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Periodontitis as a risk factor for colorectal cancer: systematic review and meta-analysis

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Abstract

Background: Primary studies on the association between periodontitis and colorectal cancer (CRC) may have insufficient statistical power to reach a reliable conclusion. In this regard, the present systematic review and metaanalysis were conducted to determine whether periodontitis is a risk factor for CRC.

Material and Methods: A systematic search was carried out in five databases, which included cohort and casecontrol studies published up to July 3, 2024, in which periodontitis was evaluated as a risk factor for CRC using relative risk (RR), hazard ratio (HR) or odds ratio (OR). The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias, and the GRADE system was used to determine the certainty of the evidence.

Results: Of 1476 articles retrieved, 8 cohort studies were included for qualitative analysis and meta-analysis. The overall synthesis showed that periodontitis is not a risk factor for CRC (RR=1.34; 95% CI: 0.96-1.89; p<0.09; I2=95%). In addition, subgroup analyses were performed according to gender, periodontitis diagnostic methods, and risk of bias, which led to the finding of an increased risk of CRC of 32% only for men with periodontitis (RR=1.32; 95% CI: 1.16-1.50; p<0.00001; I2=0%).

Conclusions: Periodontitis is not a risk factor for CRC, with very low certainty of evidence. However, the analysis of subgroups by gender showed that it is a risk factor for CRC in men, with moderate certainty of evidence.

Key words: Periodontitis, periodontal diseases, colorectal neoplasms, colorectal cancer, colorectal carcinoma, colorectal tumor.

Introduction

Periodontitis, one of the most prevalent inflammatory diseases, causes progressive and irreversible destruction of periodontal tissues, which eventually leads to mobility and tooth loss. The most serious condition of this disease affects between 10.8 and 11.2% of the world's population (1,2).

Colorectal cancer (CRC) is one of the leading causes of morbidity and mortality worldwide, and it is ranked second as regards the number of deaths associated with malignant neoplasms in both men and women. Furthermore, it is the third most commonly diagnosed form of cancer, accounting for approximately 10% of all new cases of cancer (3-6).

Numerous pathophysiological mechanisms, such as abnormal cell proliferation, cell differentiation, resistance to apoptosis, invasion of adjacent structures, and metastasis, are involved in colorectal carcinogenesis (4). These processes are initiated by the complex interaction of genetic and environmental factors, including sedentary lifestyle, obesity, alcohol consumption, smoking, and intestinal microbiota (3,4). Primary and secondary prevention and education about risk factors are essential elements for reducing the burden of this disease and improving prognosis and survival rates (5,7). Although there are systemic treatments, the rapid progress of the disease and its resistance to existing treatments have generated the need to investigate its risk factors, progression, and resistance to therapy (6).

The interaction of cancer cells with the microbiota is a unique feature in CRC compared to other types of cancer. Under normal conditions, the microbiota plays a protective role by participating in immunological homeostasis and the growth of intestinal lymphatic tissues; however, a change in balance leads to the proliferation of opportunistic pathogenic bacteria (6). In the cases of CRC, two specific species of periodontal bacteria are outstanding, namely F. nucleatum and P. gingivalis; the former has been more notable in regional lymph node metastases (8). These pathogens produce harmful metabolites, including toxins and antigens, that cause maladaptive immune responses and inflammation, damage to DNA, genomic instability, and tumor progression (6).

Translocation of periodontal pathobionts with oncogenic properties and subgingival proinflammatory mediators could potentiate carcinogenic agents, thereby changing the conditions favoring the development and progression of CRC (6,9).

Despite the growing evidence that periodontitis could be a risk factor for CRC, the primary studies may have insufficient statistical power to reach a reliable conclusion. In this sense, the present systematic review and meta-analysis were conducted to evaluate the possible association between periodontitis and the risk of CRC.

