REVIEW

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Association of Non-Tobacco Products (NTP) with Oral, Esophageal, and Pharyngeal Cancer and Oral Potentially Malignant Disorders (OPMD) in Adults: A Systematic Review and Meta-analysis

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Abstract

Introduction: Non-tobacco products (NTP) are increasingly popular as an alternative to traditional tobacco use, raising concerns about potential health risks. This systematic review and meta-analysis examine the association of NTP use with oral, esophageal, pharyngeal cancer, and oral potentially malignant disorders (OPMD) in adults. **Methods:** A comprehensive electronic search was conducted in PubMed, Embase, and Google Scholar, for observational studies that evaluated the association between NTP use, and oral, esophageal, pharyngeal cancer and OPMD, published till December 2023 in the English language. The quality of the included studies was assessed using the Newcastle-Ottawa scale. Pooled odds ratio (OR) with a 95% Confidence Interval (CI) was obtained using a random effects model, heterogeneity was assessed using I^2 statistic. Sub-group analysis was conducted based on the year of publication, a comparator for association, type of NTP user, and country. **Results:** Forty-nine studies were included in the meta-analysis with a combined total of 1,32,390 participants, revealing a significant association between NTP use and increased risk of cancers- oral (OR:5.0, 95% CI 3.3-7.7), esophageal (OR:3.0, 95%CI 1.2-7.5), and OPMD (OR:15.3, 95%CI 8.8-26.7). The proportion of the annual burden of oral and esophageal cancers attributable to NTP was 33% (30,667 cancers), and 19% (8,025 cases) respectively in India. **Conclusion:** This review provides strong evidence for the association between NTP use and increased risk of oral, and esophageal cancer and OPMD. The findings highlight the need for targeted interventions, firmer regulations, and awareness campaigns addressing NTP. Incorporating NTP as a separate category in national surveys can help reduce their burden, particularly in high-risk populations.

Keywords: Oral cancer- pharyngeal cancer- non-tobacco products- systematic review- risk- incidence- mortality

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Introduction

Non-tobacco products (NTP) users face a diverse range of health risks, with millions of individuals worldwide engaging in the practice of chewing NTP such as betel nut and areca nut [1]. This behaviour is particularly prevalent in many Asian countries and among Asian immigrant communities globally. NTP encompass a diverse range of substances, including betel quid, areca nut, and other culturally rooted oral products [2]. The combination of NTP use with tobacco further heightens the risk of various cancers, such as oral cancer, esophageal cancer, and pharyngeal cancer, and potentially malignant disorders (OPMD). The areca nut present in betel quid contains carcinogens, such as arecoline and nitrosamines, posing potential pre-neoplastic changes upon chewing. These NTP, when placed in the mouth, lead to prolonged exposure of the oral mucosa to harmful substances. The consumption of betel quid, a popular NTP, serves various purposes, including its stimulating effects, cultural traditions, and breath-sweetening properties. Over the years, the availability of traditional and professionally packaged NTP has extended beyond Asian regions, with the United Kingdom being a notable importer. Alarmingly, even young children start consuming sweetened areca nut products, eventually leading to increased NTP usage, often accompanied by tobacco consumption during adolescence [3].

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The Global Burden of Disease Study 2019, a comprehensive global survey, underscores this point by revealing that approximately 8.71 million deaths annually are attributed to tobacco-related illnesses, making it a leading cause of preventable mortality worldwide [4]. Despite global efforts to curb smoking rates, a concerning trend has emerged - the rise of NTP. NTP, including electronic cigarettes and smokeless tobacco, have garnered popularity, often perceived as safer alternatives to conventional smoking. However, recent data from the Global Adult Tobacco Survey (GATS) conducted across multiple countries highlights that approximately 41 million adults are using smokeless tobacco, with 68 million adults using electronic nicotine delivery systems (ENDS) [5]. In light of the Non-Communicable Diseases (NCD) Global Monitoring Framework's 25 by 25 strategy, aimed at reducing NCD mortality by 25% by 2025 [6], it is crucial to identify the primary causes of cancer, including NTP use, and implement effective control and prevention efforts.

