

Mouthrinses containing alcohol and oral cancer. Revision of epidemiological studies

Colutorios que contienen alcohol y cáncer bucal. Revisión de estudios epidemiológicos

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Abstract: The strong association between alcohol usage and the development of oral cancer (OC) has been reported in numerous papers. As some mouthrinses contain significant amounts of ethanol, a possible relationship to this pathology has been considered. The purpose of the present paper is to analyze several epidemiological studies which evaluated the association between commercial mouthrinses and the etiology of OC. Although some authors report an association, most of the studies are unclear and sometimes contradictory. The controversial aspects regarding the role of alcohol in OC may also make difficult to find a clear relationship between the use of mouthrinses containing alcohol and OC.

Descriptors: Mouthwashes; Oral cancer; Acetaldehyde; Alcoholic beverages.

Resumen: Existen numerosas publicaciones que informan una fuerte asociación entre el consumo de alcohol y el desarrollo del cáncer oral (CO). Debido a que algunos colutorios contienen cantidades significativas de etanol se ha considerado una posible relación entre su uso y esta patología. El propósito del presente trabajo es analizar algunos estudios epidemiológicos en los cuales se evaluó la posibilidad de que los colutorios comerciales puedan estar involucrados en la etiología del CO. Aunque algunos autores informan asociación, la mayoría de los estudios son poco claros y algunas veces contradictorios. Los aspectos controversiales respecto al papel del alcohol en el CO, dificultan el hallazgo de una relación directa entre el uso de los colutorios que contienen alcohol y el CO.

Descriptorios: Antisépticos Bucales; Cáncer oral; Acetaldehído; Bebidas alcohólicas.

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Introduction

Oral cancer (OC) is a serious public health problem that causes morbidity and mortality, with no major prognostic improvement observed in decades. There is high variability in the Oral and Pharyngeal cancer (OPC) incidence and mortality rates in different regions of the world. The incidence of OPC in men is higher in the Rhine basin area in France, in the south of India where this is the most frequent form of cancer, and in some east and central European areas.^{11,32} In women the highest incidence rate was registered in India. In Latin America and the Caribbean intermediate incidence rates have been reported, but this pattern is not homogeneous.³⁸ The lowest OC incidence rates in males are observed in Chile, Ecuador, Colombia, Venezuela, and Mexico, and the highest rates, in Puerto Rico, some areas of Brazil, Uruguay and northeast of Argentina.^{9,32} There is a lack of information about the incidence trend, but temporal series available from Sao Paulo city (Brazil) and Córdoba city (Argentina) revealed increasing trends, especially in females.^{5,30,53}

It is known that both tobacco and excessive alcohol use increase the risk of developing upper aero-digestive tract cancer in humans.^{10,21,27,33} The rising trends in OC mortality, and OC occurrence in the absence of tobacco and alcohol use^{4,48} led scientists to consider other potential risk factors like oral cavity infections and diseases, sores caused by dentures,^{22,43} deficient oral hygiene,^{21,25,27,36,42,56} poor dental status,^{18,21,25,56} dental trauma,³⁶ dietary deficiencies and low levels of nutrients present in serum such as carotenoids,^{21,27} and also the possible intervention of some viruses as the papillomavirus,⁵² herpes virus hominis and Epstein-Barr virus in the etiology of OPC.^{29,37,55} Because most commercial mouthrinses contain significant amounts of ethanol, and because mouthrinses are used by a large proportion of the adult population, some authors have also considered their possible relationship to OC. Alcohol is used in mouthrinses as a solvent of the active principles and as an antiseptic and active preservative up to 12 percent.⁴¹

The aim of this paper was to analyze the epidemiological evidence concerning the association be-

tween commercial mouthrinses containing alcohol and OPC.

Overview of epidemiologic studies

Eight studies were analyzed between 1979 and 2001 and the main aspects are summarized in Table 1.

Weaver *et al.*⁴⁷ (1979) reported a case-control study composed of 200 patients with OPC and 50 general surgical patients serving as controls. They reported that among 11 non-smokers and non-drinkers, 10 had used mouthrinses twice a day for more than 20 years. In this case, significant excess risk was found for mouthrinse use ($p < 0.001$). The majority of the mouthrinses contained 25% of alcohol and 8 of them used the same trademark. Such relationship was not evident when patients with cancer who used tobacco and alcohol were included in the comparison. The authors pointed out two limitations: the small sample size and the lack of comparability between cases and controls.

