Prevention of Caries in Cancer Patients: A Systematic Review on the Effectiveness of Dental Materials

Keywords

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ABSTRACT

This study aims to identify dental materials and their effectiveness in preventing caries in patients after chemotherapy and radiotherapy for the head and neck. The electronic search was performed in PubMed, Science Direct, Embase and Scopus. All 653 articles found passed through a double-blinded screening process. The exclusion of articles by reading titles and abstracts selected 16 articles for full reading, of which 4 were included into the study. A risk of bias analysis for non-randomized and randomized articles was performed using respectively the ROBINS I and ROB II tools. The data extraction suggested that the casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), in association with fluorine, is able to form harder surfaces compared to the control group, the intraoral fluoride-releasing system (IFRS) effectiveness is similar to the fluorine in gel and a mouthwash composed of natural enzymes (Oral7) did not demonstrate effectiveness in the prevention dental caries. New randomized controlled clinical trials are necessary to evaluate the effectiveness of prevention when applying dental materials in patients after treatment of head and neck cancer.

INTRODUCTION

Treatment for head and neck malignancies involves radiotherapy, chemotherapy, and surgical procedures, according to the particularities of the neoplasm.[1-3] Radiotherapy and chemotherapy are associated with salivary suppression and caries increase in head and neck cancer patients, and these conditions decreased the quality of life and increased risk of infections in these patients.[4-7] Thus, the search for caries preventive dental materials in patients who have undergone this type of treatment is essential and has become the research focus.

Radiation decay occurs in a widespread manner, particularly in regions with little likelihood of decay, such as cervical regions of teeth and cusp tips.[4,5,8] The color of the crown turns brownish and loses translucency, in addition, the teeth become friable, susceptible to wear, and enamel delamination occurs.[4,5,8,9] Caries caused by chemotherapy drugs that suppress salivary glands have lower scientific evidence and, unlike radiation caries, do not have specific clinical characteristics.[10-12]

The degeneration of salivary gland cells is one of the consequences of salivary gland-suppressing radiotherapies and chemotherapy drugs.[6,11,13,14] Decreased salivation favors the occurrence and evolution of dental caries due to the lack of components that stimulates proper maintenance of the dental

elements.[4,15-17] In hyposalivation conditions, the carrying of F^{-1}, Ca^{2+}, PO_4^{3-}, and HCO_{3-} ions is deficient, and the oral chemical imbalance leads to loss of Ca^{2+} from the tooth structure and consequent weakening.[16-19] In patients treated with chemotherapy and/or radiotherapy, if there is no preventive treatment for hyposalivation, caries development is favored.[5,10,18]

Prevention of caries during and after radiotherapy and/or chemotherapy treatment is possible with the distribution of rays through intensity-modulated radiotherapy (IMRT) or intensity-modulated proton therapy (IMPT), ray beam collimation, determination of ideal dosages, radioprotection of salivary glands, and surgical transplantation of the submandibular gland, when applicable.[13,20-23] In addition, a follow-up with the dentist is able to boost preventive treatments and increase patients' adherence to treatment.[24-27]

Dental materials can be used in order to prevent the mineral loss, remineralize the tooth structure, paralyze the onset of caries and prevent acute processes.[28-35] It is still not clear in the literature which materials are the best to prevent dental caries in patients after radiotherapy and/or chemotherapy. Thus, the aim of this systematic review is to identify the materials tested in the literature regarding their effectiveness in preventing radiation caries and to answer the research question: In patients after treatment by chemotherapy and/or radiotherapy of the head and neck, the dental materials show effectiveness in reducing caries?

MATERIAL AND METHODS

This systematic review is in compliance with Preferred Reporting Items for Systematic Review and Meta Analyzes Protocols (PRISMA) guidelines and was registered in The International Prospective Register of Ongoing Systematic Reviews (PROSPERO)- CRD42021261538. A PICOS strategy (P=Patients after cancer treatment by chemotherapy and radiotherapy; I=dental materials; C=control group, if any; O=dental caries; S=experimental studies) was structured according to the research question. The personalized search strategy was performed in PubMed, Science Direct, Embase, and Scopus databases *(Table 1)*.

