ORIGINAL ARTICLE

Periodontal Disease, Tooth Loss, and Squamous Cell Esophageal Cancer : A Case–Control Study

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ABSTRACT

Introduction: Recently, increasing interest has been focused on the possibility of associations between Periodontal Disease and various types of cancer. The purpose of the present report was to examine the possible relationship between Periodontal Disease parameters and number of tooth loss and risk of appearance Squamous Cell Esophageal Cancer in a representative Greek adult sample. **Materials and Methods:** The study sample consisted of 60 patients-cases diagnosed with the main histological type of esophageal carcinoma, Squamous Cell Esophageal Cancer,and 178 age and socio-economic status matched healthy individuals-controls. Clinical information on periodontal health status was obtained through a dental clinical examination and a modified questionnaire including data of their medical and dental history, and concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), number of tooth loss and the common risk factors for Squamous Cell Esophageal Carcinoma. Moreover, unadjacent and adjacent Odds Ratios (OR's) and 95% Confidence Intervals (CI's) were assessed using univariate and logistic regression models adjusted for possible confounders. **Results:** The multivariate regression analysis model application showed that lower socio-economic status (p= 0.048) (OR= 1.882, 95% CI=0.987-3.591), smoking (p= 0.052) (OR= 1.768, 95% CI= 0.931-3.359), moderate and heavy alcohol consumption (p= 0.035) (OR= 1.880, 95% CI= 0.987-3.579), and irregular tooth brushing frequency (p=0.001) (OR= 0.326, 95% CI= 0.171-0.619), were significantly associated with Squamous Cell Esophageal Cancer. **Conclusion:** Individuals with lower socio-economic status, smoking, moderate and heavy alcohol consumption, and irregular tooth brushing frequency were significantly associated with Squamous Cell Esophageal Cancer.

Key words: Periodontal disease, Squamous Cell Esophageal Cancer, Risk factors, Adults

INTRODUCTION

Periodontal Disease (PD), gingivitis and mainly chronic periodontitis, is a chronic multifactorial inflammatory disease partially responsible for tooth loss, is characterized by the progressive destruction of the tooth-supporting tissues and caused by oral microorganisms.[1]

Recently, increasing interest has been focused on the possibility of associations between PD and various systemic diseases and disorders [2,3] all of which may be attributed to systemic infection and inflammation [4], including cancer[5,6] Accumulating evidence suggests an hypothesized role of immune-inflammatory mechanisms and the potential role of inflammation in both periodontitis and cancer [7] that

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may be common to both PD and cancer.[8,9] Local chronic inflammation has been linked with cancers in several regions[10] especially those affecting the gastro-intestinal tract, such as the associations between gastric reflux disease with esophageal cancer[11], *H. pylori* ulcers with gastric cancer [12,13], inflammatory bowel disease with colon cancer, [14] and chronic pancreatitis with pancreatic cancer.[15,16] The periodontal bacteria and their by-products associated with chronic periodontitis can result in chronic systemic inflammation[17,18] not only at the oral tissue but even at distant regions.[19] Moreover, two crucial periopathogens, *Porphyromonas gingivalis* and the *Fusobacterium* species, have been revealed in esophageal or colorectal carcinomas. [20,21] These observations suggested that these periodontal bacteria may contribute to the tumorigenesis of the mentioned cancers.

There are two main types of esophageal malignancies, Squamous Cell Esophageal Cancer (SCEC), 90% of cases and Esophageal Adenocarcinoma (EAC),10%. The most important risk factors for SCEC are male gender, age over 50, tobacco smoking and drinking of alcoholic beverages, lower education level and socio-economic status, low intake of fruits and vegetables and associated marginal deficiencies in vitamins, thermal irritation from consumption of hot beverages, and food, physical irritation due to loss of teeth (poor oral hygiene), carcinogens, e.g., nitrosamines, polyaromatic hydrocarbons, HPV 16 and 18 infection [22-27] , and genetic susceptibility, e.g., loci at PLCE1, C20orf54, ADH1B and ALDH2. [28-30]

Previous and recent reports have observed an increased risk of SCEC among individuals with PD however, notable limitations of those included inadequate sample sizes and inadequate adjustment for potential confounders. Poor oral health, indicated by PD and tooth loss/decay, is a potentially important and preventable risk factor that implicates alterations in the oral microbiome that may contribute to carcinogenesis in the esophagus. [31]

Oral health assessed by tooth loss, DMFT score, periodontal health, and oral hygiene practices as tooth brushing has been examined as a risk factor for SCEC in many epidemiologic studies.[5,32-50] A positive association between tooth loss and SCEC risk has been recorded repeatedly in both case-control and large-scale prospective cohort studies conducted.[33, 35, 36, 39-51] Regular tooth brushing has been observed to have a protective effect against SCEC in several studies.[35,41-43,47,50] PD has also been associated with an increase in overall EC risk for both histological types, SCEC and EAC. [51,52]

In contrast, there have also been some reports recording no associations between poor oral health and EC risk. No associations have been revealed in prospective studies carried out in several countries. In some of the mentioned studies the researches did not distinguish between both histological types.[7,34,53-57]

The current research aimed to assess the possible role of PD indices/number of tooth loss in the development of CESC in a Greek adult population.

