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ORIGINAL ARTICLE

Risk of major cancers associated with various forms of tobacco use in India: a systematic review and meta-analysis

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Abstract

Background Several studies have established the association of various cancers with tobacco consumption. However, hardly any attempt has been made to examine the combined effect of various forms of tobacco consumption. Hence, the present study was undertaken to measure the overall risk of different cancer sites associated with various forms of tobacco used individually or in combination, and to investigate the risk variation within each site by different forms of use.

Methods Meta-analysis was carried out on the findings of 22 published studies of samples exposed to tobacco use and control groups that were not exposed to tobacco. The pooled odds ratios (ORs) for each cancer for different combinations of forms of tobacco were calculated using a random effects model.

Results Smoking was found to be associated with a 5-fold higher risk of oropharynx, larynx, and lung, a 3-fold higher risk of hypopharynx, and esophagus, and a 2-fold higher risk of oral cancer. Esophagus (OR = 3.5) and oral cancer were the only sites significantly associated with tobacco chewing. The OR associated with bidi smoking was highest for lung (6-fold) followed by esophagus (3.5-fold) and oral cancer (3-fold). Lung cancer was also significantly associated with cigarette smoking.

Conclusions The present study reported pooled ORs for different tobacco-related cancers associated with various forms of tobacco use, both individually as well as in various combinations. Collecting data on the consumption of tobacco is a complex exercise. Pooled ORs reported in this study will be useful in working out the quantum of diverse tobacco-related cancers attributable to different forms of tobacco consumption, both individually as well as in combination.

Keywords Bidi · Cigarette · Smoking · Chewing · Cancer · Meta-analysis · India

Background

Globally, oral cancer, and cancer of the pharynx account for about 5% of all cancers in men (220,000 new cases every year) and 2% of cancers in women (90,000 new cases every year) (Parkin et al. 1999). Mortality rates due to oral and other types of tobacco-related cancer (hypo pharynx, pharynx, lung, larynx etc.) vary widely across regions, but prevalence and rates of incidence are highest in developing countries such as India, Pakistan, and Bangladesh, where these (oral and other tobacco-related cancers) are the most common forms of cancer (Bhurgri et al. 2000; Parkin et al. 1997). Epidemiological evidence about the association between cigarette smoking and cancer first came into light in 1920, and its causal relationship with lung cancer was established in 1950 (Doll and Hill 1964; IARC 1986; Levin et al. 1950; Sinha et al. 2002). In 1985, an international working group of experts from the International Agency for Research on Cancer (IARC) also recognized the causal relationship between smoking tobacco and cancer of the pharynx, larynx, lung, and urinary bladder, and oral cancer (IARC 1986).

A large number of people consume smokeless tobacco and suffer from severe related health hazards, such as oral cancer,

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uterine cervical cancer, etc. (Parkin et al. 2002; Warnakulasuriya 2009). The majority of smokeless tobacco users (over 90%) live in Southeast Asian countries. Within this region, India is one of the largest producers and consumers of smokeless tobacco, where its use among 15–49 year-olds has steadily increased from 19% in 1998 to 25% in 2010, despite the adoption of stringent policy actions for controlling tobacco consumption (Awan et al. 2014).

In India, the prevalence of chewing tobacco and smoking varies widely across the states and shows a strong association with regional sociocultural characteristics. According to the third round of the National Family Health Survey, men in the age group 15–49 years are more prone to tobacco use than women; 57% of men, as compared to 11% of women, use some form of tobacco. One third of men smoke cigarettes or bidis, and 37% consume *paan* (betel quid), *gutkha* and *paan masala substitutes*, or other forms of chewing tobaccos (Bhojani et al. 2009). Moreover, the pattern of tobacco consumption in India is probably more diverse than any other country in the world, which is the reason for the regional variations in the consequential burden of tobacco-related diseases and deaths (Sinha et al. 2002). Bidi smoking is one of the earliest forms of tobacco consumption; it is practiced mostly by people belong to the lower strata of Indian society (Rahman and Fukui 2000).

The number of tobacco-attributable deaths worldwide in the late 1980s was estimated to be 630,000 per year (Conrad et al. 1992). Today, conservative estimates of tobacco-attributable deaths are between 800,000 and 900,000 per year. The major challenge for India is that it has the highest rates of oral cancer in the world, accounting for 12% of all cancers in men and 8% in women. This is partly because of the easy availability of tobacco products—smokeless, as well as for smoking. Nearly 4.5 million Indian smokers are afflicted by heart disease or angina every year, and nearly 3.9 million people develop lung diseases. Nearly half of all cancers in men are tobacco-related, while over 60% of those who are less than 40 years of age, and suffering from heart disease, are smokers. In India, there are also an estimated 12 million cases of preventable illnesses that are attributed to tobacco use (Chaudhry et al. 2001). The World Health Organization predicts that deaths related to tobacco use in India may exceed 1.5 million annually by 2020 (Stroup et al. 2000).

