REVIEW

Editorial Process: Submission:08/03/2021 Acceptance:05/04/2022

Association between Smokeless Tobacco Use and Waterpipe Smoking and the Risk of Lung Cancer: A Systematic Review and Meta-Analysis of Current Epidemiological Evidence

Imogen Rogers*, Anjum Memon, Priyamvada Paudyal

Abstract

Background: Smokeless tobacco and waterpipes are used by hundreds of millions of people worldwide and consumption rates exceed that of cigarette smoking in much of South East Asia and parts of the Middle East. However, the cancer risks of these methods of tobacco consumption are less well-characterized than those of cigarette smoking. The objective of this study was to systematically review the epidemiological evidence on the association between smokeless tobacco use and waterpipe smoking and lung cancer risk. **Methods:** The MEDLINE, EMBASE, Web of Science and OpenSIGLE databases were searched to identify eligible case-control and cohort studies (published before 1st December 2020 in any language) that adjusted for cigarette smoking or included non-cigarette smokers only. Summary odds ratio/relative risk estimates and confidence intervals were extracted, and pooled risk ratios (RRs) for lung cancer were calculated using random effects meta-analysis. **Results:** The literature search identified 2,465 publications: of these, 26 studies including 6,903 lung cancer patients were included in the synthesis (20 studies of smokeless tobacco use, five of waterpipe smoking, one of both). Our results suggest that smokeless tobacco use is associated with an increased risk of lung cancer among non-cigarette smokers, and that betel quid tobacco may be particularly hazardous. The random effects meta-analysis showed that exclusive use of any type of smokeless tobacco (pooled RR = 1.53, 95%CI 1.09 – 2.14), betel quid chewing (pooled RR = 1.77, 95%CI 1.06 – 2.95), and waterpipe smoking (pooled RR = 3.25, 95%CI 2.01 – 5.25) were significantly associated with an increased risk of lung cancer. **Conclusions:** This meta-analysis of case-control/cohort studies supports the hypothesis that use of smokeless tobacco and waterpipe smoking is associated with increased risk of developing lung cancer. Considering the widespread and increasing use of smokeless tobacco in developing countries, and increasing prevalence of waterpipe smoking in almost all societies, these findings inform formulation of public health policy, legislation and tobacco control measures at national and international level to increase awareness and decrease the prevalence of smokeless tobacco use and waterpipe smoking.

Keywords: Tobacco- smokeless- water pipe smoking- lung neoplasms- lung cancer

Asian Pac J Cancer Prev, **23 (5)**, 1451-1463

Introduction

Smokeless tobacco (ST) is used by over 300 million adults worldwide (National Cancer Institute, 2014), and is consumed orally or nasally in various forms including chewing or dipping tobacco such as betel quid, and finely cut or powdered snuff. Levels of use are particularly high in much of South and South-East Asia, with India having around 220 million ST users, Bangladesh 28 million, and Myanmar 11 million. In 2009-10, the prevalence of ST consumption in India exceeded that of cigarette smoking in both men (33% vs 24%) and women (18% vs 3%). (WHO, 2018; National Cancer Institute, 2014) Furthermore, there is evidence that prevalence of ST consumption is increasing, (Sinha et al., 2015) while the prevalence of cigarette smoking in India is starting to decline (Mishra et al., 2016). Prevalence among adolescents exceeds 10% in a number of African countries, including Congo and Namibia (National Cancer Institute, 2014). There are also around eight million ST users in the United States (National Cancer Institute, 2014) mainly in southern and mid-western states (Israel et al., 2014). ST use is relatively uncommon in Europe except in Sweden (around 21% of men and 4% of women (Leon et al., 2016)) and Norway (Lund and Lindbak, 2007) (around 16% of men and 1% of women).

The waterpipe, also known as the hookah, narghile, hubble-bubble or shisha, has been traditionally used for smoking tobacco (and other substances) in Africa and Asia for centuries (Goodman, 1993). However, recently there has a rapid increase in waterpipe use across the globe, particularly among young people (WHO, 2015). In the

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Global Youth Tobacco Survey of 13-15-year olds in the Eastern Mediterranean Region, prevalence of waterpipe smoking ranged from 9-40% in the 15 sites surveyed, increased over the survey period (1999-2007) in most sites, and generally exceeded prevalence of cigarette smoking. Surveys of female university students in Egypt, Lebanon and Jordan have found prevalence of waterpipe smoking of 38%, 23% and 19%, respectively – waterpipe smoking may be considered more socially acceptable for women than cigarette smoking which is highly socially stigmatized for Arab women (Dar-Odeh and Abu-Hammad, 2011). Although the problem is concentrated in the Middle East, high prevalence of waterpipe smoking have also been reported from Europe and North America. Surveys of university and high school students in the US and Canada have reported prevalence of waterpipe use of 8-10%, and in a recent study of secondary school students in London, prevalence of current waterpipe smoking was more than twice as high as cigarette smoking (7.6% vs 3.4%). (Maziak et al., 2015)

There is some evidence that ST use may increase the chances of cigarette smoking cessation or decrease the chances of becoming a regular cigarette smoker. As cigarette smoking is the leading preventable cause of premature mortality and morbidity globally, it has been suggested that a switch to ST use might be one way to reduce the burden of disease associated with cigarette smoking, in particular lung cancer (Henningfield and Fagerstrom, 2001; Foulds et al., 2003; Lund et al., 2010). Similarly, it appears that the increasing prevalence of waterpipe smoking may be driven partly by a perception that it is less harmful than cigarette smoking (Jackson and Aveyard, 2008), and that harmful substances in the smoke are filtered out by the water bowl.