Material and Methods

- Protocol and registration

The present systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Metanalyses checklist (PRISMA, 2020) (10), and the protocol was registered in PROSPERO under the reference number CRD42024557822.

- Focused question

The research question: Is periodontitis a risk factor for colorectal cancer in adult patients? The question was raised according to the PECOS search strategy (population/patients, exposure, comparison, results, and design of study), where P = adults, E = exposure to periodontitis, C = absence of periodontitis, O = risk of colorectal cancer, and S = cohort and case-control studies.

- Eligibility criteria and process of selection

The observational cohort design and case-control studies included published until July 3, 2024, which studied periodontitis as a risk factor for CRC in adult patients (Over 18 years of age) and calculated the odds ratio (OR), relative risk (RR) or hazard ratio (HR). The excluded studies did not have an independent statistical analysis of the risk of CRC, those with incomplete data, fewer than 1000 participants, and a follow-up period of less than 5 years.

- Operational definitions

Periodontitis was diagnosed using clinical, radiographic assessment, and epidemiological periodontal indicators. Hospital records and self-reports were also considered.

- Search strategy

The search was carried out in the electronic databases of PubMed/Medline, Web of Science, Scopus, Embase, and BVS, as well as manual searches in the reference lists of all included studies and revisions previously published. The complete search strategy, adapted according to the syntax rules of each database, is presented in Supplement 1.

- Data extraction and synthesis

The bibliographic search results were uploaded to the Rayyan application for systematic revisions (https:// www.rayyan.ai/), and the duplicate records were eliminated. Two researchers (T.H.S. and T.U.C.) independently selected the articles to be analyzed, first by title and abstract, then four researchers working in pairs (T.H.S. with T.U.C. and R.E.C with A.A.A) analyzed the complete texts. Any disagreement was discussed among the above-mentioned researchers. Therefore, the data was independently extracted and entered into an Excel spreadsheet (Microsoft® Excel® for Office 365). Afterward, the articles selected and data extracted were revised and approved by a fifth expert investigative (J.C.A.). - Risk of bias and certainty of evidence

The studies included were analyzed using the Newcastle-Ottawa Scale (NOS) tool to assess the risk of bias. The quality of evidence of the studies included in the meta-analysis was evaluated by the GRADE tool, using the GRADEpro GDT software (11).

- Statistical analysis

Data collected from the studies selected for the metaanalysis were processed using RevMan software (Review Manager v.5.3, The Cochrane Collaboration) to evaluate periodontitis as a risk factor for CRC. The random effects model was applied to develop the forest plot, and the heterogeneity between the studies was assessed using the I2 index. A sensitivity analysis was also performed to verify each study's influence on the pooled results. Subgroup analysis was performed to determine potential sources of variability. Moreover, an assessment of potential publication bias was performed using Egger's test and Stata 16.0 software (StataCorp LLC, College Station, TX).

- Summary of results

The primary outcome was periodontitis as a risk factor for CRC. The information required from each study was collected in a preliminary summarized table, and results with sufficient data to calculate an effect estimate were used for the meta-analysis.

Results

- Selection of studies

As presented in the PRISMA 2020 flowchart (12) (Fig. 1), 1476 records were retrieved. After removing duplicates and screening by title and abstract, 11 articles (10 cohort and one case-control study) remained for full-

text evaluation, of which 5 (4 cohort and one case-control) were excluded. After manually searching the references of previous systematic reviews, four additional studies were retrieved, of which two were excluded. The reasons for excluding studies are described in detail in Supplement 2. Finally, eight studies were chosen for qualitative analysis and meta-analysis.

- Characteristics of studies

In the 8 cohort studies included (Table 1), 988,897 subjects were evaluated; the study with the smallest number of participants had 1,337 (1,022 exposed and 315 unexposed) (13), and the one with the largest number had 713,201 (53,075 exposed and 660,126 unexposed) (14). The ages of the patients studied ranged from 15 (14) to 85 years (13); the shortest follow-up period was 10 years (14), and the longest was 41 years (15).

