

Alcohol-containing Mouthwash and Oral Cancer Risk: A Systematic Review

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ABSTRACT

Aim: The aim of this article is to assess any possible risk of oral cancer with increased usage of alcohol-based mouthwashes and to provide relevant information regarding the safety of using alcohol-containing mouth rinses. **Materials and Methods:** Several controversial studies regarding the prolonged use of such mouthwashes containing >25% alcohol causes oral cancers, have been reviewed and undertaken. Analyzing the number of studies done till date, it showed debatable views on the use of alcohol-containing mouthwashes and its relation with causing oral cancers. Many studies supported the use of alcohol-based mouthwashes can cause oral cancer, while few studies showed no significant relation of mouthwashes with oral cancers. **Conclusion:** To conclude, the relation between mouthwashes containing alcohol and oral cancers is still a contentious issue in the scientific community. On comparing the available reviews, it proved that prolonged use of alcohol-based mouthwashes might cause oral cancers. Thus, it's advisable for the clinicians to educate patients about the ill-effects of long-term use of alcohol-based mouthwashes and to minimize the number of times it's used per day. And to prefer the use of nonalcohol-based mouthwashes instead of the former.

Key words: Alcohol, mouthwash, oral cancer, tobacco smoking

INTRODUCTION

The oral cavity is a home to various kinds of indigenous microorganisms and is related to various health issues in humans. It is very difficult to maintain complete oral hygiene due to lack of time, stress, endogenous nutritional diet, etc. Instead, there are different methods that can be helpful to minimize the ailments related to oral hygiene like caries, periodontal problems, etc. Nowadays maintaining good oral health has become an integral part of our daily lives. Many awareness programs by oral health care providers have educated people that poor oral hygiene can become an underlying cause for many health issues.

The prior step to proper oral hygiene is tooth brushing to remove plaque (A colorless layer formed by the mass of bacteria on the tooth surface). For an effective cleaning of teeth via toothbrush, and to support tooth brushing, mouthwashes, and other inter-dental cleaners can be used for better oral hygiene. So, nowadays people have an incomplete feel without using mouthwashes even after a thorough brushing.^[1]

Bacteria such as lactobacilli and mutans Streptococci that live within dental plaque produce acids. These acids are bacterial waste products. These waste products have a pH of 4 and lower than the oral cavity pH (5.5) that means they are very acidic and can cause tooth demineralization. Hence, mouthwashes should be used with care and are beneficial in maintaining the routine oral health care. Mouthwashes are antiseptic solutions, and are intended to decrease the microbial load in the oral cavity. It can also be used as an aid in the treatment of gingivitis, periodontitis, oropharyngeal diseases and other inflammatory conditions.^[2]

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Mouthwashes that are alcohol-free and contain fluoride can also help to prevent tooth decay. From the various therapeutically active ingredients in the mouthwash, alcohol (ethanol 0-27% concentration) is an essential component present in every mouthwash. In the present analysis, it is quoted that alcohol-containing mouthwashes can cause oral cancers.

Oral cancer is a chronic disease that can take many years to develop. However, its etiology can be due to other factors also like drinking, smoking or betel nut chewing and using alcohol-based mouthwashes that are yet to be verified. Individual studies have shown the relation of alcohol-based mouthwashes with oral squamous cell carcinoma (OSCC).

OSCC is a neoplastic condition estimated with a global incidence of 275,000 cases that transforms oral keratinocytes and represents significant health issues.^[3,4] Ethanol, a carcinogenic agent present as an ingredient in mouthwashes exerts its effects through secondary mechanisms by generating carcinogenic acetaldehyde leading to lipid peroxidation and enhancement of penetration of other carcinogens.^[5,6]

This has led to a possible controversial relation of OSCC with regular use of alcohol-based mouthwashes for decades. Few epidemiological studies have been done, and they were contradictory. Thus, with reference to the different schools of thoughts done by many reviewers, the aim of this study is to find any significant relation and its impact on the use of alcohol-based mouthwashes and oral cancers after reviewing these studies and to minimize its use if it's relevant.

MATERIALS AND METHODS

The study was registered with the research center of Riyadh Colleges of Dentistry and Pharmacy and was given a registration number FRP/2015/169.