As inclusion criteria, clinical studies (randomized or not) were selected to evaluate the effectiveness of dental materials in patients after head and neck chemotherapy and/or radiotherapy without time and language restrictions. And as exclusion criteria: a) did not evaluate the caries outcome; b) does not have comparable data for before and after the intervention, c) *in vitro* research articles, review articles, case reports, conferences, book chapters, and editorials.

In the first step, H.C.A and J.D.C.T reviewers evaluated separately, through the Rayyan web app and according to the eligibility criteria, the title and abstract of the articles found in the databases after applying the search strategy and removing duplicates, in order to select the articles to be read in full. In the second stage, H.C.A and J.D.C.T independently assessed the articles selected for full reading according to the eligibility criteria. The doubts regarding the articles' inclusion or exclusion were solved by the expert A.B.V.T and by the research coordinator A.C.R.

Data were tabulated independently by the reviewers H.C.A. and J.D.C.T in an Excel spreadsheet according to the following criteria: a) author, year; b) population; c) characteristics; d) evaluation method; e) outcome; *(Table 2)*. The risk of bias analysis was performed using specific tools for each type of study, ROBINS I assessed clinical studies, and ROB 2 assessed randomized clinical studies. The figure for risk of bias was generated in Robvis (visualization tool).

Table 1. Database search strategy.

Database	Search	Found
EMBASE November 19th, 2020	('cancer patient' OR 'Head and Neck neoplasms') AND ('head and neck radiotherapy' OR 'chemotherapy') AND ('dental material' OR 'cariostatic agents') AND ('Radiation related-caries' OR 'Dental Caries')	35
PubMed November 19th, 2020	("cancer patient" OR "Head and Neck neoplasms") AND ("head and neck radiotherapy " OR "chemotherapy") AND ("dental material" OR " cariostatic agents") AND ("Radiation related-caries" OR "Dental Caries")	111
Scopus November 19th, 2020	("cancer patient" OR "Head and Neck neoplasms") AND ("head and neck radiotherapy " OR "chemotherapy") AND ("dental material" OR " cariostatic agents") AND ("Radiation related-caries" OR "Dental Caries")	6
Science Direct November 19th, 2020	("cancer patient" OR "Head and Neck neoplasms") AND ("head and neck radiotherapy " OR "chemotherapy") AND ("dental material" OR " cariostatic agents") AND ("Radiation related-caries" OR "Dental Caries")	501

Table 2. Overview of the included articles.

Author, year	Intervention and comparison	Population Characteristics	Evaluation method	Outcome
Bachok *et al.*, 2018	Experimental group: oral7® mouthwash. Control group: salt-soda mouthwash.	- Inclusion criteria: Have at least 15 years and at most 60 years, individuals that have been histopathologically diagnosed with head and neck cancer and are going to receive gland suppressive radiation, with a dose of at least 40 Gy to the parotid gland, have an ECOG performance status 0–1; - Exclusion criteria: Edentulous status, xerostomia induced by medications, sicca syndrome, and a previous history of radiotherapy or chemotherapy; - There were no relevant social-demographic differences between the groups; - Sample size: experimental group – 15 participants; control group – 15 participants.	DMFT score.	The DMFT score did not present a relevant difference between the experimental and the control group.
Katsura *et al.*, 2016	Experimental group: 10% CPP-ACP paste. Control group: non-CPP-ACP group (conventional dental management).	- Inclusion criteria: Patients who had a previous history of head and neck radiotherapy, patients had to be free of residual or recurrent disease during the study and had to have no history of allergy to milk protein; - Patients included received a total of at least 44-46 Gy to the head and neck region and additional doses were applied accordingly to primary tumor bed and high risk regions; - Characteristics among patients didn't differ significantly from one group to the other and there were no relevant differences in root surface textures between groups at baseline. - Sample size: experimental group – 12 participants; control group – 7 participants.	Root surface textures: CPI probe	Root surfaces had a smaller incidence of soft lesions and harder textures in the experimental group compared to the control group.
Meyerowitz and Watson, 1998	Experimental group: IFRS. Control group: 1.1% neutral NaF gel.	- Inclusion criterias: All participants had to have completed head-and-neck radiotherapy, with a minimum dose of 40 Gy, at least 3 months before the start of the study, they should not have received chemotherapy in the year previous to the study and should not have a history of metastasis. Patients had to have 0.5 mL/minute or less of paraffin-stimulated whole salivary flow rate, and if patients were presented with gastric ulcers or fluoride allergy they would be excluded from the study. Patients had to be older than 16 years old, have at least 10 teeth prone to develop caries, not have unrestored carious lesions and have two posterior teeth near both the parotid ducts that are able to receive the IFRS device. - The major salivary glands were covered by the radiation field. - There were no significant differences between the groups concerning age, sex, paraffin-stimulated whole salivary flow rate, and number of missing teeth. - Sample size: experimental group – 13 participants; control group – 10 participants.	Root caries: Number of lesions and severity. Coronal caries: Visual-tactile criteria (Radike) and bitewing radiographs.	In baseline, the number of filled surfaces and roots prone to develop caries was lower in the IFRS group. In the 6-month study period, one surface developed caries in the experimental group, compared to the one individual who developed two carious surfaces in the control group.
Sim *et al.*, 2019	Experimental group: 10% CPP-ACP. Control group: placebo.	- Inclusion criteria: Patients who had not been through a previous head and neck radiotherapy and were not receiving palliative care, were selected from a dental care center. Patients were going to start doing pre-radiotherapy oral health clearance and should present a minimum of 20 teeth remaining after. The minimum age for eligibility was 21 years old; - Patients received a radiation dose of 70 Gy; - Groups' general characteristics had no statistically relevant differences when it comes to age, radiation received, baseline level of carious surfaces, salivary flow rates, and saliva fluoride ion concentration between the two groups. All individuals had Chinese ethnicity. - Sample size: experimental group – 12 participants; control group – 12 participants.	Caries status: ICDAS II visual criteria.	There were 59 carious tooth surfaces in 8 subjects of the control group, and 29 carious tooth surfaces in 9 subjects of the experimental group.