Although several studies, epidemiological as well as experimental, have found a significant association between tobacco (smokeless and smoking) and several types of cancers, there has been no attempt at a systematic review of this major health issue. In an endeavor to address this gap, this study undertook a meta-analysis to quantify the overall risk of different cancer sites associated with various forms of tobacco use individually or in combination, and to examine the variation in risk at each site for different forms of tobacco use.

Material and methods

Selection of major tobacco-related cancers

In India, the National Cancer Registry Programme (NCRP) of the Indian Council of Medical Research (ICMR) has listed ten sites (lip, tongue, mouth, esophagus, pharynx, hypopharynx, pharynx unspecified, larynx, lung, and urinary bladder) as being associated with tobacco use. Lung, esophagus, and mouth cancer are the leading sites in 11, eight, and seven registries respectively, with their contribution relative to total cancers varying according to registry (NCRP 2016). These cancers are highly associated with tobacco use in both the developing world and the developed world. There are some studies in India, and many in developed countries, which showed these sites to be significantly associated with forms of tobacco use. Of these studies, all those which were freely accessible and conducted in India on oral, lung, larynx, esophagus, hypopharynx, and oropharynx cancers have been taken into account. They are presented in Figs. 2, 3, 4, 5, 6, and 7, with their separate and combined risk analyzed by a random effect model.

Literature search

A literature search was conducted using Scopus, the Science Direct database and Google Scholar for locating and accessing articles related to the forms of cancer associated with tobacco-chewing, bidi, and cigarette smoking, and which were published before April 2017. The keywords used for the search were bidi, cigarette, smoking, smokeless, chewing, oral, oral cavity, oropharynx, esophagus, larynx, hypopharynx, lung cancer, and India. Only those that were published as full-length articles and in English were considered for this study. The references listed in these articles were also accessed for additional support.

Inclusion and exclusion criteria

Studies were considered for meta-analysis if they pertained to associations between various forms of tobacco use (as exposure variables) and one or more of various kinds of cancer (oral, oropharynx, esophagus, larynx, hypopharynx, and lung) as outcome variables. Only those studies that allowed 2×2 tables to estimate ORs at 95% confidence intervals (CIs) were included in the meta-analysis. The following selection criteria were also applied to the studies:

- They must have a case–control study design;
- They must have reported 2×2 contingency tables for recalculating ORs and their corresponding 95% CIs of cancers related to bidi and cigarette smoking, and chewing tobacco consumption, *separately*.

Studies of mixed (smoking and chewing tobacco) were excluded if the effects of forms of tobacco use could not be shown separately, as well as those in which categories of case and control were not reported, which disallowed adequate classification of intake. Additionally, full-length reports that could not be accessed in English were also excluded. Overall, this study included only those articles that provided detailed information on both outcomes and forms of tobacco consumption.

A flow chart of the study selection process along with numbers selected and excluded at different levels appears in Fig. 1.

Data extraction

The epidemiological guidelines of observational studies for meta-analysis (Jussawalla and Deshpande 1971) were followed. From each study, the following information was extracted: (1) first author's last name, (2) year of publication, (3) number of exposed with different forms of tobacco consumption in cases and control, and (4) cancer sites (oral, oropharynx, esophagus, larynx, hypopharynx, and lung), for recalculating ORs as risks and corresponding 95% CIs for bidi, cigarette, and smoking and chewing tobacco separately.

Statistical analysis

For each study, 2 × 2 contingency tables were constructed to recalculate OR and the 95% CI by following the standard procedure. Separate contingency tables were developed for chewing tobacco, and bidi/cigarette smoking if data was available in the same article. The overall OR (combined for all existing case–control studies for making 2 × 2 contingency tables) and its 95% CI was calculated by using the random effects model for tobacco-chewing, bidi, and cigarette smoking, because the data used in the meta-analysis were assumed to be a random selection from all possible studies examining the association between exposure and outcomes.

The studies are hospital-based case–control and nested case–control types that were carried out in India. This is significant because of the diverse patterns of tobacco consumption in India. A forest plot was prepared using STATA-12 statistical software to describe individual studies and pooled ORs. Heterogeneity between studies was indicated by the I^2 value. I^2 statistics of less than 50% were considered as low and indicating a greater degree of similarity between studies. Statistical significance was set at a p value less than 5%.

