Epidemiological Review: Esophagus Squamous Cell Carcinoma in India

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Abstract

Worldwide the incidence of esophagus squamous cell carcinoma (ESCC), remains one of the most common causes of cancer death. ESCC is one of the leading types of cancer in the North and Northeast regions of India among both genders. Risk factors of ESCC include tobacco, alcohol, areca nut, hot beverages, low fruit diet, poor oral hygiene, unpiped water, and human papillomavirus infection. This review tries to elaborate on various modifiable risk factors for ESCC, which have been studied worldwide and need to be studied in India. PubMed was used as a search platform using keywords, such as "esophagus cancer," "esophagus squamous cell carcinoma," "epidemiology," "India," "incidence," "mortality," "risk factors," "treatment," "survival," "prevention" and their corresponding Medical Subject Heading terms, were used in combination with Boolean operators "OR" and "AND." Studies from India are mostly hospital-based case-control studies from the North region. Further research is required in India to understand the etiology, to design large-scale screening and prevention strategies.

Keywords

- esophagus squamous cell carcinoma
- esophagus cancer
- review
- epidemiology
- risk factor
- India

Introduction

Esophagus squamous cell carcinoma (ESCC) contributes a significant 90% of the total esophagus cancer (EC) cases worldwide which is an aggressive condition with poor prognosis and low survival rates.[1] Moreover, within the high-incidence region of ESCC, like South America, Africa, Iran, and Asia, the etiologies vary.[2] Consumption of alternate sorts of tobacco, alcohol, hot beverages, low fruit or vegetable diet, processed food, unpiped water, maintaining poor oral hygiene, and human papillomavirus (HPV) infection are the few possible risk factors currently being explored for ESCC worldwide. ESCC has been a major health concern in Kashmir valley and Northeastern states of India where risk factors presently are understudied. This review corroborates the necessity for conducting large-scale epidemiological studies in India to elucidate the risk factors associated with ESCC. Additionally, this review expresses the necessity of presenting the EC burden data on the basis of histological subtypes, considering the paucity of knowledge in this format, and also viewing the vast differences in their etiologies.[2]

Materials and Methods

Advanced search option of the PubMed database was used with the keywords such as "esophagus cancer," "esophagus squamous cell carcinoma," "epidemiology," "India," "incidence," "mortality," "risk factors," "treatment," "survival," "prevention," and their corresponding Medical Subject Heading terms were used in combination, like "AND" and

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"OR," to find published studies on ESCC. This review study was conducted on studies published in English, from the year 2008 to 2020 on ESCC. We excluded animal model studies, studies other than on ESCC, commentaries, clinical or observational veterinary study, and clinical trial studies. Relevant data on descriptive epidemiology and risk factors were explored using databases such as the National Health Portal of India (NHP), Central Water Commission, India (CWC), National Family Health Survey India (NHFS), National Centre for Disease Informatics and Research–Indian Council of Medical Research (NCDIR-ICMR) India, National Cancer Registry Program (NCRP) of India, Census India 2011, National Health Mission India (NHM), International Agency for Research on Cancer (IARC) Monographs, World Health Organization (WHO) guidelines, Global Cancer Observatory 2020, and Cancer Incidence in five continents XI vol. IARC (CI5 XI).

Descriptive Epidemiology

Worldwide, 604,100 new cases and 544,076 cancer death were estimated for EC in the year 2020.[3] India ranks second in EC incidence trailing China which has the highest incidence of EC. In India, it is the fifth most common cancer type in males and the sixth most common cancer type in females. In India, the number of incident cases of esophageal cancer in 2020 was 63,180 out of which 40,183 were males and 22,997 females, and the prevalent cases were 68,607.[3] The male-to-female ratio in India is 2.4:1.[4] ESCC is the most common histological subtype among all cancer registries in India. The top five cancer registries having the highest incidence rate of ESCC are Mizoram, Kamrup Urban, Cachar, Sikkim, and Tripura registries.[5] As per the hospital-based cancer registry report, the esophagus was the leading site in KMIO—Bangalore, AMC—Dibrugarh, BBCI—Guwahati, and in PGIMER—Chandigarh among 35 to 64-year-old males.[6] However, the observed incident cases in the year 2020 have already exceeded the predicted number of incident cases for the year 2035, showing a significant rise in the incident rates.[7]

Survival Data

A study from Jammu, India, suggested that the frequency of survival in ESCC patients is lowered by intake of red chili, snuff, and smoking.[8] Studies from China and Brazil show factors such as gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological reports, are independent risk factors affecting the overall survival of EC.[9,10] Other factors such as, weight loss (kg), and body mass index (BMI) variation (kg/m^2) predict the stage at diagnosis in the ESCC.[10] The Surveillance, Epidemiology, and End Results (SEER) report of 18 regions from the year 2002 to 2008 for 5-year relative survival in EC continues to be low at around 16.9%.[11] The overall survival of EC is 5 to 30% as stated by the ICMR report. The disease is mostly detected at a stage where it is inoperable in most patients (70–80%), and with an expected survival of 7 to 12 months.

Risk Factors

Recent developments and finding in epidemiological studies have led to the identification of many risk factors associated with ESCC worldwide which need to be studied in India. ►**Fig. 1**.

Strongly Associated

Tobacco Use

Exposure to tobacco smoke and chewing tobacco products has been associated with ESCC. Case-control studies in India have seen a two- to seven-fold increase in the risk of ESSC for chewing tobacco, betel quid with tobacco having a dose–response relationship.[12] In India, the risk of developing tobacco-related cancer was found highest in the Northeastern region with maximum risk found for EC in women.[13] Hospital-based studies from India suggest an increase in the risk of ESCC by smoking tobacco, in the form of cigarettes, bidi, and hookah.[14–16] Habits such as consumption of nass, snuff, paan chewers, and betel quid chewers also increase the risk of ESCC.[14,15,17] Along with cigarettes, other forms of tobacco smoking such as hookah pipes, and cigars exhibit similar risks on ESCC. A study from India on secondhand smoking and ESCC risk reported odds ratio (OR) of 1.32 in exclusive secondhand smokers (never tobacco users), and OR of 3.41 in second-hand smokers who are active chewers, suggesting additive effects of tobacco-related carcinogens[16] (►**Table 1**). However, there are only a few studies in India evaluating the risk of tobacco chewing and its association with ESCC and adjusting for potential confounders.