Search Strategy

To obtain the relevant information, a unified criterion was maintained as, alcohol-containing mouthwashes. The database search was undertaken using PubMed data, Medline, Hinari, Ebsco, Google, and medical subject headings, to identify published data that deals with alcohol-containing mouthwashes. The search terms or key titles used for the search strategy were

“mouthwash,” “leukoplakia,” “alcohol-containing mouthwash,” “non-alcohol-containing mouthwash,” “oral rinses,” “ethanol,” “oral cancer,” “squamous cell carcinoma,” “adverse effects,” “chlorhexidine (CHX),” “safety,” “tobacco chewing,” “natural mouthwash,” “smoking,” “cancer risks.”

Study Selection

Type of studies

Only English written articles were identified. For an initial search, 98 articles were obtained. The related articles for the studies were also evaluated. The relevancies of these articles were assessed by reading their titles and abstracts, from which 20 were rejected, as it was not related to the study. The remaining 78 articles were then evaluated at the conceptual level for their eligibility, out of which 20 were excluded.

Types of participants

Out of this, 58 full-text articles were subjected to inclusion-exclusion criteria [Table 1]. Reference lists of these articles were also evaluated.

Types of outcome measures

Finally in this review, 50 articles from 1977 to 2014 were included in the quantitative synthesis.

Data extraction: For each study the following data were retrieved.

Study: Publication year, design, location, age of population, gender.

Exposure: Types and duration of mouthwash usage.

Cases: Number and source of cases, types.

Controls: Matching design, inclusion and exclusion of particular type of cancer.

Table 1: Inclusion-exclusion criteria

Inclusion
English criteria
Randomized clinical trials that assess the effect of alcohol containing mouthwash on oral cancer
Cohort studies
Case-control studies
Systemic reviews of these studies
Exclusion
Case reports
Expert opinions
Patient with systemic diseases

Data Analysis

These were then subjected to preferred reporting items for systematic review and meta-analysis. [Figure 1]. The level of evidence was set according to the evidence-based medicine [Table 2].

Epidemiological Evidence

Epidemiological studies are complex and challenging. This controversial topic on a possible relation between alcohol-based mouthwashes and development of oral cancer, with less than ideal type of scientific evidence, can place a dentist in an awkward position to make ethical decisions on clinical protocols. This existence of a relation between mouthwashes and OSCC was first raised by Weaver *et al.* in a case series in 1979 where people who were examined, used mouthwashes that contained 25% alcohol.^[7] According to a review done by Currie and Farah., in 15 case-control studies and one meta-analysis, have assessed mouthwash use in OSCC patients and concluded with lack of proper evidence and research, but advised for clinicians to promote the use of non-alcoholic mouthwashes in order to minimize any potential increase in risk, and discourage long-term use of high alcohol-containing products.^[8] Many reviews tried to bring a possible relation between use of alcohol-based mouthwashes and oral cancers [Table 3], whereas some of the reviews did not support any link between them [Table 4].

Many studies (case-control, *in-vivo* and *in-vitro*) were conducted to find a possible risk between the use of alcohol-based mouthwashes and oral cancer. Guha *et al.*, reviewed and stated that use of alcohol mix mouthwashes more than twice a day, increased the chances of developing OSCC by six fold (odds ratio 5.86; 95% confidence interval = 2.91, 11.7) when compared to patients who never used mouthwashes in a multicentric case-control study.^[9] Along with Winn *et al.*, Guha *et al.*, proposed that alcohol mix mouthwash users who smoke are also at a greater risk of developing oral cancers than non-smoking users.^[10] Howie *et al.* in the year 2001, performed an *in vitro* study and stated that alcohol can cause damage to oral mucosa including epithelial atrophy associated with hyper-regeneration.^[11]

According to *in-vitro* studies done by WHO International Agency for Research on Cancer, it was found that acetaldehyde, a prime metabolite of alcohol can be metabolized by various bacteria in plaque; which

