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Tobacco Smoking and Oral Cancer: A Meta-Analysis.

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Abstract

Background: Several epidemiological studies suggest that tobacco smoking increases the risk of oral cancer. No systematic review, however, has been reported to examine how consistent the evidence is across the studies. We undertook a meta-analysis of epidemiological studies investigating the magnitude relationship between tobacco smoking and oral cancer.

Methods: Primary studies were identified through a computerized literature search of Medline. Articles abstracted were all epidemiological studies published as original articles in English during 1990-2007 provided the summary estimates of odds ratios (OR) of tobacco smoking for oral cancer compared to that of non-smokers. A total of 15 case-control studies were used for this meta-analysis. Summary of OR was calculated based on random effects model.

Result: The combined odds ratio for tobacco smoking related to oral cancer was 4.65 (95%CI, 3.19-6.77). Also, the highest combined odds ratio was belong to America continents (OR= 7.65; 95%CI, 5.11-11.45) and the lowest was in Asia (OR= 1.88; 95%CI, 0.95-3.71). There was heterogeneity in the pooled OR estimate across the studies.

Conclusion: Our results clearly indicate that tobacco smokers are at increased risk of oral cancer. The cancer risk can be reduced by controlling of tobacco smoking in different countries.

Keywords: *Mouth neoplasm, Meta analysis, Tobacco, Smoking, Iran*

Introduction

It is estimated that one in three people will develop cancer at some stage in their lives and that one in four will die from the disease. Smoking is currently responsible for a third of all cancer deaths in many western countries. It has been estimated that every other smoker will be killed by tobacco (1). Tobacco smoke play a role in the etiology of cancer of oral cavity (2, 3). Other risk factors shown or suggested for oral cancer include chewing of tobacco alone or mixtures. The primary risk factor for oral cancer is the use of tobacco in all forms. Smoking cigarettes, pipes and cigars are risk factors for all cancers associated with the larynx, oral cavity and esophagus. Over 90% of patients with oral cancer use tobacco by either smoking or chewing it. Smokers are six times more likely than nonsmokers to develop oral cancer (4, 5).

In some countries, the relation between tobacco smoking and oral cancer is investigated in the lost decades. Tobacco habits in India are unique and vary in different regions (6). In total, 4400 new cases of oral cancer were recorded in India in 2001(7). In Cuba, 82% of oral cancer cases were attributable to tobacco smoking (8). In Uruguay, smoking black tobacco cigarettes appears to be an important habit in oral and pharyngeal carcinogenesis (2). Tobacco smoking was found to be the major risk factor for oral cancer in South Africa (9).

An estimated 30,990 new cases of oral cancer are expected to be diagnosed in the U.S.

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in 2006, and approximately 7,430 people will die of the disease (10). Finally, oral cancer ranks as the seventh most common of cancer worldwide and is responsible for >400000 new cases of cancer and 210000 deaths worldwide (11).

The main purpose and the strength of our study is the meta-analysis design, to obtain a better understanding of the relation between tobacco smoking and oral cancer, using the increased power of the combined selected studies. To the best of our knowledge, this issue has not been investigated in any previous epidemiological study on cancer of oral cavity. A proven association between the risk of oral cancer and tobacco smoking would have considerable public health and prevention implication.

Materials and Methods

We sought to identify all epidemiologic studies that investigated the association between tobacco smokers and oral cancer. To identify relevant studies, we conducted a comprehensive systematic bibliographic search through MEDLINE for all medical literature published during 1990-2007. The search was performed by consecutively entering "oral cancer" in title, "tobacco smoking", and "case control" in text words. Finally, we supplemented this search by reviewing the reference lists of all retrieved publications and the most recent review articles to identify additional undetected published studies. Two investigators independently reviewed all potentially relevant articles to determine whether an article met the general inclusion criteria, and disagreement was resolved by discussion between the investigators. Studies were included in the meta-analysis if they met all of the following criteria: 1) had original data from case-control studies; 2) the primary outcome was clearly defined as at least some of the cancers of the mouth, tongue, lips, gums and cheeks; 3) provided Odds Ratio (OR) estimates and their 95% CI or sufficient data to calculate these numbers; 4) were English language studies; and 5) were published up to July 2007. If a study appeared in more than one article, data from the most recent publication were used for the statistical analysis.

