Assessment of Periodontal Disease Status, and Tooth Loss in Colorectal Cancer Patients: a Case-Control Study

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Abstract: ***Background/Objectives*:** There are known associations between Periodontal Disease (PD) and Colorectal Cancer (CRC), however, knowledge on the connections existing between the two diseases are not fully understood. The aim of the current research was to assess the possible differences regarding the periodontal condition and tooth loss between individuals suffering from localized CEC and healthy ones.

***Materials and Methods*:** The study size consisted of 130 individuals suffered from CRC and 290 matching healthy controls. The participants completed a standardized health questionnaire and clinically examined. PD status was defined by assessment of probing pocket depth (PPD), clinical attachment los (CAL), plaque index (PlI), gingival index (GI), and bleeding on probing (BOP). The number of missing teeth was also estimated. Univariate and logistic regression models were applied to assess the possible differences between CRC patients and healthy individuals.

***Results*:** CRC patients showed worst periodontal parameters such as PPD (p=0.048, OR=1.452, 95% CI=1.032-2.779), and CAL (p=0.022, OR=1.763, 95% CI=1.085-2,867) after adjustment for smoking, socio-economic and educational status, compared with healthy individuals.

Keywords: Colorectal cancer, periodontal disease, adults, risk factors.

1. INTRODUCTION

Colorectal cancer (CRC) constitutes one of the most common public health problem. In the EU, in 2020, CRC was the second most common cancer in incidence with 520,000 cases per year and the second in mortality, with 250,000 deaths annually [1]. The estimated incidence in the EU in 2023 was 42.3 cases/100,000 individuals [2].

Risk factors concern tobacco and alcohol, red or processed meat consumption, low intake of fruits and vegetables, and overweight-obesity (BMI), regardless of family history and hereditary syndromes, which represent 30% of all cases [3-6]. The rate of individuals with CRC with a positive family history appears to range from 10% to 20%, with a variable risk which depends on the degree or number of the affected relatives and also the age of CRC diagnosis.[5,6] A hereditary CRC syndrome affects about 5-7% of patients with CRC [5, 7]. Strong associations between CRC incidence and male gender or increased age have also been detected in epidemiological research. Compared to males, females experience a 25% lower incidence and mortality rate.[5]

Periodontal Disease (PD), and mainly periodontitis is the most frequent chronic inflammatory oral disease, which affects 15% of the adult population.[8] PD prevalence increases with age, cigarette abuse, and poor oral hygiene.[9]There are also complicate connections with immuno-deficiencies, osteoporosis, and various infection parameters of oral microbiota which are being investigated [10].

The inflammatory process is characterized by increased production of reactive oxygen species (ROS) and oxidative stress due to interaction with acute phase cytokines and chemokines, such as Interleukin (IL)-1 and -6, C reactive protein (Crp), which are associated with PD severity [8]. The possible role of those inflammatory biomarkers in several systemic diseases appearance could be attributed to a general inflammatory response, a systemic immune reaction to periodontal pathogens or the entry of periodontal pathogens into the blood circulation [11, 12]. Therefore, many studies have examined a possible role of periodontitis as a risk factor for systemic diseases or disorders, such as cardiovascular (CVD) and atherosclerotic disease, respiratory diseases such as COPD, diabetes mellitus, and cancer [13-15].

The possible role of PD as a risk factor in cancer development has also been investigated by several researchers in organs such as oral cavity, esophagus, stomach, pancreas, and lungs [16-20] with controversial results, even after controlling for potential confounders such as gender, age, smoking status, socio-economic level, etc.

A significant total cancer risk [20, 21] and certain location-specific types of cancer [22-24] have been associated with poor oral hygiene, PD development, and tooth loss, independent of age, smoking, and alcohol consumption. Accumulating evidence supposed an important role of immuno-inflammatory mechanisms that may be common to PD and cancer [25, 26]. However, the exact mechanisms for the po-

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tential relationship between PD and risk for cancer development still remain unknown.