MATERIALS AND METHODS

Study Population Sample and Design

A retrospective case - control research was carried out between April 2019 and September 2021.

According to Hyman et al. criteria[58], the study sample was assessed considering the SCEC incidence[59], determined with 90% Confidence Interval and relative precision 50.0%, whereas the age group was based on the World Health Organization (WHO) recommendations[60,61] for assessing PD incidence.

The study sample consisted of 147 males and 91 females. The current investigation was carried out on 60 individuals females with SCEC - cases and 178 healthy individuals controls, aged 45 to 75.

Inclusion/Exclusion Criteria of Cases and Controls

Individuals who had less than 20 natural teeth, were undergone a surgical or conservative PD treatment within the previous six months, had received a systemic antibiotics or anti-inflammatory or other systemic drugs, such as glucocorticoids the previous six weeks were excluded from the study protocol as those conditions could influence [62] the oral tissues status, and may lead to biased secondary associations.

Advanced SCEC patients under medical treatment, metastases of a primary focus at a different region, and those diagnosed in other focuses in the head-neck-thorax location (carcinogenesis field theory[63]), were excluded from the study protocol. Hospital patients were also excluded. The case group consisted of individuals whose the primary diagnosis of SCEC was based on patients' medical files with a definitive diagnosis based on histopathological examination of the intra-operatively removed tumor or its parts, using traditional histological, cytologic and histo chemical methods.

The determination of control group was based on the friendly and collegial environment of cases group in an effort to control potential confounders such as age, smoking, socio-economic level.

Questionnaire

Cases and controls responded to a modified Minnesota Dental School Medical Questionnaire[64], that contained epidemiological parameters such as age, gender, smoking status, alcohol consumption, socio-economic and education

status, and past medical/dental history. Individuals'age was classified as 45-50,51-60,61-70,71+, educational status as elementary level and graduated from University/College, socio-economic status as ≤ 1,000 and >1,000 €/month, smoking status as never smokers and former/current smokers, alcohol consumption as light ≤ 12.5 gr per day of alcohol and moderate and heavy drinking >50 gr per day.[65]

For establishment of the intraexaminer variance a randomly chosen sample of 48 (20%) individuals were re-examined clinically by the same dentist after three weeks, and no differences were recorded between the 1st and the 2nd clinical assessment *(Cohen's Kappa = 0.95*). During this time period no oral hygiene instructions were given to the participants.

Periodontal status examination

A standard number of 28 teeth was used as a reference and assessed the existed number of teeth, and then minus the number of existed teeth from 28 teeth, and the outcome was defined as some lost teeth or missing teeth.

Periodontal health status were measured at six sites in all teeth (disto-buccal, mid-buccal, mesio buccal, mesio-lingual, mid-lingual and disto-lingual), excluding third molars, and remaining roots using a manual periodontal probe (UNC-15; Hu Friedy Mfg. Co. Inc., Chicago, IL USA).

For each individual, the worst values of PPD and CAL on six sites per tooth were recorded and coded as dichotomous variables.Probing Pocket Depth (PPD) index was classified as 0-3.00 mm (absence of disease/mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [66], attachment loss (CAL) severity was classified as mild, 1-2.0 mm of attachment loss and moderate/severe, ≥3.0 mm of attachment loss [67], and tooth loss as none, 1-4, 5-10, >10 missing teeth. [68]

Ethical Consideration

The present retrospective study as a non-experimental one was not reviewed and approved by authorized committees (Ministry of Health, etc.). In Greece only experimental studies must be approved by those Authorities. An informed consent form was obtained by the individuals who agreed to participate in the current study protocol.

Statistical Analysis:

For each individual, the worst values of PPD and CAL on six sites per tooth and the presence/ absence of BOP were recorded and coded as dichotomous variables.

The distribution of missing teeth was coded as 0,1,2, and 3 for number of missing teeth none-0, 1-4,5-10,and >10, respectively. Previous/current smokers, high socio-economic (income/monthly ≥1,000 €) and educational (graduated from University/College) level individuals, individuals that reported moderate and heavy drinking (>50 gr per day), and those with regular oral hygiene (brushing ≥ 2 times per day) were coded as 1. Age groups distribution was coded as 0,1,2 and 3 for ages 45-50, 51-60, 61-70 and 71+ respectively.