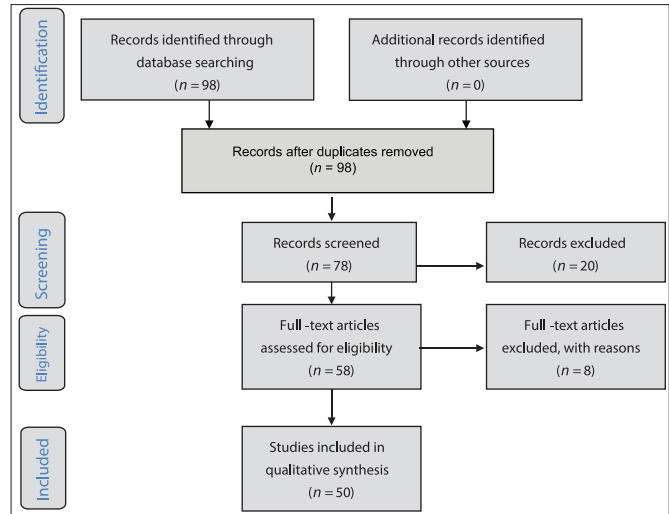


Figure 1: Preferred reporting items for systemic reviews and meta-analysis protocol used in the study

Table 2: Level of evidence

Explanation	Level of evidence
High quality systematic reviews of randomized controlled trials, individual randomized controlled trials (with narrow CI)	I
Systematic reviews of cohort studies, individual cohort study or low quality randomized controlled trials	II
Systematic review of case-control studies, individual case-control study, retrospective comparative study	III
Case-series	IV
Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	V

may support the theory that patients with poor oral hygiene are at an increased risk of oral cancer.^[12]

Seitz and Stickel in 2007 proposed that the production of carcinogenic acetaldehyde by oral bacterial flora and oral epithelial cells is one of the proposed mechanisms by which ethanol exposure contributes to oral carcinogenesis.^[6] A unifying hypothesis by Angadi *et al.*, found that when mucosal surface is exposed to environmental and carcinogenic substances like tobacco, ethanol, and betel quid, it induces undesirable molecular changes resulting in malignant foci at multiple sites.^[13]

Scully assumed in the study that the alcohol content in the mouthwash acts similar to the alcohol in beverages.^[14] Beyer *et al.*, measured the estimation of alcohol by-products (ethyl glucuronide of concentrated 50-300 ng/ml) in urine after rinsing with 12% ethanol-based mouthwash to find out that oral mucosa have a high permeability that can absorb ethanol and probably cause oral cancer.^[15] Wigmore

Table 3: Studies with evidence supporting relation between mouthwash use and development of oral cancer

Author	Conclusion	Level of evidence
Guha <i>et al.</i> ^[9]	Significant increase in risk with use of mouthwash more than once daily	III
Howie <i>et al.</i> ^[11]	Significant damage to oral mucosa, epithelial atrophy, hyper regeneration due to alcohol in mouthwash	II
Seitz and Sticke ^[6]	Ethanol exposure contributes to oral carcinogenesis	III
Angadi <i>et al.</i> ^[13]	Exposure to environmental carcinogens induces malignant foci at multiple sites	III
Scully ^[14]	Alcohol in mouthwash similar to alcohol in beverages	III
Currie and Farah ^[8]	Significant increase in risk associated with mouthwash use	III
Wynder <i>et al.</i> ^[17]	Significant increase in risk among women with use of mouthwash more than once daily	III
Blot <i>et al.</i> ^[18]	Non-significant increased risk among non-smoking females who used mouthwashes	III
Winn <i>et al.</i> ^[10]	Significant increase in risk for both men and women	III
Marshall <i>et al.</i> ^[19]	Significant increase in risk associated with mouthwash use	III
Marques <i>et al.</i> ^[20]	Significant increase in risk with use of mouthwash more than once and twice daily	III
Eliot <i>et al.</i> ^[21]	Significant increase in risk associated with use of mouthwash more than once daily	III
McCullough and Farah ^[22]	Significant increase in risk with mouthwash use	III
Rodrigues <i>et al.</i> ^[23]	Alcohol-induced mitotic recombination's was evident	II

Table 4: Studies with evidence against relation between mouthwash use and development of oral cancer