Results

Twenty-two published articles (Balaram et al. 2002; Dar et al. 2012; Das et al. 2014; Dikshit and Kanhere 2000; Gajalakshmi et al. 2003; Ganesh et al. 2011; Ihsan et al. 2014; Jussawalla and Jain 1979; Kapil et al. 2005; Madani et al. 2010; Mahapatra et al. 2015; Nandakumar et al. 1996; Nandakumar et al. 1990; Notani and Sanghvi 1974; Phukan et al. 2001; Phukan et al. 2014; Petti et al. 2013; Sapkota et al. 2007; Sehgal et al. 2012; Talukdar et al. 2013; Wasnik et al. 1998; Znaor et al. 2003) that met the eligibility criteria for this study and dealt with the association of tobacco consumption with one or more of six cancers (oral, oropharynx, esophagus, larynx, hypopharynx, and lung) were included in the study. The number of studies available was highest for esophageal (eight studies) followed by oral (seven studies) and lung cancer (six studies). All these sites were reported to be highly significantly associated with tobacco consumption. ORs pooled for different forms of tobacco consumption were

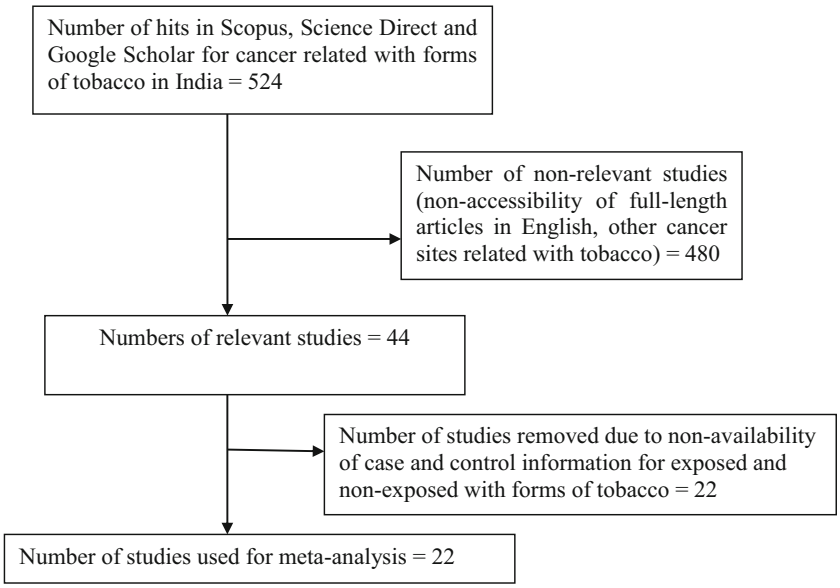

Fig. 1 Flow chart of study selection process for cancer related with tobacco use in India

around three,with a highest OR of 3.6 for oropharyngeal and lowest of 2.7 for esophageal cancer. There was a high degree of divergence among the studies dealing with different sites, with the index of heterogeneity being more than 90% (Table 1). Detailed results for individual cancer sites under study are presented in the following sections.

Oral cancer (Fig. 2)

All seven studies dealing with oral cancer reported its association with chewing and all reported a statistically significant association, with OR ranging between 4.4 and 8.5. ORs pooled for all seven studies were 6.6, with a 95% CI of 5.2 to 8.4.

Four studies reported a correlation between oral cancer and bidi smoking, and three of them reported statistically significant ORs ranging between 2.5 and 6.9. The pooled OR was 2.9 which was statistically significant, with a 95% CI of 1.5 to 5.4.

Four studies dealt with an association with cigarette smoking, and none of them reported a significant association with protective effect. Thus, there was no evidence of cigarette smoking being associated with oral cancer.

A linkage with smoking in general (without specifying type) was reported by five of the studies. It was significant in all of them, with OR being 1.5 to 3. The pooled OR was 2, with a 95% CI of 1.5 to 2.5.

Oropharynx cancer (Fig. 3)

All of the three studies dealing with oropharyngeal cancer reported its association with chewing; in two of them it was statistically significant. Pooled OR for all three studies was 2.49, with a 95% CI of 0.96 to 6.48.

As far as smoking is concerned, there was no study in the Indian context dealing with an association between oropharynx cancer and bidi or cigarette smoking separately. However, an association with smoking in general was reported by three studies. It was significant in all three studies, with ORs ranging between 2.12 and 9.28. The pooled OR was 5.26, with a 95% CI of 2.28 to 12.14.

Hypopharynx cancer (Fig. 4)

Both of the studies dealing with hypopharyngeal cancer reported a statistically significant association with chewing. However, the pooled OR of 2.59 was not statistically significant.

There was no study in an Indian context dealing with the association of hypopharyngeal cancer and bidi or cigarette smoking separately. An association with smoking in general was reported as significant by both studies, with an OR ranging between 2.44 and 4.28. The pooled OR was 3.36, with a 95% CI of 1.95 to 5.79.

Esophagus cancer (Fig. 5)

Seven of eight studies analyzed the association either for only males or for both sexes taken together, whereas one study reported the analysis for males and females separately. Thus there were nine investigations into the association of esophageal cancer with different forms of tobacco use. All of the nine analyses investigated the association with tobacco chewing, and eight of them reported a significant association, with ORs ranging between 2.44 and 6.10. The pooled OR for all nine studies was 3.46, with a 95% CI of 2.83 to 4.22.