While tobacco use has been well-established as a major risk factor for cancer related to mouth, esophagus and pharynx, emerging evidence suggests that NTP may also play a significant role in the development of these cancers, especially in populations with high NTP consumption rates. In already published systematic reviews by Guha et al., Song et al. and Gupta et al. it was noted that the reviewers tried to study the association of solely betel quid with oral, oro-pharyngeal cancers and oral precancers [7-9]. The current literature has limitations, including the exclusion of specific NTP and a lack of differentiation between different types, leading to a limited understanding. Moreover, there is a scarcity of global studies, particularly in regions with increasing NTP usage. These gaps underscore the urgent need for a thorough understanding of the health risks associated with these emerging products. While the studies by Guha et al. [7], Song et al. [8], Gupta et al. [9] have laid a solid foundation for betel quid use and associated cancer, there is still much to be explored and understood regarding the link between other NTP and their association with cancers like oral, pharyngeal, esophageal, and oral potentially malignant disorders (OPMD).

Recent evidence suggests that the NTP are associated with cancers viz oral, pharyngeal, esophageal, and OPMD [10]. Hence, this research aims to consolidate and critically evaluate the existing literature, providing a comprehensive evaluation of the overall evidence and the magnitude of the association between NTP and oral cancer, esophageal, pharyngeal cancer and OPMD [10]. This will provide valuable insights for evidence-based public health strategies, tobacco control policies, and targeted interventions, particularly tailored for the Indian population.

Materials and Methods

Literature search strategy

A comprehensive systematic electronic search was conducted for the studies published between their inception to December 31, 2023, in the following databases: PubMed, Embase and Google Scholar. The combination of Medical Subject Headings (MeSH) and free text words (e.g., betel quid without tobacco, areca nut, paan, paan masala without tobacco) were combined with search terms related to the outcome (premalignant disorders, esophageal cancer, oral cancer, and pharyngeal cancer) using Boolean operators (AND, OR and NOT). The detailed search strategy is provided in the supplement (Table S1.1-1.4). We used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses as a guide for this study [11]. (Figure1) The review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO)- CRD42021282787, and the article was written according to PRISMA guidelines.

Selection Criteria

The review included studies that fulfilled the following inclusion criteria: 1) conducted on adults (more than 18 years of age), 2) any study design that evaluated the association between usage of betel quid, areca nut, paan and other NTP and the risk of development of oral, pharyngeal, esophageal cancers and other OPMD as outcome, 3) for the case control design comparator were those without cancer or those with cancers other than the sites included in the current study and for the cohort study design the comparator were those who are not exposed to NTP and 4) sufficient data must be available in the study to calculate the OR between the NTP exposure and outcome, and 5) studies in English language or summary in English. Studies were excluded if: 1) the exposure was tobacco containing product and 2) conference abstracts, editorials, letters, opinion papers, and grey literature. The NTP used in the study include 1) betel leaf and areca nut 2) betel leaf, 3) areca nut, 4) NTP not specified and 5) all NTP are addictive and have harmful effects on health. As per GATS 2 report, among the NTP, betel quid without tobacco is the most prevalent product [5]. The operational definition of betel quid for the study was - a 'betel quid' (synonymous with 'pan' or 'paan') generally contains betel leaf, areca nut and slaked lime, and may contain tobacco [1]. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard, or sweeteners, are added according to local preferences. (Details of search strategy given in Table S1.1-1.4)

Study selection

All the retrieved studies from the databases were uploaded to the Rayyan software for screening [12]. After confirming the most recent and comprehensive version, the duplicates were removed. Based on the selection criteria, two reviewers (PD and RAD) independently screened all the titles and abstracts. The third author (AL), who handled any selection disputes, made the final decision. In case of missing information, the authors were contacted. The full texts were retrieved for all the selected abstracts and further screened for inclusion. Reference lists of the retrieved studies were also screened for additional sources.