Author	Conclusion	Level of evidence
Gandini <i>et al.</i> ^[27]	No significant relation between mouthwash use and oral cancer	II
La Vecchia ^[30]	Lack of dose-response relationship	III
Winn <i>et al.</i> ^[31]	No association between mouthwash use and oral cancers	II
Macfarlane <i>et al.</i> ^[36]	No significant risk with use of mouthwashes once or twice per day	III
Young <i>et al.</i> ^[34]	No increase in risk or differences when stratified by smoking/drinking among males or females	III
Kabat <i>et al.</i> ^[35]	No significant risk among females. Most cases likely used mouthwashes to mask tobacco/alcohol odors	III
Talamini <i>et al.</i> ^[37]	No increase in risk with use of mouthwashes more than twice per week	III
Divaris <i>et al.</i> ^[38]	No increase in risk or differences when stratified by smoking/drinking	III
Chang <i>et al.</i> ^[39]	No significant risk with mouthwash use; insufficient statistical power	III
Elmore and Howitz ^[40]	No supportive link to associate relation between mouthwash use and oral cancer	III
Cole <i>et al.</i> ^[32]	No increase in risk with mouthwash use and oral cancers	III
Carretero Peláez <i>et al.</i> ^[41]	No justification to establish relation between mouthwash and oral cancer	III
Lewis and Murray ^[42]	No increase in risk with mouthwash use and oral cancer	III
Warnakulasuriya ^[43]	No supportive evidence between mouthwash use and oral cancer	III

and Leslie implied that the effect of alcohol in the oral cavity was greater on rinsing using alcohol-based mouthwashes than actual alcohol consumption after checking with breath analyzers.^[16] A retrospective case-control study by Wynder *et al.*, based on gender and their use of alcohol-based mouthwashes found that women who were non-smokers and non-drinkers were more prone to oral cancers on using mouthwashes daily more than once, when compared to men.^[17] Blot *et al.* conducted a case-control study in North Carolina with 206 women and found a non-significant increased risk for oral and pharyngeal cancers among women who were non-smokers and used alcohol-based mouthwashes.^[18] In Western New York, a case-control study by Marshall *et al.* on 290 cases stated that there is a significant increase in risk related to mouthwash use but did not find any association with the duration of its use.^[19]

Marques *et al.* conducted a hospital based case-control study in South Eastern Brazil with 309 patients and found a significant association to oral and pharyngeal cancer with use of mouthwashes more than twice per day.^[20] A case-control study in by Eliot *et al.* on 513 cases and 567 controls, affirmed that head and neck squamous cell carcinoma was associated with use of mouthwashes more than once daily, be it alcohol-based or nonalcohol-based mouthwashes.^[21] McCullough and Farah, in a non-systematic narrative review stated that according to selected case-control studies reviewed, there is a risk of oral cancer with long-term use of alcohol-based mouthwashes.^[22] In an *in-vitro* study, Rodrigues *et al.* investigated the ability of three different mouthwashes to induce genetic mutation using *drosophila melanogaster* somatic mutation and recombination test. It was found that ethanol (16.8%) induced mitotic recombination's

than the antimicrobial components in the mouth washes.^[23]

From the above studies, long-term use of alcohol-containing mouthwashes when used with poor oral hygiene, smoking and drinking can cause oral cancer. And thus concluded in their reviews that it is advisable, to limit its use. Gandini *et al.*, stated that from his several studies, carcinogenicity of alcohol mix in mouthwash is due to the formation of acetaldehyde as first metabolite.^[5,24-27] They showed that alcohol-containing mouthwashes forms acetaldehyde in the oral cavity for up to 10 min in the saliva,^[26] which was confirmed with research done by Nummi *et al.*^[28] and Moazzez *et al.*^[29] Their studies detected that acetaldehyde formation in the saliva is comparatively more on using alcohol-based mouthwashes than compared to drinking alcohol and smoking on using alcohol-based mouthwashes. In another quantitative meta-analytical study done by Gandini *et al.*, it was determined that there was no significant relation between daily use of mouthwash ($P = 0.11$) and OSCC.^[27] La Vecchia, highlighted the lack of a dose-response relationship after focusing on two papers that conducted two studies conducted by U S National Cancer Institute.^[30] The first study stated that the risk of oral cancer was associated with its regular use and varied in proportion to dose, duration and frequency of mouthwash use and concentration of alcohol in it. The second study was a reanalysis of the first study, done by Winn *et al.*^[31] and Cole *et al.*^[32] and they commented no association between mouthwash usage and true oral disease as it can also be due to use of mouthwashes by “smokers” and “drinkers” to camouflage breath odors which was supported by other studies.^[17,33-35] Macfarlane *et al.*, performed a case-control study in Europe to find out relation between smoking and alcohol consumption to cancers in oral cavity, pharynx, larynx, and esophagus but affirmed no association of oral cancer risk with use of mouthwashes once or twice per day.^[36] A case control study was conducted by Young *et al.* among males and females to investigate the risks of oropharyngeal cancers with poor health, mouthwash use, occupation, histories of tobacco and alcohol use and other factors. Their study showed no significant relation to an increased risk to oral cancers among males and females on using mouthwashes.^[34] Another case-control study in 125 women was conducted by Kabat *et al.*,^[35] to assess the role of mouthwash with oral cancer and found no significant risk associated with the use of mouthwash more than once daily. Most of the women used mouthwashes to mask the odor of

