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Smokeless tobacco use: A meta-analysis of risk and attributable mortality estimates for India

DN Sinha[1], KM Palipudi[2], PC Gupta[3], S Singhal[4], C Ramasundarahettige[4], P Jha[4], A Indrayan[5], S Asma[2], G Vendhan[6],

[1] World Health Organization, Regional Office for South-East Asia, New Delhi, India
[2] Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[3] Healis Sekhsaria Institute for Public Health, Navi Mumbai, Maharashtra, India
[4] Michael's Hospital and University of Toronto, Toronto, Canada
[5] Ex department of Biostatistics and Medical Informatics, Delhi University College of Medical Sciences, New Delhi, India
[6] Epidemiological Research Centre, Chennai, Tamil Nadu, India

Correspondence Address:
D N Sinha
World Health Organization, Regional Office for South-East Asia, New Delhi, India

Abstract

Background: Use of smokeless tobacco (SLT) is widely prevalent in India and Indian subcontinent. Cohort and case-control studies in India and elsewhere report excess mortality due to its use. **Objective:** The aim was to estimate the SLT use-attributable deaths in males and females, aged 35 years and older, in India. **Materials And Methods:** Prevalence of SLT use in persons aged 35 years and older was obtained from the Global Adult Tobacco Survey in India and population size and deaths in the relevant age-sex groups were obtained from UN estimates (2010 revision) for 2008. A meta-relative risk (RR) based population attributable fraction was used to estimate attributable deaths in persons aged 35 years and older. A random effects model was used in the meta-analysis on all-cause mortality from SLT use in India including four cohort and one case-control study. The studies included in the meta-analysis were adjusted for smoking, age and education. **Results:** The prevalence of SLT use in India was 25.2% for men and 24.5% for women aged 35 years and older. RRs for females and males were 1.34 (1.27-1.42) and 1.17 (1.05-1.42), respectively. The number of deaths attributable to SLT use in India is estimated to be 368127 (217,076 women and 151,051 men), with nearly three-fifth (60%) of these deaths occurring among women. **Con Clusion:** SLT use caused over 350,000 deaths in India in 2010, and nearly three-fifth of SLT use-attributable deaths were among women in India. This calls for targeted public health intervention focusing on SLT products especially among women.

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Full Text

Introduction

Tobacco smoking has attracted worldwide attention, and smoking-attributable deaths have been estimated in several studies. [1],[2] According to World Health Organization (WHO), six million deaths are attributable to tobacco use globally, of which nearly 1.2 million occur in South-East Asia. [3],[4],[5] Smoking-attributable deaths in India were estimated at 0.9 million for 2010, [6] however smokeless tobacco (SLT) use-attributable deaths have not been estimated so far.

Countries (WHO South-East Asia Region [SEAR]) in Indian subcontinent are home to over 250 million SLT users out of which 206 million lives in India.

High prevalence of SLT use in many countries of Indian subcontinent is notable both among males in Myanmar (51.4%), India (32.9%), Nepal (31.2%) and Bangladesh (26.4%), [5] and among females was in Bangladesh (27.9%), India (18.4%), Bhutan (17.5%) and Myanmar (16.1)%). [5]

SLT contains carcinogens, tobacco-specific nitrosamines, nitrosamine acids, polycyclic aromatic hydrocarbons, aldehydes, and metals. [7],[8],[9] In India and Indian subcontinent, in addition to other cancers, a major disease consequence of SLT use is oral cancer. [8],[9],[10],[11],[12],[13],[14] Myocardial infarction and other cardiovascular diseases. [15],[16],[17] Apart from specific diseases all cause premature deaths due to SLT use has been reported from different parts of the world including India. Relative risks (RRs) of all-cause mortality due to SLT use are available for Sweden, [18],[19] USA [20] and India. [21],[22],[23],[24],[25]

SLT has been consumed in various forms in countries of India and Indian subcontinent. [26],[27],[28],[29],[30],[31],[32],[33] SLT products are either chewed as a dry or moist tobacco mixture or applied over teeth and gums. Betel quid with tobacco is chewed. It is a traditional form of tobacco chewing (India 6.2%), however, cheaper products such as tobacco lime mixture (Khainee in India 11.6%, areca nut, tobacco, lime and other additive mixtures (gutka in India 8.2%) are replacing traditional chewing. Some SLT products are applied over gums and teeth as dentifrice in the form of gul, gudaku, mishri, masheri, or tapkir (India 4.7%), and one product, tuibur, can even be gargled in India. As India is the hub of SLT use, it is important to know all-cause mortality effect at the national level. This paper provides meta-analysis of all-cause mortality and an estimate of SLT use-attributable deaths in India for the first time.