Data extraction

The data extraction was done using a pretested spreadsheet to collect information on authors, the year of publication, socio-demographic characteristics of the population, details of exposure such as type, duration, comparator, the disease being studied, and outcome estimates such as odds ratio and corresponding 95% CIs. When a risk estimate was not presented, we extracted appropriate data (i.e., exposed/unexposed cases and controls) to permit its calculation. When there was a cell with a count of 0, we added 0.5 to all cells to allow for calculation of the OR and 95% CIs (continuity correction). Two authors (PD and RAD) independently extracted the data, and any disagreements were resolved by the third reviewer (AL).

Risk of Bias Assessment

The methodological quality of the included studies was assessed using Newcastle -Ottawa scale (NOS) [13] for case-control and cohort study and a modified version of NOS [13] was used for cross-sectional studies. Studies were assessed under the following three key domains for case-control, cross-sectional and cohort study: 1) Selection, 2) Comparability and 3) Exposure/Outcome. A maximum score of four (selection), two (comparability) and three (exposure/outcome) can be given to each study (case-control and cohort design) assessed using NOS scale and a score of five (selection), two (comparability) and three (outcome) can be given to each study of cross-sectional study design. Based on the score obtained from each study, it was classified as high quality (≥7), moderate (3-6) and low quality (<3) studies. The details of risk of bias assessment of included studies in given in (Table S5). The compliance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist are given in the supplementary file. (Figure 1)

Statistical analysis

Summary estimates of pooled odds ratios were estimated with 95% confidence intervals to gauge the precision of the summary estimate. Forest plots were used to graphically display the pooled odds ratio and corresponding 95% confidence intervals. Heterogeneity was assessed by Cochrane's Q statistic test and I2 statistic (percentage of residual variation attributed to heterogeneity). I^2 value > 50% was considered to indicate presence of heterogeneity. Random-effects meta-analysis was performed in R software [14] To address the heterogeneity, subgroup analysis was performed for each outcome (oral cancer, esophageal cancer, pharyngeal cancer and OPMD) based on the following categories: 1) on the basis of year of publication (before 2005 vs after 2005), 2) On the basis of comparator (no habits and non NTP with other risk factors), 3) Type of user (exclusive user vs non-exclusive user and current vs ever user), 4) based on country (Indian sub-continent, Taiwan, and others).

We employed the population attributable fraction (PAF) method to assess the impact of NTP use on the occurrence of cancer cases. The data source for calculating the prevalence of NTP use among adults aged >15 years (after excluding individual using smokeless tobacco) in India was obtained from the GATS 2016-17 survey dataset [5]. To estimate the annual number of incident cancer cases, we retrieved relevant data from published reports of the Indian cancer registry programme, focusing on the year closest to 2015 [15]. The outcomes were categorised based on ICD-10 coding: C00-C06 for oral cancer, C10-C14 for pharyngeal cancer and C15 for esophageal cancer [16]. Through the aforementioned data, we derived the PAF and the annual number of cancer cases attributable to NTP use for the year 2015. The PAF was calculated using the formula PAF= [Pe (OR-1)]/ [Pe (OR-1) +1], where Pe represents the proportion of the population exposed to NTP use and OR denotes the odds ratio derived from this meta-analysis. The total number of attributable cases (AC) for the specific cancer type was then computed using the formula AC=PAF*TC, with PAF representing the population attributable fraction and TC indicating the total number of annual incident cases for that cancer.

Results

Study selection

A total of 3102 potentially relevant studies were considered for the review. Full texts of 136 studies were screened, of which 87 were excluded, and finally, 49 studies were included in the systematic review and meta-analysis (Figure 1). The most common reason (48%) for excluding full-text articles was wrong exposure as shown in (Table S 6.1-6.3).

Characteristics of included studies

A total of 49 studies included in the review yielded a combined total of 1,32,390 participants, of which 40 studies were case-control, seven cross-sectional and two cohort study as shown in Table S (A-C). Of the total studies included in this review, 12 studies were conducted in urban area. The studies were from Indian sub-continent, Taiwan, US, and Papua New Guinea (PNG). The exposures in the included studies were 1) betel leaf and areca nut 2) betel leaf, 3) areca nut, 4) NTP not specified and 5) all NTP. In the included studies, the odds ratio ranged from 0.9 to 62.8 for oral cancer, 0.3 to 19.3 for pharyngeal cancer, 0.4 to 17.4 for esophageal cancer and 3.8 to 1655.0 for OPMD with corresponding 95% CIs.