Alcohol Use

Alcoholic beverages are known to be casually associated with ESCC as reported by IARC monograph.[18] A hospital-based case-control study from India found an increased risk of ESCC when associated with alcohol consumption, but without adjusting for all potential confounders, that is, tobacco chewing and smoking habits.[14] Another study from India, by Singh et al, reported statistically significant multivariate OR of 2.21, among ever alcohol drinkers for ESCC.[17] Although alcohol intake has a strong association with ESCC, few studies have observed a **J**-shaped relationship (rather than a linear relationship) between alcohol consumption and increased risk of ESCC.[19,20] Hence, designing health care policies is a challenge[21] (►**Table 2**).

Possibly Associated

Areca Nut

IARC has considered areca nut (AN) as a group-1 human carcinogen in 2003.[22] AN is consumed widely in Asian countries like India, Pakistan, Bangladesh, and Sri Lanka, with consumption observed higher in females.[23] A Taiwan study indicated that AN chewing history is significantly associated with the onset of cancer from a younger age and with poor response to chemoradiotherapy, in ESCC patient.[24] A meta-analysis study from Asia suggested that chewing AN was independently and significantly associated with an increased risk of ESCC.[25] Studies from India have shown a dose–response relationship and combined effect of tobacco consumption and AN (►**Table 3**).

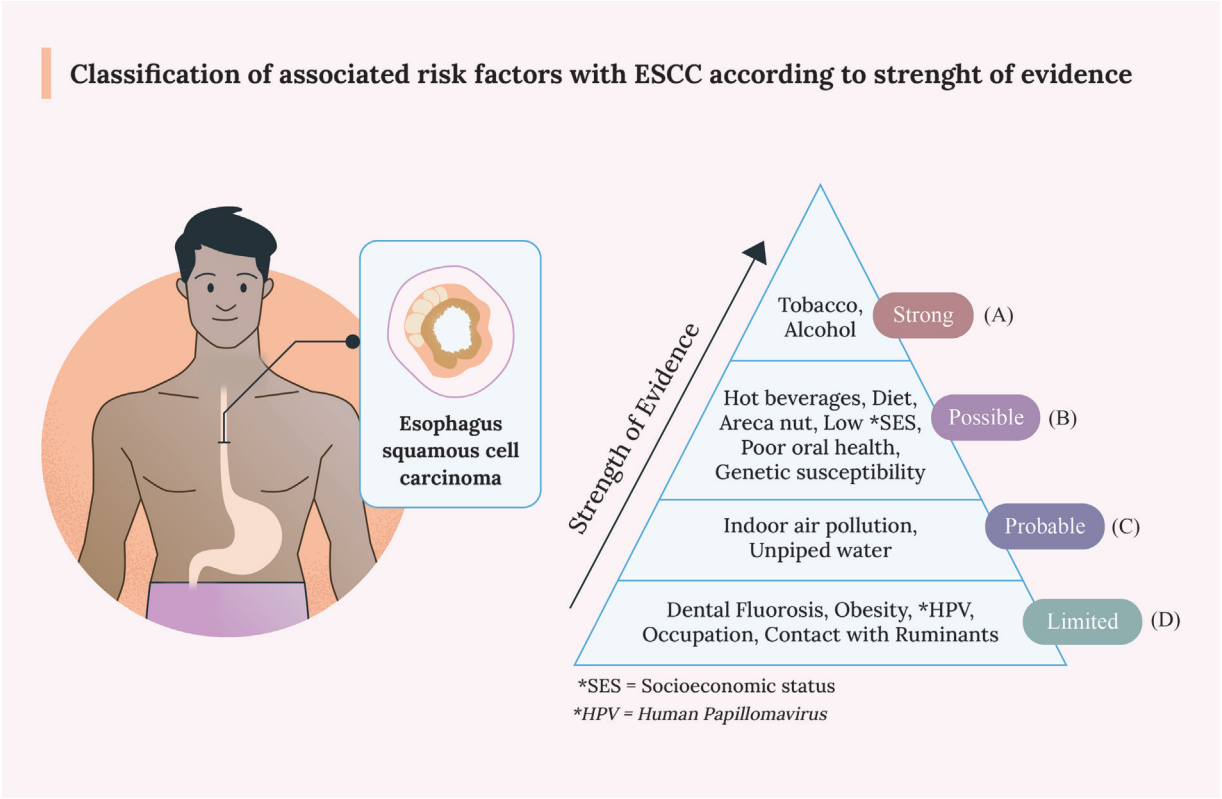

Fig. 1 Classification of associated risk factors with ESCC according to strength of evidence. (**A**) Strong: risk factors having strongest association as per literature are mentioned in this group followed by (**B**) Possibly associated risk factors, (**C**) Probably associated risk factors, and (**D**) risk factors having limited evidence. ESCC, esophagus squamous cell carcinoma

Poor Oral Health

A population-based case-control study from China, indicating habits of tooth brushing once or less per day, compared with tooth brushing twice or more per day, among nonsmokers and nondrinkers showed significant association with a 1.81-fold increased risk of ESCC.[24] The Golestan cohort study from Iran suggested that tooth loss is independently and positively associated with ESCC.[26] A recent case-control study from Africa showed increased ESCC risk when associated with decayed teeth and missing teeth[27] (►**Table 4**). A research study from India, Kashmir region showed an inverse association between cleaning teeth and ESCC risk, especially with toothbrushes compared with sticks or other tools of brushing, supporting previous studies from other high-risk countries.[28] A cross-sectional study published in 2019 from rural India to understand the prevalence of oral disease concluded that the prevalence of dental caries was 76.4%. The decayed, missing, and filled teeth (DMFT) score of subjects who did not use toothbrushes and toothpaste was significantly higher and the awareness about oral hygiene was observed to be low in the general population.[29]