tobacco and alcohol than the odors due to food and dental infections.^[35] In Italy, Talamini *et al.* performed a case-control study and found no associated risk in using mouthwashes more than twice per week.^[37] Divaris *et al.*^[38] carried out a population-based case-control study in North Carolina to assess the risk for head and neck squamous cell carcinoma with oral health and periodontal diseases, mouthwash use and frequency of dental visits. Their study showed no significant risk in association with mouthwash use.^[38] Another case-control study was conducted by Chang *et al.*^[39] to analyze the association between oral hygiene and head and neck cancer, whether it differed with use of alcohol, cigarettes, betel quid, genetic polymorphisms. Their study found no difference in risk between alcohol-containing mouthwash use and had insufficient statistical power.^[39] A methodological and systemic review of seven case-control study was conducted by Elmore and Horwitz^[40] in year 1995 and evaluated that neither the data nor the analysis done in the few available studies on mouthwash use and risk of oropharyngeal cancer supported a link between them.^[40] Cole *et al.*, reviewed nine epidemiologies and concluded that there is no significant relation between alcohol-based mouthwash and oropharyngeal cancer.^[32] In a narrative review, Carretero Peláez *et al.*, stated that there is no justification to establish a relation between the use of alcohol-based mouthwash and oral cancer.^[41] La Vecchia conducted a case-control study and stated that there is no supported epidemiological evidence against the relation between mouthwash and oral cancer risk.^[30] Lewis and Murray, 2006^[42] and Warnakulasuriya, 2009^[43] conducted a narrative review and affirmed that evidences does not support relation between use of alcohol-based mouthwashes and oral cancers.

Some of the reviewers had mixed responses about the incidence of oral cancer in association with alcohol-based mouthwashes [Table 5]. In their studies and reviews, it was evident that oral cancers can be caused due to many other aggravating factors like its excessive use per day, smoking, drinking, and betel quid usage. Adverse effects of alcohol-containing mouthwashes were noted in the studies conducted by Settembrini *et al.*^[44] 1995 and Weiner *et al.*^[45] 1997 which showed that alcohol can cause burning mouth, drying of oral mucosa, softening effects on composite filling materials and mucosal pain in some patients. Salaspuro^[46] 2007, Lachenmeier *et al.*^[26] 2009, McCulloch *et al.*^[47] 2012, conducted *in vivo*-studies which stated that a brief exposure to alcohol-

Table 5: Studies with evidence having mixed responses relation between mouthwash use and development of oral cancer

Author	Conclusion	Level of evidence
Settembrini <i>et al.</i> and Weiner <i>et al.</i> ^[44,45]	Adverse effects evident with use of alcohol-based mouthwashes, but no potential risk highlighted	III
Lachenmeier <i>et al.</i> McCullough <i>et al.</i> ^[26,50,47]	Potential mutagenic effect with increase in salivary acetaldehyde	III
McCullough and Farah ^[22]	Contradictory regarding benefits and risks with long-term use of alcohol-based mouthwashes	III
D'Souza <i>et al.</i> ^[48]	Oropharyngeal cancer associated with oral HPV infection than mouthwash use	III
Shapiro <i>et al.</i> ^[49]	No risk of oral cancer with use of mouthwash but suggested due to tobacco/alcohol use	II
Lemos and Villoria ^[51]	Contradictory about safe use of mouthwashes	III

HPV: Human papillomavirus

containing mouthwashes can increase the level of salivary acetaldehyde to a potential mutagenic effect to cause oral cancer. However, their studies concluded that more investigative studies are required to relate the association of alcohol in mouthwashes can cause oral cancers; as Lachenmeier *et al.*^[26] stated uncertainty regarding the safe use of alcohol-based mouthwashes, and McCulloch and Farah,^[22] surmised against the use of such mouth rinses.^[46] A hospital based case-control study was performed by D'Souza *et al.*^[48] to find an association with increased use of tobacco and alcohol with oropharyngeal cancer but found no significant relation. Their study highlighted that oral human papillomavirus infection is strongly associated with oropharyngeal cancer rather than mouthwashes.^[48] Shapiro *et al.* suggested in a statistical commentary review that the use of alcohol-based mouthwashes along with heavy alcohol and tobacco use, may raise the risk of oropharyngeal cancer even under the hypothesis that mouthwash does not cause cancer.^[49]

Eugeniu *et al.*^[50] in the year 2014 CHX has been used in various concentrations (0.002-2%) with different periods of contact time between the disinfectant and various microorganisms.

