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The association between smokeless tobacco use and pancreatic adenocarcinoma: A systematic review

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Abstract

Background—Smokeless tobacco is a possible risk factor for developing pancreatic adenocarcinoma. This systematic review addressed the question: Is there an association between smokeless tobacco use and pancreatic adenocarcinoma diagnosis?

Methods—Five electronic databases, grey literature, and citations of relevant articles were searched to identify studies. Six researchers double-reviewed records for inclusion in the review. The information extracted from these studies was selected using criteria outlined in the Newcastle–Ottawa Quality Assessment Scale for observational studies. A qualitative synthesis of included studies was performed.

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Authorship contribution statement

All of the above-listed authors: (1) made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; (2) contributed to drafting the article or revising it critically for important intellectual content; and (3) provided final approval of the version to be published.

None of the authors disclosed any conflicts of interest. Shari Feirman and Matthew D. Burkey contributed equally to this study.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Results—The search of electronic databases resulted in a total of 1747 citations. Eleven studies met the inclusion criteria for this review, including three cohort studies, seven case control studies and one study that pooled data from multiple case-control studies. Studies were heterogeneous in their assessment of exposure intensity and ascertainment of outcomes. Quality of the studies varied. Existing investigations of the association of interest appear to exhibit several types of biases including selection bias, information bias and bias in the analysis.

Conclusion—The association between smokeless tobacco use and pancreatic adenocarcinoma is inconclusive. More definitive conclusions regarding this relationship await the results of more methodologically rigorous epidemiologic studies.

Keywords

Pancreatic neoplasms; Pancreatic cancer; Smokeless tobacco; Tobacco products; Systematic review

1. Introduction

Pancreatic adenocarcinoma, the most common form of pancreatic cancer, is the fourth leading cause of cancer deaths in the United States; it is estimated that approximately 38,460 Americans died of pancreatic cancer [1]. Despite new chemotherapeutic agents, improved surgical technique, and growing experience in the last two decades, mortality from pancreatic cancer remains unchanged [2]. Thus, preventative approaches, such as identifying and understanding risk factors, are important in reducing the harm caused by this disease.

Major known risk factors for pancreatic cancer include tobacco smoking [3], diabetes [4], and obesity [5]. The association between smokeless tobacco use and pancreatic adenocarcinoma is unknown, but smokeless tobacco has been identified as a possible risk factor contributing to the development of this disease [6–8]. Some smokeless tobacco products contain over 30 recognized carcinogens, and the consumption of such products represents the highest known non-occupational exposure to carcinogenic nitrosamines [9,10]. One of these nitrosamines (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)) and its metabolite (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)) have been shown to cause pancreatic cancer in rat models [11].

The detrimental health effects of smokeless tobacco have come under scrutiny as global sales of smokeless tobacco have increased over the past decade [12]. Among public health researchers, a debate has emerged as to whether smokeless tobacco products should be promoted as a harm reduction strategy in order to lessen the burden that cigarette smoking inflicts on the public's health [13]. Indeed, research suggests that, when used alone, these products may present a decreased risk of tobacco-related disease when compared to cigarettes [14]. However, these products may pose unique risks (such as oral cancer and esophageal cancer [15]) and, if they are used in addition to cigarettes or other tobacco products, may actually increase the risk of harm to tobacco users [14]. In the U.S., approximately 60% of smokeless tobacco users also use cigarettes [16].

Previous syntheses of evidence examining the effect of smokeless tobacco use on pancreatic cancer have found varying associations. Boffetta [15] found a relative risk of 1.66 (95% CI:

1.06–2.62) for ever users of smokeless tobacco as compared to never users in Norway, whereas two meta-analyses found no significant association between smokeless tobacco use and pancreatic cancer [17,18]. One of the studies showing no association was sponsored by a major tobacco company [18].

The objective of this study was to update and expand upon previous systematic reviews that investigate the association between smokeless tobacco use and pancreatic adenocarcinoma. This update is needed to address potential conflicts of interest inherent in previous studies, and to expand the scope of analysis to assess for studies performed outside of Europe and North America given the widespread use of smokeless tobacco worldwide. Furthermore, regular updates to systematic reviews are recommended every two years in order to assess new evidence [19]; the most recent systematic review on smokeless tobacco use and pancreatic cancer included studies through May 2008 [17]. This study was designed to address the etiologic question: Is there an association between smokeless tobacco user status and pancreatic adenocarcinoma diagnosis?