Social Economic Status

Higher incidence of ESCC is observed in low or middle-income countries as compared with high-income countries.[30] A population-based case-control study from Golestan, Iran, indicates a strong inverse association between education, wealth, and being married with the risk of developing ESCC. A Swedish cohort study showed that divorce, widowhood, living alone, low educational attainment, and low income increased the risk for ESCC along with other subtypes of EC.[31] A study from China published in 2018 showed higher education (OR = 0.60), larger house area per person (OR = 0.71), and higher wealth score (OR = 0.43) were associated with a low risk of ESCC, and patients possessing several household appliances (>5 years) also had a lower ESCC risk.[32] Similar findings from a case-control study published in 2013, from Kashmir, India, observed that low socioeconomic status is associated with a high risk of ESCC.[33] Another study from North India suggests poor socio economic status results in lack of fresh fruit and vegetable intake and which is suspected to be one of the risk factors in development of esophageal cancer[34] (►**Supplementary Table S1**; available in the online version).

Although socioeconomic status is observed to be associated with esophageal cancer, it is not the direct cause in the development of esophageal cancer. The low socioeconomic status affects esophageal cancer through various causal pathways which include its association with poor nutrition, higher rates of tobacco consumption, and higher proportion of infection with HPV.

Diet

High consumption of fruits and vegetables showed an inverse association with the development of ESCC as reported in a

Table 1 Characteristics of tobacco studies (chewing, smoking, and inhalation) for ESCC in the population of India and worldwide

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–tobacco									
Tobacco chewing with other products									
Paan chewers with tobacco (more than 20 years)	OR = 1.5 77/204	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Nass chewing (ever chewer)	OR = 2.88 201/192	Dar et al[15]	2012	23033008	Kashmir	ESCC	702/1,663	Case control	Age, ethnicity, religion, place of residence, education level, cumulative use of cigarette, hookah, ever use of bidi, cannabis, gutka, alcohol, daily fruit, and fresh vegetable consumption
Tobacco inhalation									
Snuff	OR = 3.86 136/71	Sehgal et al[12]	2012	23107978	Jammu	ESCC	200/200	Case control	Not mentioned
Chewing products other than tobacco									
Betel nut chewer (ever chewer)	OR = 2.79 68/52	Singh et al[17]	2015	26045981	Assam	ESCC	99/75	Case-control	Not mentioned
Tobacco smoking									
Smoking tobacco	OR = 1.97 110/63	Sehgal et al[12]	2012	23107978	Jammu	ESCC	200/200	Case control	Not mentioned
Cigarette smoking	OR = 2.0 40/90	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Bidi smoking	OR = 1.8 122/252	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Water pipe tobacco smoking									
Hookah (waterpipe tobacco smoking ever users)	OR = 1.85 420/699	Dar et al[15]	2012	23033008	Kashmir	ESCC	702/1,663	Case control	Age, ethnicity, religion, place of residence, education level, cumulative use of cigarette, hookah, ever use of bidi, cannabis, gutka, alcohol, daily fruit and fresh vegetable consumption
Indian study–Second hand smoking									
Secondhand smoker (never tobacco users)	OR = 1.32 31/60	Rafiq et al[16]	2016	26735535	Kashmir	ESCC	703/1,664	Case control	Age, ethnicity, religion, place of residence, income, gender, education, the wealth score, ever use of alcohol, salt tea consumption, frequency of close contact with animals, house type, cooking fuel, fruit and vegetable intake
Secondhand smoker (tobacco chewers)	OR = 3.41 15/11	Rafiq et al[16]	2016	26735535	Kashmir	ESCC	703/1,664	Case control	Age, ethnicity, religion, place of residence, income, gender, education, the wealth score, ever use of alcohol, salt tea consumption, frequency of close contact with animals, house type, cooking fuel, fruit and vegetable intake, tobacco smoking and smokeless tobacco use
International studies–tobacco									
Cigarette or pipe (ever)	RR = 1.33	Tran et al	2005	15455378	China	ESCC	1,958	Cohort	Age

Table 1 (*Continued*)

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Ever smoker	HR = 1.36	Fan et al	2008	18444169	Shanghai	EC	101	Cohort	Level of education, body mass index, number of drinks consumed per day, number of years of drinking, and summed intakes of preserved food items, fresh fruits, and fresh vegetables
Smoking tobacco index (daily tobacco intake × duration of smoking) overall survival	HR = 1.21	Liu et al	2020	32071596	China	ESCC	944	Cohort	Multivariate
Smokeless tobacco users	OR = 2.06–12.8	Gupta et al	2018	30264755	Eastern Mediterranean	EC	80 studies	Meta-analysis	
Ex-smokers	HR = 1.29	Cho et al	2017	28973012	Korean	EC	9,171	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and alcohol
Current smokers	HR = 1.87	Cho et al	2017	28973012	Korean	EC	9,171	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and alcohol

Abbreviations: BMI, body mass index; CI, confidence interval; EC, esophagus cancer; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio; RR, relative risk.

few studies.[35] Processed food is a source of N-nitroso amines compounds which play important role in the high risk of ESCC. N-Nitroso amines in processed meats are labeled as carcinogenic (group 1) in 2015 by IARC monographs and also red meat is classified as (group 2A) carcinogenic.[36,37] A cohort study from the Netherlands showed that the consumption of vegetables and fruits has an inverse association with ESCC.[38] A population-based case-control study in China mentioned a strong association between consumption of salted meat and ESCC.[39] A case-control study from the Golestan region in Iran indicated direct association between red meat consumption and ESCC.[40] Another cohort study from Golestan showed that a dietary deficiency of zinc and calcium is associated with ESCC.[41] A study from India, observed that lower intake of fresh vegetables and fruits is suspected to be a major risk factor for the development of ESCC[34] (►**Supplementary Table S2**; available in the online version). In India, the high-risk regions of ESCC consume majorly processed red meat, fermented vegetables, fermented black mustard seeds, and fermented fish to enhance the flavors and preserve the food during scarcity.[42]