There are, however, good reasons to believe that both ST and waterpipe use may be causally associated with an increased risk of lung cancer. In addition to the well-established association with oral cancer (Gupta and Johnson, 2014; Asthana et al., 2019), ST use has been associated with the risk of cancer of more distant sites, such as the stomach, pancreas and cervix (Znaor et al., 2003; Boffetta et al., 2008; Sinha et al., 2016). A large number of toxic and carcinogenic substances are present in ST products, including polycyclic aromatic hydrocarbons, nitrate, nitrite, nicotine, acroline, formaldehyde and acetaldehyde. The tobacco-specific nitrosamines (TSNA) found in chewing tobacco are known to have carcinogenic effects, in particular N-nitrosonornicotine (NNN) and 4-(methyl-nitrosamino)-1-(3 pyridyl)-1-butane (NNK) are both classified as Group 1 carcinogens, and have been found in the body fluid of ST users (Hecht et al., 2007). One of the primary target tissues of NNK is the lung – rats given drinking water treated with NNK developed lung tumours. NNK, NNN, N-nitrosoanabasine (NAB), N-nitrosoanatasine (NAT) and their metabolites have been measured in the urine of ST users and generally found to be higher than in cigarette smokers (Stepanov and Hecht, 2005). The effect of ST use on inflammation is a further possible mechanism, circulating inflammation markers have been found to be prospectively associated with the risk of lung cancer (Shiels et al., 2013), and a study of 47 ST users and 44 non-users in India found that Cox-2 expression and levels of pro-inflammatory cytokines including TNF-α and iNOS were higher in the ST users (Biswas et al., 2015). The composition of waterpipe smoke has been less extensively studied than that of cigarette smoke, but has been found to contain a wide range of potential carcinogens, including polycyclic aromatic hydrocarbons, TSNAs, aldehydes and primary aromatic amines (Goodman, 1993; Cohn et al., 2017). In addition, there is evidence that exposure to smoke-related toxicants from waterpipe smoking may be considerably higher than from cigarettes (Cobb et al., 2011; Jacob et al., 2013; St Helen et al., 2014a; St Helen et al., 2014b).

The aim of this systematic review and meta-analysis was to summarize the findings from studies investigating the association between ST use and waterpipe smoking and the risk of lung cancer. Previous literature reviews and meta-analyses on this topic have generally focussed on particular geographical regions (Lee and Hamling, 2009; Sinha et al., 2016), or have included studies which have not adjusted for cigarette smoking (Akl et al., 2010), resulting in less clear understanding of the relationship between ST and waterpipe use and lung cancer. This review restricts the analysis to studies with appropriate control/adjustment for cigarette smoking, provides the updated epidemiological evidence and expands the meta-analysis to include all available studies from all regions.

Materials and Methods

This systematic review was undertaken in accordance with PRISMA guidelines (Moher et al., 2009). The MEDLINE, Embase, Web of Science and OpenSIGLE databases were searched to find cohort and case-control epidemiologic studies published before 1st December 2020. A combination of MESH terms and keywords were used including lung cancer, smokeless tobacco, snuff, snus, betel quid, gutka, naswar, zarda, maras, toombak, chimo, iqmik, mishri, qiman, paan, shammah, waterpipe and shisha. Full details of the literature search strategy are given in Appendix 1 in the supplementary material. The references of identified articles were also searched for relevant articles. All relevant cohort and case-control studies reporting primary data analyses were included irrespective of language. Two investigators (IR and PP) screened the titles and abstracts to select full-text articles for assessment, then reviewed the selected full-text articles for eligibility for inclusion in the systematic review. Data were independently abstracted from all full text articles selected for inclusion by both reviewers, discrepancies were solved by consensus.

Studies reporting the association between use of an alternative tobacco product and risk of lung cancer as an Odds Ratio, Relative Risk or Hazard Ratio, or that reported sufficient information for calculation of the effect size, were included in the review. For studies with insufficient information, we first contacted the authors to ask if they could provide the relevant data, if this was not successful the finding of the study was included in the discussion of the results.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale, which evaluates various aspects of case-control and cohort studies relating to selection and comparability of cases and controls and the exposed and non-exposed cohort, ascertainment of exposure and outcomes, and follow-up and non-response rates (Wells et al., 2021). Scores on the scale range between zero and nine. In line with previous literature, (de Souza et al., 2015; Montazeri et al., 2017) scores of above seven were taken to indicate "good" quality, and scores of 4-6 and 3 or less to indicate respectively "fair" and "low" quality studies. All studies were assessed by both IR and PP, discrepancies were resolved by consensus.

Statistical Analyses and Data Extraction

The information extracted from each study included: first author, year of publication, country where the study took place, the study design (case-control or cohort), number and sex of participants (cases and non-cases), age range and median age, the type of alternative tobacco exposure, whether or not smokers were included in the analysis, and any covariates adjusted for. Relevant results extracted included the Odds Ratio (OR), Relative Risk, or Hazard Ratio (HR) and 95% confidence intervals (CI), p-values, and the number of cases and non-cases exposed and not exposed to alternative tobacco products. The principle summary measure extracted was the risk of lung cancer among those ever exposed to alternative tobacco products compared to those not exposed, the risks associated with different durations or intensities of alternative tobacco product use were also extracted if available. Where necessary and sufficient data were available, we estimated the OR and 95% CI. Where risk estimates were presented for different levels of ST or waterpipe use, the risk estimate for ever versus never use was taken in preference if available. Where studies reported on the use of more than one type of ST, the risk estimate for the type of ST most commonly used in the study population was taken in preference. Where studies had overlapping data, the risk estimate derived from the study with the greatest sample size was used.

Meta-analyses were conducted based on the extracted risk estimates and corresponding 95% CI. Only risk estimates which were adjusted for cigarette smoking, or which were derived from non-smokers only were included in the meta-analyses. The standard errors used in the meta-analyses were calculated from the stated ORs and lower and upper limits of the 95% CI given in the included papers.

We assessed heterogeneity with I^2 and Cochran's Q. However, as the included studies covered diverse populations and included a wide range of alternative tobacco products, we fitted random effects models throughout. Meta-analyses were conducted for studies of ST and waterpipe smoking. Within these tobacco types, subgroup analyses were conducted by study type (case-control or cohort) and by geographical regions (Africa, Asia, Europe and North America). Separate analyses were also conducted for samples restricted to non-smokers, and for studies of betel quid tobacco.

Sensitivity analysis and testing for publication bias

For all meta-analyses including 10 or more risk estimates, we tested for publication bias by examining the funnel plot, and the Eggers test for funnel plot asymmetry. Where there was evidence of funnel plot asymmetry, the pooled risk estimate was recalculated using the trimfill method. We also performed a sensitivity analysis to investigate the influence of single studies by recalculating the pooled risk estimate omitting one study each time. All analyses were carried out in R 3.5.0(R Core Team, 2013) using the metafor package (Viechtbauer, 2010).

