ORIGINAL ARTICLE

Periodontal Disease Indices and Colorectal Cancer Risk in Greek Adults: A Case–Control Study

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ABSTRACT

Introduction: The previous researches have recorded positive associations between periodontal disease (PD) and risk of cancer at various locations. The aim of the present case–control study was to investigate the possible associations between PD indices and the risk of colorectal cancer (CRC) development in a sample of Greek outpatients referred to a medical and dental private practice. **Materials and Methods:** A total of 342 individuals were interviewed and underwent an oral clinical examination, and 85 of them were suffered from CRC at various anatomic locations. The evaluation of the possible associations between CRC and PD indices was performed using a regression analysis model. **Results:** Clinical attachment loss (CAL) ($P = 0.042$, odds ratio [OR] = 1.78, 95% confidence interval [CI] = 1.02–3.11) was significantly associated with the risk of developing CRC. CRC family history ($P = 0.002$, OR = 2.33, 95% CI = 1.35–4.03) and smoking ($P = 0.019$, OR = 1.96, 95% CI = 1.12–3.45) were also significantly associated with the mentioned risk, whereas smoking was found to be nota confounder regarding the estimated association between moderate/severe CAL with the risk of developing CRC. **Conclusion:** CAL as an index for PD severity was statistically significantly associated with the risk of developing CRC.

Key words: Adults, chronic inflammation, colorectal cancer, periodontal disease, risk factor

INTRODUCTION

Colorectal cancer (CRC) is relatively a frequent human cancer and is considered as the 3rd most common cancer in males and the 2nd in females, whereas it has been estimated that more than 50.0% of CRC cases occur nowadays in industrialized countries.[1,2] CRC also consists the 4th most common cause of cancer mortality and is responsible for 600,000 deaths annually.[3,4] Its incidence could be attributed to the Western lifestyle mainly[5] and remains one of the main health diseases worldwide. The main cause for CRC relatively high mortality is the lack of reliable biomarkers that could lead to early diagnosis and treatment. The 5-year relative survival increased significantly from 53.0% to 62.0% and from 51.0% to 65.0% for colon and for rectal cancer, respectively, despite the fact that the majority of CRC cases are presented with advanced stages at the time of initial diagnosis, and already malignancy cells are present in various organs, leading to a clinical situation which eliminate the possibility of a radical surgical intervention.[6] CRC develops in the colon or the rectum and genetic, behavioral, environmental, and other unknown risk factors are implicated in its etiology. A great number of CRC cases are sporadic;[7] however, genetic risk factors include inherited cancer syndromes, such as Lynch syndrome, hyperplastic, familial juvenile, and hamartomatous polyposis. That parameter of genetic predisposition is responsible for 2.0-5.0% of all colon and rectal cancers.[8,9] The environmental and behavioral risk factors include high red or processed meat daily consumption, heavy alcohol daily consumption, low consumption of fresh fruits and vegetables, obesity, smoking, physical inactivity, and other unknown factors.[10,11] The previous studies have observed that nonsteroidal anti-inflammatory drugs, such as aspirin associated with a lower risk of CRC.[12] In addition,