2. Methods

2.1. Criteria for inclusion in this review

Retrospective cohort studies, prospective cohort studies, and case control studies were eligible for this review. These types of controlled observational studies were selected in order to evaluate the temporal association between smokeless tobacco use and the development of pancreatic adenocarcinoma. Case reports, case series, and cross-sectional prevalence studies were excluded from the analysis because they either lack sufficient numbers of participants to make valid statistical conclusions, they do not include control groups, or they do not include adequate information about temporal relationships between the exposure and outcome of interest.

Studies were included if they assessed smokeless tobacco use and pancreatic adenocarcinoma diagnosis in participants. Smokeless tobacco products include: snuff (dry and moist), snus (tea-bag like pouches that do not require spitting), dip, chewing tobacco, gutka (which is popular in Southeast Asia), and dissolvable tobacco products that come in the form of orbs, sticks and strips [20,21]. The use of such products does not involve the burning of tobacco; these products are consumed either orally or nasally. The primary outcome of interest was diagnosis of pancreatic adenocarcinoma. Studies specifically evaluating non-adenocarcinomatous pancreatic tumors were excluded given their distinct pathogenesis and risk factors.

There were no restrictions with respect to age, gender, ethnicity, geographic location, comorbidities, or the number of participants. Only articles that were written in English, Spanish or Chinese were included; these languages were selected based on the availability of reviewers who speak these languages.

2.2. Search methods for identification of studies

Five electronic databases were searched for relevant articles: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Pubmed), CINAHL, LILACS, and

EMBASE. In consultation with a university librarian, search strategies were tailored for each database. The searches included combined controlled vocabulary terms and related keywords for smokeless tobacco use and pancreatic adenocarcinoma. Several linguistic variations of smokeless tobacco were included in the search to reflect the variety of terms applied to this category of exposures colloquially and worldwide [22]. Examples of smokeless tobacco terms that were searched include: “snuff,” “snus,” “gutka,” “oral tobacco,” “betel quid,” “naswar,” “dip” and “non-cigarette tobacco.” Search terms related to pancreatic cancer included: “pancreatic tumor,” “pancreatic neoplasm,” “pancreatic adenocarcinoma,” and “pancreatic malignancy.” The databases were searched on February 22, 2013. A similar search strategy was employed to search OpenGrey for unpublished studies including theses, unpublished abstracts, and other unpublished sources. The OpenGrey database search was conducted on March 12, 2013. Citations from relevant papers were hand-searched in order to identify articles that may not have been identified in electronic searches.

2.3. Selection of studies

A team of six researchers (SF, HW, SC, SG, MB, FJ) reviewed the search results. The study selection process included two steps: (1) review of title and abstracts for inclusion in a full text review, and (2) review of full texts for final inclusion assessment. In each stage, two of the six researchers independently reviewed studies for inclusion. Studies were classified as “exclude,” “unsure” or “include.” The reviewing pairs discussed articles classified as “unsure” or for which there was disagreement until classification status could be agreed upon based upon study inclusion criteria.

2.4. Data collection

After papers were chosen for inclusion, two of the six reviewers independently extracted and recorded data from each included study. An electronic data collection form was developed in order to ensure standardization in the extraction process. The form was pilot tested on two articles, which were reviewed by all six researchers. Disagreements were resolved by discussion between the reviewing pair, or by group consensus when necessary. Abstracted data included: study identification information, study design and methods, participant characteristics, exposure, outcome, results, and discussion (author’s key conclusions, reviewer comments).

During the data extraction process, the researchers also collected information to assess the risk of bias in each study. The information extracted was selected using criteria outlined in the Newcastle–Ottawa Quality Assessment Scale for observational studies [23]. Pairs of reviewers independently assessed sources of bias in each study. Disagreements between reviewers were resolved by group consensus. The studies were assessed for vulnerability to selection bias, information bias, and bias in the analysis.

3. Results

3.1. Search results

The search of electronic databases resulted in a total of 1747 citations, including: 578 studies from LILACS, 573 from Embase, 509 from Pubmed, 46 from CINAHL, and 41 from COCHRANE. After removing duplicate records, 1312 records remained. During the review of titles and abstracts, 1238 articles were excluded because they did not meet the inclusion criteria. Of the remaining 74 articles eligible for full text review, articles were excluded because they did not meet the language requirement, the outcome or exposure of interest was not assessed, or the study design criteria were not met. The citations for eligible studies and relevant review studies were hand-searched in order to identify additional papers; four studies were identified during this process. The flowchart in Fig. 1 provides details on the study selection process.