Materials and Methods

Current use of smokeless tobacco

Various forms of SLT use may have differential risk of death. However, the cohort and case-control studies used in the calculation of this study cover most popular varieties of SLT products used in India and Indian subcontinent. Current exclusive SLT use in any form has been considered for this analysis. Prevalence estimates of SLT use for persons aged 35 years and older in, India were obtained from the Global Adult Tobacco Survey (GATS), which was conducted in 2009-2010. [27] They are based on face-to-face interviews of nationally representative samples of persons aged 15 years and above. Respondents self-reported their SLT use. This survey provides the most comprehensive information on SLT use.

Age and sex wise population

For calculating the number of SLT users and total deaths in 2008, age-sex population (aged 35 and older) data were obtained from the United Nations (UN) estimates [34] (2010 revision). Total deaths in persons aged 35 years and older have also been computed from UN estimates [35] and used in this report to estimate attributable deaths. UN estimates are for the five years period from 2006-2010 and one-fifth of these estimates have been considered for 2008.

Relative risks

Relative risks were used to estimate the attributable deaths for India: A SEAR country. These were calculated by conducting a meta-analysis of past studies from the countries from WHO SEAR. PRISMA guidelines were utilized to search medical databases, such as EMBASE and Ovid MEDLINE. The words used in the search strategy were based on the Population, Exposure, Control, Outcome, and Study design framework. The selection criteria included adults of age 35 years and older, who were exposed to some form of chewing tobacco and were no longer alive. Adults of the same age with no exposure to tobacco were selected as controls. Cohort study designs were studies of choice for the meta-analysis as they can establish causation between exposure of chewing tobacco and death. Any study that included chewing tobacco as exposure and death due to any cause as the outcome was included. Studies, for which the main outcome was incidence or prevalence of any disease, instead of death, attributable to chewing tobacco, were excluded. Using the Boolean method, search terms were combined. Endnote software was used to import all of the searches and to remove duplicates. Fifty-three articles resulted from the search, out of which, four relevant articles were considered for the final analysis. [21],[22],[23],[24] Three of the studies had analysis for males and females separately, and one of the studies was having analysis only for males. Studies eliminated after the title stage were due to having incidence or prevalence of cancers as outcomes or because the effect of SLT could not be observed in isolation. The complete elimination strategy is depicted in a flowchart [Figure 1]. The reference lists of relevant studies were also reviewed to include any study that might not have shown up during databases search; however, no new study could be retrieved. To reduce publication bias, results from an unpublished large study were also pooled in [25] [Table 1]. Funnel plot analysis was also performed to check for publication bias.{Figure 1}{Table 1}

As the sample size varied quite a lot among studies selected, we conducted the random effects model for our meta-analysis. The random effects model assured that estimates are not overly influenced by any one population; we were not discounting a small study by giving it a smaller weight and were not giving too much weight to a larger study. Risks were adjusted for smoking, age and education, as in the original articles, provided by their respective authors.

Pooled RRs for males (1.17) and females (1.34) were used [Table 2] for calculation in this study.{Table 2}

Calculation of smokeless attributable deaths

We used the population attributable fraction (PAF) method to estimate attributable deaths: [33]

Attributable deaths = PAF X number of deaths,

Where,

[INLINE:1]

p = Prevalence of current SLT use, and,

RR = Meta-RR of death among current SLT users compared to never users.

Results

The prevalence of exclusive SLT use in India was 25.2% for men and 24.5% for women aged 35 years and older. A summary of the studies considered for this analysis is included in Table 1. All the studies reported an increased risk of excessive mortality among male and female chewers.

Before combining the data into a summary estimate (meta-RR), we assessed publication bias through the use of funnel plots [Figure 2] and [Figure 3]. Evidence of significant publication bias is noted at $P < 0{\cdot}05$. Evidence of significant heterogeneity between studies is noted at I 2 > 40% [Figure 4] and [Figure 5], [Table 2].{Figure 2}{Figure 3}{Figure 4}{Figure 5}

Pooled RR derived from adjusted RRs of individual studies (risks were adjusted for age or age and education) for all-cause mortality from chewing tobacco that is estimated to be 1.34 (1.27-1.42) for women and 1.17 (1.05-1.31) for men [Table 2]. SLT use-attributable deaths in India at a pooled rate is 368,127 people (217,076 women and 151,051 men) [Table 3], with nearly three-fifth (60%) of these deaths occurring among women.{Table 3}

Discussion

Although the prevalence of SLT use among men (25.2%) and women (25.9%) in India is similar, meta-analysis found higher RR for women (1.34) when compared to men (1.17). Hence estimated number of SLT use-attributable deaths in women (217,076) is significantly higher than among men (151,051).

