Indian population. It differs significantly from one community to another, and varies across various cities within the same geographic location, majorly depending upon the practices and lifestyles of the people in that location.[15] Furthermore, there are several factors associated with an increased risk of HNC such as diverse demographical, socio-economical, clinicoepidemiological, clinicopathological, and biological characteristics of Indian HNC patients that will benefit the study in understanding the precise difference between these factors.

How will our study address this?

This study will be the first of its kind to use meta-analysis in the evaluation of HNC risk factors in 29 Indian states and seven union territories. The meta-analysis offers an accurate degree of consistency by quantifying the extent of the variation compared to narrative synthesis. Quantitative synthesis will allow enumerating the diverse roles of the published risk factors of HNC to develop an HNC risk prediction model for future clinical research in India. The pooled effect size of HNC risk factors and the relative weight to the overall meta-analysis of the published studies from diverse Indian states and territories can contribute to

achieving the precision model to assess the specific dose-response association between multi-level risk factors and risk of HNC.

How will it help?

Since, India is cosmopolitan in culture, while being quite economically and socio-demographically distinct from other western countries, our findings will also be useful in further research for developing risk prediction models of HNC. This proposed systematic review and meta-analysis protocol will provide comprehensive and up-to-date information on the different combinations of risk factor relationship with HNC. This will also identify more appropriate HNC risk factor reports and studies published in this context. This extracted data will aid in filling the knowledge gaps of HNC risk factor distribution in 29 states and seven union territories of India. The effect size estimates of risk factor distribution will help to address the research priorities identified by World Health Organisation (WHO) and National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR). This protocol outlines the strategies for a systematic review and meta-analysis that could be helpful to Indian oral health and care, public health and political actions leading to personalising interventions for individuals at risk of HNC. This protocol provides in-depth information on HNC with the study objectives and design, search strategies, eligibility criteria, data extraction and synthesis, that is most appropriate to cancer researchers, clinicians and epidemiologists. This systematic review and meta-analysis will prospectively help in improving the early detection by addressing the percentage of prevalence and geographical distribution of risk factors in addition to early screening and treatment facilities thereby creating awareness among the high-risk Indian population. These public health measures will have an impact on reducing HNC mortality in India.

This protocol aims to describe the methodological approach for conducting systematic review and meta-analysis on risk factor distribution of HNC in the Indian demography. Given the potential importance of this study, the systematic review and meta-analysis are to quantify HNC incidence in association with risk factor prevalence in different Indian cities. The subgroup analysis with varying combinations of risk factors would further aid in figuring out the likelihood of developing HNC on a city-specific scale and predicting the endemic high-risk zones.

METHODS

Study design and participants

The authors will consider reports and also all published studies as well as unpublished studies from conference proceedings. The anticipated date of commencement of literature search for identifying studies is on 15 July 2018 and anticipate date of completion is on 15 December 2018. The study will include all studies that have clearly defined HNC risk factors expressed both individually as well as in combinations. Authors will also include studies describing the general human population in different geographic regions of India diagnosed with laboratory and clinically confirmed HNC from all ethnicities and socioeconomic backgrounds.

There will be no limits on study participants in terms of:

(a) demographic parameters such as age, gender, ethnicity, and employment;
(b) clinicopathological parameters such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, histological grade; and
(c) clinical outcomes such as recurrence (local and regional) and patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Authors will include risk factor studies pertaining to incidence, prevalence, and mortality of HNC in India. These studies will be carried out independently and will not be based on any global or national cancer registry for the statistical data of HNC risk factor distribution. Studies will be selected according to the criteria outlined below.

Study selection criteria

Inclusion criteria

- The HNC risk factor study has performed independent data extraction and has not relied on any state, national or global cancer registries
- Study provides statistical data regarding the risk factor associated with HNC incidence in India
- Study talks about the city-wise risk factor prevalence within India
- The inclusion of the factor based on the strength of the factor and the availability of at least three levels of interactions such as dose, exposure, and level of associated risk.
- Language: English

Exclusion criteria

- The study has stated HNC screening.
- The study uses different HNC *in-vitro* analysis and evaluations.
- Review articles and studies comparing the different genetic profiles in HNC

Selection criteria for participants

Inclusion criteria

1. Participants of any age with HNC or receiving HNC treatment will be considered.
2. Participants with a clearly confirmed diagnosis of HNC.
3. Participants based in India.

Exclusion criteria

1. Participants' age or age range not clearly mentioned.
2. Study participants' confirmative diagnoses of HNC have not been clearly identified.
3. 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 and authors will include studies at all levels of healthcare setting (such as primary, secondary, and tertiary healthcare) and those conducted in the community.