The investigators discussed their evaluation; discrepancies were resolved through discussion and rereading.

All data from the studies were independently reviewed and extracted with a standardized data-collection form by 2 investigators. Differences between reviewers were resolved by discussion and, when necessary, through consultation. The following characteristics were recorded from each study: 1) the first author's name, year of publication, and country of the population; 2) the study design; 3) the classification used for the disease; 4) the number of the subjects; 5) any confounding factors for matching or adjustment; 6) the methods used for collection of data on exposure; and 7) the odds ratio (OR) of oral cancer associated with tobacco smoking and the corresponding 95% CI in each subgroup. For this meta-analysis we selected all case control studies on the relationship between tobacco smoking and the incidence, mortality, or prevalence of oral cancer. Furthermore, a retrospective assessment of the tobacco smoking was feasible because oral cancer is not immediately fatal. For the published results of each of the selected studies, data were extracted to permit the calculation of adjusted ORs with 95% CIs to estimate the association between tobacco smokers and the risk of oral cancer.

Potential sources of heterogeneity between the studies were examined by using the method developed by DerSimonian and Laird (12), which calculates the between-study variation based on the Q statistic. We considered that there was statistically significant heterogeneity when the P value between the results of the included studies was below 0.5. In cases with heterogeneity, we applied random-effects models as opposed to fixed-effect models because the former include both within-study sampling error (variance) and between-study variation in the assessment of the

uncertainty (95% CI) of the results of a meta-analysis.
Data analyses were performed with NCSS and PASS 2000 Released December 2005.

Results

We identified a total of 41 potentially relevant studies that described the association between the cigarette smoking and oral cancer, but after obtaining and reading the articles, our predetermined inclusion criteria were met by only 15 studies, which were then included in the meta-analysis (2, 3, 8, 13-20). A list of the excluded papers is available from the authors. Articles were excluded from the analyses for any one of the following reasons: 1) the article was a review paper; 2) the results from the same subjects had already been partially or completely published in another included article; 3) the article was a survey study; 4) the article had insufficient published data for determining an estimator of OR and a 95% confidence interval; 5) the data on oral cancer were mixed with that of other cancers.

The summary characteristics of all studies included in the meta-analysis are described in Table 1. The sample size of the 15 included studies varied between 67 and 630 for the case subjects and between 67 and 1456 for the control subjects. Most of the study populations involved Americas (n= 8), 3 studies were conducted in the Africa, 2 studies in Europe and 2 were conducted in Asia.
When all the extracted data were pooled, 2533 subjects and 4306 controls were eligible for analysis. The meta-analysis data that explored the effect of smoking on the risk of oral cancer based on different continents is shown in Fig. 1. Table 2 shows the odds ratio and homogeneity test for oral cancer risk related to oral cancer in different continents. According to the Table, the highest odds ratio is belong to America continents (OR= 7.65; 95% CI, 5.11-11.45) and the lowest is in Asia (OR= 1.88; 95% CI, 0.95-3.71). The Table shows, the combined odds ratio for tobacco smoking related to oral cancer is 4.65(95% CI, 3.19-6.77). Also, this Table shows the results of the homogeneity test. This test shows that using random effect model is appropriate.