The included studies were conducted in the United States (13,16-20), Sweden (15), and Korea (14). All studies declared that they had been funded; while five (14-17,19) mentioned that there was no conflict of interest, two (13,20) did not mention it, and one (18) indicated that the financing agent participated in the design and data collection.

- Risk of bias

As shown in Table 2, most of the studies included in the present analysis had a low risk of bias (13,14,16,17,19,20). The NOS categories with the lowest compliance were the representativeness of the cohort exposed and the determination of exposure.



Fig. 1: Flow chart for inclusion of the studies evaluating periodontitis as a risk factor for CRC.

Table 1: General characteristics of cohort studies inc
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	Author					No. of Pa	rticipants	The			
N°	(coun- try, year of publica- tion)	Data- base	De- sign	Fol- low-up period (years)	Age (Years)	Exposed	Non- exposed	primary loca- tion of colorec- tal cancer	Periodon- tal charac- teristic	Covariables	Conclusions
1	Kim (Korea, 2022)	Korean National Health Insur- ance Cohort Database	Retro- spec- tive	10	Peri- odonti- tis: 49 (39-60) Con- trols: 31 (15-46)	Total: 53075 Men: 27310 Women: 25765	Total: 660126 Men: 325796 Women:- 334330	Colon	Community periodontal index: Code 3: presence of moderate pocket (4-5 mm) Code 4: Deep pock- et (probing equal to or greater than 6 mm)	Age, sex, level of in- come, residential areas, BMI, smoking history, and comorbidities (MI, CHF, PVD or rest pain, any history of CVA, dementia, COPD, CTD, PUD, DM, moderate to severe CKD, hemiple- gia, leukemia, malig- nant lymphoma, ascites or esophageal varices, disseminated cancer, and AIDS)	Periodontitis was associ- ated with an increased risk of cancer. Diagnosis of periodontitis was associ- ated with an increased risk of colon cancer.
2	Momen- Heravi (USA, 2017)	Nurses' Health Study	Pro- spec- tive	18	30 - 55	Total: 9725 Women: 9725 Men: 0	Total: 59931 Women: 59931 Men: 0	Colorec- tal, co- lon and rectum	Self-report- ed peri- odontitis	Age, race, alcohol consumption, intakes of folate, calcium, vitamin D, red meat and processed meat, multivitamin use, BMI, physical activity, cigarette smoking, his- tory of sigmoidoscopy/ colonoscopy screening, family history of CRC, aspirin use, Type 2 DM and PMH use.	Women with fewer teeth and possibly moderate or severe bone loss may have a slightly higher risk of developing colorectal cancer, sug- gesting a possible role of oral health in colorectal carcinogen- esis.
3	Michaud (USA, 2018)	Athero- sclerosis Risk in Com- munities (ARIC cohort study)	Pro- spec- tive	14.7	44 - 66	Total: 4346 The data provided were ex- pressed in per- centages without specify- ing the total number of men and women sepa- rately.	Total: 1710 The data provided were expressed in per- centages without specifying the total number of men and women separately.	Colorec- tal	Probing depth and clinical attachment loss (CAL);	Age, race, educational status, field center, BMI, DM, HRT in women smoking and drinking status.	The risk of cancer, es- pecially lung and colorectal cancer, was higher in individuals with peri- odontitis.
4	Michaud (USA, 2016)	Health Profes- sionals Follow- up Study (HPFS)	Pro- spec- tive	26	No PD and 17- 32 teeth: 52.2 (±9.56); No PD and <17 teeth: 61.3 (±9.20); PD and 17-32 teeth 56.5 (±9.59); PD y <17 teeth: 64.8 (±8.06)	Total: 1945 Men: 1945 Women: 0	Total: 17988 Men: 17988 Women: 0	Colorec- tal	Self-report of peri- odontitis	Age, height, BMI, physical activity, eth- nic origin, DM, high cholesterol, high blood pressure, NSAID, multivitamin, daily dietary intake (calories, vitamin D, alcohol)	Periodontitis was not as- sociated with colorectal cancer.