Language

Authors will include articles reported in the English language.

Information sources

The authors will develop a comprehensive literature search strategy using Medical Subject Headings (MeSH) and text words related to the prevalence of Head and Neck Cancer risk factors in India. The authors will scan the reference list through Cochrane Library, EMBASE, MEDLINE, PubMed, Science Direct, Scopus and Web of Science. The authors will also search multiple electronic bibliographic databases to identify the grey literature and unpublished studies from conference proceedings. The authors will circulate the bibliography of the included articles to the systematic review team.

Searching other resources

The major metropolitan city and hospital-based cancer registries in 29 states and 7 union territories of India will be integrated with the following reports by national and international cancer registries:

- Cancer Incidence in Five Continents (CI5) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- Global Cancer Observatory (GCO) by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- GLOBOCAN 2012 by World Health Organisation (WHO): International Agency for Research on Cancer (IARC)
- Global Heath Estimate (GHE) 2012 by WHO: Department of Health Statistics and Information Systems (DHSIS)
- Three-Year Report of Population-Based Cancer Registries 2012-2014 by National Centre for Disease Information & Research (NCDIR) - National Cancer Registry Program (NCRP) initiated by Indian Council of Medical Research (ICMR)

Search strategy

The systematic review and meta-analysis team will consider both qualitative as well as quantitative HNC risk factor studies primarily focusing on the Indian demography. All authors will provide their inputs for the draft Scopus search strategy to ensure that it retrieves a high proportion of eligible studies. After the Scopus strategy is finalised, it will be adapted to the syntax and subject headings of the other electronic bibliographical databases to be searched. The specific search strategies will be created by all authors after consultation with the review team

Draft Scopus Search

1. “Head and Neck Cancer” [Topic] AND “India” [Topic]
2. “Head and Neck Cancer” [Topic] AND “Risk Factors” [Topic] AND “India” [Topic]
3. “Head and Neck Cancer” [Topic] AND “Risk Factors” [Topic] AND “India” [Topic]] AND “Geographical incidence” [Topic]
4. “Head and Neck Cancer” [Topic] AND “Alcohol” [Topic] AND “India” [Topic]
5. “Head and Neck Cancer” [Topic] AND “Smoking” [Topic] AND “India” [Topic]
6. “Head and Neck Cancer” [Topic] AND “Betel” [Topic] AND “India” [Topic]
7. “Head and Neck Cancer” [Topic] AND “HPV” [Topic] AND “India” [Topic]

Study records

Data management

The HNC risk factor literature will be fed into a reference management software EndNote™. This will contribute to a strong working relationship among the review team during the study selection process. The reviewers will select the studies based on selection criteria and will upload relevant studies into EndNote™. This will yield a PRISMA flow diagram after the screening process by the HNC risk factor review team. HNC reviewers will also be using the traditional forms of data management in this process. Authors will avoid duplications when compiling together from multiple reports of the same study by including study design, HNC participants’ characteristics and risk factor associations. The corresponding authors will be contacted for missing information in the studies.

Selection process

The author team will review the titles and abstracts related to HNC risk factors in India. They will obtain the full-length of all titles that meet the selection criteria. Authors will screen the

full-length articles and confirm whether the screened articles meet the selection criteria.

Data collection process

The references extracted from the full-length articles will be reviewed to identify other publications of interest. References cited in the retrieved, as well as selected publications, will be considered to find additional articles in this context. The HNC risk factor data extraction form will be created and used by the review team during the data collection process. This particular form will be piloted on randomly selected eligible studies of HNC risk factors. Any discrepancies between the two groups will be sorted out via mutual discussion.

Data items

Authors will extract the various parameters using the HNC risk factor data extraction form. The key data items include:

(a) characteristics of studies (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 studies such as cross-sectional studies, observational studies and longitudinal studies);

(b) characteristics of the study participants consist of three classifications: HNC participants' demographic characteristics (such as age, gender, ethnicity, and employment);

(c) clinicopathological characteristics (such as anatomical sites, tumour stage, nodal status, nodal stage, postoperative radiotherapy, and histological grade);

(d) clinical outcomes (such as recurrence (local and regional);

(e) patients' survival such as Overall Survival (OS), Disease Free Survival (DFS) and Disease Specific Survival (DSS));

(f) characteristics of individual HNC risk factors (such as alcohol consumption, tobacco smoking, HPV, and betel-quid chewing) and their combinations (such as alcohol and HPV, and tobacco smoking and HPV, and tobacco chewing and HPV);

(g) prevalence of HNC risk factors in different cities in India and its associations with HNC incidence

Outcomes

Primary outcomes

The primary outcome is to evaluate the risk factor prevalence and its associations with HNC in India.