Table 1: Characteristic of case-control studies of tobacco smoking on oral cancer from published studies

Study	Country	Sex	OR (95% CI)	Type of smoking	Study characteristics	Level of smoking	Confounding Variables considered
Thomas SJ, 2007	New Guinea	Male and Female	2.63(1.32, 5.22)	Tobacco smoking	Population based control	Daily smokers	Betel quid chewing, Sex, Age, Alcohol
Thomas SJ, 2007	New Guinea	Male and Female	4.63(1.32, 5.22)	Tobacco smoking	Population based control	Heavy smokers	Betel quid chewing, Sex, Age, Alcohol
Chandran R, 2005	South Africa	Male and Female	4.63(1.74, 12.30)	Tobacco smoking	Hospital based control	Smokers	Sex, Age, Ethnicity, Drinkers
Xie H, 2004	Puetro Rico	Male and Female	9.5(3.0, 30.0)	Tobacco smoking	Population based control	Heavy smokers	GSTM1-present genotype, Sex, Age, Alcohol
Xie H, 2004	Puetro Rico	Male and Female	1.8(0.6, 5.2)	Tobacco smoking	Population based control	Heavy smokers	GSTM1-null genotype, Sex, Age, Alcohol
Shiu MN, 2004	Taiwan	Male and Female	1.36(0.69, 2.68)	Tobacco smoking	Hospital based control	Smokers	Alcohol, Betel quid, Sex, Age
Lieweiiyn CD, 2004	England	Male and Female	2.1(1.1, 4.0)	Tobacco smoking	Population based control	More than 21 year smoking	Alcohol, Age, Sex, Area of residence
De Stefani E, 1998	Uruguay	Male and Female	12.1(7.6, 19.4)	Black tobacco	Hospital based control	Black tobacco	Sex, Age, Residence, Education, Alcohol
De Stefani E, 1998	Uruguay	Male and Female	8.7(5.6, 13.4)	Hand rolled cigarettes	Hospital based control	Hand rolled cigarettes	Sex, Age, Residence, Education, Alcohol

Table 1: Continued: ….

Zheng T, 1997	China	Male and Female	2.73(1.26, 5.91)	Tobacco smoking	Population based control	Smokers	Sex, Age, Alcohol
Jaber MA, 1999	UK	Male and Female	4.38(2.6, 7.2)	Tobacco smoking	Hospital based control	More than 20 cigarettes per day	Sex, Age, Ethnicity, Alcohol
Garrote LF, 2001	Cuba	Male and Female	20.8(8.9, 48.3)	Cigarette smoking	Hospital based control	More than 30 cigarettes per day	Sex, Age, Residence, Education, Alcohol
Zheng Z, 2001	USA	Male and Female	6.1(1.5, 25.0)	Cigarette smoking	Hospital based control	Heavy smokers	Sex, Age, Race, Alcohol
Zheng Z, 2001	USA	Male and Female	3.7(1.1, 12.0)	Cigarette smoking	Hospital based control	Light smokers	Sex, Age, Race, Alcohol
Vecchia CL, 1999	USA	Male and Female	6.18(4.62, 8.26)	Cigarette smoking	Population based control	Smokers	Sex, Age, Education, Alcohol

Table 2: Odds ratio and homogeneity test of tobacco smoking related to oral cancer in different continents

Continent	**OR and 95% CI**			**Homogeneity Test**		
	OR	**Lower**	**Upper**	**Cochran's Q**	**df**	***P***
Africa	3.62	2.40	5.48	1.76	2	0.410
America	7.65	5.11	11.45	23.69	7	0.002
Asia	1.88	0.95	3.71	2.53	1	0.112
Europe	3.12	1.52	6.40	4.38	1	0.037
Combined	4.65	3.19	6.77	86.75	14	<0.001