Table 1: Cont.

5	Arora (Swe- den, 2010)	The Swedish Twin Registry	Pro- spec- tive	41	No PD: 50.6 (±9.4); PD: 58.7 (±9.7)	Total: 908 The data provided were expressed in per- centages without specify- ing the total number of men and wom- en sepa- rately.	Total: 12592 The data provided were expressed in per- centages without specifying the total number of men and women separately.	Colorec- tal	Self-report- ed peri- odontitis: If at least half of the pa- tient's teeth showed mobility, this was indicative of advanced disease.	Sex, age, education, employment, number of siblings, smoking sta- tus, smoking status of partner, alcohol status, BMI, DM	Periodontitis was associ- ated with an increased risk of colorectal cancer.
6	Michaud (USA, 2008)	Health Profes- sionals Follow- up Study (HPFS)	Pro- spec- tive	18	No PD: 53.7 (±9.7); PD: 58.3 (±9.2)	Total: 7863 Men: 7863 Women: 0	Total: 40512 Men: 40512 Women: 0	Colorec- tal	Self-report of peri- odontitis	Age, height, BMI, physical activity, race, smoking history, disease history (DM, Cholecystectomy), medication use (aspirin, NSAID, multivitamin) daily dietary intake (calories, vitamin C, vitamin D, alcohol).	No as- sociation was found between periodontitis and colorectal cancer.
7	Mai (USA, 2016)	Women's Health Initiative (WHI) Observa- tional	Pro- spec- tive	12.2	53 - 85	Total: 1022 Men: 0 Women: 1022	Total: 315 Men: 0 Women: 315	Colorec- tal	Radio- graphic assessment: loss of al- veolar ridge height.	Age at the visit, race, the highest level of educa- tion, smoking history, secondhand exposure to smoke, alcohol consumption, physical activity, total energy intake, fruit and veg- etable intake, red meat intake, caffeine intake, lactose intake, hormone use plus progesterone, current regular use of NSAID, current dietary supplement use (any vitamin, calcium, and vitamin D), history of diagnosis of DM, dental hygiene (frequency of toothbrushing, tooth flossing, and dental visits), family history of cancer, age at meno- pause, age at menarche, parity, and use of oral contraceptives, BMI, smoking history in- cluded smoking status, packs smoked per day, age when the patient started smoking.	There were no statistically significant associations between the severity of periodontitis and the risk of total or site-specific cancer.
8	Nwizu (USA, 2017)	Study at the Buffalo Clinical Center	Pro- spec- tive	15	50 - 79 Mean: 68.3	Total: 17103 Men: 0 Women: 17103	Total: 48766 Men 0 Women: 48766	Colorec- tal, co- lon and rectum	Self-report of history of PD	Age, race/ethnicity, edu- cational level, region of residence, family history of cancer, history of DM, recreational physical activity, smoking status, pack-years of smoking, exposure, pt secondhand smoke, alcohol con- sumption, total dietary energy intake, fruit and vegetable intake, total (dietary & supplement) intake of calcium and vitamin D and MHT use, frequency of dental visits, BMI.	No as- sociation was found between PD and colorectal cancer.

Abbreviations: PD = periodontal disease, CRC = colorectal cancer MI = myocardial infarction, CHF = congestive heart failure, PVD = peripheral vascular disease, CVA = cerebrovascular accident, CTD = connective tissue disease, PUD = peptic ulcer disease, CKD = chronic kidney disease, BMI = body mass index, HRT = hormone replacement therapy, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, AIDS = acquired immune deficiency syndrome, PMH = post-menopausal hormone, NSAID = non-steroidal anti-inflammatory drug, MHT = menopausal hormone therapy.