Blot *et al.*² (1983) published a case-control study based on a five-minute telephone interview involving 206 women with OPC and 352 controls, who were asked about the patterns of mouthrinse use. No significant overall increase in risk was found among users. The relative risk adjustment for snuff-dipping and smoking habits was 1.15 (95% CI 0.8, 1.7); this relative risk associated with mouthrinse use increased to 1.94 (95% CI 0.8, 4.7), however, among women abstaining from tobacco. Consistent dose-responses were not observed for this subgroup. The alcohol content of the product used was unknown, as were the reasons for mouthrinse use.

Wynder *et al.*⁵⁴ (1983) reported a hospital-based investigation of 568 controls and 571 patients with OPC. The frequency of mouthrinse use was separated in different categories depending on the duration of the use in years. The study results were negative for the association between daily mouthrinse use and OPC among men. In women (157 cases and 157 controls) the crude data indicated moderate association (RR of 2.8); but no dose-response relationship with increased duration of use was observed in non-smoking, non-drinking women as well. Multiple

Table 1 - Epidemiological studies concerning the association between mouthrinses containing alcohol and oral cancer.

Publication	Study	Characteristics and limitations of the study	Mouthwash alcohol content	Conclusions
Weaver <i>et al.</i> ⁴⁷ (1979)	<ul style="list-style-type: none"> • Case/control • 200/50 (11/10) 	<ul style="list-style-type: none"> • Small sample. • Lack of comparability between cases and controls. 	Considered	<ul style="list-style-type: none"> • Significant excess risk only in non-smokers and non-drinkers.
Blot <i>et al.</i> ² (1983)	<ul style="list-style-type: none"> • Women • Telephone interview • Case*/control • 206/352 	<ul style="list-style-type: none"> • No consistent dose-response relationship. 	Unknown	<ul style="list-style-type: none"> • No association. • Slightly increased risk in non-smokers.
Wynder <i>et al.</i> ⁵⁴ (1983)	<ul style="list-style-type: none"> • Hospital-based investigation • Case*/control • 571/568 (157/157 women) 	<ul style="list-style-type: none"> • Lack of comparability between cases and controls. • No dose-response relationship in non-smoker and non-drinker women. • Possibility of confounding by tobacco and alcohol use considering the underreporting bias. 	Not reported	<ul style="list-style-type: none"> • No association among men. • Doubtful moderate association in women.
Mashberg <i>et al.</i> ²⁸ (1985)	<ul style="list-style-type: none"> • Veterans Hospital-based • Case*/control • 95/913 males at risk 	<ul style="list-style-type: none"> • Tobacco and alcohol consumption was considered. 	Considered	Inverse association between mouthwash use and OPC, regardless of the amount of alcohol consumption.
Young <i>et al.</i> ⁴⁵ (1986)	<ul style="list-style-type: none"> • Multi-hospital-based • Case*/control • 317/306 	<ul style="list-style-type: none"> • Neither tobacco nor alcohol consumption was controlled. 	Not reported	No association.
Kabat <i>et al.</i> ¹⁸ (1989)	<ul style="list-style-type: none"> • Multi-hospital-based • Case*/control • 125/107 women 	<ul style="list-style-type: none"> • Frequency, duration of use, dilution or rinsing practices were considered. 	Not reported	No association.
Winn <i>et al.</i> ⁵⁰ (1991)	<ul style="list-style-type: none"> • General population • Case*/control • 866/1,249 	<ul style="list-style-type: none"> • Adjusted by tobacco and alcohol consumption. • Increased risk related to duration and frequency of mouthrinse use. 	Considered	Increased risk, 40% in male and 60% in female.
Winn <i>et al.</i> ⁵¹ (2001)	<ul style="list-style-type: none"> • General population • Case/control • 342/521 	<ul style="list-style-type: none"> • Unable to evaluate the accuracy of reporting of tobacco, alcohol or mouthrinse use. • No evidence of a dose-response effect for any of several measures of mouthrinse use. 	Considered	No association

*Include lips, hypopharynx, larynx and salivary glands.

logistic regression including all factors of interest showed inconsistent results for duration and frequency of mouthrinse use. The authors concluded that “due to the absence of a dose-response relationship and the possibility of confounding by tobacco and alcohol use, and considering the underreporting bias on alcohol in women, it was not possible to attribute causal significance to the association between daily mouthrinse use and OC in women”.