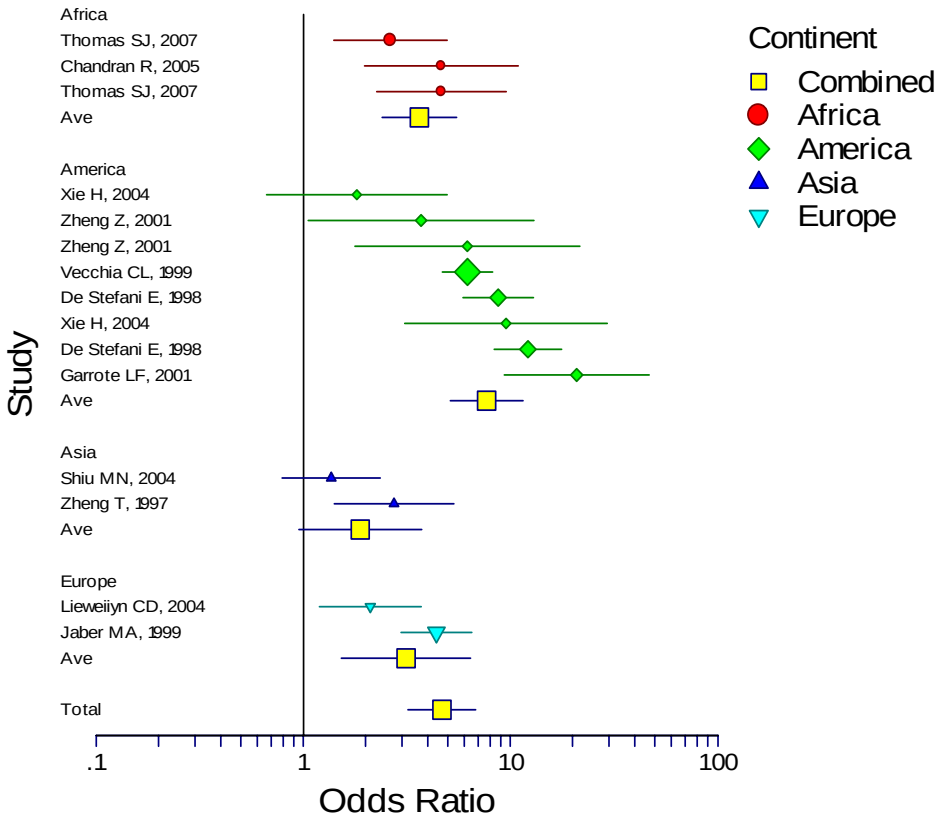

Fig. 1: The meta-analysis data exploring the effect of smoking on the risk of oral cancer based on different continents

Discussion

We investigated the association between smoking and the risk of oral cancer through a meta-analysis of existing epidemiologic studies. Meta-analysis is a statistical analysis that combines or integrates the results of several studies to provide increased power for the combined studies (21). This meta-analysis was performed on fifteen case control studies. The strengths of the present meta-analysis include the acceptable methodological quality of the studies on which the analysis is based, as well as the considerable number of studies and subjects include.

In this study we had both hospital- based and population-based control data, and this can reduce a main limitation of the study.

Our analysis was performed with a homogeneity test and random effect model to recognize an appropriate model for interpretation of oral cancer risk related to tobacco smoking in different areas. So, this report has indicated continent-specific risk estimates for smoking and oral cancer. Selected case-control studies for this meta-analysis have been conducted in USA, New Guinea, South Africa, Puerto Rico, Taiwan, England, Uruguay, China and Cuba, which included information on tobacco smoking and oral cancer. Finding of this meta-analysis showed a significant difference of risk between the continents. The value of the current meta-analysis compensates for the individual lack of precision in most of the studies, a problem that was alleviated by pooling the data of all the studies. The major finding of the present meta-analysis provides support for the observation that smoking plays an important role as a risk factor for development of oral cancer.

Our study provided a unique opportunity for the mentioned purpose, because we performed a meta-analysis that aimed to use all relevant published literature from observational studies to arrive at a quantitative conclusion about the risk of oral cancer related to tobacco smoking and the countries which the relevant studies are performed.

In summary, the evidence from the published studies and finding of this meta-analysis lends support that tobacco smoking play a strong role in the etiology of oral cancer, and oral cancer risk can be reduced by controlling of tobacco smoking in different countries.

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