Very Hot Beverages/Food

Drinking very hot beverages (≥65°C) is one of the probable risk factors for ESCC as reported by the IARC monograph and is classified as group-2A carcinogen.[43,44] A recent cohort study from Iran and a case-control study from Kenya strengthen the evidence for a strong association between very hot beverage consumption and risk of ESCC.[27,45] A population-based cohort study from China observed an increase in EC associated with a combination of hot tea, excessive alcohol, and tobacco.[46] A study from South America showed that hot mate drinking was associated with ESCC risk.[47] In India, a case-control study from Kashmir indicated that the habit of drinking salt tea was strongly associated with the risk of developing ESCC and not the consumption of hot tea. Although, it could be due to variations in reporting tea-drinking temperature[48] (►**Supplementary Table S3**; available in the online version).

Probably Associated

Indoor Air Pollution

Indoor air pollution or household air pollution occurs from the combustion of cooking fuel and has been studied as one of the risk factors for esophageal cancer. In the rural area of the developing countries where the incidence of ESCC is high, cooking fuels like coal, charcoal, wood, crop residue, animal dung, and other smoke-producing fuel are used for daily cooking. Compared to males, females are at a higher risk of indoor air pollution since most of the cooking is done by females in developing countries and where most of them are non-smokers or non-drinkers.[49] These fuels generate smoke containing Polycyclic Aromatic Hydrocarbons (PAH) which are classified as group 1, that is, carcinogenic to humans as per IARC.[50] A study from Iran, indicated that PAHs played a causal role in the etiology of esophageal cancer in high-risk population.[26] A study from Northern India suggested that

Table 2 Characteristics of alcohol studies for ESCC in the population of India and worldwide

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–alcohol									
Alcohol	OR = 1.8 66/131	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence and occupation
Alcohol	OR = 2.21 41/22	Singh et al[17]	2015	26045981	Assam	EC	110/75	Case control	Not mentioned
Zu (local liquor)	OR = 1.34 32/28	Lalpawimawha	2016	Not found	Mizoram	EC	138/276	Case control	Betel quid consumption, tobacco consumption, smoking, BMI at 20 years of age and family history of cancer; education level and income level, dietary habits and physical activity except for each independent variable
Zu (local liquor) + commercial	OR = 9.82 21/12	Lalpawimawha	2016	Not found	Mizoram	EC	138/276	Case control	
International studies–alcohol									
Mild-to-moderate drinkers	HR = 1.52	Cho et al	2017	28973012	Korean	EC	5,839	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and smoking status
Heavy drinkers	HR = 3.13	Cho et al	2017	28973012	Korean	EC	5,839	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and smoking status
Light drinker	RR = 1.25	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	16 studies	Systematic review and meta-analysis	Systematic review and meta-analysis
Moderate drinker	RR = 2.32	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	27 studies	Systematic review and meta-analysis	Systematic review and meta-analysis
Heavy drinkers	RR = 5.38	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	20 studies	Systematic review and meta-analysis	Systematic review and meta-analysis

Abbreviations: BMI, body mass index; CI, confidence interval; EC, esophagus cancer; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table 3 Characteristics of areca nut studies for ESCC in population worldwide

Exposure	Risk estimates (95% CI)	Study	Year	PMID	Location	Case type	Sample size	Study design
International study–areca nut								
Areca nut	OR = 3.05	Akhtar et al[25]	2013	23224324	Kuwait	ESCC	12 case-control study	Meta-analysis
Areca nut and tobacco smoking	OR = 6.79	Akhtar et al[25]	2013	23224324	Kuwait	ESCC	6 case-control study	Meta-analysis

Abbreviations: CI, confidence interval; ESCC, esophagus squamous cell carcinoma; OR, odds ratio.

using cooking fuels, like electricity (OR = 0.24), and LPG (OR = 0.10) were associated with lower ESCC risk in comparison to using less expensive fuels in the region, like animal dung, firewood, and biomass[33] (►**Supplementary Table S4**; available in the online version).

Unpiped water/Drinking Water Contamination

Relation between drinking water quality and cancer has been studied for a long time. Drinking water contaminants like arsenic (group 1), nitrates (group 2A), and disinfection by-products (groups 2B and 3), all are classified as carcinogenic by IARC monograph classification.[51] However, a study from Sri Lanka showed contradicting results where pipe-borne water was seen to have a six-fold risk for EC compared with the present study with other sources of water, but it could be due to other factors of water storage, and sanitization after collection of water.[52] Whereas, a study from Golestan observed a dose–response relationship between the duration of drinking unpiped water and ESCC[26,40] (►**Supplementary Table S5**; available in the online version). On the National Health Portal (NHP) of India, it is mentioned that the total urban and rural population consumes only 43.5% of their drinking water from the tap, the remaining population drinks water from unpiped sources, that is, well (11%), tube well (8.5%), hand pump (33.5%), spring (0.5%), river or canals (0.6%), pond or lake (0.8%), and other source (1.5%),[53] making it a necessary exposure to be studied.

Limited Data or No Data Associated

Obesity

Waist-to-hip ratio (WHR) and body mass index (BMI) are strong factors representing obesity in a population. Obesity is strongly associated with esophagus adenocarcinoma (EAC) as per many published studies worldwide. There are limited studies studying obesity as a risk factor in association with ESCC.[30] A recent study published from the United Kingdom, Biobank cohort, suggested that no significant associations were observed with anthropometric measurements or body fat composition in men,[54] and in women measurements, like weight, BMI, hip circumference, waist circumference, waist-to-height ratio, body fat, and trunk fat percentage were all inversely associated with ESCC[55] (►**Supplementary Table S6**; available in the online version). In India, this exposure in association with ESCC is still quite unexplored.