Risk of bias assessment

In the assessment of quality across the three domains, it was found that four cross-sectional studies achieved a score of seven or higher, indicating a high quality and one study was of moderate quality. Among the case-control studies, 19 studies were rated as high quality, scoring seven or above, while 21 studies fell into the moderate quality category with scores ranging from three to six. The cohort study included in this review, was of moderate quality, as detailed in Table S5.

Association between NTP use and various cancers

The pooled odds ratio for the association between NTP use with oral cancer, pharyngeal cancer, esophageal cancer, OPMD & oral cancer and OPMD was 5.0

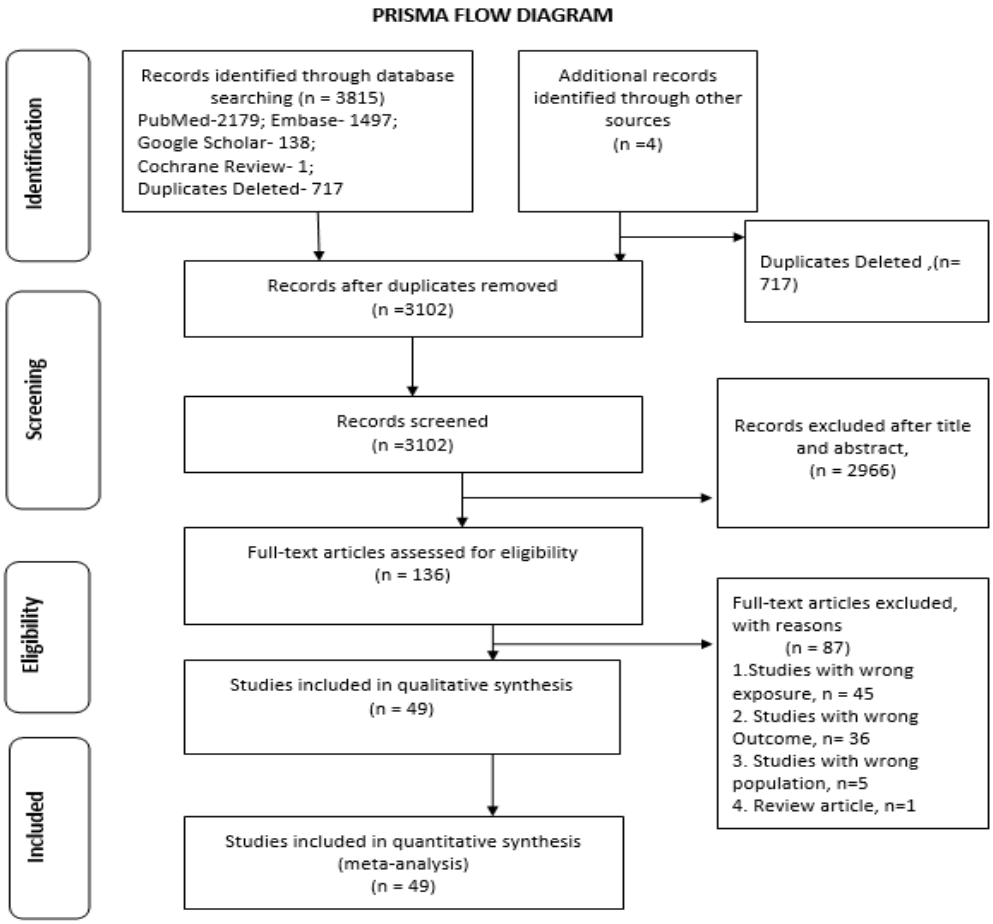

Figure 1. Prisma Flow Diagram

(95%CI:3.3-7.7, p-value<0.01, n=29), 1.9 (95%CI:0.8-4.9, p-value 0.16, n=7), 3.0 (95%CI:1.2-7.5, p-value 0.02, n=6), 15.3 (95%CI:8.8-26.7, p-value<0.001, n=15), and 1.0 (95% CI: 0.2-6.1, p-value< 0.01, n=2) respectively.