DMFT: Decayed, Missing and Filling Teeth; CPI: Community Periodontal Index; ICDAS II: International Caries Detection and Assessment System; CPP-ACP: Casein phosphopeptide-amorphous calcium phosphate; IFRS: Intraoral Fluoride-Releasing Systems; ECOG: Eastern Cooperative Oncology Group; NaF: Sodium Fluoride; Gy: Gray

RESULTS

The search strategy *(Table 1)* resulted in 653 articles and, after removing the duplicates, 639 articles were evaluated according to title and abstract. For full reading, 16 studies were selected, of which 4 articles *(Table 2)* met the eligibility criteria (shown in *Figure 1*) and were included, and 12 articles were excluded *(Table 3)*. Considering the heterogeneity of the included studies, it was not possible to perform a meta-analysis as there were different dental materials for caries prevention, different types of head and neck cancer, and varying time related to chemotherapy and/or radiotherapy treatments.

Among the studies analyzed, the dental materials for caries control in patients who underwent radiotherapy and/or chemotherapy in the head and neck region were: Intraoral fluoride release system (IFRS),[36] casein phosphopeptide-amorphous calcium phosphate (CPP-ACP),[37,38] and a mouthwash composed of natural salivary enzymes (Oral7 mouthwash).[39]

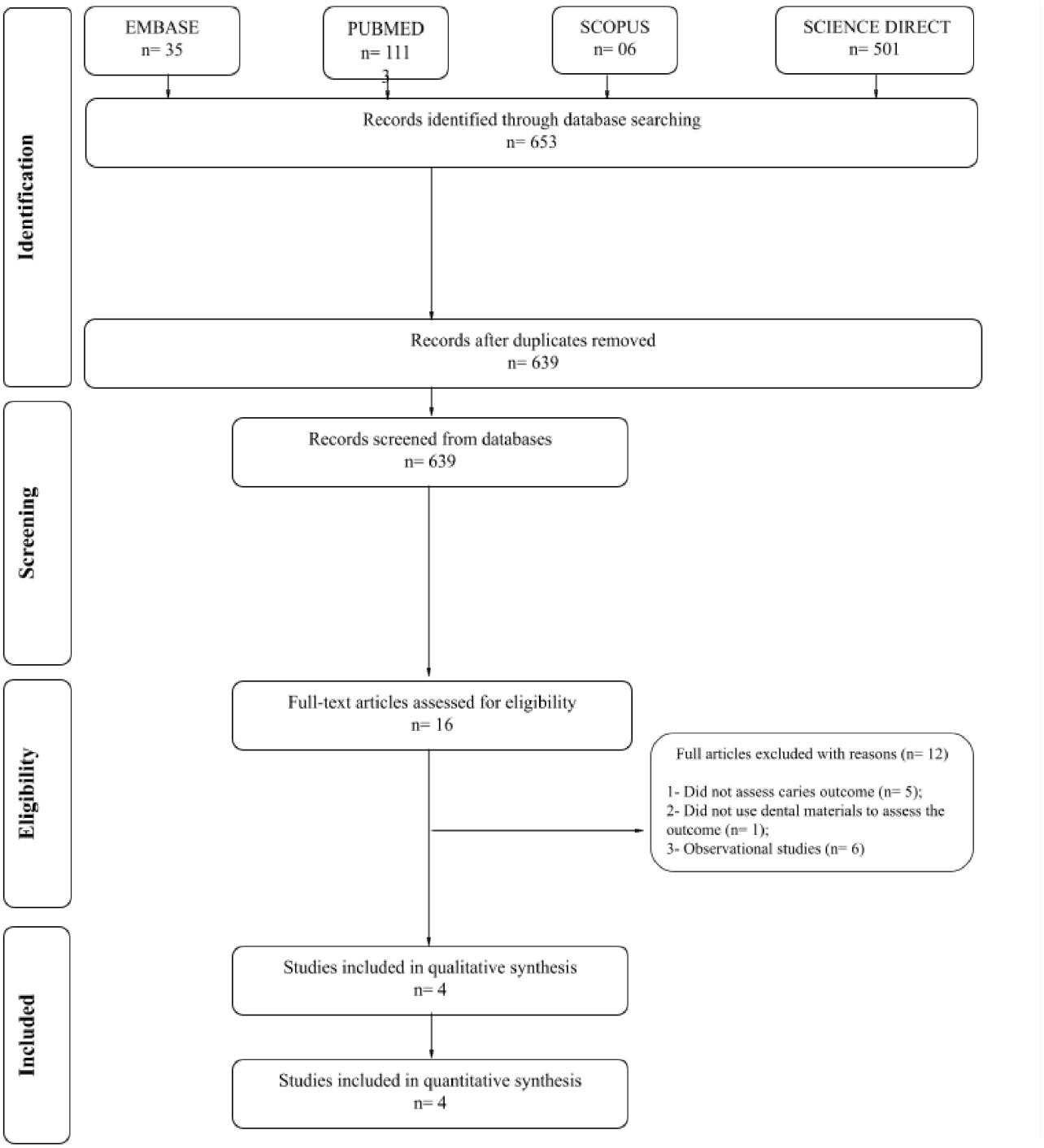

Figure 1: Flow diagram of literature search and selection criteria.

Table 3. Excluded articles and reasons for exclusion.

Author, Year	Reason for exclusion
Meca *et al.* 2009 [9]	1
O'Sullivan *et al.* 1993 [10]	1