Bidi smoking was stated by four studies to be significantly associated, with ORs varying from a low of 2.76 to a high of 12.08. The pooled OR was 3.63, with a 95% CI of 2.41 to 5.45.

An association with cigarette smoking was also reported by four studies, and two of them reported a significant association with OR from 2.11 to 3.59. The pooled OR was 1.17, with a 95% CI between 0.65 and 2.08.

All nine studies dealing with tobacco consumption studied the role of smoking in general without specifying the type, and eight of them reported a significant association, with a low variation in ORs. ORs ranged from a low of 2.05 to a high of 4.50. The pooled OR was 2.67, with a 95% CI of 2.06 to 3.47.

Larynx cancer (Fig. 6)

All three studies dealing with laryngeal cancer reported its association with chewing, but only one of them was found to be statistically significant. The OR pooled for these three studies was 1.42, with a 95% CI of 0.69 to 2.90.

Table 1 Number of studies for different tobacco-related sites with pooled odds ratio (OR), 95% confidence interval (CI) and measure of heterogeneity (I^2)

Cancer sites	No. of studies included	OR (CI)	I^2 (%)	*P* value
Oral cancer	7	2.83 (1.91–4.18)	97.6	< 0.0001
Oropharynx	3	3.61 (1.67–7.80)	97.4	< 0.0001
Hypopharynx	2	2.90 (1.59–5.30)	91.7	< 0.0001
Esophagus	8	2.74 (2.18–3.43)	91.7	< 0.0001
Larynx	3	2.79 (1.55–5.03)	96.6	< 0.0001
Lung	6	3.19 (2.05–4.97)	96.8	< 0.0001