		Se	election		Compara- bility				
Study	Represen- tativeness of the exposed cohort	Selec- tion of the non-ex- posed cohort	Ascer- tain- ment of expo- sure	Demonstra- tion that outcome of interest was not present at the start of the study	Compa- rability of cohorts based on the design or analysis	Assess- ment of out- come	Was follow- up long enough for outcomes to occur?	Ade- quacy of follow- up of cohorts	NOS
Kim, 2022	*	*	*	*	**	*	*	*	9
Momen-Heravi, 2017	-	*	*	*	**	*	*	*	8
Michaud 2018	-	*	*	-	**	*	*	-	6
Michaud 2016	-	*	-	*	**	*	*	*	7
Arora, 2010	-	*	-	*	**	*	*	-	6
Michaud 2008	-	*	-	*	**	*	*	*	7
Mai, 2016	-	*	*	*	**	*	*	*	8
Nwizu, 2017	-	*	-	*	**	*	*	*	7

Table 2: Summary of the risk of bias assessment for cohort studies - New Castle Ottawa.

- Meta-analysis of synthesis

The 8 cohort studies were analyzed using the random effects model and considering the relative risk (RR) as the measure of effect. The global synthesis showed a RR of 1.34 (95% CI: 0.96-1.89) and p=0.09, with considerable general heterogeneity (I2=95%; p<0.00001), as shown in the forest plot of Fig. 2. In this sense, because the CI crosses the line of no effect, periodontitis would not be a risk factor for CRC.

- Analysis of subgroups

Analysis of the subgroups, which included gender, methods of diagnosis of periodontitis, and risk of bias, was performed, as shown in Table 3. The heterogeneity drastically decreased in the subgroup gender in the studies that included only men (I2=0%, p=0.68), only women (I2=0%, p=0.38), and an unclear risk of bias (I2=0%, p=0.36). A decrease in heterogeneity, although moderate, was also found when the method of periodontitis diagnosis was self-reported (I2=59%, p=0.12). In this sense, the analysis showed an increase of 32% in the CRC risk for men with periodontitis (RR=1.32; 95% CI: 1.16-1.50; p<0.00001). The forest plot of the analysis of subgroups may be visualized in Supplement.

- Publication bias and sensitivity analysis

The Egger test was used, and no publication bias (t=0.40, p=0.7026) was detected, which was confirmed by the Harbor test (t=0.21, p=0.8407) and the Begg test based on the Kendall score (z=1.11, p=0.2655).

The sensitivity analysis is shown in Table 4, in which the study of Momen-Heravi *et al.* (16) was omitted. An association was found between periodontitis and CRC (RR=1.43; 95%CI:1.00-2.03; p=0.05). Moreover, omitting the study of Kim *et al.* (14) decreased the heterogeneity to 53%. However, the decision was to maintain these studies due to the statistical power of the sample.



Fig. 2: Forest plot of the studies evaluating periodontitis as a risk factor for CRC.

Subgroups		No. of	Hete	rogeneity	Effect		Meta-anal	Meta-		
		studies	I ² (%)	р	model	RR	95% CI	р	regression	
	Male	2	0	0.68	Random	1.32	1.16-1.50	< 0.00001		
Gender	Female	3	0	0.38	Random	0.98	0.86-1.13	0.82	0.004	
	Male and female	3	86	0.0007	Random	1.65	0.98-2.76	0.06		
Method of	Clinical-radiographic	6	95	< 0.00001	Random	1.4	0.94-2.07	0.09	0.500	
diagnostic	Self-report	2	59	0.12	Random	1.32	0.97-1.79	0.47	0.500	
Disle of hiss	Low risk of bias	6	96	< 0.00001	Random	1.36	0.91-2.03	0.13	0.800	
KISK OF DIAS	Unclear risk of bias	2	0	0.36	Random	1.27	0.93-1.75	0.13	0.800	

Table 3: Results of subgroup analysis.