Association between individual NTP with various cancers

Areca nut consumption showed statistically significant association with esophageal cancer [7.0 (95%CI:1.2-42.1, p-value 0.03, n=2)] and OPMD [5.5 (95%CI:4.0-7.6, p-value 0.88, n=3)] as shown in Figure 2. Betel leaf consumption showed significant association with OPMD [6.7 (95%CI:2.1-21.1, n=1)] (Table S3.4). Consumption of areca nut and betel quid showed significant association with oral cancer [5.9 (95%CI:3.7-9.5, p-value<0.001, n=24)], and OPMD [22.7 (95%CI:12.1-42.7, p-value<0.001, n=11)] as shown in (Figure S6.1) Non specified NTP use showed significant association with oral cancer [2.1 (95%CI:1.6-2.7, p-value<0.001, n=2)] as shown in (Figure S6.4).

Sub-group analysis

Sub-group analysis was conducted for oral cancer, pharyngeal cancer, esophageal cancer and OPMD based on year of publication (before and after 2005), comparator (no-habits and non NTP with other risk factors), type of user (exclusive and non-exclusive) and country (India, Taiwan, and others). NTP use was significantly associated with oral cancer and OPMD on the basis of year of publication, comparator, type of user and country as shown in (Table S4.1 and S4.4) NTP use also showed a statistically significant association with pharyngeal cancer as well as with esophageal cancer on the basis of year of publication and country.

Publication bias

Funnel plots were made for estimation of publication bias for the outcome oral cancer, and OPMD (Figure S8.1-S8.2). There was no evidence of bias, and it was statistically confirmed by egger's test (P-value for oral cancer was 0.57 and for OPMD was 0.39) [17].

Table 1. Attributable Burden of Incident Cancers due to NTP Use among Adults in India

Cancer Site	Prevalence of NTP use among adults as per GATS 2016 (%)	Population Attributable Fraction (PAF) with 95%CI	Total number of annual incident cases	NTP attributable annual incident cases with 95% CI
Both sexes				
Oral cancer	12.1	0.33 (0.22,0.45)	94029	30667 (20471, 42099)
Esophageal cancer	12.1	0.19 (0.02,0.44)	41184	8025 (973, 18131)