Registration details

The study protocol is registered with PROSPERO (number CRD42017077909) (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=77909).

Role of the funding source

This work was supported by the University of Brighton. The funders had no role in the study design, collection, analysis and interpretation of data, or the decision to submit the paper for publication.

Results

A flowchart describing the study selection process is given in Figure S1 in the supplementary material. A total of 34 studies were eligible for inclusion in the synthesis. Of these, a further 10 studies were excluded from the meta-analysis due to overlapping samples, insufficient data or lack of appropriate adjustment for cigarette smoking (these studies are summarized in Table S1 in the supplementary material). This resulted in 20 studies of ST, five of waterpipe smoking, and one of both ST and waterpipe smoking eligible for inclusion in the meta-analyses (Table 1). These provided 22 risk estimates for ST (14 from case-control and eight from cohort studies including 646,672 individuals), and 6 risk estimates for waterpipe smoking (all from case-control studies including 1,620 individuals) for inclusion in the synthesis.

Use of all types of smokeless tobacco and lung cancer

Ten studies had estimates of risk derived from non-smokers only (Figure 1). The meta-analysis of these risk estimates found an overall significant positive association with risk of lung cancer with a pooled Risk Ratio (RR)of 1·53 (95% CI 1·09 – 2·14, I^2=48.0%, p=0.02), varying from 1·45 (95% CI 1.02 – 2·06) to 1·71 (95% CI 1·30 – 2·26) in the sensitivity analyses. The results were largely unchanged on restricting the analysis to cohort studies (pooled RR = 1·51 (95% CI 1·06 – 2·15, I^2=50.7%, p=0.03)). There were two case-control studies in never-smokers, which yielded a pooled RR of 1·07 (95% CI 0·14 – 2·82). The meta-analysis of all studies of any ST use and smoking-adjusted lung cancer risk found no overall association, with a pooled RR of 1·24 (95% CI 0·98 1·56, I^2=84.6%, p<0.0001) (Figure S2 in supplementary data). There was evidence of publication bias (p funnel plot asymmetry = 0·0002), with the trim fill method suggesting 6 studies missing on the left side of the funnel plot (Figure S3 in supplementary data), and

Table 1. Summary of Studies Included in the Meta-Analysis.

Reference and country	Population studied	Participants (N) and sex	Age (Median, range)	Type of tobacco exposure	Exposed (Cases/controls)	Unexposed (Cases/controls)	Smokers included	Covariates included	OR/RR (95%CI) for ever use
Smokeless tobacco case-control study									
(Williams and Horm, 1977) United States	Cancer patients in the Third National Cancer Survey and age and race matched controls with other cancers (subjects 97.5% White)	7518 (M/F NR)	NR	CT and snuff	(36/164) in M	(532/1624) in M	Y	Age, smoking, race	0·67 (0·46 – 0·97)* (M only)
(Hsairi et al., 1993) Tunisia	Lung cancer patients diagnosed between December 1988 – May 1989 and community controls matched on age, sex and cigarette consumption	110 cases, 110 controls (107M/3F) for both	61·1†(2·8)‡ for cases	Snuff use	(20/8)	(90/112)	Y	Age, sex, daily cigarette consumption, certain occupational exposures (e.g. Nickel, Chromium)	2·2 (0·9 – 5·6) §
(Notani et al., 1993) India	Lung cancer cases in Bombay and population controls	246 cases, 85 controls (all M)	NR	CT	NR		Y	Age group (4 categories) and smoking status (2 categories)	0·80 (0·5 – 1·4) (NR)
(Dikshit and Kanhere, 2000), India	Lung cancer cases in Bhopal from 1986-1992 and population controls	163 cases, 260 controls (all M)	NR	CT	(52/108)	(111/152)	Y	Age and smoking	0·7 (0·4 – 1·2) §
(Bhurgri et al., 2002), Pakistan	Lung cancer patients in Karachi and sex- and age-matched controls (hospital and visitors)	314 cases (282M/32F), 640 controls (561M/79F)	22 – 90	CT (mostly BQ) and snuff	(79/110) for CT, (33/56) for snuff	(241/530) for CT, (287/584) for snuff	Y	Sex, age, hospital and cumulative tobacco smoking	1·1 (0·7 – 1·7) for CT 1·9 (1·0 – 3·7) for snuff
(Pacella-Norman et al., 2002), South Africa	Black lung cancer patients and non-tobacco related cancer patient controls attending hospitals in Greater Johannesburg between 1995 – 1999	146 cases (105M /41F), 2174 controls (1370M/804F)	18-74y	Snuff	(0/28) in M, (8/302) in F	(103/772) in M, (33/1065) in F	Y	Place of birth, education, age, heating fuel 20 years ago, work category, tobacco smoking, alcohol consumption	0·9 (0·4 – 2·1) (F only)
(Sasco et al., 2002), Morocco	Lung cancer cases diagnosed between January 1996 – January 1998 and age, sex and residence matched hospital controls in Casablanca (subjects 91% white, 9% Black/Mixed)	118 cases (114M/4F) and 235 controls (230M/5F)	59·3 (35 – 82) for cases, 58·8 (34 – 82) for controls	Snuff	(9/11)	(83/206)	Y	Smoking and passive smoking, hashish use, history of chronic bronchitis, occupational exposures, cooking and heat source, lighting source, ventilation of kitchen	1·05 (0·28 – 3·85)
(Gajalakshmi et al., 2003), India	Lung cancer cases and healthy and non-tobacco-related cancer controls in Tamil Nadu and Kerala	778 cases, 3430 controls (all M)	≤34y to ≥75y	CT	NR	NR	Y	Age, recruitment center and smoking pack years	0·74 (0·57-0·96) (All) 0·30 (0·04 – 2·30) (NS only)
(Shah et al., 2008), India	Patients with squamous cell carcinoma of the lung and ethnicity, socio-economic and geographical location matched controls in Northern India	200 cases, 200 controls (all M)	43†(12)‡ for cases, 56†(9)‡ for controls	CT	(27/23)	(53/115)	N	None	2·55 (0·79 – 4·29)*
(Yadav et al., 2010), India	Lung cancer cases diagnosed in 3 hospitals in NE India from 2006 to 2008 and age, sex and ethnicity matched controls	101 cases, 221 controls, (number M/F not stated)	53†(10)‡/ 49†(10)‡ for cases/ control in Assam, 59†(11)‡/62†(10) ‡ in Sikkim, 63† (10) ‡/63† (10) ‡ in Mizoram	CT and BQ	(55/123) for CT, (79/130) for BQ	(46/98) for CT, (22/91) for BQ	Y	Smoking and GSTT1, GSTM1 and GSTP2 genotypes, BQ analyses also adjusted for tobacco chewing, CT analyses also adjusted for BQ chewing	0·73 (0·42 – 1·27) for CT 2·16 (1·05 – 4·43) for BQ
(Ganesh et al., 2011), India	Lung cancer patients and cancer-free controls attending hospital in Mumbai between 1997-1999.	408 cases, 1383 controls (all M)	56·2† for cases, 46·5† for controls	CT	(23/103)	(385/1280)	Y	Cigarette and bidi smoking, alcohol drinking, consumption of milk, coffee, chicken, red meat, fish and chillies, and pesticide exposure	0·6 (0·3 – 1·2)