Dental Fluorosis

Natural fluoride belts are found in regions from Jordan, Egypt, Libya, Algeria, Sudan, Kenya, Turkey, Iran, Afghanistan, India, Northern Thailand, and China, and similar fluoride belts are observed in the United States and Japan.[56] Fluoride carcinogenicity in humans is understudied and is being classified in group 3 as per IARC monograph.[36] ESCC is plausibly associated with dental fluorosis as per recent findings from a case-control study in Kenya[27] (►**Supplementary Table S7**; available in the online version). Dental fluorosis is endemic as per the data published in the National Health Profile report 2019 from India and, presents a total number of 10,379 rural habitations from 16 states, showing exceeding levels of fluoride in their source of drinking water and highlights the need for safe drinking water in these habitations.[53] Studies in India show a high groundwater fluoride level correlation with a high prevalence of dental fluorosis in regions like the Northwest, South, and East, including the Gangetic Plains which warrants the needs to study it as a risk factor in the development of ESCC.[57–59]

Heavy Metals Consumption

Heavy metals, like cadmium, lead, chromium (IV), and arsenic, have been found in drinking water and farm soil, all of which have been, classified as carcinogenic(group-1) by IARC monograph.[51] A study from Taiwan suggested an increased level of nickel in farm soil is associated with the prevalence of EC.[60] A study from Iran observed high-lead intake from vegetables could be prevented in high-risk regions of ESCC which is beyond suggested levels by WHO[61] (►**Supplementary Table S8**; available in the online version). In developing countries, like India, most of the population is dependent on surface water and groundwater as a source of drinking water, hence most of the habitats are exposed to the presence of excess arsenic in the drinking water source.[62]

Human papillomavirus (HPV) Infection

A meta-analysis study conducted in the Chinese population reported pooled OR of 6.36 for HPV 16 infection and EC.[63] Another meta-analysis study on HPV types in ESCC observed OR of 3.55 for HPV 16 infection and OR of 1.25 for HPV 18 infection.[64] HPV 16 was found to be the most frequently observed genotype in ESCC (►**Supplementary Table S9**; online only).

Table 4 Characteristics of poor oral health studies for ESCC in population of India and worldwide

Exposure	Risk estimates (95% CI) Case | control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–poor oral health									
Cleaning of teeth with brush	OR = 0.11 Case | Control 50/528	Dar et al[28]	2013	23900216	India	ESCC	703/1,664	Case control	Age, ethnicity, residence, education, wealth score, fruit and vegetable intake, bidi smoking, gutka chewing, alcohol consumption and cumulative use of hookah, cigarette, and nass
Cleaning of teeth with finger	OR = 0.51 Case | Control 488/957	Dar et al[28]	2013	23900216	India	ESCC	703/1664	Case control	
International studies–poor oral health									
Frequency of brushing teeth <= 1	OR = 1.81 486/510	Chen et al	2017	27778330	China	ESCC	616/770	Case control	Age, gender, education, marital status, tobacco smoking, alcohol drinking, tea drinking, family history of ESCC, daily consumption of pickled vegetables, daily consumption of fresh fruits, and wealth score
≥6 tooth loss (after age 20)	OR = 1.48 266/330	Chen et al	2017	27778330	China	ESCC	616/770	Case control	
Excessive tooth loss (≥12 excess tooth loss)	HR = 1.66	Sheikh et al[26]	2019	30611753	Northeastern Iran	ESCC	50,045 individuals	Cohort	Age, gender, residence counties, ethnicity, quartiles of the socioeconomic status, opium consumption through smoking, opium consumption through ingestion, drinking hot tea at ≥60°C, daily intake of fruits, daily intake of vegetables, drinking un-piped water, indoor air pollution, daily contact with ruminants, alcohol drinking, cigarette smoking, nass chewing
Mswaki stick	OR = 1.7 133/75	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	Gender, ethnicity, alcohol and tobacco, alcohol intensity, beverage drinking, family history of EC, and continuous: age, education score, tooth brushing frequency + brush type + DMFT (not for lost/decayed teeth), leukoplakia, dental fluorosis
No. of missing teeth ≥ 6	OR = 1.3 87/55	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
No. of decayed teeth ≥ 3	OR = 4.4 131 | 37	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
DMFT count ≥ 8	OR = 3.0 133/54	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
Frequency of brushing teeth (never) tobacco users–fully adjusted	OR = 2.53 222/324	Abnet et al.	2009	18990747	Golestan, Iran	ESCC	283/560	Case control	Age, gender, place of residence, ethnicity, alcohol drinking, use of tobacco, opium, or both, education in three categories, number of appliances, and fruit and vegetable intake
Frequency of brushing teeth (never) alcoholic beverage drinkers–fully adjusted	OR = 2.15 222/324	Abnet et al.	2009	18990747	Golestan, Iran	ESCC	283/560	Case control	
Teeth loss	OR = 1.31	Chen et al	2015	26462879	China, Iran, Japan, India, the United States, Finland	ESCC	6 studies	Meta analysis	Not mentioned (Forest's plot)
teeth brushing	OR = 0.57	Chen et al	2015	26462879	China, Iran, Japan, India, the United States, Finland	ESCC	4 studies	Meta analysis	Not mentioned (Forest's plot)

Abbreviations: CI, confidence interval; DMFT, decayed, missing, and filled teeth; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio.

Occupation

Occupational hazard as a risk factor in association with ESCC has received less attention. A population-based case-control study conducted in China showed OR of 1.69 in jobs involving high physical labor.[32] In India, a few studies conducted in Kashmir published that the risk of workers who are highly physically active or who are engaged in physically strenuous work are at higher risk of developing ESCC[33,65] (►**Supplementary Table S10**; available in the onlineversion).