In contrast to the mentioned reports, few studies have investigated the periodontal health status or the oral conditions in patients suffered from various types of cancer, such as gastric, lung cancer, glioblastoma, *etc*. [29-32]. Epstein *at al.* [33] in a literature review reported that 14.1% of the patients with Multiple Myeloma (MM) presented some types of oral lesions. A retrospective study [34] found mandible lesions occurring in 15.6% and oral mucosa lesions affecting 2.6% of them.

In Greece similar prospective or retrospective studies which investigated the possible differences in periodontal status between colorectal cancer patients and healthy ones have not been carried out. The current research was designed to estimate the possible differences in periodontal health status between individuals who suffered from CRC and healthy ones.

2. MATERIALS AND METHODS

2.1. Research Population Sample and Design

Study size assessment was based on CRC prevalence [35] and the EPITOOLS guidelines (https://epitools.ausvet.com.au) determined with 95% Confidence Interval (CI) and desired power 0.8, whereas the age group was based on the World Health Organization (WHO) recommendations [36] for assessing periodontal condition incidence. The study was carried out between October 2024 and November 2025.

The study sample consisted of 420 individuals, 238 males and 182 females aged 48-77 years recruited from two medical and a dental private practice. 130 individuals suffered from CRC-cases and 290 were healthy individuals-controls. Cases and controls completed a medical and a dental standardized health questionnaire and were clinically examined regarding their periodontal condition and the number of missing teeth.

CRC definitive diagnosis was confirmed by an histopathological examination of suspicious tissue (biopsy or polyp) removed during the endoscopic procedure colonoscopy [37].

2.2. Patients and Healthy Individuals Eligibility Criteria

To be eligible, CRC patients and healthy individuals should not have been cured by a conservative or a surgical procedure in their oral tissues in the last six months, or prescribed for systemic glucocorticoids or immuno-suppression agents or antibiotics within the same time period. In addition, CRC patients should not have been received chemotherapy, targeted therapy, and immunotherapy in the last four to eight weeks after surgery, and no later than eight weeks post-operation (Adjuvant Chemotherapy) [38].

CRC patients and healthy individuals should also have more than 15 teeth and periodontitis from stage I to IV [39]. In case they suffered from CVD, diabetes mellitus, rheumatoid arthritis, acute pulmonary diseases or any other type of malignancies were excluded from the study protocol, as the mentioned conditions could possible affect oral and periodontal tissues [40] and could lead to biased secondary associations. 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, as already mentioned [40].

To avoid selection biases, CRC patients and healthy individuals, were recruited from the same city population, whereas healthy individuals' selection was based on CRC patients' environment, such as friends, colleagues, *etc*., but not from the same family. Moreover, cases and controls were matched regarding their gender, age, socio-economic and smoking status.

No oral hygiene instructions was given to CRC patients group for a period of two weeks after the definitive diagnosis of the disease and before the application of any medical treatment, i.e. targeted therapy, immunotherapy, corticosteroids and chemotherapy as improvement of oral hygiene could be affect the intra-examiner variance.

A sample of 84 (20%) individuals randomly selected was clinically re-examined by the same Dental Surgeon after two weeks in order to assess the intra-examiner variance. After consideration of the ID's of the double examined individuals no differences were recorded between both clinical examinations *(Cohen's Kappa= 0.97).*

The current case-control study was not an experimental one and was not reviewed and approved by authorized committees (Greek Dental Associations, Health Ministry, *etc*). However, it was carried out in full accordance with the World Medical Association Declaration of Helsinki. Individuals who agreed to participate in the study design and protocol signed an informed consent form.

2.3. Research Questionnaire

CRC patients and healthy individuals completed a modified Minnesota Dental School Medical questionnaire [41], which consisted of various epidemiological parameters such as age, smoking, educational and socio-economic status, BMI, current diseases and disorders, and past medical/dental history.