Table 1. Continued

Reference and country	Population studied	Participants (N) and sex	Age (Median, range)	Type of tobacco exposure	Exposed (Cases/controls)	Unexposed (Cases/controls)	Smokers included	Covariates included	OR/RR (95%CI) for ever use
Smokeless tobacco case-control study									
(Ihsan et al., 2011b), India	Lung cancer patients diagnosed between December 2005 – 2008 and age, sex and ethnicity matched controls selected from healthy relatives of cancer patients	161 cases (120M/41F), 274 controls (202M/72F)	NR	BQ and CT	(88/134) for CT, (133/168) for BQ	(73/140) for CT, (28/105) for BQ	Y	Smoking, alcohol consumption, p53 genotypes, tobacco chewing also adjusted for BQ chewing, and BQ chewing adjusted for tobacco chewing	1·04 (0·65 – 1·67) for CT 3·54 (2·01 – 6·25) for BQ
(Phukan et al., 2014), India	Lung cancer cases and age-, sex- and ethnicity matched community controls in Northeast India	151 cases, 151 controls (82M/69F for both)	59·0†(33 – 85) for cases, 58·5†(34 – 82) for controls.	CT	(110/96)	(41/55)	Y	Smoking, education, occupation, alcohol consumption	1·59 (0·96 – 2·64) §
(Saikia et al., 2014), India	Lung cancer cases and sex, age and ethnicity matched controls in NE India	272 cases (130M/142F), 544 controls (260M/284F).	61·96†(21 – 88) for cases, 61·79†(21 – 89) for controls	BQ	(187/336)	(85/208)	Y	Smoking, sex, age, exposure to wood combustion, exposure to cooking oil fumes	1·36 (0·99 – 1·87) §
Smokeless tobacco, cohort study									
(Accortt et al., 2002), United States	Participants in First National Health and Nutrition Examination Survey Epidemiologic Follow Up Study (White and Black subjects)	3130M and 3675F	Aged 45-75 at baseline in 1975, followed up for 20y	Smokeless tobacco	(0/NR) in M, (4/NR) in F	(6/NR) in M, (3/NR) in F	N	Age, race, poverty index ratio, region of residence, alcohol, recreational physical activity, and fruit/vegetable intake	9·1 (1·1, 75·4)‖ (F only)
(Boffetta et al., 2005), Norway	Systematic sample of general population from 1960 census and relatives of Norwegian migrants to United States, enrolled in 1966 and followed up to 2001	10 136 (all M)	NR	Snus use	(72/NR)	(271/NR)	Y	Smoking and age	0·80 (0·61 – 1·05) ¶ (All) 0·96 (0·26 – 3·56) ¶ (NS only)
(Henley et al., 2005), United States	Men in CPSI Study (enrolled in 1959, followed up to 1972) and in CPSII Study (enrolled in 1982, followed up to 2002)	77 407 in CPSI, 114 809 in CPSII (all M)	Median age at enrolment for never and current users of spit tobacco was 53 and 62 in CPSI, and 56 and 57 in CPSII	Spit tobacco (CT or snuff)	(18/7727) in CPSI, (18/2470) in CPSII	(116/69546) in CPSI, (378/111104) in CPSII	N	Age, race, educational level, BMI, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, aspirin use in CPSI and plus employment status and type in CPSII	1·08 (0·64 – 1·83) ‖ (CPSI never v current 1·96(1·27 – 3·01)* (CPSII)
(Luo et al., 2007), Sweden	Construction workers completing at least one health check between 1978 – 1992	279 897 (all M)	35†(13) ‡ (<30 to ≥ 60)	Snus use	(18/37737)	(136/87685)	N	Age, BMI	0·7 (0·6 – 0·7) ¶ (All) 0·8 (0·5 – 1·3) ¶ (NS only)
(Pednekar et al., 2011), India	87 222 men aged ≥ 35y recruited in Mumbai in 1991-1997	87 222 (all M)	35y to >70y	Smokeless tobacco	(34/NR)	(17/NR)	N	Age, education, religion, mother tongue, BMI category	1·59 (0·87 – 2·90)‖
(Andreotti et al., 2017), United States	Subjects including pesticide applicators and their spouses in Iowa and North Carolina (subjects 96% White)	53 071 M/ 30 944 F	<30y to > 70y	Smokeless tobacco (CT or snuff)	(10/NR) smokeless tobacco	NR	N	Gender, age, state of residence, race, education, BMI, alcohol consumption, fruit and vegetable intake	2·21 (1·11 – 4·42)‖
(Fisher et al., 2019), United States	Participants in the National Longitudinal Mortality Study surveyed between 1993 and 2005	1863 current ST users (88.4%M), 124 457 never users (37.4%M)	Mean age at interview 39.6y for current ST users, 44.6y for never users	Smokeless tobacco	(3/1860)	NR	N	Gender, race, age, educational attainment, family income, health status	2.98 (0.91 – 9.76) ‖ for current ST use versus never use

