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Review

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.
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.

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

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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, co-morbidities, 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