Ruminants

Contact with the animal has been a risk factor which has not studied extensively, but we have a few case-control studies that mention the risk of ESCC from the contact with ruminants. A case-control study from India observed the association between daily close contact with animals and increased risk of ESCC as compared with no animal contact group. Animal contact for more than 50 years was associated with an increased risk, showing a dose–response association with ESCC.[66] Another case-control study from Iran showed an increased risk of ESCC when in contact with canines and ruminants in the ever contact group as compared with the group which was never in contact. Also, there was a dose–response relationship observed with the level of contact with the animals[67] (►**Supplementary Table S11**; available in the online version).

Prevention

Lifestyle modifiable changes could be adapted to prevent the risk of developing ESCC. Strong evidence suggests cessation of smoking tobacco, chewing tobacco, and drinking alcohol should be followed in high-risk populations. Improving socioeconomic status reduces the risk of EC.[32,33,68] Studies recommend a healthy diet with fresh vegetables and fruits that will help reduce the risk of developing ESCC. Pickled and salted food intake needs to be avoided, along with processed meat.[35,37–39,69] Behavioral changes are needed in a high-risk region where the intake of hot beverages is a common tradition.[43] Endoscopic screening and surveillance for conditions, such as dysplasia in the esophagus can lead to a reduction in the incidence of ESCC and reduce in the mortality rate.[70] Management of symptoms that can lead to conditions, like dysplasia, can be decreased with the help of pharmaceutical drugs, lifestyle changes, diet modifications, and diagnostic testing. Early detection and classification of high-risk populations can be done with help of a risk prediction model. Vaccination programs for a defined high-risk population can prevent cancer incidences. Maintaining regular oral hygiene prevents tooth loss and helps in preventing injury in the inner lining of the esophagus. Early age lifestyle modifications can help maintain health in the context of ESCC prevention.[71]

Discussion on Gaps in the Literature, Indian Perspective

In India, tobacco smoking in males is 19% and in females is 2%. On the another hand, smokeless tobacco prevalence in males is 29.6% and in females is 12.8%.[72] Association of different types of chewing tobacco and betel nut needs to be identified. Similarly, association with different types of tobacco smoke products, including bidi, needs to be studied in the Indian population adjusting for potential confounders. The duration of consumption and content of the local liquor consumed in high-risk regions of India in association with ESCC have not been studied yet. Traditional alcoholic beverages carrying cultural significance are commonly consumed during various special occasions in the high ESCC incidence region of India.[42] Similarly, raw ANs or fermented ones are commonly consumed alone or with betel leaf in high ESCC incidence region of India, thus they need to be studied in association with ESCC. Fermented, spicy, and processed food are consumed extensively in the high ESCC incidence region of India to meet their needs in extreme environmental conditions. Therefore, research on understanding the carcinogenic factors developed during food processing can help to design preventive policies for food preservations and cooking in high ESCC incidence regions.

In India, according to NHFS4 data, 55.7% of the rural population uses wood as their source of cooking fuel, and only 44% of the total urban and rural households had clean cooking fuel.[73] Indoor air pollution and socioeconomic status could be related since the population which has high social economic status (SES) can afford clean fuel for cooking and has low exposure to indoor air pollution. To understand the relation between indoor air pollution and the risk of ESCC development, we need further investigation. As per the NHFS4 survey data of India, rural households rely most on tube wells or boreholes (51%), followed by water piped into their dwelling, yard, or plot (18%).[73] In India, since more than half of the population lives in rural areas where tap water is unavailable most of the time, unpiped water consumption could be a potential risk for ESCC.

Conclusion

ESCC carcinoma affects millions of people worldwide every year having a poor prognosis and poor survival rate, especially in developing countries. A rapid increase in the incidence rate of ESCC needs the implementation of new strategies for diagnosis, treatment, and containment of the disease. The review studies modifiable risk factors, like obesity, unpiped water, dental fluorosis, heavy metals, diet, SES, and HPV, showing very few or no studies from India. The review indicates that there is a need to conduct descriptive, as well as large-scale analytical studies in India for generating evidence for risk factors associated with ESCC. Strict actions against the usage of modifiable risk factors leading to ESCC can be opted by the government policymakers to prevent such health conditions and improve overall public health.

Conflict of Interest
None declared.

References

1 Yang J, Liu X, Cao S, Dong X, Rao S, Cai K. Understanding esophageal cancer: the challenges and opportunities for the next decade. Front Oncol 2020;10:1727