Table 1. Continued

Reference and country	Population studied	Participants (N) and sex	Age (Median, range)	Type of tobacco exposure	Exposed (Cases/controls)	Unexposed (Cases/controls)	Smokers included	Covariates included	OR/RR (95%CI) for ever use
Waterpipe case-control study									
(Qiao et al., 1989), China	Lung cancer cases aged 35-80y who were alive in 1985 in Geiju area and age-matched controls working for YTC	107 cases, 107 controls (all M)	61† (49 – 78) for cases, 62† (47 – 79) for controls	Waterpipe	(24/23)	(3/5)	N	Age	1·9 (0·4 – 9·4)
(Lubin et al., 1992), China	Lung cancer cases reported to the Geiju City Cancer Registry between 1984 and 1988 and age-matched controls (employees of YTC and city controls)	544 cases, 1043 controls (all M)	62·9† and 62·6† for cases (YTC and city), 62·5† and 62·1† for controls	Pipe use (primarily waterpipes)	56/151	Sep-72	N	Age, source of subject (city or YTC), type of respondent and years of work underground	1·78 (0·8 – 4·2)
(Hsairi et al., 1993), Tunisia	Lung cancer patients diagnosed between December 1988 – May 1989 and community controls matched on age, sex and cigarette consumption (+- 5 cigarettes/day)	110 cases, 110 controls (107M/3F for both)	61·1† (2·8) ‡	Waterpipe	(13/3)	(107/117)	Y	Age, sex, daily cigarette consumption, snuff use and cannabis use	5.7 (1·2 – 27.6) §
(Gupta et al., 2001), India	Lung cancer patients in Chandigarh recruited between January 1995 – June 1997 and hospital controls	265 cases (235M/30F), 525 controls (435M/90F)	< 50 to ≥70	Waterpipe	(12/31) in M	(26/172) in M	N	Age and education	1·94 (0·85 – 4·44) (M only)
(Koul et al., 2011), India	Lung cancer cases in Kashmir diagnosed from June 2005 to December 2006 and healthy age- and area of residence matched controls	251 cases (209M/42F), 400 controls (328M/72F)	58·4† in M, 56·5† in F	Waterpipe	(120/100)	(57/277)	N	None	5·83 (3·95 – 8·60)
(Kudhair et al., 2020), Iraq	Lung cancer cases in Najaf city diagnosed between December 2017 and June 2019 and healthy age and ethnicity-matched controls (recruited from Mahdi Al-Attar clinic Najaf province).	123 lung cancer patients and 129 controls (all M)	61.1% and 38.9% of cases and 56.6% and 43.4% of controls ≤ 50y and >50y respectively	Waterpipe	(86/51)	(37/78)	N	None	3.6 (2.1 – 6.0)

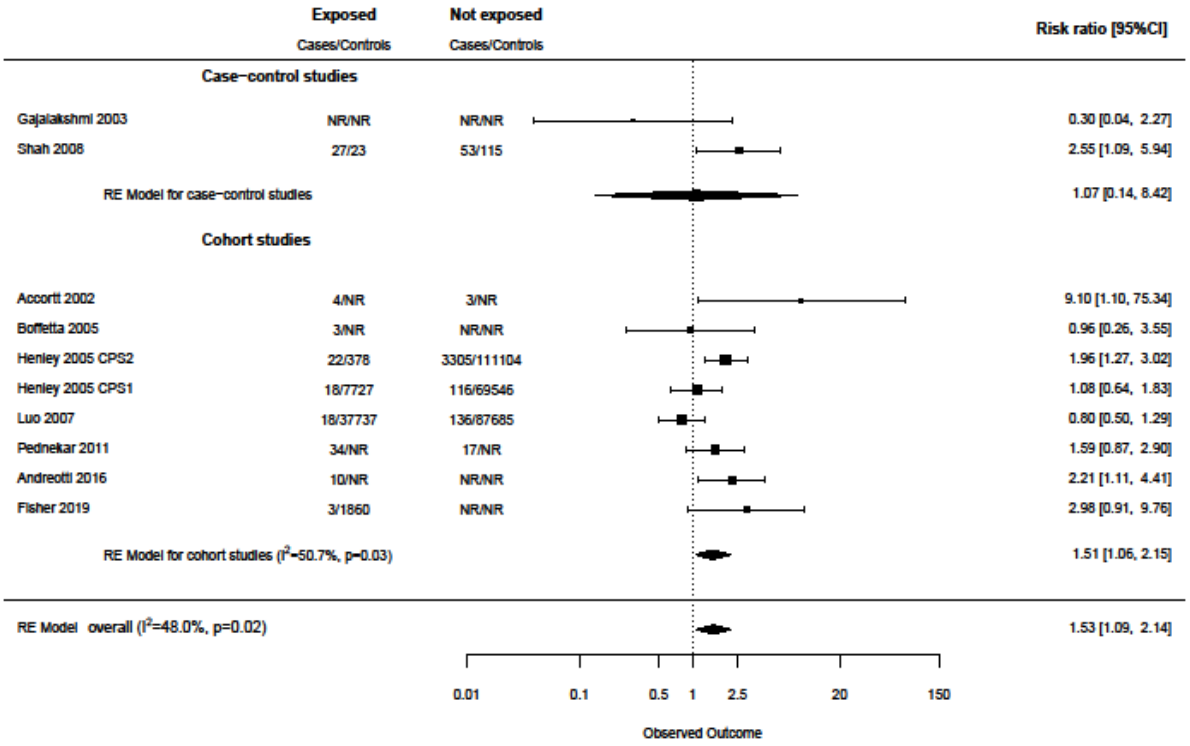

Figure 1. Random Effects Meta-Analysis of the Association between Ever Use of Smokeless Tobacco and Lung Cancer among Non-Smokers. The ORs fore each study are presented as squares, with the position of the square corresponding to the point estimate and the 95% CI shown by horizontal lines. (95% Cis for each study shown in the forest plot are obtained by back transformation using the calculated standard error shown in the analysis and do not always conform exactly to the stated confidence intervals in the paper). The area of the square Is inversely proportional to the variance in the OR. The diamond represents the pooled OR and it's 95% CI

giving a revised pooled RR (including imputed missing data) of 1·01 (95% CI 0·78 – 1·31).