Table 4: Sensitivity analysis.

Omited study	No. of	Hete	rogeneity	Meta-analysis			
Onneu study	studies	I ² (%)	р	RR	95% CI	р	
Arora, 2010	7	96	< 0.00001	1.32	0.92-1.91	0.13	
Kim, 2022	7	53	0.05	1.16	0.99-1.35	0.06	
Mai, 2016	7	96	< 0.00001	1.31	0.92-1.85	0.13	
Michaud, 2008	7	95	< 0.00001	1.35	0.89-2.05	0.16	
Michaud, 2016	7	95	< 0.00001	1.36	0.93-1.99	0.11	
Michaud, 2018	7	95	< 0.00001	1.38	0.96-1.99	0.09	
Momen-Heravi, 2017	7	94	< 0.00001	1.43	1.00-2.03	0.05	
Nwizu, 2017	7	94	< 0.00001	1.41	0.99-2.02	0.06	

- Quality of evidence

As presented in the SoF Table in Fig. 3, periodontitis was not a risk factor for CRC, with very low certainty of evidence, indicating that the probability of a different result for future studies would be very high. Considering the finding that periodontitis was a risk factor for CRC in the male gender, a second GRADE analysis was performed (Fig. 4) with the studies included in this subgroup, obtaining a moderate certainty of evidence, which suggested a good indication of the probable effect.

Summary of findings:

[periodontitis] c	[periodontitis] compared to [non periodontitis] in [increase risk of colorectal cancer]								
Patient or population: [increase risk of colorectal cancer] Setting: Intervention: [periodontitis] Comparison: [non periodontitis]									
	Anticipated absolute effects* (95% Cl)			Nr = 6	Certainty of				
Outcomes	Risk with [non periodontitis]	Risk with [periodontitis]	Relative effect (95% Cl)	participants (studies)	the evidence (GRADE)	Comments			
Colorectal cancer (CRC) assessed with: medical diagnosis follow-up: range 10 years to 41 years	6 per 1000	9 per 1000 (6 to 12)	RR 1.34 (0.96 to 1.89)	937927 (8 non- randomised studies)	⊕OOO Very low ^{a,b}	Periodontitis is not a risk factor for colorectal cancer. However, the evidence is very uncertain and the likelihood of a different outcome is very high.			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there

is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of

effect.

Explanations

a. Due to considerable inconsistency (I2 = 95%) we decided to reduce 2 certainty levels. b. OIS criterion is met ((at least 2000 patients) and the 95% CI include no-effect (CI includes RR of 1.0). For this reason, we decided to reduce 1 certainty level.

Fig. 3: SoF table of the eight studies evaluating periodontitis as a risk factor for CRC.

Summary of findings:

Periodontitis compared to non periodontitis in increase risk of colorectal cancer in men

Patient or population: increase risk of colorectal cancer in men Setting: Intervention: periodontitis

Comparison: non perio	Anticipated absolute effects* (95% CI)			Nr. of	Containty of		
Outcomes	Risk with non periodontitis	Risk with periodontitis	Risk with eriodontitisRelative effect (95% CI)	participants (studies)	the evidence (GRADE)	Comments	
Colorectal cancer in men (CRC in men) assessed with: medical diagnosis follow-up: range 18 years to 26 years	21 per 1000	28 per 1000 (24 to 32)	RR 1.32 (1.16 to 1.50)	68308 (2 non- randomised studies)	⊕⊕⊕O Moderate	Periodontitis probably results in a slight increase in colorectal cancer in men.	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Fig. 4: SoF table of the studies evaluating periodontitis as a risk factor for CRC in men.

Discussion

In recent years, studies have suggested a link between periodontitis and the risk of gastrointestinal cancer. The exact biological mechanisms of this association have not yet been fully understood. Some potential pathways have, however, been identified, such as the production of carcinogenic metabolites by specific oral microorganisms and the induction of chronic low-grade systemic inflammation, leading to the release of free radicals and cytokines (21).