Wahlin *et al.* 1989 [12]	1
Epstein *et al.* 1991 [5]	1
Banava *et al.* 2015 [1]	1
Rudat *et al.* 2000 [11]	2
Breslin *et al.* 2020 [2]	3
Cubukcu *et al.* 2008 [3]	3
Epstein *et al.* 1989 [4]	3
Epstein *et al.* 1996 [6]	3
Keene *et al.* 1987 [7]	3
Keene *et al.* 1994 [8]	3

1) Did not assess caries outcome; 2) Did not use dental materials to assess the outcome; 3) Observational studies.

The use of a mouthwash composed of natural salivary enzymes, such as glucose oxidase, lactoperoxidase, lysozyme, and lactoferrin, showed no significant difference when compared to a placebo mouthwash formulated of salt-soda mouthwash (1 tablespoon of sodium chloride, 1 tablespoon of sodium bicarbonate and four cups of water). An amount of 15 ml was used 4 times a day for 5 minutes and was applied on patients one week before, during, and until 6 weeks after radiotherapy treatment, with or without chemotherapy.[39]

Daily applications of CPP-ACP associated with fluorine (0.412% stannous fluoride (SnF_2) in gel (1000 ppm), 0.32% sodium fluoride (NaF) present in toothpaste or fluorine in gel (9000 ppm)), was highly effective in caries prevention. Katsura *et al.*[37] study demonstrated that after 12 months the experimental group, who received daily application of 10% CPP-ACP in custom fitted trays and conventional (with the topical application of 9000 ppm F gel every 3 months), displayed a harder root surface compared to the control group, that received only conventional dental management. Both experimental and control groups consisted of post-treatment radiotherapy patients.