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some previous reports have been recorded that plasma levels of inflammatory biomarkers or pro-inflammatory cytokines such as interleukin-8 (IL-8), soluble tumor necrosis factor receptor 2, and IL-6 were correlated with an increased risk of CRC; however, other similar studies have not confirmed such observations.[13-16] In addition, chronic inflammatory diseases such as Crohn's disease and ulcerative colitis have been associated with an increased risk of CRCs cancers, however, those diseases can explain only 1.0–2.0% of all CRC cases.[7,17,18] Based on the mentioned observations, it has been suggested that chronic inflammatory conditions could be implicated in development and/or cancer progression as chronic inflammation may cause alterations in cellular signaling pathways in relation to mutagenesis, epithelial cell proliferation, inhibit programmed cell death, decrease the adaptation to oxidative stress, increase the inflammatory mediators accumulation, and contribute to the angiogenic process.[19] Periodontal disease (PD) is a chronic inflammatory disease of the supporting tissues of the teeth.[20] Severe periodontitis and edentulism influence 743 and 158 million individuals worldwide, respectively.[21,22] The chronic infection of periodontal tissues can cause systemic effects and results in an increased plasma concentration of inflammatory cytokines and chemokines that are linked to PD severity, such as C-reactive protein, IL-1, and IL-6. Despite the fact that the mentioned inflammatory biomarkers may be implicated in systemic inflammations, it remains unclear whether bacterial invasion to host systemic blood circulation, activation of systemic inflammatory response or immune response to periodontal infective bacteria may influence the risk for various systemic diseases development.[23,24] PD has been associated with several systemic diseases and disorders, such as diabetes mellitus, cardiovascular disease, respiratory disease, inflammatory bowel disease,[25] cancer,[26] and systemic infections.[27,28] The previous researches have recorded positive associations between PD and risk of cancers at various locations including oral, pharynx, lung, pancreas, breast, esophagus, and stomach.[29-41] In addition, similar studies have suggested that tooth loss, as a PD indicator, was independently associated with an increased risk of cancer in organs such as head and neck, esophagus, and lungs.[30,37,42,43] However, the possible association between PD, tooth loss, and CRC has not been sufficiently investigated. Few studies have been carried out but recorded no associations between PD and CRC risk.[4,37,44,45] On the contrary, only one study showed that PD was associated with high rates of CRC mortality.[46] Poor oral health or hygiene, as indicators of PD, is possible risk factors for cancer in different organs according to recent prospective and case–control epidemiological studies.[30,32-35] It has been suggested that poor oral health might enhance systemic inflammation, local excessive immune response and probably is able to alter microbiota by pathogens that cause PD, condition that could be implicated in CRC development.[47,48] Therefore, despite the fact that oral health might play an important role in colorectal (CR) carcinogenesis, relevant epidemiological studies are limited and have not resulted in definitive outcomes. The present retrospective case–control study was carried out to investigate the possible association between PD indices and the CRC risk in a sample of Greek adults.

MATERIALS AND METHODS

Study sample

A total of 342 individuals, 176 males and 166 females, aged 45–71+ years, referred by two private practices were included in the study sample. Participants responded to a medical and dental health questionnaire and examined clinically in their oral and dental status by a well-trained and calibrate dentist.

Participant's selection criteria

Patients-cases and healthy individuals-controls should have at least 20 natural teeth and should meet the criteria of established periodontitis,[49] namely, at least two teeth with clinical attachment loss (CAL) ≥6 mm and more than one site with probing pocket depth (PPD) ≥5 mm. Participants should not have been treated by any conservative or surgical periodontal therapy, during the previous 6 months or received systemic antibiotics or an inflammatory or other systemic drugs the previous 6 weeks.[50] To avoid possible confounding effects on the research indices examined, cases and controls with the following diseases or pathological conditions were excluded from the study protocol: Acute infections, diabetic mellitus, cardiovascular diseases, rheumatoid arthritis, patients on immunosuppression caused by hematological malignancy or recent organ transplantation, and patients who received general glucocorticoids. CRC patients in an advance stage under medical supervision, with CR metastases of a primary focus at a different location and hospital CRC patients were also excluded from the study. The mentioned conditions may have potential effects on the oral tissues and the variables examined. Cases group included individuals, in which the diagnosis was set initially by histological examination during the endoscopic procedure, whereas before the application of any CRC therapeutic treatment, surgery, radiotherapy, or chemotherapy, oral hygiene instructions were given. Controls group was selected by the friendly and collegial environment of cases group to avoid as much as possible effects of potential confounders such as socioeconomic status.

Dental and oral clinical examination

Cases and controls dental and oral clinical examination was performed at two private practices and concerned the following clinical indices of periodontal tissues: PPD, CAL, and bleeding on probing (BOP) were measured to the nearest mm for each tooth except for the remaining roots and the 3rd molars by a William's 12 PCP (PCP 10-SE, Hu-Friedy Mfg. Co. Inc., Chicago, IL, USA) at six sites (facial, mesiofacial,

distofacial, lingual, mesiolingual, and distolingual). PPD index was categorized as follows:[51]

- Score 0: Moderate periodontal pockets, 4–6.0 mm and
- Score 1: Advanced periodontal pockets, >6.0 mm.