Mashberg *et al.*²⁸ (1985) included 95 cases and 913 controls as a part of a large case-control study on a male veteran population at risk (drinking and smoking) for OPC, which provided complete histo-

ries in a questionnaire that included data on mouthrinse use. They considered the mouthrinses’ alcohol content. The authors found no significant differences in the frequency of mouthrinse use in cancer cases *versus* controls. When a logistic regression analysis was performed to simultaneously remove the effects of age, or smoking and drinking habits, OPC did not appear related to mouthrinse use.

Young *et al.*⁴⁵ (1986) described a multi-hospital-based case-control study of 317 OPC cases and 306 control subjects who had a cancer of head and neck “not thought to be related to tobacco use” or cancer of the larynx. The results of this study were clearly

negative but there were limitations related with the study design; for example, the study finds negative incidence for mouthrinse use despite the fact that neither smoking nor drinking were controlled.

Kabat *et al.*¹⁸ (1989), in a multi-hospital-based investigation, obtained interviews from 125 women with OC and 107 female controls. The authors found no association between mouthrinse use and OC in terms of frequency, duration of use, dilution or rinsing practices; no information was available regarding the alcohol content of the product used. The relationship between OC and mouthrinse use could not be established because women used mouthrinses to disguise breath odors of tobacco or alcohol.

Winn *et al.*⁵⁰ (1991) reported interviews with 866 OPC patients and 1,249 controls of similar age and gender from the general population in four areas of the United States. This study revealed increased risks of OPC associated with the regular use of mouthrinses by 40% among male and 60% among female mouthrinse users after adjusting for tobacco and alcohol consumption. Risks in both sexes generally increased in proportion to duration and frequency of mouthrinse use. The increased risks were confined to users of mouthrinses high in alcohol content, consistent with the elevated risks associated with drinking alcoholic beverages.

Ten years later, the same authors⁵¹ performed a similar analysis with 342 cases of OPC registered in Puerto Rico and 521 population-based controls. They found that one fourth of the cases of OC in men and half of the cases in women were not related to tobacco or alcohol. An elevated but non-significant risk was observed in non-smokers/non-drinkers, among whom an effect of alcohol-containing mouthrinses would be most likely evident. This study appears to have been generally well conducted, but the authors acknowledge that they were unable to “evaluate the accuracy of the reporting of tobacco, alcohol or mouthrinse use”. There was no evidence of a dose-response effect for any of several measures of mouthrinse use. They concluded that there was no overall increased risk of OC associated with mouthrinse use.

White lesions, associated to misuse or long-term use of alcohol-containing mouthrinses, have been

observed in human oral mucosa and in laboratory animals.^{1,31} Nevertheless the validity of these reports is doubtful, considering that, in the first case³¹, the authors reported the effects of undiluted mouthrinses containing 70% of alcohol and, in the second study, Bernstein *et al.*¹ (1979) performed the experiment applying buccal cheek pouches to hamsters during 45 minutes daily for 41 days. All these studies are controversial and more investigation is necessary.

Possible role of alcohol in oral carcinogenesis

The above information does not support a straightforward relationship between alcohol-containing mouthrinses and OC, although a strong association between alcohol and tobacco use and the development of OC has been reported in numerous papers. These results agree with the studies of Carretero-Peláez *et al.*⁵ (2004), Elmore *et al.*⁸ (1995) and Cole *et al.*⁶ (2003). In a review⁴⁹, Wight, Ogden (1998) reported that in most studies alcohol is considered as an independent factor in increasing the risk of oral carcinogenesis.⁴⁹ Nevertheless these authors reported in that paper many controversial aspects regarding the possible role and the action mechanism of alcohol. There is also high controversy due to the type of alcohol consumed. Differences in the fermentation, distillation and maturation processes may also result in specific impurities or contaminants in the alcoholic beverage which can also be carcinogenic themselves including acetaldehyde, nitrosamines,^{39,46} aflatoxines, ethyl carbamate (urethane), asbestos and arsenic compounds.¹⁷ Nevertheless, according to the literature and considering also some studies in animals, it seems that the total amount of alcohol¹⁹ and the duration of alcohol consumption²⁰ are more important factors than the type or constitution of the beverage consumed. On the other hand, Huang *et al.*¹⁶ (2003) found that heavy consumers of liquor had strongly increased the risk of OC in a case-control population-based study, suggesting that alcohol concentration is a risk factor for OC independently of the total amount consumed. Studies have been carried out in Western France (where there is a high inci-