After the review process, twelve studies [6–8,24–32] were deemed appropriate for the data extraction phase of the study. Two of the studies [6,24], however, utilized the same dataset, so only the more recent study was included in the analysis for a total of eleven included studies. Three of these studies were cohort studies [7,24,25] and seven were case-control studies [8,26–30,32]. One additional study utilized data from 6 case-control studies in order to calculate a pooled odds ratio for the association between smokeless tobacco use and pancreatic cancer [31] and was included because it contained data from otherwise unpublished studies.

3.2. Description of studies and qualitative synthesis

Tables 1 and 2 summarize descriptive details from the included cohort and case control studies, respectively. All three of the cohort studies [7,24,25] included analyses that examined the risk of pancreatic cancer in ever smokeless tobacco users versus never smokeless tobacco users, regardless of smoking status. Boffetta [24] and Zheng [7] reported positive associations between smokeless tobacco use and pancreatic cancer ((RR 1.66, 1.06–2.62) and (RR 1.70, 0.90–3.10), respectively), while Luo [25] reported a (non-significant) negative association (RR 0.90, 0.70–1.20). Boffetta and Luo also conducted analyses that excluded smokers. In these analyses, Boffetta found a negative relationship between snus use and pancreatic cancer (RR 0.85, 0.24–3.07), while Luo found a positive association (RR 2.00, 1.20–3.30).

It is possible that the heterogeneity of these results can be attributed to differences in the designs of these studies, including the choice of comparison groups, populations studied, and methods for ascertainment of exposure and outcome. While participation in all three studies was restricted to males, the studies were situated in different locations and examined different populations: Boffetta [24] examined a cohort intended to be representative of the general adult Norwegian population, as well as a cohort of Norwegians with family members who had migrated to the United States; Zheng [7] examined White men in the United States who were life-insurance policy holders; and Luo [25] examined male Swedish construction workers. Boffetta and Zheng both assessed exposure status via questionnaires, whereas Luo assessed exposure via interviews with nurses. Boffetta and Luo examined snus

use, and Zheng did not specify the type of smokeless tobacco being examined. Boffetta and Luo assessed the outcome by tracking population and health registries, while Zheng tracked death certificates.

As with the cohort studies, the case control study findings were heterogeneous. Three of the seven case control studies provided effect measures with confidence intervals; smokers were excluded from these analyses [8,28,29]. Muscat [8] and Alguacil [28] found positive associations between smokeless tobacco use and pancreatic cancer ((OR 3.6, 1.0–12.8) and (AOR 1.4, 0.5–3.6), respectively), while Hassan [29] found negative associations (AOR for chewing tobacco: 0.7, 0.4–1.1; and AOR for snuff: 0.6, 0.3–1.1). All three studies were conducted in the United States, though in different regions of the country. Participants in the studies conducted by Muscat and Hassan were drawn from hospital samples (Hassan included healthy hospital visitors as controls), while Alguacil conducted a population-based study. Data in all three studies were collected directly from the individuals with pancreatic cancer.

The remaining case-control studies all found negative or no association between smokeless tobacco use and pancreatic cancer. However, these studies did not provide confidence intervals for their effect measures and, thus, the precision of their estimates is difficult to assess. Farrow [30] reported an OR of 0.8 and stated that the confidence interval included 1.0. Ghadirian [27] stated that use of chewing tobacco was “not associated with increased risk” of pancreatic cancer, but did not provide quantitative support for this conclusion. Falk [26] reported that use of smokeless tobacco products was not associated with excess risk of pancreatic cancer, but the authors did not provide an estimate of effect size. Williams [32] reported an OR of 0.31 for individuals with a lower level of smokeless tobacco use, and an OR of 0.26 for individuals with a greater level of tobacco use; however confidence intervals were not provided. All case-control studies were set in diverse regions within the United States with the exception of Ghadirian [27], which was set in Montreal, Canada. Data collection methods were heterogeneous: Farrow [30] collected data via surrogate interviews; Ghadirian [27] and Falk [26] used both direct and surrogate interviews to collect data; and Williams employed direct interviews. The study by Falk [26] was a hospital-based study, and the remaining studies were population-based.