CAL severity was categorized as follows:[52]

- Score 0: Mild, 1–2.0 mm of attachment loss and
- Score 1: Moderate/severe, ≥3.0 mm of attachment loss.

Presence/absence of BOP was categorized as follows:

- Score 0: Absence of BOP and
- Score 1: Presence of BOP and regarded as positive if it took place within 15 s of probing.

Questionnaire

Cases and controls groups were responded to a self-administered health questionnaire which included epidemiological variables such as age, gender, smoking status (active/former never-smokers), socioeconomic and educational status, CRC family history, alcohol and red/processed meat daily consumption, and information with reference to their general medical history several chronic systemic disorders or diseases and medication. To establish the intraexaminer variance, the same dentist reexamined a random sample of 68 (20.0%) individuals, cases, and controls, after a period of 3 weeks and no differences were observed between the two clinical examinations (Cohen's Kappa = 0.96), whereas during that time period, no oral hygiene instructions were given to the participants.

Ethical consideration

The current study was a retrospective, no experimental case–control study. In Greece, only experimental studies must be reviewed and approved by authorized committees (Ministry of Health, Dental Associations, etc.). An informed consent form was signed by the individuals who agreed to participate in the present case–control study.

Statistical analysis

The worst values of PPD and CAL at the mentioned sites per tooth and the presence/absence of BOP for each individual were measured and coding of dichotomous variables was applied. Females, never smokers, participants with a low socioeconomic (income/monthly <1000 €) and educational (graduated from primary/elementary school) level, no CRC family history participants, and those who consume <30 g of alcohol daily[53] and <20 g of red/processed meat daily[54] were coded as 0. Age groups distribution was coded as 0, 1, 2, and 3 for ages 45–50, 51–60, 61–70, and 71+, respectively. The statistical model of univariate analysis was carried out to assess the association between the independent variables examined and the CRC risk, separately, using Chi-square test. Multivariate regression analysis model was performed to evaluate the associations between the dependent variable, CRC, and independent ones that were defined by the enter method. Adjusted odds ratios (ORs) and 95% confidence interval (CI) were also estimated. Finally, the independent variables were included in stepwise method to assess gradually those which showed a significant association with the dependent one. Cochran and Mantel–Haenszel statistical method was carried out to control possible confounders, such as smoking and socioeconomic status to avoid biased associations. Statistical analysis was carried out using the statistical package of SPSS ver.19.0, and *P*-value <5% ($P < 0.05$) was considered to be statistically significant.

RESULTS

The study sample had a mean age of 63.2 years (±5.3). Eighty-five individuals, 38 males and 47 females, suffered from CRC in several locations. The histological type was adenocarcinoma and the anatomic distribution of CRC was rectum 27.7%, sigmoid colon 23.4%, cecum 15.8%, ascending colon 8.2%, rectosigmoid junction 7.6%, colon, overlapping, and unspecified 7.3%, descending colon 6.2%, and transverse colon 3.8%. Table 1 shows univariate analysis of cases and controls in regard to the examined variables. Epidemiological variables such as age, educational level, smoking, CRC family history, red meat consumption, and the total number of PD indices examined were statistically significantly associated with CRC risk. Table 1 also presents unadjusted ORs and 95% CI. After the performance of the first method (Step 1a) of the regression model, it was found that educational level, smoking, and CRC family history were significantly associated with CRC risk [Table 2]. The stepwise final method (Step 6a) shows that smoking, CRC family history, and CAL were significantly associated with CRC risk [Table 2]. Table 3 also presents adjusted ORs with 95% CI. CAL was also significantly associated with CRC risk after adjusting for confounders, such as smoking and socioeconomic status [Table 3].

DISCUSSION

The present case–control research showed that CAL was associated with an increased CRC risk, after controlling for possible confounders such as smoking and socioeconomic status. Despite the fact that more investigation is required to confirm such observations, the current findings suggest that improvement of oral hygiene status and smoking cessation could be an effective preventive measure against CRC development. The role of gender as a cancer risk factor is known; however, it is considered to be a confounder. The results revealed no association between gender and CRC risk, finding that was in accordance with those from the previous reports.[55,56] Although older individuals are in a higher risk for total cancer, CRC,[56,57] initiation, and progression of PD,[58] age is also considered as a confounder. In the current study, no association was recorded between age and CRC risk.