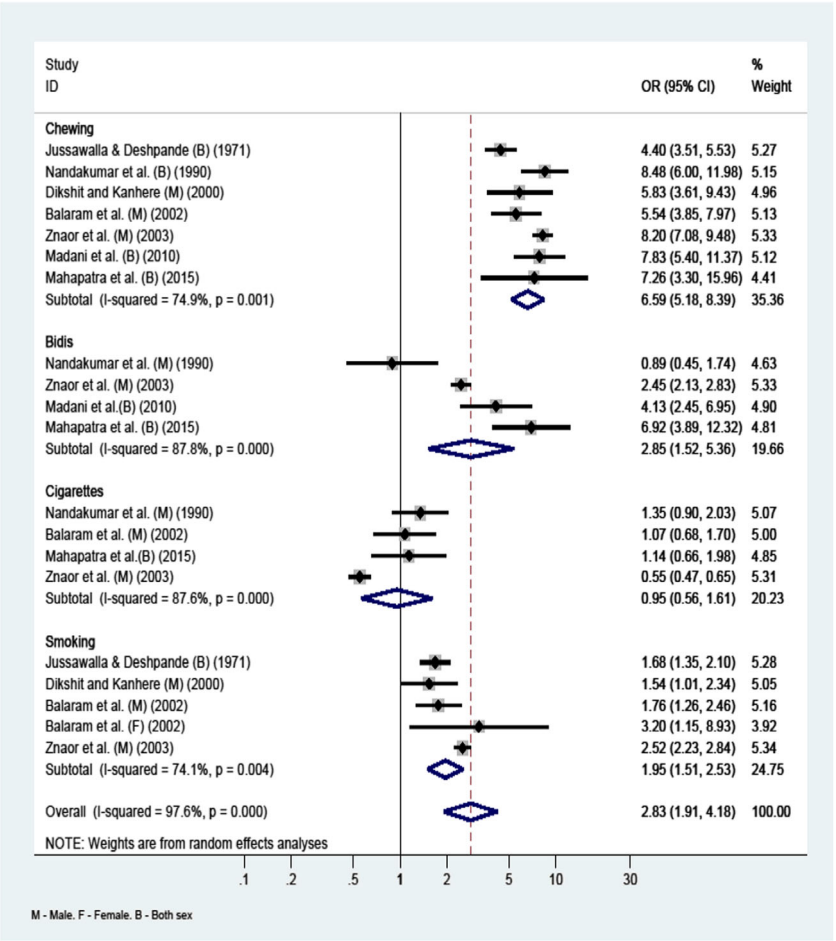

Fig. 2 Forest plot for risk of oral cancer by forms of tobacco

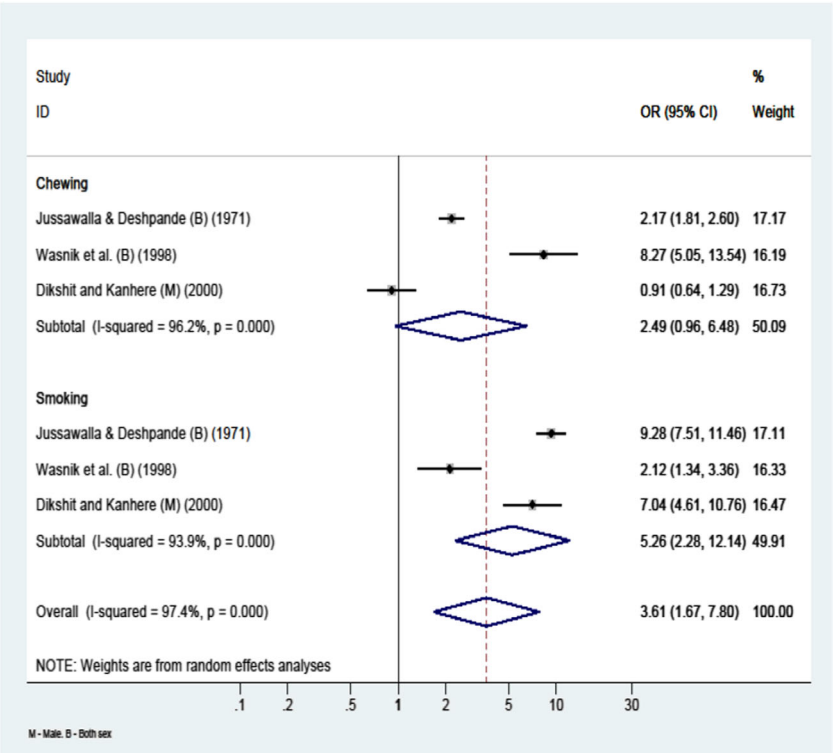

Fig. 3 Forest plot for risk of oropharynx cancer by forms of tobacco

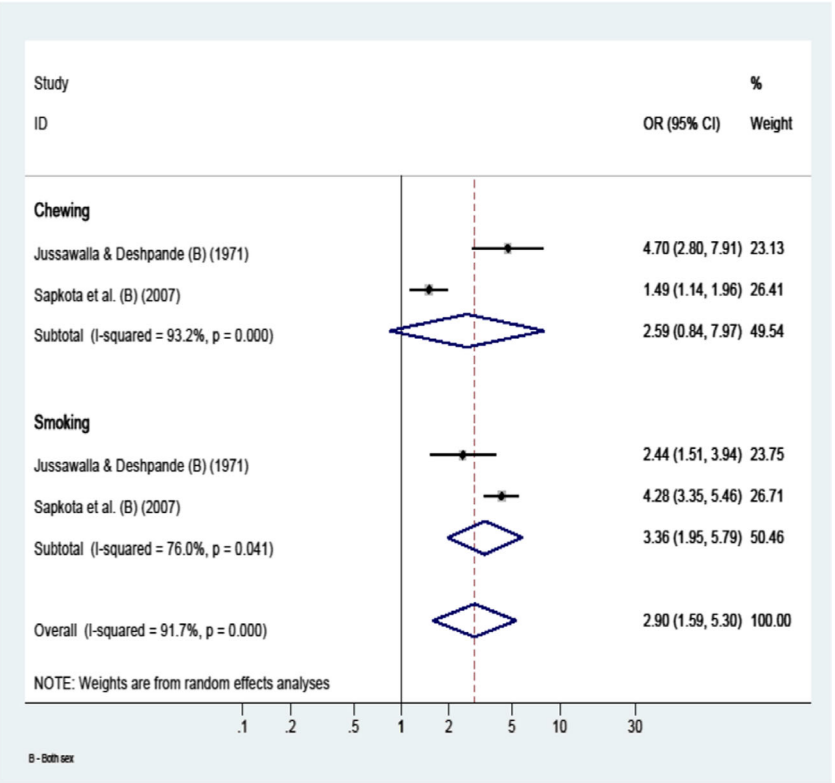

Fig. 4 Forest plot for risk of hypopharynx cancer by forms of tobacco

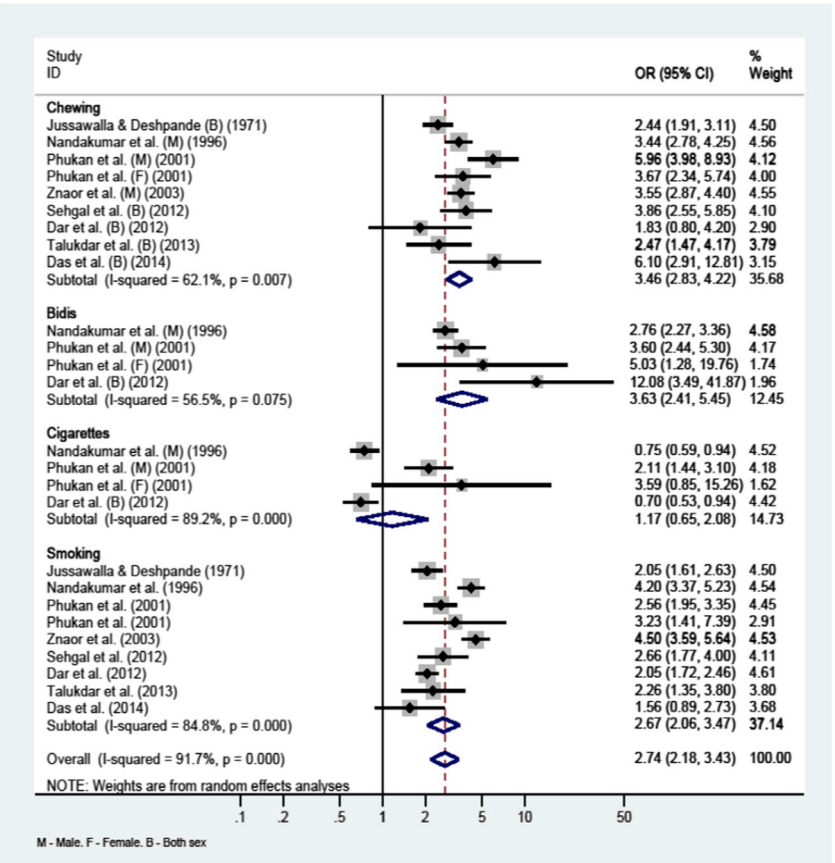

Fig. 5 Forest plot for risk of esophagus cancer by forms of tobacco

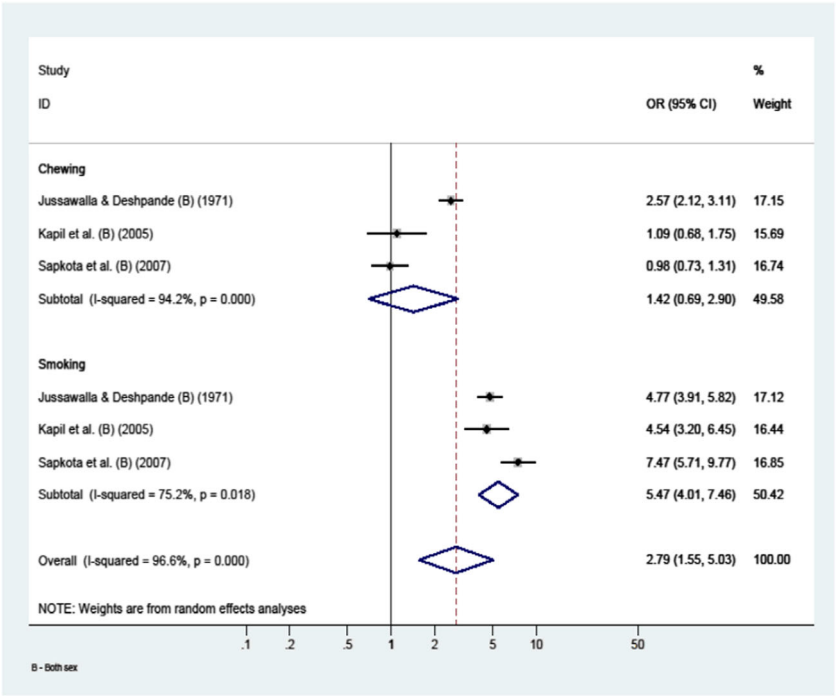

Fig. 6 Forest plot for risk of larynx cancer by forms of tobacco

There was no study in the Indian context dealing with an association between laryngeal cancer and bidi or cigarette smoking separately. An association with smoking in general was reported by all three studies, with ORs ranging between 4.54 and 7.47. The pooled OR was 5.47, with a 95% CI of 4.01 to 7.46.

Lung cancer (Fig. 7)

Four of the studies investigated the association between lung cancer and tobacco chewing, but only one of them reported a significant association. The pooled OR was not statistically significant.

Bidi smoking was reported by all four studies to be significantly associated, with ORs varying from a low of 2.2 to a high of 11. The pooled OR was 5.9, with a 95% CI of 2.7 to 13.1.

An association with cigarette smoking was also reported by all four studies, and three of them reported a significant association, with ORs from 1.8 to 6.4. The pooled OR was 2.2, with a 95% CI ranging from 1.2 to 3.8.

All six studies dealing with tobacco consumption studied the role of smoking in general, without specifying the type, and all of them reported a significant association; however there was a high variation in ORs, ranging from a low of 1.8 to a high of 15.8. The pooled OR was 5.1, with a 95% CI of 2.4 to 10.7.