2 Hull R, Mbele M, Makhafola T, et al. A multinational review: oesophageal cancer in low to middle-income countries. Oncol Lett 2020;20(04):42
3 Cancer today. Accessed March 22, 2021 at: http://gco.iarc.fr/today/home
4 Choksi D, Kolhe KM, Ingle M, et al. Esophageal carcinoma: An epidemiological analysis and study of the time trends over the last 20 years from a single center in India. J Family Med Prim Care 2020;9(03):1695–1699
5 Bray F, Colombet M, Mery L, , et al; World Health Organization. Cancer Incidence in Five Continents, Vol. XI. Accessed March 22, 2021 at: https://publications.iarc.fr/_publications/media/download/6371/8015478d4d1381e2d10b7df95e6762987b34a20e.pdf
6 National Centre for Disease Informatics and Research, National Cacer Registry Programme. Consolidated report of hospital based cancer registries: 2012–2014. Accessed March 30, 2021 at: https://ncdirindia.org/ncrp/ALL_NCRP_REPORTS/HBCR_REPORT_2012_2014/index.htm
7 National Centre for Disease Informatics and Research, National Cacer Registry Programme. Consolidated report of population based cancer registry: 2012-2014. Accessed March 30, 2021 at: https://ncdirindia.org/ncrp/Annual_Reports.aspx
8 Sehgal S, Kaul S, Gupta BB, Dhar MK. Risk factors and survival analysis of the esophageal cancer in the population of Jammu, India. Indian J Cancer 2012;49(02):245–250
9 He Y, Liang D, Du L, et al. Clinical characteristics and survival of 5283 esophageal cancer patients: A multicenter study from eighteen hospitals across six regions in China. Cancer Commun (Lond) 2020;40(10):531–544
10 Tustumi F, Kimura CMS, Takeda FR, et al. Prognostic factors and survival analysis in esophageal carcinoma. Arq Bras Cir Dig 2016;29(03):138–141
11 Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19(34):5598–5606
12 Gupta P, Arora M, Sinha D, Asma S, Parascandola M. Smokeless Tobacco and Public Health in India. Ministry of Health & Family Welfare, Government of India. New Delhi, India: Govt. of India; 2016
13 Asthana S, Patil RS, Labani S. Tobacco-related cancers in India: a review of incidence reported from population-based cancer registries. Indian J Med Paediatr Oncol 2016;37(03):152–157
14 Ganesh B, Talole SD, Dikshit R. Tobacco, alcohol and tea drinking as risk factors for esophageal cancer: a case-control study from Mumbai, India. Cancer Epidemiol 2009;33(06):431–434
15 Dar N, Bhat G, Shah I, et al. Hookah smoking, nass chewing, and oesophageal squamous cell carcinoma in Kashmir, India. Br J Cancer 2012;107(09):1618–1623
16 Rafiq R, Shah IA, Bhat GA, et al. Secondhand smoking and the risk of esophageal squamous cell carcinoma in a high incidence region, kashmir, india: a case-control-observational study. Medicine (Baltimore) 2016;95(01):e2340
17 Singh V, Singh LC, Singh AP, et al. Status of epigenetic chromatin modification enzymes and esophageal squamous cell carcinoma risk in northeast Indian population. Am J Cancer Res 2015;5(03):979–999
18 IARC. Alcohol Drinking: IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans Volume 44. Accessed March 31, 2021 at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Alcohol-Drinking-1988
19 Kim MK, Ko MJ, Han JT. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health insurance corporation's health examinee cohort in 2000. Cancer Causes Control 2010;21(12):2295–2302
20 Islami F, Fedirko V, Tramacere I, et al. Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: a systematic review and meta-analysis. Int J Cancer 2011;129(10):2473–2484
21 Chokshi DA, El-Sayed AM, Stine NW. J-shaped curves and public health. JAMA 2015;314(13):1339–1340
22 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2004;85:1–334
23 Shah G, Chaturvedi P, Vaishampayan S. Arecanut as an emerging etiology of oral cancers in India. Indian J Med Paediatr Oncol 2012;33(02):71–79
24 Chen CH, Lu HI, Wang YM, et al. Areca nut is associated with younger age of diagnosis, poor chemoradiotherapy response, and shorter overall survival in esophageal squamous cell carcinoma. PLoS One 2017;12(02):e0172752
25 Akhtar S. Areca nut chewing and esophageal squamous-cell carcinoma risk in Asians: a meta-analysis of case-control studies. Cancer Causes Control 2013;24(02):257–265
26 Sheikh M, Poustchi H, Pourshams A, et al. Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan cohort study. Gastroenterology 2019;156(05):1416–1427
27 Menya D, Maina SK, Kibosia C, et al. Dental fluorosis and oral health in the African Esophageal Cancer Corridor: Findings from the Kenya ESCCAPE case-control study and a pan-African perspective. Int J Cancer 2019;145(01):99–109
28 Dar NA, Islami F, Bhat GA, et al. Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. Br J Cancer 2013;109(05):1367–1372
29 Salunke S, Shah V, Ostbye T, et al. Prevalence of dental caries, oral health awareness and treatment-seeking behavior of elderly population in rural Maharashtra. Indian J Dent Res 2019;30(03):332–336
30 Wild CP, Weiderpass E, Stewart BW. World Cancer Report: Cancer Research for Cancer Prevention. Accessed March 22, 2021 at: https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-Cancer-Research-For-Cancer-Prevention-2020
31 Lagergren J, Andersson G, Talbäck M, et al. Marital status, education, and income in relation to the risk of esophageal and gastric cancer by histological type and site. Cancer 2016;122(02):207–212
32 Gao P, Yang X, Suo C, et al. Socioeconomic status is inversely associated with esophageal squamous cell carcinoma risk: results from a population-based case-control study in China. Oncotarget 2018;9(06):6911–6923
33 Dar NA, Shah IA, Bhat GA, et al. Socioeconomic status and esophageal squamous cell carcinoma risk in Kashmir, India. Cancer Sci 2013;104(09):1231–1236
34 Khan NA, Teli MA, Mohib-Ul Haq M, Bhat GM, Lone MM, Afroz F. A survey of risk factors in carcinoma esophagus in the valley of Kashmir, Northern India. J Cancer Res Ther 2011;7(01):15–18
35 About the global cancer update programme. Accessed March 24, 2021 at: https://www.wcrf.org/int/continuous-update-project
36 IARC. Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations. Accessed March 23, 2021 at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Aromatic-Amines-Anthraquinones-And-Nitroso-Compounds-And-Inorganic-Fluorides-Used-In-Drinking-water-And-Dental-Preparations-1982
37 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Red Meat and Processed Meat. Lyon (FR): International Agency for Research on Cancer; 2018
38 Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Int J Cancer 2011;129(11):2681–2693
39 Lin S, Wang X, Huang C, et al. Consumption of salted meat and its interactions with alcohol drinking and tobacco smoking on