2.4. Assessment of Covariates

Socio-demographic variables, and potential CRC risk factors included as covariates in the statistical analysis. Cases and controls' age was classified as 48-50, 51-60, 61-70, and >71 years old, socio-economic status was classified as ≤ 1,000 and >1,000 €/month, and, educational level was classified as elementary and higher education (University/College) level. Cigarette smoking was classified as never (individuals who smoked less than 100 cigarettes during their lifetime), and former (those who smoked at least 100 cigarettes in their lifetime and reported that they now smoke "not at all")/present smokers (those who smoked at least 100 cigarettes in their lifetime and reported they now smoke "every day" or "some days"). BMI is an obesity index and was classified as normal (< 30 Kg/m^2) and high (≥ 30 Kg/m^2) [42].

2.5. Oral Clinical Examination

The periodontal tissue recorded concerned the following indices, Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), Plaque Index (PlI), Bleeding on Probing (BOP), the number of missing teeth, and included all permanent teeth, except 3rd molars and the remaining roots using a Williams probe with a controlled force of 0.2 N (DB764R, Aesculap AG & Co. KG, Tuttlingen, Germany), at six sites per tooth (disto-facial, facial, mesio-facial, disto-lingual, lingual and mesio-lingual).

2.6. Probing Pocket Depth (PPD)

PPD was dichotomously assessed as score 0: stage I [maximum PPD ≤ 4.0 mm] and score 1: stage II-IV [PPD ≤ 4.0 - ≥ 6.0 mm] [40].

2.7. Clinical Attachment Loss (CAL)

CAL severity was classified as mild, 1.0-2.0 mm of attachment loss and moderate/severe,≥ 3.0 mm of attachment loss [43].

2.8. Gingival Index (GI)

The presence or absence of gingival inflammation was defined by the GI, and concerned the mentioned sites. Gingivitis severity was coded as follows: -score 0: gingival tissue normal situation and/or mild gingival inflammation, which corresponds to Löe and Silness[44] classification as score 0 and 1, respectively, and score 1: moderate/severe gingival inflammation which corresponds to Löe and Silness classification as score 2 and 3, respectively.

2.9. Plaque Index (PlI)

PlI was assessed by Silness and Löe[45] at the mentioned sites. The presence of dental plaque was defined whether it was visualized with naked eye or existed abundance of soft matter on the tooth and gingival margin and/or within the gingival pocket (score 2 and 3, respectively, according to PlI) and considered as present if at least one site showed the characteristic sign.

2.10. Number of Missing Teeth

The number of missing teeth was coded as none, 1-4, 5-10, >10 missing teeth [46].

2.11. Bleeding on Probing (BOP)

The presence/absence of BOP was recorded and coded as dichotomous variables.

2.12. Statistical Analysis

For each CRC patient and healthy individual, the worst values of PPD, CAL, PlI, GI, the BOP presence/absence, and number of missing teeth were recorded and classified as dichotomous variables, as already mentioned. Categorical data presented as frequencies and percentages.

Univariate analysis model was applied to assess the possible association between cases/ controls and the independent variables examined. Logistic regression model was carried out to assess the mentioned associations using the Enter and Wald methods. Unadjusted and Adjusted OR's and 95% CI were also recorded. The SPSS ver.19.0 package was used, an a p-value of less than 5% *($p<0.05$)* was regarded significant for all statistical test applied.

3. RESULTS

The mean ages were 62.5±2.6 years and 63.5±2.4 years for CRC patients and healthy individuals, respectively. Univariate model was used to compare indices between cases and controls for categorical variables. The outcomes showed that cases with CRC family history (p=0.006) and smokers (p=0.015) were statistically significant greater compared to healthy individuals, whereas no statistically significant differences were observed among the PD indices examined between CRC patients and healthy individuals (Table **1**). Unadjusted OR's and 95% CI are displayed in the same Table. After applying logistic regression model, the final step (Wald method), was found that deep periodontal pockets (PPD) (p=0.048), moderate/severe attachment loss (CAL) (p=0.022), and the mentioned parameters, were statistically significant different between cases and controls (Table **2**). Adjusted OR's and 95% CI are also shown in the same Table.