In an additional study, Bertuccio [31] performed a pooled analysis to combine results from 11 case control studies that examined the odds of having pancreatic cancer among various tobacco exposure groups. Among the studies, smokeless tobacco use data was available for 6 of the included studies (of these, 1 study was not published and 3 did not include smokeless tobacco in their published reports). Bertuccio’s pooled analysis found no association between smokeless tobacco use and pancreatic cancer (OR 0.98, 0.75–1.3) in ever smokeless tobacco users compared with never tobacco users. The result was more suggestive of a negative association when the association was examined among smokeless tobacco-only users (i.e. excluding smokeless tobacco users who also smoked) (OR 0.62, 0.37–1.04).

3.3. Risk of bias assessment

The quality of the studies that met the inclusion criteria varied and, as a whole, the literature investigating the association between smokeless tobacco use and pancreatic adenocarcinoma appears to be vulnerable to a number of different types of bias.

Vulnerability to selection bias was apparent in several of the included studies. First, there was a high rate of attrition (23% of participants) in the cohort followed by Zheng [7]. However, a sensitivity analysis conducted by the authors did not suggest differential loss by cancer risk factors. Second, the representativeness of the study samples to the general population at risk of pancreatic cancer was questionable in several of the selected studies. For example, Zheng [7] examined the association between smokeless tobacco use and pancreatic cancer among White male life-insurance policy-holders who were over the age of 35 and Luo [25] examined data from male Swedish construction workers. In order to attempt to increase representativeness of our findings, we specifically included search terms that described smokeless tobacco products from multiple world regions and did not limit our inclusion criteria to studies published in English; however, all of the studies identified for this review were conducted in North America and Europe. As smokeless tobacco products and their carcinogenic effects may differ from country to country, the findings in this review cannot necessarily be generalized to regions beyond North America and Europe.

We found that four studies may have been vulnerable to information bias. Measurement error was likely in the papers by Zheng [7], Farrow [30], and Ghadirian [27] as these studies did not quantify amount of smokeless tobacco use. Zheng [7] did not specify what type of smokeless tobacco participants used, how frequently participants used smokeless tobacco, or for how long they had been using smokeless tobacco. Misclassification error was also possible due to the case ascertainment methods used. For example, Zheng [7] assessed pancreatic cancer via death certificates, which may have underestimated the effect of the association by excluding individuals who were diagnosed with pancreatic cancer but died of another cause. The study by Boffetta [24] does not appear to have assessed pancreatic cancer at baseline which may have resulted in misclassification of prevalent cases at the time of enrollment; however, the effect of any misclassification is likely to be non-differential and its magnitude reduced by the natural history of pancreatic adenocarcinoma (e.g. short life expectancy) and the long duration of follow-up (35 years) in this study.

Given the associations between smoking, alcohol, diabetes and pancreatic adenocarcinoma – as well as the associations between smoking and use of other forms of tobacco (including smokeless tobacco) – the possibility of confounding was a major concern and was identified in several included studies. Neither Boffetta [24] nor Luo [25] controlled for alcohol use, and the latter did not control for diabetes. All but one study adjusted for smoking, though the adjustment often did not account for intensity, duration, or timing of smoking and thus may not have fully accounted for smoking's confounding effects. To account for smoking, Alguacil [28] and Bertuccio [31] excluded smokers from the primary analysis, Luo [25], and Hassan [29] included subgroup analyses excluding smokers, and others adjusted for smoking intensity.

Two of the studies in this review were included in the analysis conducted by Bertuccio [31] which pooled data from 11 case-case control studies in order to calculate a summary odds ratio for the association between smokeless tobacco use and pancreatic cancer. We contacted the authors but were unable to obtain more information about the individual unpublished studies.