Findings

Table 2 summarizes the findings of our study in the form of ORs of different tobacco-related sites of cancer associated with various types of tobacco consumption. The risk of oral cancer is about seven times higher among chewers and three times higher among bidi smokers. Similarly, the risk of esophageal cancer is about four and three times higher among chewers and bidi smokers respectively. These two sites are not significantly associated with cigarette smoking. On the other hand, four other sites under study, namely, oropharynx, hypopharynx, larynx, and lung, were also significantly associated with smoking and not only with chewing. The risk for lung cancer associated with bidi smoking was around six times higher.

Discussion

Chewing and smoking tobacco are among the most well-established causes of various forms of cancer. The magnitude of risks varied from study to study, and was calculated based on extracted information about case and control among both exposed and non-exposed individuals and different forms of tobacco consumption. Information on case and control was obtained from a systematic review of published articles. The objective of the study was to arrive at a reasonably accurate assessment, based on the various methods of sampling and analysis in the articles studied, of the risks of cancers due to

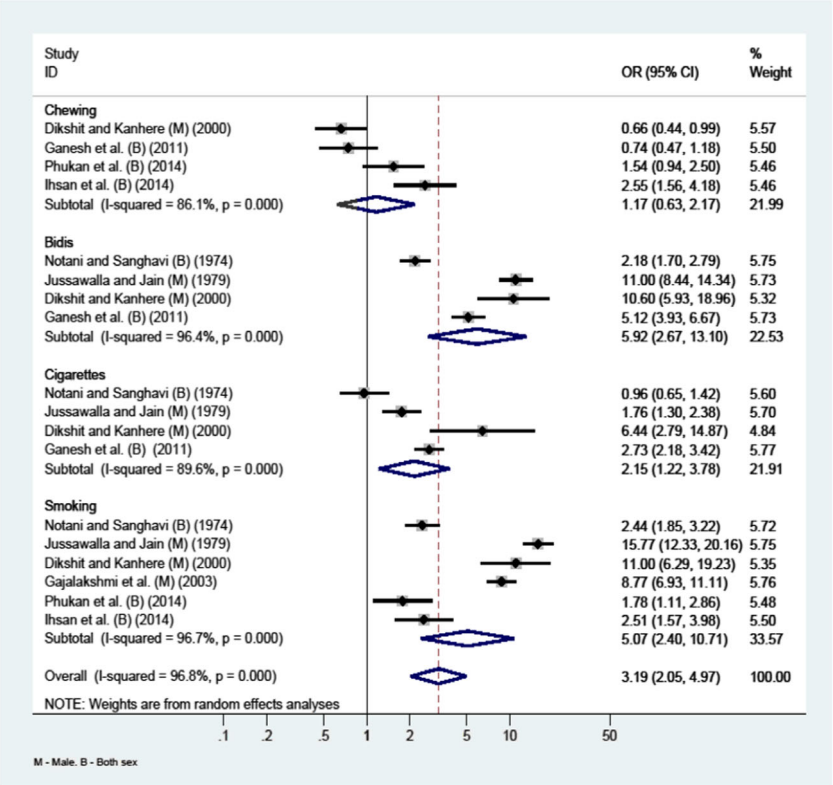

Fig. 7 Forest plot for risk of lung cancer by forms of tobacco

tobacco consumption. The study used a random effect model, with the assumption that each study used randomly selected samples for analysis. The high heterogeneity observed in the studies of each cancer type was due to the different periods in which the studies were carried out, and the diversity of locations, cultures and economic status.

Many systematic reviews have been carried out regarding the association between chewing tobacco and oral cancer in the developing and developed worlds (Awan and Patil 2016; Bhawna 2013; Boffetta et al. 2008; Critchley and Unal 2003; Guha et al. 2014; Gupta and Ray 2003; Gross et al. 1995; Khan et al. 2014; Lee and Hamling 2009). Among them, a study by Gupta et al. is regarded as one of the most extensive. It reported a high pooled OR for oral cancer (Lee and Hamling 2009), and found a significant association between chewing tobacco and oral cancer. The finding added strong evidence-based support to the IARC's inclusion of chewing (smokeless) tobacco in the list of risk factors associated with oral cancer (Awan and Patil 2016; Khan et al. 2014). Awan and Patil found a 7-fold higher risk of oral cancers due to betel-quid chewing (Gupta and Ray 2003). A similar risk level was also observed for other types of chewing tobacco. The risk of oral cancer was higher among females, most likely because of the nature of their mucosa, which is more susceptible to spoil on exposure to tobacco, and/or lack of knowledge and awareness about tobacco use (Balaram et al. 2002; Lee and Hamling 2009). The causal relationship observed between exposure to chewing tobacco and oral cancer is consistent with IARC reports. However, a review of some studies in Europe and North America reported conflicting outcomes (Blot et al. 1988; Lee 2011; Weitkunat et al. 2007). This may be because of the differences in the types of smokeless tobacco available,

Table 2 Odds ratios (ORs) of tobacco-related sites with different forms of tobacco consumption along with statistical significance