Significantly, a high RR for all-cause mortality among SLT users is not restricted to India alone. Two large cohort studies from Sweden and two large cohort studies from United States (US) have reported significantly elevated RRs for all-cause mortality in SLT users. [18],[19],[20] In Indian studies RR for men ranged between 1.1 and 1.9; and for women ranged between 1.3 and 1.4.

In Cancer Prevention Study I (CPS-I), follow-up study of over one million US adults (456,487 men and 594,544 women) in 1959 and in CPS-II, nearly 1.2 million US adults (676,306 women and 508,351 men) in 1982 found that men who currently used snuff or chewing tobacco at baseline had higher death rates from all causes than men who did not in both CPS-I (hazard ratio [HR]'O1.17, 95% confidence interval [CI]'O1.11-1.23) and CPS-II (HR'O1.18, 95% CI'O1.08-1.29). [20]

Both Swedish studies found RR 1.2 for men and 1.4 for women. [18],[19] Although SLT habits, confounders and effect modifiers differ across the world, however, similar RR in Swedish and Indian studies confirm higher SLT use-attributable mortality among SLT users; more among women than men. [18],[19] One Swedish study was of 135,036 construction workers (including 6297 SLT users), which were followed from 1974 to 1985. The RR for all-cause mortality in this study was 1.4 (95% CI: 1.3-1.8). [18] The other Swedish study followed 20,333 participants for 29 years from 1973 to 2002. Of these, 867 never daily smokers who ever used snus daily had a HR for all-cause mortality of 1.23 (95% CI: 1.09-1.40). [19] Both of these studies found RR as 1.2 among men and 1.4 among women. [18],[19]

Studies reported in the 1980s from South India [20],[21] showed RR for males ranging from 1.20 (0.68-2.11) to 1.95 (1.17-3.27) and for females ranging from 1.30 (0.93-1.81) to 1.35 (1.19-1.54). In India, a large cohort study in Mumbai showed elevated RRs of death for SLT users (mainly in the forms of mishri and betel quid). Interim results were based on 5-6 years of follow-up of 52,000 people, with 114,980 person-years for female and 57,890 for male SLT users. The age-adjusted RR for SLT users compared with non-tobacco users was 1.22 among men, and 1.35 among women, with the suggestion of a dose-response relationship for daily frequency of use. [22] However, the next report from the same cohort [23] reported lower RRs (RR = 1.16 for males and RR = 1.25 for females). A large unpublished national study (Million Deaths Study, India), covering more than one million households in India, shows RR for females and males 1.36 (1.26-1.47) and 1.11 (1.05-1.16), respectively. Some authors of this article also took part in the Million Death Study, hence data were accessible for calculation in this article. [25]

The higher RR for women compared with men for SLT use opposes the results generally reported for smoking. The differential, however, is related to the maturity of the smoking epidemic in this population. As the epidemic is maturing, the RRs among women and men are becoming comparable. For SLT use in India, there is little differential in maturity of the epidemic between men and women since SLT use by women is socially and equally acceptable. It is also possible that men are exposed to many more risk factors compared with women, thereby increasing their risk of mortality in the non-SLT user group and decreasing their RR estimate in the SLT group.

Over 350,000 SLT-attributable deaths in India calls for immediate attention for continued monitoring of SLT and policy interventions targeted to SLT use in India, particularly among women and the specific high prevalence populations.

Although these RRs are comparable to those reported from Sweden, there is a lack of consistency in reports from different cohort studies. Risks included in the meta-analysis adjusted for age and education, but not for other risk factors which older cohorts, especially people from low economic sections, are exposed. Due to insufficient data, it was not possible to separate the all-cause mortality risk into specific causes of death. Estimates of the prevalence have age-restrictions, but those do not seem highly restrictive. Due to dual use of tobacco products (both smoking and smokeless), there is an implied assumption that the excess risks from smoking and SLT use are independent, but that has not been corroborated.

Considering that the heterogeneity ($I2 > 40\%$) and publication bias ($P < 0.05$) among the studies, the estimate from a meta-analysis may have additional limitations. However, the attributable mortality estimates presented here are most conservative based on available data. These studies clearly demonstrate the need for further research. Nevertheless, this paper provides precise estimates of SLT-attributable mortality in the India, probably for the first time.

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Disclaimer

The author alone is responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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