While, Sim *et al.*[38] when evaluating patients one week before, during, and 12 weeks after radiotherapy treatment, reported that the daily applications of CPP-ACP crème, associated with 0.412% SnF_2 gel (1000 ppm fluoride) and of 0,32% NaF dentifrice applications, resulted in a 51% reduction in caries incidence in the experimental group when compared to the control group that received a placebo crème with the same constituents as the CPP-ACP crème, except for the CPP-ACP itself, associated with 0.412% SnF_2 (1000 ppm F) gel and 0,32% NaF dentifrice.

The IFRS, suggested in the Meyerowitz and Watson study,[36] contains a system with 35 mg of NaF, that releases 0.12 mg of F- per day for 130 days, fixed bilaterally in the maxilla posterior teeth. After six months the IFRS presented caries preventive action similar to the control group, in which 1.1% NaF gel was applied in custom trays. All participants of the study were post-radiotherapy patients and were using fluoridated dentifrice.

As for the risk of bias analysis of the included studies, it was analyzed according to the type of study, so that, the randomized studies were assessed through ROB2 tool (shown in *Figure 2*),[36,38] and the two not randomized studies were assessed through ROBIS I (shown in *Figure 3*).[37,39] After analysis, the Sim *et al.*[38] study showed low risk of bias, and the Meyerowitz and Watson study raised concerns about the risk of bias.[38,36] The risk of bias from the non-randomized studies presented a serious risk of bias.

Among the included studies assessed for the risk of bias using the ROB 2 tool, Sim *et al.*[38] showed a low risk of bias for all domains. Meyerowitz and Watson,[36] on the other hand, had flaws in the randomization process, since there was no standardization regarding the initial condition of oral hygiene between the intervention group and the experimental group, the IFRS group had fewer surfaces and restorations at risk of developing caries. As for the non-randomized studies, assessed for risk of bias using the ROBINS I tool, presented a serious risk of bias. Bachok *et al.*[39] did not adequately control the confounding variables present in the oral hygiene practices of the participants and presented two domains with moderate risk of bias. One was the lack of information regarding the participant's adherence to the treatment, which made it difficult to analyze deviations in the intended interventions. And the other domain with moderate risk is due to biases that interfere in the analysis of the results, such as the measurement of the results being operator dependent and the presence of a potential type II error of low statistical power reported by the author.[39] Katsura *et al.*[37] also presented serious risk of bias as the application of chemotherapy concomitantly with radiotherapy were detected in some patients, which represents a confounding variable not properly controlled. In addition, missing data from patients excluded after the start of interventions, deviations in intervention classifications (as interventions were assigned according to the choice of participants), and two domains had moderate risk of bias: selection of participants, with the exclusion of patients after the start of the intervention, and in the measurement of the results, since the operator-dependent analyzes were not performed blindly. In addition, all included studies showed a small sample size,[36-39] with a reduced number of participants in the experimental and control groups, and Sim *et al.*[38] and Bachok *et al.*[39] had a short follow-up, which limits the reliability of the results.