Table 1: Univariate analysis of cases and controls regarding each independent variable examined

Variables	Cases (*n*) (%)	Controls (*n*) (%)	*P*-value	Odds ratio	95% Confidence interval
Gender					
Males	38 (44.7)	138 (53.7)			
Females	47 (55.3)	119 (46.3)	0.151	0.69	0.43–1.14
Age (years)					
45–50	8 (9.4)	67 (26.1)			
51–60	29 (34.1)	80 (31.1)	0.013*	-	-
61–70	38 (44.7)	87 (33.9)			
71+	10 (11.8)	23 (8.9)			
Socioeconomic level					
Low	38 (44.7)	107 (41.6)			
High	47 (53.3)	150 (58.4)	0.619	1.13	0.69–1.86
Educational level					
Low	30 (35.3)	149 (58.0)			
High	55 (64.7)	108 (42.0)	0.000*	0.40	0.24–0.66
Smoking					
No	27 (31.8)	134 (52.1)			
Yes	58 (68.2)	123 (47.9)	0.001*	0.43	0.26–0.72
Cancer family history					
No	29 (34.1)	146 (56.8)			
Yes	56 (65.9)	111 (43.2)	0.000*	0.39	0.24–0.66
Red meat consumption (g/daily)					
<30	31 (36.5)	137 (53.3)			
>30	54 (63.1)	120 (46.7)	0.007*	0.50	0.30–0.83
Alcohol consumption (g/daily)					
>30	37 (43.5)	133 (51.8)			
<30	48 (56.5)	124 (48.2)	0.189	0.72	0.44–1.18
Periodontal pockets					
Depth 4.0–6.0 mm	32 (37.6)	159 (61.9)			
Depth >6.0 mm	53 (62.4)	98 (38.1)	0.024*	0.37	0.22–0.62
Clinical attachment loss					
Mild 1–2.0 mm	24 (28.2)	185 (72.0)			
Moderate/severe ≥3.0 mm	61 (71.8)	72 (78.0)	0.000*	0.15	0.08–0.26
Bleeding on probing					
No	28 (32.4)	133 (51.8)			
Yes	57 (67.6)	124 (48.2)	0.003*	0.46	0.27–0.77

**P*-value: Statistically significant

Another crucial confounder is socioeconomic level; however, it has been proven its possible role as a CRC risk factor.[59-61] Individuals in low socioeconomic status had a higher risk of developing CRC compared to those in higher socioeconomic status, observation that could be attributed to differences regarding the access to and use of health-care services, as individuals in low socioeconomic status have lower rates of CRC screening.[59] However, other studies showed that high socioeconomic status individuals were in a higher risk of developing CRC.[62,63] No association was observed in the current study between those variables examined. The possible role of educational level as a risk factor of developing CRC has been investigated according to the previous reports with conflicting outcomes.[62,64,65] However, it is supposed that high-educated individuals take care of their own oral hygiene more than low-educated ones.[66,67] In the current study, no

Table 2: Presentation of correlation between independent variables and colorectal cancer according to enter (first step) and Wald method (backward) of multiple logistic regression analysis model

Variables in the equation	B	S.E	Wald	df	Sig.	Exp. (B)	95% CI for exp. (B)	
							Lower	Upper
Step 1a								
Gender	0.392	0.277	1.998	1	0.157	0.676	0.392	1.164
Age	0.356	0.154	5.366	1	0.051	1.427	1.056	1.929
Socioeo_lev	0.365	0.284	0.000	1	0.986	1.005	0.577	1.752
Educ_lev	0.460	0.282	11.627	1	0.031	2.613	1.504	4.537
Smok_stat	0.691	0.295	5.501	1	0.019	1.997	1.120	3.558
Ca_fam_history	0.785	0.286	7.526	1	0.006	2.193	1.251	3.842
Redmeat_cons	0.324	0.293	1.223	1	0.269	1.383	0.778	3.459
Alcoh_cons	0.161	0.286	0.317	1	0.573	1.175	0.671	2.055
P_p_d	0.514	0.287	3.206	1	0.073	1.671	0.953	2.932
C_a_l	0.488	0.298	2.653	1	0.056	1.628	0.909	2.918
B_o_p	0.110	0. 0.284	0.001	1	0.342	0.990	0.567	1.728
Constant	2.877	0.541	38.324	1	0.000	0.032		
Step 6a								
Age	0.358	0.152	3.558	1	0.068	1.431	1.062	1.927
Educ_lev	0.998	0.278	3.880	1	0.055	1.713	1.003	2.678
Smok_stat	0.675	0.288	5.492	1	0.019*	1.964	1.117	3.454
Ca_fam_history	0.847	0.279	9.227	1	0.002*	2.332	1.350	1.028
P_p_d	0.504	0.282	3.196	1	0.074	1.655	0.953	2.874
C_a_l	0.577	0.284	4.120	1	0.042*	1.781	1.020	3.109
Constant	2.454	0.436	42.637	1	0.000	0.032		