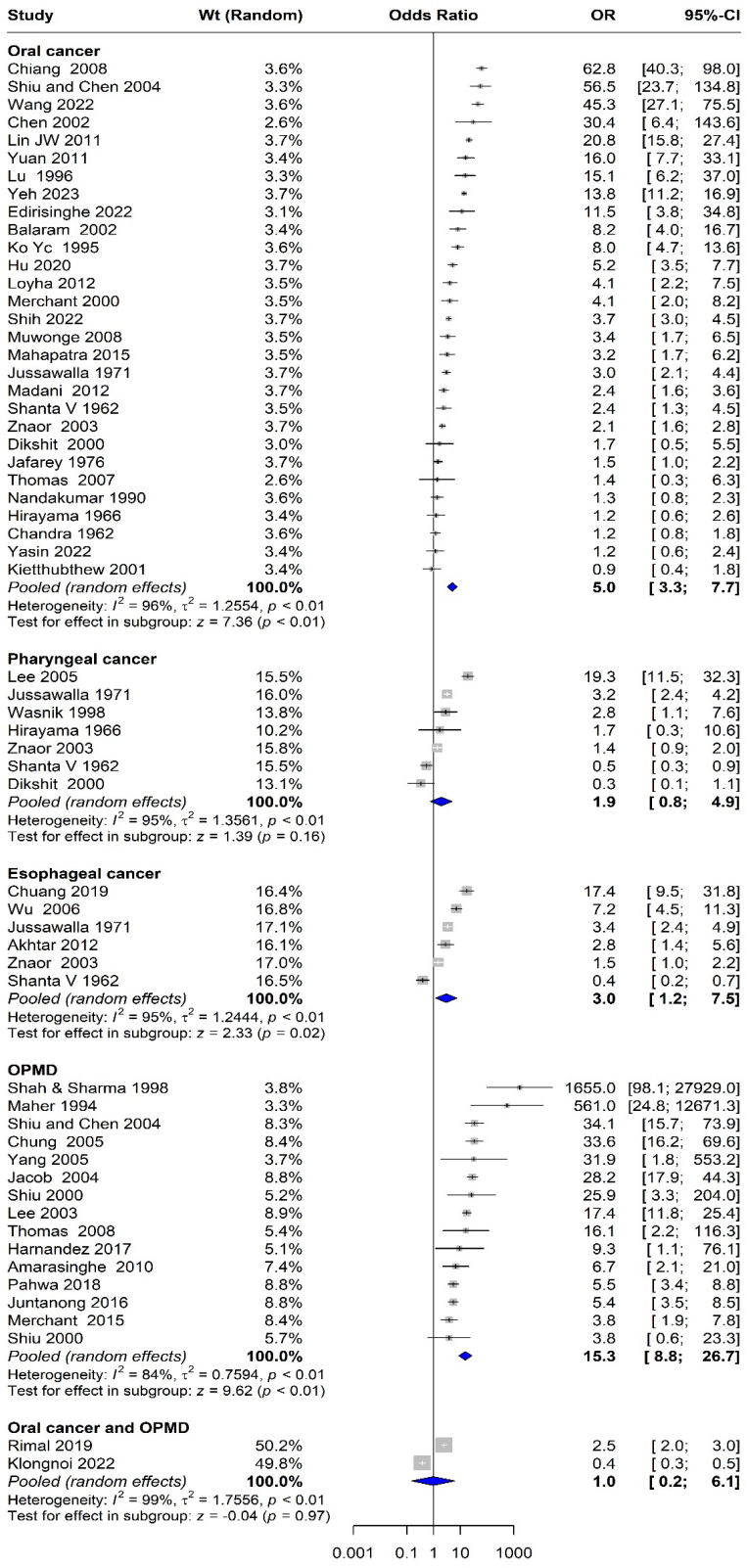

Figure 2. Association of NTP with Various Cancers and OPMD

Attributable burden of incident cancer cases

The burden calculation was carried out for two cancers (oral, and esophageal). The annual number of NTP attributable cancer cases were 30,667 for oral cancer (33% of all oral cancers), and 8,025 for esophageal cancer (19% of all esophageal cancers) as shown in (Table 1).

Discussion

Summary of the study results

In this systematic review and meta-analysis, we analysed data from 49 studies conducted in India, Pakistan, Taiwan, US, Sri Lanka, and Papua New Guinea, and estimated the pooled odds ratio for different NTP and their

association with oral, pharyngeal, esophageal cancers and OPMD. We found varying levels of association between NTP (NTP) and different types of cancers and OPMD. The strongest association was observed for OPMD and NTP use. Likewise, the NTP use was also associated with oral and esophageal cancer.

Credibility of findings

Several factors second for the credibility of our findings. We searched multiple databases like PubMed, Embase and Google Scholar for retrieving relevant records and did not restrict the search strategy to any specific geographic location for robust evidence generation. Secondly, we considered various outcomes which includes oral, pharyngeal, & esophageal cancer and OPMD as per the International Agency for Research on Cancer (IARC) "Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 85" [1]. Thirdly, risk of bias was assessed for all studies using a standard tool as per the study design and the results are presented for the clear comprehension of the findings. Fourthly, funnel plots were made to address the publication biases. Lastly, we performed sub-group analysis to assess the robustness of the estimates to account for the potential biases and heterogeneity. All these efforts increase our confidence in the validity of the estimates and in turn in our review.