4. DISCUSSION

The most frequent indices used for estimating periodontal condition are clinical indices such as PPD, CAL, GI, PlI, BOP, Bleeding Point Index (BPI), Alveolar Bone Loss (ABL), number of missing teeth/remaining teeth, *etc*., [47].

Previous researches have reported that oral lesions were the first manifestation of various cancer types such as MM [48-50], lung cancer [31], and gastric cancer [30].

The results showed not statistically significant differences between cases and controls, regarding socio-demographic characteristics such as gender, age, SES, and educational level, variables which have been considered as possible risk factors for CRC development.[5]

Smoking is regarded as a potential risk factor for initiation and progression of PD and various types of cancer [51], however acts as a confounder in studies which examine the possible association between PD and several types of malignancies in which smoking is implicated in cancer development. In the present study a statistically significant difference was observed between smokers CRC patients and smokers-healthy individuals. The same difference was detected, regarded CRC patients with a CRC family history compared to healthy individuals with CRC family history.

The outcomes showed that PPD in cases group was statistically significant greater than in control group, finding that remained after adjusting for possible confounders as smoking, SES and educational status. PPD reflects the destructive process of a chronic inflammatory response and is an indicator for estimating PD severity [52]. A similar prospective cross-sectional research, recorded that individuals with oral or oropharyngeal cancer had PPD 6.0 mm or greater of 76.0 % of the patients, whereas only 10.0% in the control group showed the same PPD severity [19]. A recent case-control study in lung cancer patients [30] showed that

PPD was statistically significantly different between cases and controls whereas in another one in gastric cancer patients that finding was not observed [29].

CRC patients did not show significantly worse mean values in gingival inflammation severity, according to GI compared with controls, finding that was not confirmed by previous studies as similar reports have not been carried out, except for a recent study in which that finding was confirmed in gastric cancer patients [29]. It must be noted that GI use is limited in such epidemiological studies despite the fact that reflects the gingival tissue inflammatory load, whereas Hujoel *et al.* [17] suggested that gingival inflammation could be a risk factor for several types of cancer development.

BOP index reflects the host's vascular response in terms of hyperemia, the capillaries' dilation and increased blood flow in the inflammation region. BOP is a widely used criterion to diagnose gingival inflammation, however it has been suggested that periodontal pockets with a probing depth of greater than or equal to 5.0 mm showed a significantly higher incidence of BOP [53]. BOP is a crucial indicator of a periodontal diagnosis, and the most reliable indicator of PD activity [53]. No statistically significant difference was recorded regarding BOP between cases and controls, finding which was in accordance with the gingival inflammation scores recorded in both groups. Similar findings have not been reported by other studies.

In a recent review by Xavier de Almeida *et al.* [54], gingival bleeding was observed in almost 10.0% of the reported cases in MM patients. The gingival bleeding assessed by the Gingival Bleeding Index (GBI) currently suggests localized gingivitis [55, 56]. GBI has been defined as the percentage of sites with G-Index ≥ 2 [57]. A similar research showed that the mean GBI of the male patients (12.61±9.27%) was much lower than the female's mean GBI (22.35±20.5). The same study also recorded a statistical significance regarding gingival bleeding between elders and middle-age females *(p=0.05)* among MM patients. Although gingival bleeding is strongly associated with inadequate dental plaque control, hormonal changes throughout life in middle-aged and older females may explain the higher GBI values [58].