Variable (s) entered on step 1: Gender, age, socioc_lev, smok_stst, ca_fam_history, redmeat_cons, alcoh_cons, p_p_d_, c_a_l, b_o_p.
CI: Confidence interval

Table 3: Application of Cochran and Mantel-Haenszel, statistical method for controlling possible confounders

Variables	Exp. (B)	95% CI
Clinical attachment loss		
Non-smokers	1.838	0.597–3.126
Smokers	1.987	0.651–3.201
Low socioeconomic level	1.372	0.458–1.822
High socioeconomic level	1.314	0.501–1.927

CI: Confidence interval

association was recorded between educational level and CRC risk. CRC family history was found to be significantly associated with the CRC risk, finding that was in accordance with those from the previous reports.[8,9] It has been recorded that the first-degree relatives who suffer from colon or rectal cancer or hereditary non-polyposis or familial adenomatous polyposis have an increased risk of CRC developing, suggestion that could be attributed to the influence of hereditary and environmental factors.[68] In a meta-analysis by Butterworth *et al*.,[68] after the consideration of cohort and case–control studies was confirmed the risk of first-degree relatives to develop CRC. Smoking is a causal risk factor of total cancer and CRC.[69-71] Several pathways which include? Carcinogenic compounds in tobacco such as polycyclic aromatic hydrocarbons, nitrosamines, and arylamines have been described. In addition, exposure to tobacco smoke has been linked to mutational or epigenetic alterations in KRAS and BRAF cellular signaling pathways, which are also, identified in most CRC cases.[72] The current study confirmed its role as a causal risk factor. On the other hand, smoking is a risk factor for PD development and progression[73,74] and a proven confounder as well. That was the main reason why the Cochran and Mantel–Haenszel model was carried out in an effort to clarify if possible significant correlations between both diseases could be attributed to smoking status or not. The model showed that smoking was not a confounder of CAL. According to the results, CAL was associated with an increased CRC risk after controlling for certain confounders such as smoking and socioeconomic status. Similar reports that have investigated the possible associations between PD indices and CRC risk or total cancer have not been carried

out. Few epidemiological studies have investigated the association between PD and CRC risk;[32,37,44,45] however, no significant associations were recorded between tooth loss, as PD indicator, and CRC risk. Only in a study by Ahn *et al*.[46] was recorded that periodontitis-associated mortality was in higher rates of CRC (relative risk = 3.58, 95% CI = 1.15–11.16). Such epidemiological studies in which PD and cancer share common risk factors such as smoking and socioeconomic status may lead to biased associations due to the influence of possible confounders. Similarly, unknown factors could lead to such outcomes, for example, genetic predisposition. Another factor that could be lead to biased association is the accuracy definition of PD which is essential to establish on reliable and reproductive indices.[75] Finally, a great number of similar reports have based on epidemiological prospective or retrospective methods and it has been used several methods to control possible systematic and selection biases mainly and confounding. However, smoking remains a possible interpretation as the correlations that have reported concerned smokers, whereas no correlations have been reported between PD and cancer in non-smokers. It is important to highlight that the present study was a first attempt to approach that possible association in Greece.

CONCLUSION

PD parameters such as CAL were associated with an increased risk of developing CRC after adjusting for certain confounders such as smoking and socioeconomic status.

DISCLOSURE OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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