esophageal squamous-cell carcinoma. Int J Cancer 2015;137(03): 582–589
40 Golozar A, Etemadi A, Kamangar F, et al. Food preparation methods, drinking water source, and esophageal squamous cell carcinoma in the high-risk area of Golestan, Northeast Iran. Eur J Cancer Prev 2016;25(02):123–129
41 Hashemian M, Poustchi H, Abnet CC, et al. Dietary intake of minerals and risk of esophageal squamous cell carcinoma: results from the Golestan Cohort Study. Am J Clin Nutr 2015;102(01): 102–108
42 Narzary Y, Brahma J, Brahma C, Das S. A study on indigenous fermented foods and beverages of Kokrajhar, Assam, India. Journal of Ethnic Foods 2016;3(04):284–291
43 Loomis D, Guyton KZ, Grosse Y, et al; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of drinking coffee, mate, and very hot beverages. Lancet Oncol 2016;17(07):877–878
44 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Drinking Coffee, Mate, and Very Hot Beverages. Lyon (FR): International Agency for Research on Cancer; 2018.
45 Islami F, Pourshams A, Nasrollahzadeh D, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. BMJ 2009;338:b929
46 Yu C, Tang H, Guo Y, et al; China Kadoorie Biobank Collaborative Group. Hot tea consumption and its interactions with alcohol and tobacco use on the risk for esophageal cancer: a population-based cohort study. Ann Intern Med 2018;168(07):489–497
47 Lubin JH, De Stefani E, Abnet CC, et al. Maté drinking and esophageal squamous cell carcinoma in South America: pooled results from two large multicenter case-control studies. Cancer Epidemiol Biomarkers Prev 2014;23(01):107–116
48 Dar NA, Bhat GA, Shah IA, et al. Salt tea consumption and esophageal cancer: a possible role of alkaline beverages in esophageal carcinogenesis. Int J Cancer 2015;136(06):E704–E710
49 WHO. Fuel for life: household energy and health. Accessed March 23, 2021 at: https://www.who.int/publications/i/item/9789241563161
50 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum 2010;92:1–853
51 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some drinking-water disinfectants and contaminants, including arsenic. IARC Monogr Eval Carcinog Risks Hum 2004;84 (01):1–477
52 Talagala IA, Nawarathne M, Arambepola C. Novel risk factors for primary prevention of oesophageal carcinoma: a case-control study from Sri Lanka. BMC Cancer 2018;18(01):1135
53 National Health Portal of India, Gateway to Authentic Health Information. Health tips. Accessed April 7, 2021 at: https://www.nhp.gov.in/
54 Sanikini H, Muller DC, Sophiea M, et al. Anthropometric and reproductive factors and risk of esophageal and gastric cancer by subtype and subsite: Results from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Int J Cancer 2020;146(04):929–942
55 Sanikini H, Muller DC, Chadeau-Hyam M, Murphy N, Gunter MJ, Cross AJ. Anthropometry, body fat composition and reproductive factors and risk of oesophageal and gastric cancer by subtype and subsite in the UK Biobank cohort. PLoS One 2020;15(10): e0240413
56 Khairnar MR, Dodamani AS, Jadhav HC, Naik RG, Deshmukh MA. Mitigation of fluorosis - a review. J Clin Diagn Res 2015;9(06): ZE05–ZE09
57 Chaudhry M, Prabhakar I, Gupta B, Anand R, Sehrawat P, Thakar SS. Prevalence of dental fluorosis among adolescents in schools of Greater Noida, Uttar Pradesh. Journal of Indian Association of Public Health Dentistry 2017;15(01):36
58 Kotecha PV, Patel SV, Bhalani KD, Shah D, Shah VS, Mehta KG. Prevalence of dental fluorosis & dental caries in association with high levels of drinking water fluoride content in a district of Gujarat, India. Indian J Med Res 2012;135(06):873–877
59 Podgorski JE, Labhasetwar P, Saha D, Berg M. Prediction modeling and mapping of groundwater fluoride contamination throughout India. Environ Sci Technol 2018;52(17):9889–9898
60 Lee CP, Lee YH, Lian IB, Su CC. Increased prevalence of esophageal cancer in areas with high levels of nickel in farm soils. J Cancer 2016;7(12):1724–1730
61 Zafarzadeh A, Rahimzadeh H, Mahvi AH. Health risk assessment of heavy metals in vegetables in an endemic esophageal cancer region in Iran. Health Scope 2018;7(03): . Doi: 10.5812/jhealthscope.12340
62 Ministry of Jal Shakti, Department of Water Resources, River Development and Ganga Rejuvenation, GoI. Central Water Commission. Accessed March 27, 2021 at: http://www.cwc.gov.in/
63 Zhang SK, Guo LW, Chen Q, et al. The association between human papillomavirus 16 and esophageal cancer in Chinese population: a meta-analysis. BMC Cancer 2015;15:1096
64 Yong F, Xudong N, Lijie T. Human papillomavirus types 16 and 18 in esophagus squamous cell carcinoma: a meta-analysis. Ann Epidemiol 2013;23(11):726–734
65 Shah I, Bhat G, Rafiq R, et al. Strenuous occupational physical activity: Potential association with esophageal squamous cell carcinoma risk. Proceedings of Singapore Healthcare 2019; 28:201010581986086
66 Dar NA, Islami F, Bhat GA, et al. Contact with animals and risk of oesophageal squamous cell carcinoma: outcome of a case-control study from Kashmir, a high-risk region. Occup Environ Med 2014; 71(03):208–214
67 Nasrollahzadeh D, Ye W, Shakeri R, et al. Contact with ruminants is associated with esophageal squamous cell carcinoma risk. Int J Cancer 2015;136(06):1468–1474
68 Islami F, Kamangar F, Nasrollahzadeh D, et al. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. Int J Epidemiol 2009;38 (04):978–988
69 IARC. Fruit and Vegetables: IARC Handbooks of Cancer Prevention Volume 8. Accessed March 24, 2021 at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Fruit-And-Vegetables-2003
70 Jankowski JAZ, de Caestecker J, Love SB, et al; AspECT Trial Team. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet 2018;392(10145):400–408
71 Etemadi A, Golozar A, Kamangar F, et al. Large body size and sedentary lifestyle during childhood and early adulthood and esophageal squamous cell carcinoma in a high-risk population. Ann Oncol 2012;23(06):1593–1600
72 GATS2 (Global Adult Tobacco Survey) Fact Sheet, India, 2016–17. Accessed July 20, 2022 at: https://www.tobaccofreekids.org/assets/global/pdfs/en/GATS_India_2016-17_FactSheet.pdf
73 National Family Health Survey. Accessed April 5, 2021 at: http://rchiips.org/nfhs/factsheet_NFHS-4.shtml