PlI assesses dental plaque accumulation. In a previous study was found that poor oral hygiene, as reflected in the amount of dental plaque, was associated with increased cancer mortality, as based on the findings, the high bacterial load on tooth surfaces and in gingival pockets over a prolonged time could play a role in carcinogenesis.[59] The current report showed no statistically significant differences regarding PlI between cases and controls. Only a study by Czerniuk *et al.* [60] confirmed that PlI in MM patients could lead to more severe infection of periodontal tissues according to PlI measurements, whereas Critchlow *et al.* [61] observed that head and neck cancer patients showed poor oral health and therefore more dental plaque accumulation at the time of diagnosis, whereas PD and dental caries were suggested as important clinical issues.

CAL is another index for assessing periodontitis severity [52] and also refers to the long term stages of chronic inflammation including destructive processes signs of a chronic inflammatory response. The present report showed statistically significant differences between the cases and the controls, regarding CAL values. Similar findings have not been reported by other investigators regarding the CAL index.

Similarly, few studies [62-64] have investigated the possible differences between cancer patients and healthy individuals concerning the number of missing teeth. The present report showed no statistically significant differences between the groups examined and tooth loss, whereas Bezerra *et al*. [56] investigated the oral status of elders and middle-aged MM patients observed that the elderly group showed to have significantly more missing teeth *(p=0.05)* than the middle-aged group. To be more specific the elders had a mean of 22.7±6.25 missing teeth and the middle-aged individuals, 14.4±9.5, whereas males had a mean of 16.0±9.38 missing teeth, and females, 21.8±7.42.

The increased risk of periodontal tissue destruction in cancer patients has been suggested to be a result of psychological burden rather than disturbances in patients' nutrition or alterations in the oral cavity regarding the saliva quantity/quality, or in the balance of microbiological and immunological parameters in the oral cavity that could be affected because of the chemotherapy or radiotherapy or targeted treatment [65, 66]. It is also possible that cancer patients with poor prognosis could be more susceptible to the progression and destruction of periodontal tissue than the healthy population, suggestion that could be attributed to the fact that prognosis varies according to age and is worse in individuals over 65 years when compared to younger ones [30, 31].

In general, a limited amount of research has been carried out in the literature regarding the oral or periodontal health status in patients who suffered from various types of cancer. The aim of the current study was to investigate a comparison between CRC patients and epidemiologically matched healthy individuals regarding several PD indices, and number of missing teeth and not to explore a possible association between PD indices, as etiological or risk factors, and CRC development.

Some certain limitations should be taken into account during results interpreting. Case-control studies in contrast to prospective ones, do not have the reliability of the prospective ones, whereas selection, recall, random biases and the effect of known and unknown confounders are possibly higher in retrospective studies and could lead to biased secondary associations regarding the indices examined. Another drawback is that the validity of the study could be affected by the fact that retrospective studies are based on questionnaires. Ultimately, the decision to be enrolled in the current study older individuals who had at least 15 natural teeth would lead to an underestimation as those individuals with previous PD may have had teeth extracted for periodontal reasons.

Strengths of the current study were the adequate and representative study sample and that it was a matched case-control study, as was used a randomly selected population-based sample, methodology which warrants interval validity.