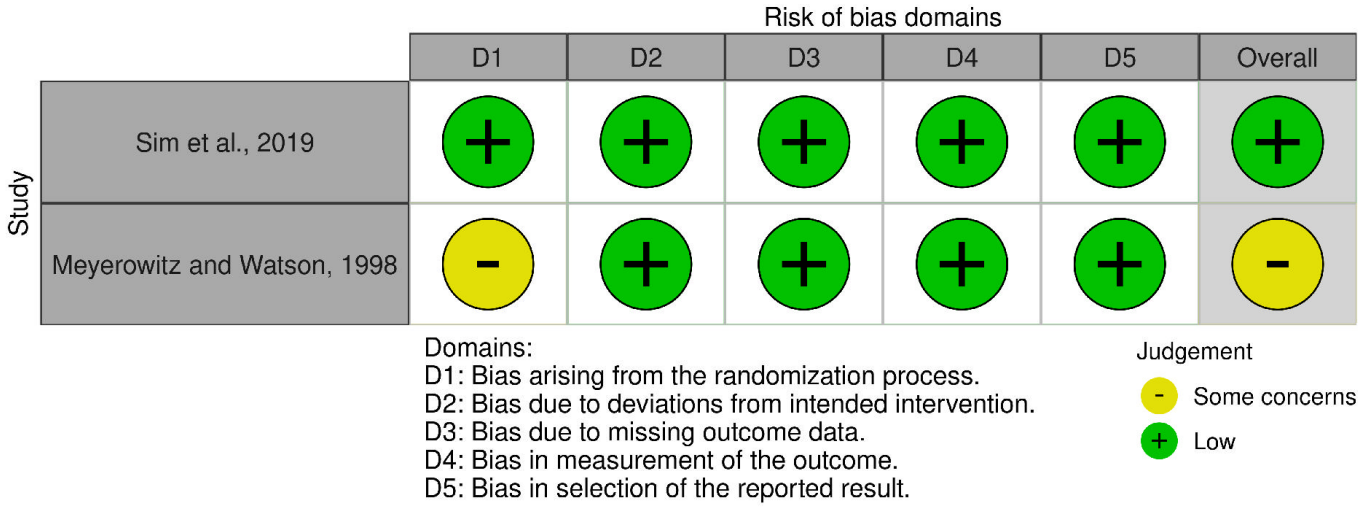

Figure 2: Risk of bias from randomized studies.

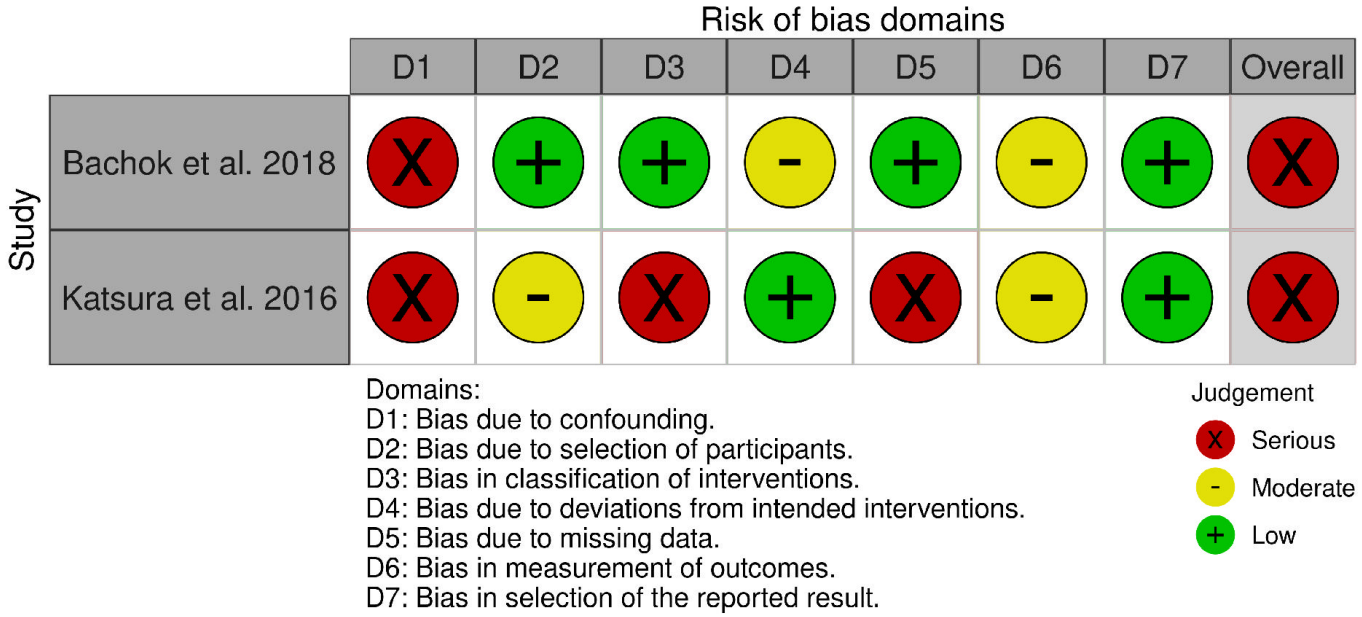

Figure 3: Risk of bias from non-randomized studies.