In addition to the risks of bias noted above, we also identified a number of other issues that may limit the inferences that can be drawn from the results of the included studies. First, the small number of exposed subjects in many of the studies limits their statistical power to confirm or exclude the possibility of a true underlying relationship between smokeless tobacco exposure and pancreatic adenocarcinoma. Since the methodologic and statistical heterogeneity (see below) of the included studies precluded a meta-analysis, we are limited to making inferences from results of the individual studies [19]. Second, several of the studies did not report measures of effect size, confidence intervals, or adequate information to calculate measures of effect size in their reports, therefore limiting the strength of the conclusions that can be drawn from existing studies. For example, the study by Farrow [30] stated that the adjusted odds ratio for ever users of chewing tobacco was 0.8; while noting that the confidence interval included 1.0, their paper does not report the confidence interval limits. Falk [26] and Ghadirian [27] did not provide effect measures and Ghadirian's report only mentions that "study groups for these variables were small." Similarly, the study by Williams [32] reports that three participants with pancreatic cancer were exposed to smokeless tobacco without providing an effect size for the association.

3.4. Assessment of heterogeneity and quantitative synthesis

Per standard practice [19], we assessed the heterogeneity of included studies with I^2 . The results of these tests demonstrated moderate to high heterogeneity between studies ($I^2 = 64.2\%$; where I^2 values of 50% to 90% indicate substantial heterogeneity [19].) As noted in the descriptions of individual studies above, there were also considerable sources of methodologic heterogeneity. Specific areas of concern included: use of different comparison groups, inconsistent controlling for smoking exposure, variable methods of assessing and classifying both the exposure and outcome, and study quality (e.g. small sample sizes). Thus, the studies were not considered appropriate for quantitative synthesis in a meta-analysis.

4. Discussion

Based on the studies included in this review, we found that the evidence for an association between smokeless tobacco use and pancreatic adenocarcinoma is inconclusive. In part, this finding stems from the quality of the included studies. As noted above, many of the included studies were found to be at risk for one or more types of bias, which potentially diminished the validity of their results. Additionally, the heterogeneity of the included studies precluded a quantitative synthesis of the results. Thus, we were not able to analyze the results in a way that may have produced a more definitive picture of the association between smokeless tobacco use and pancreatic adenocarcinoma.

While this inconclusive finding does not significantly differ from a 2008 review [18], our study differed methodologically from the previous study in ways that may enhance the scope and credibility of our conclusions. First, we searched five databases in order to identify studies, did not restrict our search to North America and Europe, and did not perform a meta-analysis of our results due to substantial between-study heterogeneity. The current review may also address inherent conflicts of interest that appear to have existed in a previous analysis, as two of the three authors were employed by a tobacco company at the time they wrote their manuscript [18]. Notably, the similarities between our findings and those of previous reviews underscores the need for more research to be conducted outside of North America and Europe; despite including a variety of databases and not limiting our search by geographic area, we did not find studies conducted out of these two regions. Conducting studies in a variety of countries is crucial for understanding how smokeless tobacco use may impact pancreatic adenocarcinoma, because the tobacco products differ by culture and country and modifying risk factors may be distributed differently by region.

The present study delineates specific gaps that may be addressed by future research attempting to investigate the association between smokeless tobacco use and pancreatic adenocarcinoma. Future studies would benefit from more detailed assessments of smokeless tobacco exposure frequency, intensity, and timing in relationship to pancreatic adenocarcinoma diagnosis and from adjusting for smoking status, given its strong confounding effect in the relationship between smokeless tobacco use and pancreatic adenocarcinoma. Understanding the health effects of smokeless tobacco will help determine how it should be regulated, and how governments should respond to the increase in smokeless tobacco use.

5. Conclusions

The results of available studies reviewed in this paper suggest that the association between smokeless tobacco use and pancreatic adenocarcinoma is inconclusive. The heterogeneity and quality of included studies limited our ability to draw a conclusion regarding the direction of an association between the exposure and outcome, if one exists. All of the included studies originated from North America and European countries, and, as such, our findings may not be generalizable to populations in other regions where patterns of use and product formulations vary. Studies were heterogeneous in their assessment of exposure intensity and their ascertainment of outcomes. The generalizability of these results is also limited by the analysis of population subgroups; for example, multiple studies included only males or only a subgroup of males (e.g. based on occupational status). More definitive conclusions about the relationship between smokeless tobacco use and pancreatic adenocarcinoma await the results of more methodologically rigorous epidemiologic studies.

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Fig. 1.
Flowchart illustrating study selection process.

Table 1

Study characteristics—cohort studies.