dence of OPC) to look at various constituents of alcoholic beverages produced in this area. Loquet *et al.*²³ (1981) found that many constituents of the alcoholic beverages in this region are mutagenic. However, animal studies have shown no increase in esophageal cancer in rats treated with these locally produced beverages.²⁶

The alcohol metabolism in the organism also should be considered to understand its possible role in oral carcinogenesis. Ethanol and water are the main components of alcoholic beverages. Ethanol is mainly metabolized in the liver through the following steps: oxidation to acetaldehyde via the enzyme alcohol dehydrogenase (ADH); conversion to acetate by the aldehyde dehydrogenase (ALDH); and oxidation to carbon dioxide, water and fatty acids. Extra-hepatic metabolism in oral, gastric and esophageal mucosa has also been reported and, interestingly, the activity of ALDH in oral mucosa is less than the activity of ADH, which could allow the accumulation of acetaldehyde in oral tissues;⁷ the concentration of this substance is influenced by the different genotypes of ADH and ALDH.^{12,44} Oral physiological microflora may also lead to an increase in salivary acetaldehyde production from ethanol in patients with poor dental status.¹⁴ Experimental work has shown that acetaldehyde is highly toxic, mutagenic and carcinogenic while pure ethanol is not carcinogenic itself and could be considered more as a co-carcinogen rather than a tumor initiator. To this extent, different studies support the observation that alcohol may increase the penetration of carcinogens in the oral mucosa. Howie *et al.*¹⁵ (2001) suggest that short-term exposure to ethanol may act as a permeability enhancer, possibly by molecular rearrangement of the permeability barrier instead of the result of lipid extraction. Nevertheless it seems that more *in vitro* and animal studies are necessary to investigate these possible roles of alcohol in carcinogenesis. Experimental work has also been performed to study the morphological changes in the oral mucosa. Epithelial atrophy of esophageal mucosa after prolonged exposure to ethanol was found. It was due to a decrease in cellular size, with a statistically signifi-

cant reduction in mean cytoplasmic area and mean nuclear area^{34,35} and not to a decrease in the number of cellular layers;^{3,25,35} other authors observed different degrees of cellular damage depending on alcohol concentration.³⁴ In the long-term exposure, they found dysplastic changes with keratosis and increasing density of basal cell layer.^{3,24,34}

Final considerations

Ethanol has a carcinogenic effect mainly caused by its metabolite acetaldehyde.^{12,44} The high long-lasting levels of this substance microbiologically produced in saliva of alcohol consuming subjects could be a biological explanation for the epidemiological findings.¹³ On the other hand, if the mouthrinses contain high concentrations of alcohol, they contribute to decrease the amount of oral bacteria and consequently the concentration of acetaldehyde in the oral cavity. These authors¹³ reported that *in vivo* acetaldehyde production is significantly reduced after 3-days use of an antiseptic mouthrinse (chlorhexidine).

In many cases, mouthrinses are used to disguise alcohol or tobacco smell and also to disguise breath odors due to mouth infections or dental problems,¹⁸ which are risk factors themselves. No cause-effect relationship can be suspected unless the use of mouthrinses precedes, rather than follows, the earliest manifestations of the OC, which is not easy to identify. Many experimental results indicate that antiseptic mouthrinses significantly reduce the production of acetaldehyde; it is therefore unlikely that the use of these mouthrinses increases the risk of developing OPC, and further studies are necessary. All the above mentioned controversial aspects make difficult to find a clear relationship between alcohol-containing mouthrinses and OC. In addition, few of the studies adhere to basic methodologic principles of case-control design.⁸ In the future, it would be necessary at least to homogenize the samples in order to obtain conclusive results.⁴⁰

In conclusion, up to now it has not been possible to establish a causal relationship between the use of alcohol-containing mouthrinses and the development of OC.

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