Although the overall synthesis showed an RR of 1.32, in the present meta-analysis, the CI crossed the line of no effect, indicating that periodontitis was not a risk factor for CRC. This was in disagreement with the findings of Wang et al. (21) and Li et al. (22), who reported that periodontal disease (PD) increased the risk of CRC by 21% and 44%, respectively. These authors used HR as a measure of effect, and although this can be interpreted as an RR, it can convey different information. The former quantifies the instantaneous relative risk, while RR quantifies the cumulative risk; therefore, these two estimates may differ considerably for the same data (23). It should be noted that the metaanalysis by Wang et al. included one study (24) that did not evaluate CRC directly; instead, it evaluated benign and malignant colorectal tumors and found an association only for the former. Likewise, the review by Li et al. included one study (25) that evaluated mortality. In contrast, both reviews evaluated PD (gingivitis and periodontitis) and not specifically periodontitis, accentuating the discrepancy.

When performing subgroup analysis, a 32% increase in the risk of CRC was found for men with periodontitis, coinciding with the findings reported by Li *et al.* (22). This is due to the differences in exposure to risk factors such as alcohol and tobacco, dietary patterns and sex hormones. Considering that men diagnosed with CRC had a worse prognosis and a 40% higher mortality rate than women (26), strategies for early detection of periodontitis and colonic lesions with oncogenic potential should be considered for this group.

A limitation to be considered for the present review would be the high heterogeneity, possibly due to the large difference in sample sizes, population characteristics, criteria for classifying exposed/non-exposed participants, and indicators for periodontitis diagnosis, among other factors. Concerning sample sizes, the study by Mai et al. (13) had a sample of only 1337 participants, while Kim et al. (14), Momen-Heravi et al. (16), and Nwizu et al. (17) had samples larger than 50,000 participants, which would contribute to the power of the meta-analysis for detecting real effects (27-29). Similarly, the study by Kim et al. (14) showed a significant difference in the ages of their exposed vs. unexposed groups, with mean ages of 49 [39-60] and 31 [15-46], respectively. This difference in ages could be critical, considering that CRC occurs more frequently in patients over 50 years of age (26,30), and the approximate period in which malignancy findings may occur in the colorectal region is 10 and 15 years, mainly in cases of polyps or in patients with Lynch syndrome (26,31). Moreover, concerning the diagnosis of periodontitis,

the majority of studies included in this analysis were based on self-reports validated in previous studies by radiographic bone loss or clinical examination. Only a few used a periodontal index or clinical and/or radiographic diagnosis, the latter being, according to Heitz (32), the standard method for periodontitis diagnosis. While it is true that the use of self-reported data could be susceptible to recall bias or patients could modify their responses to align with concepts they considered socially acceptable, an interesting finding of the present systematic review and meta-analysis was that the selfreport subgroup data did not differ from those of the clinical-radiographic diagnosis of periodontitis, which would suggest that self-report could be a reliable method for use in this type of studies.

According to the GRADE assessment of the eight studies included in the meta-analysis, there was great uncertainty in the results, and further studies on the subject would likely provide substantially different results. However, when assessing studies that included men, a moderate certainty of evidence was obtained, indicating that the results probably reflect the situation that occurred in reality. From this aspect, we do recommend that future studies must focus on the presence or predominance of bacterial complexes with evidence of oncogenic properties, such as Fusobacterium nucleatum and Porphyromonas gingivalis (33-35), and show specific results according to gender. Likewise, the periodontal epidemiological index should be homogenized to classify the exposed group and incorporate the evaluation of biomarkers of chronic systemic inflammation.

Conclusions

Periodontitis is not a risk factor for CRC, with very low certainty of evidence and high heterogeneity of the studies included. However, periodontitis is a risk factor in males, with moderate certainty of evidence and without heterogeneity.

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