DISCUSSION

In this systematic review, it was found that the use of the dentifrice containing 10% of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) was effective in preventing caries, the intraoral fluoride release system (IFRS) had similar results to the application of 1.1% NaF gel, and the mouthwash composed of natural salivary enzymes (Oral7) did not show effectiveness in preventing caries in patients after head and neck chemotherapy and/or radiotherapy treatment.

Phosphopeptide casein (CPP) is a milk-derived protein that has an anti-cariogenic capacity. The CPP-ACP complex acts through the supersaturation of calcium phosphate in saliva, which is helpful in the remineralization process, antibacterial action, and alleviates salivary deficiency's effects on dental structures.[28,40-46] Calcium binds to the dental element film are stronger than those to bacterial cell membranes, so the selective occupation of binding sites decreases bacterial adherence to biofilm.[28,45,47] Furthermore, the high amount of Ca^{2+}, phosphate (PO_4^{3-}), and free F+ forms a layer of calcium fluoride (CaF_2) on the tooth surface that acts as a fluoride reservoir in cases of acid attack.[44,46,48]

Katsura *et al.*[37] and Sim *et al.*[38] observed that mechanisms of action promoted by CPP-ACP in association with 9000 ppm of sodium fluoride (NaF) or 0.32% of NaF dentifrice and 1000 ppm of stannous fluoride (SnF_2), had as an outcome the prevention of caries. In a randomized controlled clinical trial where CPP-ACP, amorphous calcium phosphate casein phosphopeptide with fluoride (CPP-ACFP), and NaF varnish were compared to determine the caries prevention potential of each material, it was concluded that CPP-ACFP is the

product with the greatest capacity for remineralization, which highlights the adjuvant action that CPP-ACP can promote to fluoride during treatment.[49] Furthermore, Maden *et al*.[44] demonstrated that the association of CPP-ACP with fluoride is effective in repairing dental erosion caused by soft drinks. CPP-ACP alone is a remineralizing agent of tooth structures and its association with fluoride increases the remineralization capacity of the product.[19,49,50]

Despite the positive results of the CPP-ACP in the included studies,[37,38] caution should be exercised when considering them, since these studies showed some biases. Sim *et al*.[38] showed a low risk of bias according to ROB 2 tool analysis, however, they presented a small sample size and short follow-up. In Katsura *et al*.[37] study, a small number of participants were included and some were excluded after the beginning of the intervention (without data about them); the outcome was not measured with blinding; in addition to treatment with chemotherapy concurrent with radiotherapy in some participants, which may be a confounding variable. Other studies in the literature[19,44,49,50] support the results of CPP-ACP in caries prevention, however, more controlled and randomized clinical trials can be performed to prove its effectiveness in preventing caries in patients after head and neck chemotherapy and/or radiotherapy treatment.

Fluoride application was considered the best therapy for caries prevention in several studies due to its capacity for dental remineralization.[4,35,40,48,51-55] It can often be associated with other materials to improve its action. Patient compliance with fluoride applications directly influences the effectiveness of caries prevention treatment.[26,27,56] The IFRS is a fixed application method of fluoride and does not depend on patient compliance.[57,58] Meyerowitz and Watson[36] found that the IFRS use did not have a significant difference from 1.1% NaF gel applications in personalized trays. However, it should be considered that this study presented a small sample size and a bias in the randomization process since the participants included in the IFRS group had fewer surfaces and restorations at risk of developing caries than the control group, which may induce a similar result between the IFRS and NaF gel treatments. Despite this, other studies corroborate these results by concluding that the IFRS action is effective and corresponds to fluorine gel (5000 ppm) applications and daily applications of fluorine gel in personalized trays (1100 ppm).[57-59] In addition, there are other materials most commonly used capable release fluoride slowly, such as glass ionomer cement and sealants, which can be recharged.[32,60-63]