To fully evaluate the consistency or divergence of our findings, we compared our findings with multiple systematic reviews on NTP and their association with oral cancer, esophageal cancer, pharyngeal cancer, and OPMD, including studies from different regions, for a comprehensive understanding and identification of patterns across global studies. Our findings are consistent with a systematic review and meta-analysis conducted by Guha et al, in 2013, which focused on the association between betel quid consumption and the risk of oral cancers [7] Their study concluded that betel quid, irrespective of the presence of added tobacco, was a substantial independent risk factor for oral cavity and oropharyngeal cancers. The alignment between their conclusions and our study findings strengthens the evidence supporting the significant association between betel quid use and the development of these cancers.

In line with our study objective, a systematic review and meta-analysis conducted by Song et al. [8] published in 2013 aimed to investigate the association between betel quid, free from tobacco, and oral cancer & precancer (OPMD). Their analysis revealed that betel quid is a potential risk factor for the development of oral cancer and precancer. These consistent findings further support the evidence regarding the detrimental effects of betel quid use on oral health. In 2014, Gupta et al. conducted a systematic review and meta-analysis that focused on the association between betel quid without tobacco and oral cancer in South Asia and the Pacific region. Their comprehensive analysis revealed a significant and independent positive association between the consumption of betel quid without tobacco and the risk of oral cancer within this specific population [9] This aligns with our study findings, further emphasizing the consistent evidence regarding the role of betel quid without tobacco in oral cancer development in these regions. Our study stands apart from previous studies by investigating a wide array of NTP in relation to oral cancer, esophageal cancer, pharyngeal cancer, and OPMD. Unlike earlier studies focusing solely on betel quid without tobacco, our research provides a comprehensive and updated perspective on the association between diverse NTP and these critical health conditions. While earlier studies often mixed smokeless tobacco and NTP, our study takes a focused approach, concentrating solely on NTP. This targeted analysis ensures a more accurate understanding of the impact these specific products have on the outcomes under scrutiny. Also, this approach allows us to capture the complexities of modern habits and their implications on public health comprehensively.

Implications of the study

Our analysis found varying levels of association between NTP and different cancers and OPMD. However, the association with pharyngeal cancer was inconclusive. These results hold particular importance for policymakers, especially considering that oral cancer has the highest age-standardized incidence in the WHO South-East Asia region [18]. In countries such as India with a high burden of oral, pharyngeal, and esophageal cancers, policymakers should identify all potential risk factors and develop comprehensive strategies to combat their prevalence. From our review, it is obvious that NTP have significant association with various cancers and OPMD. It also opens room for more studies on the association of NTP with lesser studied cancers like esophageal and pharyngeal cancers.

NTP use has seen an alarming increase among children, particularly in rural areas. Wang et al. [19] conducted a large-scale survey in Taiwan, involving 10,288 students, which found that 3.9% of adolescents used betel quid, with higher usage among boys (6.6%) compared to girls (1.5%). The prevalence varied across different locations, with rates ranging from 0.8% in cities to 4.3% in towns and 7.6% in the countryside. Peer pressure was identified as the primary influencing factor, followed by fathers introducing their children to betel quid. Another survey in northern Taiwan, China, conducted by Huang et al. in 2009 [20] among fourth-grade elementary students, revealed different rates of ever chewers, with a prevalence of 10.8% in city schools and a significantly higher rate of 56.6% in mountain schools, indicating a greater prevalence among the aboriginal population residing in mountainous areas [20]. These findings highlight the need to prioritize adolescent populations in future for NTP prevention and control programs.

The use of NTP poses multiple risks and challenges especially among adolescents as these products have a higher likelihood of transitioning to traditional cigarettes, increasing overall tobacco consumption and health risks [21]. Nicotine's addictive effects are particularly concerning for adolescents, impacting their cognitive development and well-being. The use of NTP also has social and behavioural implications, influenced by

peers and leading to increased experimentation [22]. The popularity among adolescents and adults raises public health concerns, potentially undermining cancer prevention efforts. Raising awareness, implementing regulations, and educational programs are crucial to address the risks and consequences associated with NTP use.