Use of betel quid tobacco products and lung cancer

Four eligible studies examined the association between the use of betel quid tobacco products and lung cancer (Figure 2), all of which were case-control studies and included both smokers and non-smokers. The meta-analysis found a significant positive association between betel quid tobacco use and smoking-adjusted

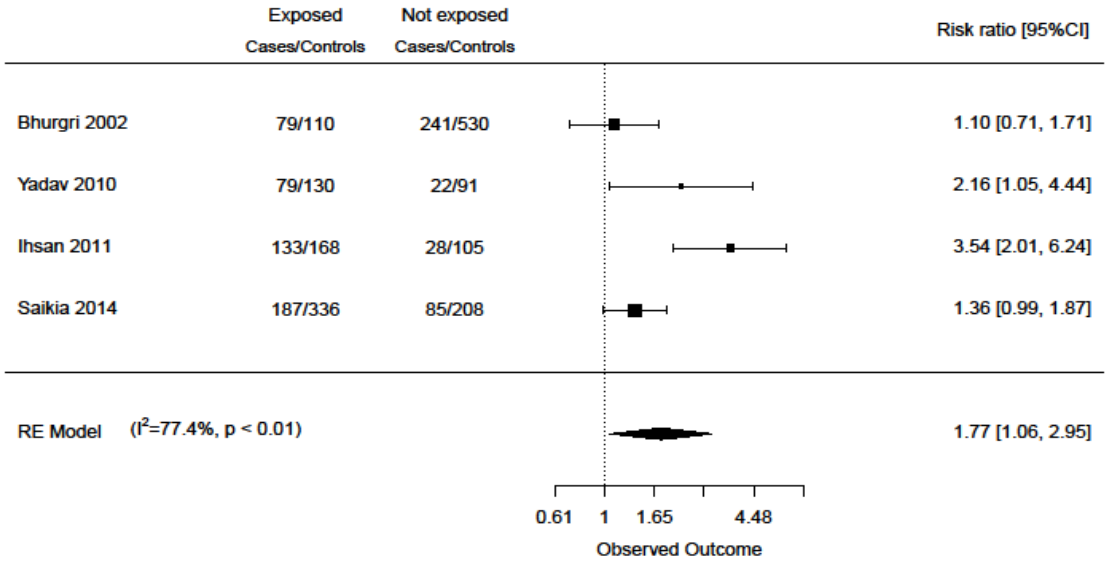

Figure 2. Random Effects Meta-Analysis of the Association between Ever Use of Betel Quid/Tobacco Mixes and Lung Cancer. The ORs fore each study are presented as squares, with the position of the square corresponding to the point estimate and the 95% CI shown by horizontal lines. (95% Cis for each study shown in the forest plot are obtained by back transformation using the calculated standard error shown in the analysis and do not always conform exactly to the stated confidence intervals in the paper). The area of the square Is inversely proportional to the variance in the OR. The diamond represents the pooled OR and it's 95% CI

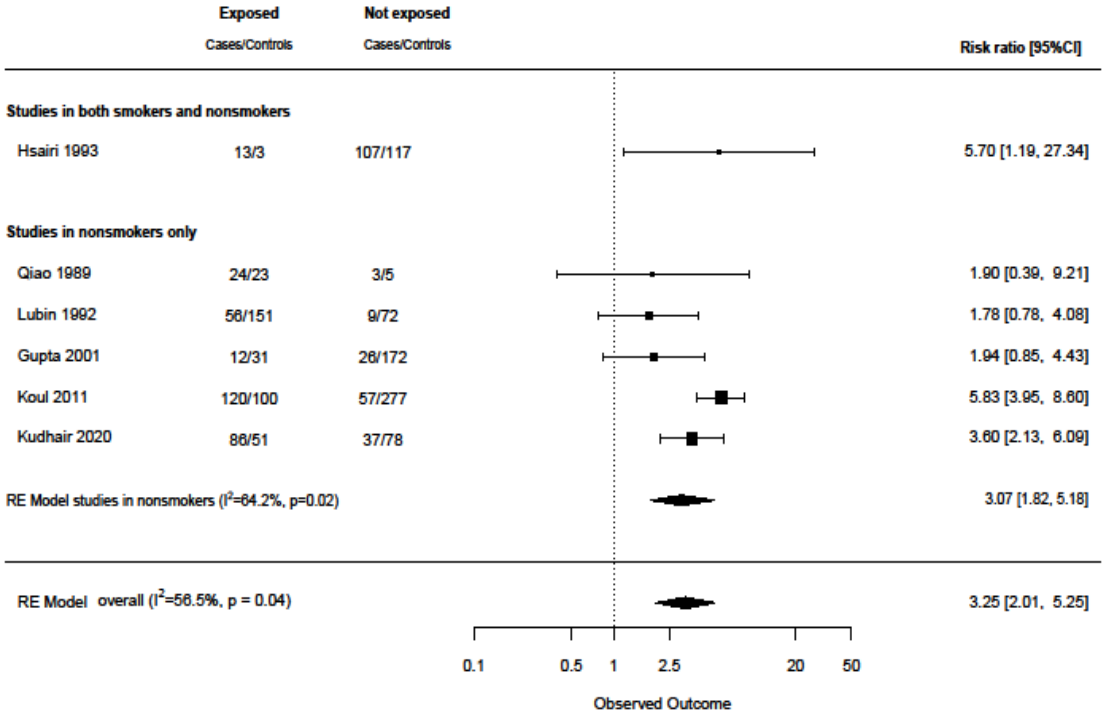

Figure 3. Random Effects Meta-Analysis of the Association between Ever Use of Smokeless Waterpipe Smoking and Lung Cancer. The upper limit for one of the included studies65 was altered as we believe that the value reported in the paper is a typographical error. The CI reported in the published paper is 1.2 – 7.6 and we changed the upper limit to 27.6 to make the CI log symmetrical. We attempted to contact the authors to confirm this but were unsuccessful. The ORs fore each study are presented as squares, with the position of the square corresponding to the point estimate and the 95% CI shown by horizontal lines. (95% Cis for each study shown in the forest plot are obtained by back transformation using the calculated standard error shown in the analysis and do not always conform exactly to the stated confidence intervals in the paper). The area of the square Is inversely proportional to the variance in the OR. The diamond represents the pooled OR and it's 95% CI

lung cancer risk, with a pooled RR of 1·77 (95% CI 1·06 – 2·95. I^2=77.4%, p <0.01), varying between 1·35 (95% CI 1·06 – 1·72) and 2·10 (95%CI 1·17 – 3·78) in the sensitivity analysis.