The saliva's role in protecting tooth structures and caries prevention is known.[17-19,34,64,65] The Oral7 mouthwash, evaluated by Bachok *et al*.,[39] consists of natural enzymes such as lysozyme and lactoferrin present in saliva, however, was not effective in preventing caries in patients after head and neck chemotherapy and/or radiotherapy treatment. According to the authors,[39] the similarity between interventions is due to the small sample size and short follow-up, which led to low statistical power. In addition, biases as confounding variables not controlled by the study, such as radiation dosage and no standardization of the participants' oral hygiene, interfered with the results. Contrary to this result, Kobus *et al*.[65] analyzed the association of the enzymes lysozyme and lactoferrin with the mean number of decayed, missing, and filled permanent teeth (DMFT) and the mean number of decayed, missing, and filled primary teeth (dmft) of 34 patients with juvenile idiopathic arthritis and 34 age and sex-matched controls, and identified an inversely proportional relationship between lysozyme concentration in saliva and dmft, observing a positive result with the use of these natural enzymes.

Salivary substitutes containing lysozyme and lactoferrin had superior antibacterial characteristics compared to saliva in terms of adherence to hydroxyapatite and proliferation of *Streptococcus mutans*.[64] This microorganism, together with *Lactobacillus spp*., releases bacterial acids and causes demineralization of the dental substrate, initiating the carious process.[17-19,34] The saliva prevents cellular aggregation of these microorganisms, provides intraoral pH balance and favors ionic exchanges with the dental element, a process that regulates teeth demineralization and remineralization.[17-19,34] However, the reduction in saliva production, known as hyposalivation, is a common condition in patients who have undergone treatment for head and neck cancer.[37]

Chemotherapy and/or radiotherapy treatment directly interfere with saliva production by the salivary glands.[6,7,18,66] Chemotherapy is capable of inducing salivary gland hypofunction in about 50% of patients and, unlike radiotherapy, the effects of chemotherapy are transitory shortly after the end of treatment.[10,18] In this study, it was not possible to establish the isolated influence of chemotherapy on caries development, as in the selected articles chemotherapy was associated with radiotherapy, in addition, information regarding chemotherapy treatments was not detailed.[37,39]

The technique, field, and radiation dose directly affect salivary glands, especially serous glands, such as the parotid and the submandibular gland, that contribute to watery secretions.[13,18] Intensity-modulated radiotherapy (IMRT) is able to modulate the doses directed to each structure and spare the parotid and submandibular glands from high doses of radiation.[18,20-22] According to Pedersen *et al*.[18] doses greater than 60 Gy are associated with irreversible damage to the salivary glands and doses of 30 Gy to 50 Gy can be reversible. The salivary gland recovery capacity after radiotherapy depends on cell regeneration capacity and the dose administered to the tissue.[18,67,68]

In addition to the effects that salivary gland hypofunction exerts on the teeth of patients who underwent head and neck radiotherapy, some studies reveal that the direct incidence of radiation on dental elements promotes chemical and mechanical changes in mineralized structures, which suggests a relationship with the formation of radiation caries.[9,69,70] The study by Lu *et al*.[69] demonstrated that doses above 30 Gy are able to promote degeneration of mineralized tissue, such as

changes in enamel microhardness and modulus of elasticity, and doses above 60 Gy promote even greater destruction. This characteristic may be related to the decreased capacity of the tooth to resist masticatory forces, even months after the end of radiotherapy.[69] The irradiation doses used in the selected studies were 40 Gy,[36,39] 70 Gy[38] and 44 to 46 Gy.[37] Two of the studies also highlighted only the inclusion of patients in which the radiation field involved major salivary glands, the main source of salivary production.[36,39]

Thus, it was noticed in this systematic review that caries incidence in patients with head and neck cancer is related not only to the use of dental materials, prevention, and dental management before, during, and after chemotherapy and radiotherapy treatment, but also to variations in the cancer treatment.

The dental materials evaluated by the included studies to reduce caries in patients after treatment for head and neck cancer must be considered with caution due to the small number of studies that matched the eligibility criteria and had a small sample size, biases, and some, a short follow-up. Thus, it is recommended that controlled clinical trials be carried out, with larger sample sizes and follow-up, to reach a more concise and evidence-based conclusion.

CONCLUSION

The findings of this systematic review suggest that dentifrice or créme based on 10% of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) showed efficacy, the intraoral fluoride release system (IFRS) had similar results to fluorine topical application, and the Oral7 mouthwash did not demonstrate significant results to reduce caries in head and neck cancer patients who underwent chemotherapy and/or radiotherapy.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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