All these findings consistently highlight the alarming trend of NTP initiation among younger age groups, emphasizing the urgent need for attention. This underscores the importance of early monitoring and surveillance of NTP use among young children. Health promotional activities should be conducted to address the adolescents about the harmful effects of NTP, so that the burden of associated cancers could be reduced in the future. Furthermore, the limited research on the association between NTP and various cancers has resulted in their exclusion from national survey questionnaires as an independent risk factor. It is imperative to address this gap and include NTP in regulations aimed at combating cancer, like measures taken against tobacco in smoke and smokeless forms. The Global Youth Tobacco Survey (GYTS) is a self-administered survey of students in grades related to 13 to 15 years old that is conducted at schools. Its goal is to improve the ability of nations to monitor youth tobacco use and to provide guidance for the implementation and evaluation of tobacco prevention and control programs [10]. The survey can be utilised for surveillance and to optimise the efforts in combating the use of NTP. The results of the survey can be utilised in making NTP specific rules and regulations which can be a helping hand in combating the burden of NTP associated cancers and OPMD.

Strength and Limitations

To the best of our knowledge, this study represents the first comprehensive assessment of the association between different NTP and the risk of oral, pharyngeal, and esophageal cancers, as well as OPMD. The study employed a standardized search strategy, conducted quality assessments using established tools, performed sub-group analysis to address heterogeneity, and included studies of various designs without geographic restrictions. The outcomes and the exposures considered were in line with the IARC Monograph "Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 85" [23]. These rigorous efforts enhance the validity of our findings [23].

However, there were a few limitations in our study. We only included studies reported in English, which may have excluded relevant studies published in other languages. We had pooled the results from 49 studies from different parts of the world for our analysis. However, in some included studies, adequate information on the type of exposure consumed was not specified, which makes it a limitation. Additionally, we did not consider grey literature and the inclusion of a few low-quality studies with moderate to high heterogeneity in the analysis might limit the generalizability of the findings.

Conclusions and policy recommendations

Understanding the distinct risks associated with various NTP is pivotal for shaping effective public health strategies. This study provides compelling evidence linking the use of NTP to heightened risks of oral cancer, esophageal cancer, and OPMD. The comprehensive analysis underlines the urgent need for targeted interventions. The findings emphasize the critical importance of countering the emerging threat posed by alternative products, ensuring a holistic approach to tobacco control efforts.

To address the burden of NTP usage, stringent regulatory measures are imperative, encompassing production, marketing, and sales. Concurrently, comprehensive public education campaigns, targeting both current users and potential initiators, are vital. Educational institutions should integrate awareness regarding NTP from an early age. Likewise, NTP should be included as a distinct category in national health surveys to gather comprehensive data on the burden, and usage patterns. Integrating NTP prevention strategies into existing national tobacco control programme ensures comprehensive care for NTP users. Additionally, robust support for cessation programs tailored to diverse demographics is crucial. International collaboration and continuous surveillance are essential, ensuring the exchange of best practices and informing evidence-based policies to combat the evolving landscape of NTP usage effectively. These strategies collectively form a roadmap towards mitigating the significant health risks posed by NTP.

Author Contribution Statement

Conceptualization: Ayush, Pooja; Data curation: Pooja, Ayush, Roy; Formal analysis: Rizwan, Ayush, Pooja; Investigation: Pooja, Roy, Ayush, Deependra; Methodology: Ayush, Rizwan, Roy, Pooja; Project administration: Ayush, Ankur, Rama; Resources: Ayush, Rizwan; Supervision: Rizwan, Ankur, Rama, Ayush; Validation: Ayush, Rizwan; Visualisation: Ayush, Rizwan; Writing - original draft: Pooja, Roy Ayush; Writing -review and editing: Pooja, Roy, Ayush, Rizwan, Deependra, Rama, Ankur, Devashish.

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Approval

This study was not a part of a student thesis. Primary data collection involving human subjects was not required for this study. The study includes the compilation of already published data. The protocol of this study was registered under PROSPERO with registration number CRD42021282787.

Ethical Declaration

This study is exempt from ethical review and approval. It is a meta-analysis aggregating freely available data from published research. The informed consent and all due ethical proceedings were already satisfied by the authors of the individual eligible articles.

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