Secondary outcomes

The secondary outcome is to link the variations in HNC risk factors with different geographic locations in India in addition to other demographical, clinico-pathological and clinical parameters.

Risk of bias in individual studies

The authors will collect the risk factor information from individual studies during their data synthesis phase using defined procedures for possible risk of bias. The defined procedures

will include study validity based on specific parameters such as a number of HNC patients, year of publication, mention of ICD code, disease diagnosis and confirmation, study locations, and study period. The review team will decide on possible risk of bias within the extracted information from the included studies, either high-risk or low-risk. Two authors will independently make these decisions and disagreements will be resolved by team decision and consultation with the third author. The studies will be assessed for risk of bias using guideline formulated by Effective Health Care Program[15], and we will also use Newcastle-Ottawa Scale (NOS)[16] for the methodological assessment of cohort studies.

Data synthesis

Authors will describe the risk factor prevalence with reference to ICD code for HNC (Lip and oral (C00-08), nasopharynx (C10), other pharynx (C09-10, C12-14), and larynx (C32)). The authors will also include different clinical studies with the different combination of risk factors and different age ranges and studies with varying times of follow-up. This process will be performed in two phases. The first phase consists of identification and dissemination of risk factor resources collected, followed by critical study and participant data items extracted. The second phase will focus on utilisation of retrieved data items to estimate the survival trends among the HNC participants using Comprehensive Meta-Analysis Software™. The software analysis will yield the information about the heterogeneity of Odds Ratio (OR) using Cochran's Q test and Higgins' (I^2) statistic.[17] Heterogeneity between the HNC risk factor studies will be assessed using the I^2 statistic, wherein substantial heterogeneity would be indicated by obtaining an I^2 value greater than 50%. Fixed or random effects model will be applied depending upon the heterogeneity. Q test statistical significance will be considered at a P-value of <0.01. Publication bias will be assessed using Harbord-Egger's bias indicator test[18], Orwin's classic fail-safe N test[19], Begg and Mazumdar's rank correlation test[20], Duval and Tweedie's trim and fill calculation[21], and inverted funnel plot.

Subgroup analysis and meta-regression model

Subgroup analysis will be performed on primary outcomes with subgroups defined by different study locations throughout India of reported incidence. Different combinations of the HNC risk factors and its associations with HNC incidence and prevalence will be measured. The source of heterogeneity will be assessed using meta-regression analysis of fitting co-variables. Heterogeneity will be considered significant if *P*-value is <0.05. The heterogeneity of proportional contributions of risk factor associations with one or more study variable will be assessed using meta-regression analysis. The impact of proportional contributions of risk factor and combination of risk factors on fitting co-variables including gender distribution, methods of data collection, sample size, research quality, and sampling procedure will be calculated using meta-regression model. It needs a large ratio of studies for assessing the impact of combinations of risk factors to calculate true regression.

Patient and Public Involvement

No patients will be involved in this study.

Ethics and dissemination

The study does not require formal ethics approval by a human research ethics committee because this review protocol collects risk factor data from publicly published reports and studies. We plan to publish the results of this systematic review and meta-analysis in a peer-reviewed journal and present at relevant conference proceedings.

DISCUSSION

The precise risk factor analysis with respect to HNC incidence cannot be sufficiently explained in the published studies. Most published clinical studies focus on major referral centre, or city-wise, or state-wise HNC incidence and prevalence.[22 23] Estimation of a national risk factor prevalence is an urgently needed agenda from the perspective of epidemiologists to identify low-risk and high-risk endemic zones.[24] Further evaluations apart from our defined scope of this study are not advisable. Structuring a systematic review and meta-analysis around the framework of a registered protocol will offer a more consistent strategy.[25] Furthermore, a reviewed protocol will allow more in-depth analysis. HNC incidence is on a staggering rise.[26-29] A large portion of this increase is attributed to adults who indulge in the multifarious HNC risk factors widely prevalent in India.[24 30] Immediate introductions of control measures would be a proactive step in order to curb the rising HNC incidence.[31 32]

Abbreviations HNC: Head and Neck Cancer

Authors' Contributions RJ conceived this study and provided supervision and mentorship to AP and RA. RJ and AP led the development of the study protocol and design, wrote the first draft of the protocol, and coordinated and integrated comments from co-authors. RJ, KMG, NR and AP critically revised and edited successive drafts of the manuscript and gave input to the final draft of the protocol. RJ provided methodological guidance on the overall development of the protocol. All authors read and approved the final version of the manuscript.

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Competing Interests None declared

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 therein are those of the authors and not those of their institutions.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page no
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3,4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	-

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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