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

Variables	Cases No %	Controls No %	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	78 (60.0)	160 (55.2)	0.356	1.219 (0.801-1.856)
Females	52 (40.0)	130 (44.8)		
Age (year old)				
48-50	21 (16.2)	52 (17.9)		
51-60	37 (28.5)	87 (30.0)		
61-70	55 (42.3)	116 (40.0)	0.935	———
>71	17 (13.1)	35 (12.1)		
Socio-economic status				
Low	45 (34.6)	108 (37.2)	0.605	0.892 (0.579-1.375)
High	85 (65.4)	182 (62.8)		
Education level				
Low	68 (52.3)	147 (50.7)	0.759	1.067 (0.705-1.614)
High	62 (47.7)	143 (49.3)		
CRC family history				
Absence	38 (29.2)	204 (70.3)	**0.000***	0.174 (0.111-0.274)
Presence	92 (70.8)	86 (29.7)		
Cigarette Smoking				
Never	41 (31.5)	128 (44.1)	**0.015***	0.583 (0.377-0.902)
Previous/Current	89 (68.5)	162 (55.9)		
Body Mass Index (BMI)				
<30 Kg/m^2	55 (42.3)	117 (40.3)	0.705	1.084 (0.713-1.650)
≥30 Kg/m^2	75 (57.7)	173 (59.7)		
Probing pocket depth (PPD)				
≤ 4.00 mm	47 (36.2)	113 (39.0)	0.583	0.887 (0.578-1.362)
≤ 4.0 - ≥ 6.0 mm	83 (63.8)	177 (61.0)		
Clinical Attachment Loss (CAL)				
Absence/Mild: 1.00-2.00 mm	42 (32.3)	118 (40.7)	0.102	0.696 (0.450-1.076)
Moderate/Severe: ≥ 3.0 mm	88 (67.7)	172 (59.3)		
Gingival Index (GI)				
Absence/Mild Inflammation	61 (46.9)	140 (48.3)	0.798	0.947 (0.626-1.434)
Moderate/Severe Inflammation	69 (53.1)	150 (51.7)		
Plaque Index (PlI)				
Absence	64 (49.2)	154 (53.1)	0.463	0.856 (0.566-1.296)
Presence	66 (50.8)	136 (46.9)		
Bleeding on Probing				
Absence	52 (40.0)	121 (41.7)	0.740	0.931 (0.611-1.419)
Presence	78 (60.0)	169 (58.3)		

Tooth Loss				
None	11 (8.5)	32 (11.0)		
1-4 Teeth	29 (22.3)	54 (18.6)		
5-10 Teeth	48 (36.9)	110 (37.9)	0.748	———
> 10 Teeth	42 (32.3)	94 (32.4)		

* p-value :statistically significant.

Table 2. Presentation of association between independent variables and CRC according to Enter (first step) and Wald (final step) method of multiple logistic regression analysis model.

Variables in the Equation									
-		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	gender	,067	,249	,073	1	,787	1,070	,656	1,744
	age	,115	,131	,775	1	,379	1,122	,868	1,451
	educ.level	,030	,242	,015	1	,902	1,030	,641	1,655
	socioec.status	-,004	,251	,000	1	,986	,996	,609	1,627
	smok.stat	,944	,245	14,784	1	**,000***	2,569	1,588	4,156
	bmi	,476	,244	,198	1	,755	,927	,574	1,495
	crc.fam.hist	1,821	,244	55,664	1	**,000***	6,178	3,829	9,968
	pr.pock.dep	,492	,257	2,128	1	**,081***	1,696	1,063	2,812
	cl.att.loss	,624	,283	4,862	1	**,027***	1,866	1,072	3,249
	ging.ind	,226	,274	,680	1	,409	,798	,466	1,365
	bl.on.prob	,091	,304	,090	1	,764	1,096	,604	1,986
	pl.index	,078	,285	,087	1	,895	,963	,551	1,684
	tooth.loss	,017	,127	,017	1	,896	1,017	,793	1,304
	Constant	2,836	,540	27,549	1	,000	,059		
Step 11[a]	smok.stat	,948	,242	15,392	1	**,000***	2,581	1,607	4,145
	crc.fam.hist	1,788	,241	55,267	1	**,000***	5,980	3,732	9,583
	pr.pock.dep	,443	,233	2,205	1	**,048***	1,452	1,032	2,779
	cl.att.loss	,567	,248	5,233	1	**,022***	1,763	1,085	2,867
	Constant	2,603	,301	74,636	1	,000	,074		

a.Variable(s) entered on step 1: gender, age, educ.level, socioec.status, smok.stat, bmi, crc.fam.hist, pr.pock.dep, cl.att.loss, ging.ind, bl.on.prob, pl.index, tooth.loss.

* p-value :statistically significant

CONCLUSION

Patients suffering from CRC presented deeper periodontal pockets, and worse attachment loss than healthy individuals after adjusting for known confounders

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