In a case-control study, regarding the safety of mouthwash use and oral cancer by Lemos and Villoria in 2008, it was evident and stated about the contradiction whether it's safe to use mouthwashes with alcohol without proper guidance and instructions or not.^[51]

Reviewing the above studies, it was evident that the conflicting issues regarding the safe use of alcohol-containing mouthwashes is still contradictory. With the possible risks of oral cancer caused by alcohol-based mouthwashes, there is still controversy regarding its long-term use. Ethanol, being an essential ingredient, had led to increased scrutiny of its presence in mouthwashes. Thus, it's advisable that clinicians

educate their patients regarding any potential risks involved with its long-term use.

RESULTS

Through the literature searches, 50 full-text articles were found that were considered for inclusion in the review. Among which, 15 articles supported the risk factors for oral cancer, 14 articles against risk causing oral cancer and the remaining 13, showed a mixed response. From the referred reviews, it was evident that long-term use of alcohol-based mouthwashes along with improper oral hygiene and habitual smoking, drinking might have aggravated the risk of oral cancer. The supportive reviews stated in their studies that use of alcohol-based mouthwashes induced undesirable molecular changes leading to carcinogenesis, whereas, other reviews didn't show any significant relation between use of alcohol-containing mouthwash and oral cancer. Some studies indicate that these alcohol-containing formulations proved to be effective in preventing periodontal diseases and have reduced the incidence of posting-surgical inflammations. These factors are contributing to its continued used in the field of dentistry. Non-alcoholic mouthwashes available in the market also proved to be as useful as an alcohol-based mouthwash. Thus, from the included studies a possible risk of bias is likely to the increasing demand for alcohol-based mouthwashes.

DISCUSSION

A potential link between use of alcohol mix mouthwash and risk of oral cancer has been a debatable topic for several decades, since its observation by Weaver *et al.*^[7] ethanol being the main content in alcohol mixed mouthwashes has a carcinogenic effect mainly caused by its metabolite acetaldehyde.^[27] In this study, a quantitative analysis of the potential effect of alcohol mix mouthwash on the risk of oral cancer was assessed.

All the reviewed articles were identified thoroughly through their literature and reference list. Fifty full-text articles suitable for inclusion were selected, to ensure the maximum amount of information on the subject. It was observed from the reviews that long-term use of alcohol mix mouthwashes are likely to cause oral carcinogenesis even with risk determinant factors such as tobacco smoking, alcohol drinking, betel nut chewing, and poor oral hygiene. Although, individual reviews emphasized there is no significant relation between uses of alcohol-based mouthwash and oral cancer risk. However, in the future it would be necessary to do more clinical based studies and homogenize the samples to obtain a better conclusive result.

CONCLUSION

From the current analysis of studies and literatures reviewed, it's observed that despite of certain undesirable effects like burning sensation, drying of oral mucosa, mucosal pain; the association between mouthwash use and oral cancer risk may be a combination of risk determinants, effect modifiers and cofounders involved. Although, previous studies suggest the minimal use of alcohol-based mouthwashes, there is still a lack of evidence to establish its association to oral cancer. Further, studies are required to re-evaluate and reanalysis of alcohol-based mouthwash on the basis of epidemiological and mechanistic studies. It is also mandatory to investigate the cellular and molecular events related to alcohol-based mouthwash and to focus on certain aspects of the use of alcohol mix mouthwash and development of oral cancer due to its use. On the contrary, a benefit of alcohol in mouthwash is not negligible, and its risk of oral cancer is difficult to quantify. So, ethically giving priority to patient safety, it's advisable that clinicians and dental professionals must guide their patients to minimize it's long-term use and to follow proper instructions while using alcohol-containing mouthwashes. And to adopt nonalcohol-based mouthwashes that have equal effect when compared to alcohol-based mouthwashes with lesser adverse effects.

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