Use of smokeless tobacco and lung cancer by region

The pooled RR for the 11 eligible studies conducted in Asia was 1·26 (95% CI 0·91 – 1·75, I^2=79.5%, p<0.0001), for the eight studies conducted in Europe and North America was 1.22 (95% CI 0·80 – 1·88, I^2=90.0%, p<0.0001), and for the three studies (all of snuff use) conducted in Africa was 1·29 (95% CI 0·69 – 2·41, I^2=18.0%, p=0.34) (Figs S4a, S4b and S4c respectively in the supplementary data). In a meta-regression of all studies of ST use, there was no moderating effect of region on the association between ST use and lung cancer risk (p = 0·382).

Waterpipe smoking and lung cancer

The meta-analysis of waterpipe smoking and lung cancer risk is shown in Figure 3. The meta-analysis found a significant positive association with lung cancer risk, with a pooled RR of 3·25 (95% CI 2.01 – 5·25, I^2=56.5%, p=0.04), varying from 2·68 (95% CI 1·76 – 4.07) to 3.73 (95% CI 2.30 – 6.05) in the sensitivity analysis. The sub-group analysis of the four studies of never-smokers found similar results with a pooled RR of 3.07 (95% CI 1.82 – 5·18, I^2=64.2%, p=0.02), varying from 2.50 (95% CI 1.58 – 3.95) to 3.53 (95% CI 2.04 – 6.09) in the sensitivity analyses.

Study quality

Of the 24 studies included in the meta-analyses, 13 scored seven or more on the Newcastle Ottawa assessment (considered to be good quality), 12 scored between four and six (fair quality), and one scored three (low quality). Details of the scoring are given in Appendix 2 in the supplementary material. No studies were excluded on the basis of quality.

Results of studies not considered eligible for inclusion in the meta-analysis (Table S1, supplementary material)

Six case-control and three cohort studies of ST provided an estimate of the association between ST use

and lung cancer but were not eligible for inclusion in the meta-analysis – one did not provide enough information to calculate a confidence interval for the association, and it was not possible to contact the author of this study. One had a sample that overlapped with another study(Bolinder et al., 1994), and one study included only smokers(Henley et al., 2007). Six studies did not adjust for cigarette smoking in the analysis(Doll and Bradford Hill, 1952; Pisani et al., 2006; Sapkota et al., 2008; Ihsan et al., 2011a; Singh et al., 2011), of these four found ORs for lung cancer of <1 among users of ST. There were also two case-control studies of waterpipe smoking(Lubin et al., 1990; Aoun et al., 2013) which did not adjust for cigarette smoking, both found strong positive associations between waterpipe use and lung cancer risk. We contacted the corresponding author of one of these studies(Aoun et al., 2013) to confirm that the results presented were not adjusted for cigarette smoking and to request smoking-adjusted results, but these were not available.

Discussion

Main finding of this study

To our knowledge, this is the most comprehensive review on the association between use of alternative tobacco products and the risk of lung cancer. Among non-cigarette smokers, the pooled data showed an approximately 50% increased risk of lung cancer associated with the use of ST. Our results suggest that the use of betel quid tobacco may be particularly hazardous, with about 80% increase in the risk of lung cancer among the users. We also found a strong association between waterpipe smoking and lung cancer risk, with approximately three times increased risk of lung cancer in waterpipe smokers.

What is already known on this topic

Previous meta-analyses of the association between use of ST and lung cancer have concentrated on particular geographical regions. The Lee and Hamling (2009) and Boffetta et al., (2008) meta-analyses included studies conducted in Europe and North America, so excluded all studies from South-East Asia, the region with the highest number of ST users, whereas the Sinha et al., (2016) meta-analysis included only studies conducted in India and so only had six studies available for the pooled analysis. They did not find an association between ST use and lung cancer risk, however, while all the meta-analyses included only studies where some adjustment for cigarette smoking had been made, such adjustment frequently fails to account for factors such as daily cigarette consumption or duration of smoking habit. A Swedish study found that use of ST (snus) was associated both with lower daily cigarette consumption among current smokers and with an increased probability of quitting smoking (Gilljam and Galanti, 2003). ST might therefore act as a marker of reduced cigarette consumption, potentially resulting in reduced, or spurious negative associations between ST use and lung cancer (Luo et al., 2007). In the current study, the pooled analysis of all studies of ST use in all subjects did not find a significant association with lung cancer risk, but the association was strengthened and became significant on restricting the analysis to studies of non-smokers. Only the Lee and Hamling (2009) review presented results from studies restricted to non-smokers, finding a pooled OR of 1.34 (95%CI 0.80 – 2.23) similar to our own combined estimate of 1.53 (1.09 -2.14), although their result did not reach statistical significance. We are aware of three other meta-analyses on the association between waterpipe smoking and lung cancer, the Akl et al.(2010) review, and the Montazeri et al., (2017) and Waziry et al., (2017) reviews. Two of these (Akl et al., 2010; Waziry et al., 2017) reported a pooled OR of 2·12 (95%CI 1·32 – 3·42) derived from the same four studies. The Montazeri et al., (2017) review reported a pooled OR of 4·58 (95%CI 2·61 – 8·03) derived from three studies, however, one of the risk estimates included (from the Aoun et al., (2013) study) was an unadjusted OR derived from a sample that included cigarette smokers . The Montazeri et al., (2017) review excluded the studies of Chinese tin miners(Qiao et al., 1989; Lubin et al., 1992) on the basis the results may have been confounded by radon exposure. We repeated our meta-analysis excluding these studies and the association with lung cancer was slightly strengthened (pooled OR 3·94 (95%CI 2.38 – 6.94).