Tobacco-related site	Chewing	Bidi smoking	Cigarette smoking	Smoking in general	Pooled for all types
Oral cancer	6.6	2.9	1.0[a]	2	2.8
Oropharynx	2.5[a]	–	–	5.3	3.6
Hypopharynx	2.6[a]	–	–	3.4	2.9
Esophagus	3.5	3.6	1.2[a]	2.7	2.7
Larynx	1.4[a]	–	–	5.5	2.8
Lung	1.2[a]	5.9	2.2	5.1	3.2

[a] Not statistically significant. All other ORs statistically significant at 5% level

and different environmental, ethnic and socioeconomic, conditions between South Asian and European/North American populations. Moreover, the duration of chewing habits may also play a part. It has been observed that a longer duration of chewing (exposure) is linked with a higher risk of oral cancer (Rahman et al. 2003).

Our meta-analysis indicates that bidi smokers have a 3-fold higher risk of oral cancer than non-smokers. However, the study did not find a significant relationship between cigarette-smoking and oral cancer. Another study also showed a significantly high association with bidi smoking but an insignificant one with cigarette smoking (Rahman et al. 2003). This is because of the toxicity, as measured by nicotine, tar carbon monoxide, hydrogen cyanide, ammonia, other volatile phenols, and carcinogenic hydrocarbons, benz[a]pyrene, benz[a]anthracine and radioactive uranium, which are higher in bidi smoke than cigarette smoke (Sankaranarayanan et al. 1991). Moreover, bidi wrappers are made from tendu leaves, which are less porous than cigarette paper and are also less combustible. This results in higher intake of tar, nicotine, and carbon monoxide (Narayan et al. 1996).

In India, 21% of urban and 42% of rural adult males choose to expose themselves to bidi smoking (Rahman and Fukui 2000), most of whom are from disadvantaged sections of the society. The pooled OR for cancer of the esophagus (3.6 times) and lung (5.9 times) are higher in bidi smokers than for other forms of tobacco consumed. Some other studies also indicate that bidi smoking has a greater OR than cigarette smoking in developing cancers of the lung, esophagus, and larynx and other chronic conditions (Humans 2012; Jayanta et al. 1983; Notani et al. 1977; Phukan et al. 2001; Petti et al. 2013; Sankaranarayanan et al. 1990; Znaor et al. 2003). Aggressive combating of bidi smoking is therefore necessary to prevent thousands of deaths from cancers associated with it.

The pooled OR of oropharynx, hypopharynx, larynx, and lung cancers had an insignificant association with chewing tobacco, while other forms of tobacco were significantly associated with them. However, Lee et al. reported a significant association between chewing tobacco and larynx cancer, while evidence in the IARC's report and Western studies was equivocal (Lewin et al. 1998; Stockwell and Lyman 1986; Weitkunat et al. 2007; WHO 2011). Although our meta-analysis found a high OR and significant association between chewing and esophagus cancer, as Lee and Hamling also showed, there is an insignificant association on the basis of Western studies (Weitkunat et al. 2007). Meta-analysis showed that smoking tobacco has a high association with esophagus cancer. Heterogeneity among these studies was also higher than esophagus cancer associated with use of chewing tobacco. This variation might be due to small and insignificant associations with cigarette smoking and/or socioeconomic inequality.

The present study also showed a definite association between smoking tobacco and oral, oropharynx, hypopharynx, esophagus, larynx, and lung cancers. The proportion of bidi users in this group is high. Most bidi smokers belong to the vulnerable lower socioeconomic groups in India and cancer pushes them even further into poverty. These groups are often not able to access appropriate treatment, which exacerbates their situation.

Strict implementation of effective tobacco control measures can prevent globally about 900,000 deaths per year associated with smoking and smokeless (chewing) tobacco. Our meta-analysis also found a high and significant association between smoking and lung cancer (OR = 5.1; CI 2.40–10.71). This supports WHO estimates that smoking is the cause of over 70% of lung cancers (WHO 2011). The findings of this study will help to generate and raise awareness, educate the masses, and inform policy makers when taking the necessary actions to combat rampant tobacco use. Smoking and smokeless tobacco are both dangerous for health.

Conclusions

This study has reported pooled ORs for different tobacco-related cancers associated with different forms of tobacco use, both individually as well as in different combinations. Collecting data on the consumption of tobacco is a complex phenomenon. Pooled ORs reported in this study will be useful in working out the quantum of various tobacco-related cancers attributable to different forms of tobacco consumption, both individually as well as in combination. In addition, it may be concluded from pooled ORs that chewing and bidi smoking were responsible for the large burden of oral and esophagus cancers. For lung cancer, bidis were more significantly linked than cigarettes. The study also confirms the insignificant association of chewing tobacco with larynx and lung cancer.

Compliance with ethical standards

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of supporting data This meta-analysis study was based on secondary data sources (published studies).

Competing interests The authors declare that they have no conflict of interest.

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