Author (y)	Country	Study population	Sample size	Sex	Baseline assessment (y)	Follow-up (end year)	Exposure ascertainment	Smokeless tobacco type	Smokeless tobacco measure	Outcome	Adjusted for	Relative risk (CI)	Loss to follow-up (%)
Boffetta et al. [24]	Norway	General adult Norwegian population, and relatives of Norwegian migrants to the USA	10,136	M	1964	2001	Questionnaire	Snus	Regular current/regular former/never or occasional use	Incident pancreatic cancer	Age, amount of tobacco smoking	1.67 (1.12–2.50)	0.15%
Zheng et al. [7]	USA	Life-insurance policy holders of the Lutheran Brotherhood Insurance Society	17,633	M	1966	1986	Questionnaire	(Not specified)	Ever use	Cause-specific mortality	Age, alcohol, smoking	1.7 (0.9–3.1)	23.0%
Luo et al. [25]	Sweden	Swedish construction worker cohort	279,897	M	1978–1992	2004	Interview	Snus	Never/previous/current use; <10 or >= 10 g per day	Incident pancreatic cancer	Age, BMI, smoking	Entire cohort: 0.9 (0.7–1.2) Excluding smokers: 2.0 (1.2–3.3)	0.0%

Abbreviations: CI = confidence interval; M = male; F = female; BMI = body mass index.

Table 2

Study characteristics—case-control studies.

Author (y)	Country	Cases/ controls	Sex	Years	Case definition	Control selection	Matching	ST type	ST measure	Data collection method	Adjusted for	Adjusted OR (CI)	Response rate (%) for cases/ controls
Falk et al. [26]	USA	363/1234	M/F	1979–1983	Histopathology (84%), radiology (16%)	Hospital	Race, sex, age (±5 years)	S,C	Not described	Cases: 50% proxy, <50% direct. Controls: 13% proxy, 87% direct	Not described	“No excess risk”	86%/87%
Farrow and Davis [30]	USA	148/188	M	1982–1986	Histopathology (46%); medical records (54%)	Population based	Frequency matched: age (±5 years)	C	Not described	Cases & controls: 100% proxy	Race, education	0.8 (CI: N/A; non- significant)	77%/71%
Ghadirian et al. [27]	Canada	179/239	M/F	1984–1988	Histopathology (83%), clinical or radiology (17%)	Population based	Sex, area of residence, age (±5 years)	C	Not described	Cases: 75% proxy, 25% direct Controls: 17% proxy, 83% direct	Age, sex, smoking, education, data source (proxy)	“Not associated with increased risk”	60%/NA
Muscat et al. [8]	USA	290/572	M/F	1985–1993	Histopathology (100%)	Hospital	Sex, age (±5 years), race, hospital, year	S,C	Current, never, former	Cases and controls: 100% direct	Not Described	3.6 (1.0–12.8)	51%/63%
Alguacil and Silverman [28]	USA	154/844	M/F	1986–1989	Histopathology (85%); other (chart review for clinical or radiologic evidence: 15%)	Population based	Frequency matched: sex, age, race	S,C	Ounces/wk, years used	Not described	Age, sex, race, cigar, smoking, site	0.7 (0.4–1.1)	46%/78%
Hassan et al. [29]	USA	808/808	M/F	2000–2006	Histopathology (100%)	Hospital visitors	Frequency matched: age (±5 years), race, sex, city	S,C	Low (20 time-years); high (>20 time-years)	Cases and controls: 100% direct	Age, sex, race, smoking, diabetes, alcohol, education, area of residency, marital status	Chewing tobacco: 0.7 (0.4–1.1); Snuff: 0.6 (0.3–1.1)	NA/NA
Bertuccio et al. [31] [/]	USA, Canada, Netherlands, Poland, Australia	1404/3014	M/F	1983–1989; 2000–2009	Histopathology, clinical, or radiology (%’s NA)	Clinic, hospital, population- based, hospital visitors	Unmatched analysis	S,C	Ever, never	Direct and proxy (%’s NA)	Center, race, sex, age, education, diabetes, BMI, alcohol	0.98 (0.75–1.27)	46–93%/27– 84% (NA for 1 included study)

Abbreviations: NA = not available, ST = smokeless tobacco, OR = odds ratio, CI = confidence interval, M = male, F = female, S = snuff, C = chewing, U = unspecified, time-years = frequency of daily intake multiplied by duration of exposure (in years).

[/] Pooled analysis of 6 studies, includes data from 2 other studies included in Table 2: Alguacil and Silverman [28] and Hassan et al. [29].