What this study adds

Our synthesis has several strengths. To our knowledge, this is the first systematic review and meta-analysis of the association between ST and lung cancer to include studies from all geographic regions, increasing the statistical power to detect any associations. Our results are robust as only studies that adjusted for cigarette smoking status have been included, and the associations between any ST or waterpipe smoking and lung cancer are retained in pooled analyses restricted to non-smokers. Also, we present subgroup analysis by study design and geographical region. Separate meta-analysis was carried out for studies of the use of betel quid tobacco and lung cancer, for which only studies derived from samples which included cigarette smokers were available. Although all these studies made some attempt to adjust for tobacco smoking, only one (Bhurgri et al., 2002) included adjustment for a measure of smoking intensity and duration. It is possible that the positive association observed between betel quid chewing and lung cancer may reflect residual confounding by cigarette smoking. There is limited data on the relationship between betel quid chewing and smoking intensity, but in the Bhurgri et al., (2002) study it was stated that heavy betel quid chewing and heavy smoking were positively associated.

Our literature search also included terms relating to e-cigarettes and vaping (Appendix 1 in the supplementary material). We did not identify any studies describing the risk of lung cancer associated with the use of e-cigarettes. As these products have only recently begun to be widely used, this is unsurprising, but given their popularity, data on the potential lung cancer risk associated with e-cigarettes are urgently required.

Limitations of this study

There are a number of limitations in the data available

for the synthesis. These relate particularly to the substantial array of different commercial and home-prepared tobacco products available, as indicated by our literature search strategy which included over 40 different terms for ST. These may be very variable in terms of other substances added, processing and storage, and therefore in terms of carcinogenicity, but there is generally limited information in the studies about exactly what types of ST are included. A further complication is that the same term may be associated with a range of products with different compositions and methods of use, for example "snuff" may refer to either moist snuff, which is air or fire cured and taken orally, or dry snuff, a fermented tobacco product frequently containing flavourings and other additives which may be taken nasally.

There is likely to be regional variation in the composition of ST. In Asia, ST products are commonly kept unrefrigerated in warm conditions for long periods, with the result that fermentation and increases in the tobacco-specific nitrosamine (TSNA) content will occur. This is less likely in Europe and North America, but there will probably have been changes over time in the composition of ST, with the ST used in older studies having a higher TSNA content (Lee and Hamling, 2009). In addition, there may be considerable within region variation in the composition of products. For example, American chewing tobacco products are generally fermented, whereas Swedish snus is heat treated – these different tobacco products contain different types and amounts of TSNAs and other carcinogens, and may have different effects on health (Stepanov et al., 2008; Rutqvist et al., 2011). Stepanov et al., (2008) analysed a wide range of ST products marketed in India – levels of the TSNAs NNN and NNK varied from 76·9 and 28·4 µg/g in Raja brand khaini, to less that 1µg/g in most brands of Gutka. In Asia, tobacco is commonly chewed as betel quid mixes containing areca nut. Betel quid and areca nut without tobacco are classified as human carcinogens, and are known to cause oral, pharyngeal and oesophageal cancers (2004). We found a significant association with lung cancer in the meta-analysis of studies that specified an exposure to betel quid tobacco; insufficient information was available to investigate the association of other type of ST with lung cancer. However, we did not find a marked difference in the strength of association between use of ST and lung cancer in different geographical regions, despite the more common use of betel quid in Asia.

As with ST, the types of tobacco used for waterpipe smoking and their potential health effects are likely to vary by region. In China and India, waterpipe tobacco is generally unflavoured and heated directly by charcoal. In the West and Middle East waterpipe smokers tend to use flavoured processed tobacco mixes which are indirectly heated, (Akl et al., 2010; Sahin et al., 2016) such as maasel, the introduction of which in the 1990s may have helped to fuel the growing popularity of waterpipe smoking(Maziak et al., 2015). However, there were too few studies of waterpipe smoking and lung cancer to allow a regional analysis.

A further limitation of the available data is that unlike cigarette smoking, where measurement of consumption is relatively straightforward, there is no standard way of measuring the intensity of use of ST or waterpipe (Akl et al., 2010; Waziry et al., 2017) Few of the studies presented information on lung cancer risk by alternative tobacco product usage level, so it was not possible to investigate dose-response relationships. Many studies failed to adjust for important potential confounding variables such as measures of socioeconomic status, which is associated both with ST and waterpipe use and with lung cancer risk independently of cigarette smoking (Hovanec et al., 2018). It is possible that the positive associations observed between ST use and lung cancer among never smokers might reflect unmeasured confounding. Cigarette smoking is associated with a range of other unhealthy behaviours which may predispose towards lung cancer e.g. poor diet, excessive alcohol consumption and low physical activity levels, (Nuttens et al., 1992; Kang et al., 2010) the same may also be true of tobacco chewing and waterpipe smoking.

In summary, our results suggest that ST use may be associated with a significantly increased risk of lung cancer among non-smokers, and that betel quid tobacco may be particularly hazardous. We also found waterpipe use to be associated with a significantly increased risk of lung cancer. If causal, these associations represent an important cancer burden given the very high prevalence of ST use in much of the developing world and the growing global popularity of waterpipe smoking. More studies are needed with accurate measurements of intensity and frequency of use, detailed information on cigarette smoking history, and details of the specific types of ST or waterpipe tobacco being used. Public health policies and international tobacco control efforts should also focus on the risks associated with ST use and waterpipe smoking.

Author Contribution Statement

The authors confirm contribution to the paper as follow: study conception and design: PP; data collection; IR; analysis and interpretation of results: IR, PP, AM; draft manuscript preparation: IR, PP, AM. All authors reviewed the results and approved the final version of the manuscript.

Acknowledgements

This work was supported by the University of Brighton (grant holder PP). The data underlying this article are available in the article and in its online supplementary material. The study protocol is registered with PROSPERO (number CRD42017077909) (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=77909). The authors declare no conflict of interest. Ethical approval was not required for this study as it was a review of published work.

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