Univariate analysis model was applied to examine the relationship between the independent variables examined and SCEC risk, separately, by using chi-square test. Multivariate regression model was carried out to examine the associations between the dependent variable, SCEC, and independent ones that were determined by the enter method. Unadjusted and Adjusted Odds Ratios (OR's) and 95% CI were also assessed. Finally, the independent variables were included to stepwise method in order to estimate gradually the indices that showed significant associations with the dependent one. Statistical analysis was carried out using the SPSS ver.19.0 package. A p-value of less than 5% ($p< 0.05$) was considered significant for all statistical test conducted.

RESULTS

The mean age of the sample was 55.6 ± 4.2 years. The main histological type was SCEC, as in the study protocol were not included the Adenocarcinoma cases as its etiology differs. The epidemiological variables of SCEC patients and controls after carrying out the univariate analysis are presented in Table 1. Higher socioeconomic status (p= 0.03), and irregular tooth-brushing frequency (p= 0.000) were statistically significantly associated with risk for SCEC development. Table 1 also shows Unadjusted Odds Ratio and 95% Confidence Interval (CI) for each variable examined.

After performance of the first method (step 1a) of the logistic regression model was found that socioeconomic status (p= 0.053), smoking (p= 0.067), moderate and heavy alcohol consumption(p=0.051), and irregular tooth brushing frequency (p= 0.001) were significantly associated with SCEC risk (Table 2). Table 2 also shows Unadjusted Odds Ratio and 95% CI for each variable examined. The final step of multivariate regression analysis model (Wald method) is presented in Table 2, socio-economic status (p=0.048), smoking (p= 0.052), moderate and heavy alcohol consumption (p=0.035), and irregular tooth brushing frequency (p=0.001) were significantly associated with SCEC risk.

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

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	38(63.3)	109(61.2)	0.772	1.093(0.597-2.003)
Females	22(36.7)	69(38.8)		
Age				
45-50	7 (11.7)	22 (12.4)		
51-60	16 (26.7)	47 (26.4)		
61-70	25 (41.7)	77 (43.3)	0.986	_____
71+	12 (20.0)	32 (18.0)		
Educational level				
Low	24(40.0)	91 (51.1)	0.136	0.637 (0.352-1.155)
High	36 (60.0)	87 (48.9)		
S/economic level				
Low	19 (31.7)	85 (47.8)	**0.030***	0.507 (0.273-0.941)
High	41 (68.3)	93 (52.2)		
Smoking status				
No	21 (35.0)	84 (47.2)	0.100	0.603 (0.329-1.105)
Yes	39 (65.0)	94 (52.8)		
Tooth brushing frequency				
<1 times/day	42 (70.0)	78 (43.8)	**0.000***	2.991 (1.599-5.597)
≥2 times/day	18 (30.0)	100 (56.2)		
Alcohol consumption				
<12.5 grams/day	20 (33.3)	82 (46.1)	0.085	0.585 (0.317-1.080)
>50 grams/day	40 (66.7)	96 (53.9)		
Probing pocket depth				
0-3.00 mm	28 (46.7)	86 (48.3)	0.825	0.936 (0.521-1.682)
≥ 4.0 mm	32 (53.3)	92 (51.7)		
Clin. Attachment Loss				
1.00-2.00 mm	24 (40.0)	93 (52.2)	0.101	0.609 (0.336-1.104)
≥ 3.0 mm	36 (60.0)	85 (47.8)		
Tooth Loss				
None	6 (10.0)	16 (9.0)		
1-4 teeth	8 (13.3)	37 (20.8)		
5-10 teeth	28 (46.7)	78 (43.8)	0.645	_____
> 10 teeth	18 (30.0)	47 (26.4)		

* p-value statistically significant

Table 2. Presentation of association between potentially risk factors and BC according to Enter(first step-1a) and Wald (last step 12a) method of multivariate 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]	gander	,005	,333	,000	1	,988	1,005	,523	1,931
	age.group	,243	,160	2,287	1	,131	,785	,573	1,074
	socioecon.stat	-,587	,339	3,000	1	,063	1,798	,926	3,494
	educ.level	-,467	,330	2,009	1	,156	1,595	,836	3,043
	smok.status	,543	,340	2,558	1	,067	1,722	,885	3,351
	alcoh.consum	,699	,342	4,182	1	,051	2,011	1,029	3,929
	toothbr.frequency	-1,188	,345	11,874	1	,001	,305	,155	,599
	prob.pock.dep	,547	,381	2,058	1	,151	,579	,274	1,222
	clin.att.loss	,804	,385	2,370	1	,037	1,134	1,051	2,747
	tooth.loss	,343	,196	3,059	1	,080	1,409	,959	2,069
	Constant	2,347	,700	11,247	1	,001	,096		
Step 7 [a]	socioecon.stat	-,633	,330	3,685	1	**,048***	1,882	,987	3,591
	smok.status	,570	,327	3,028	1	**,052***	1,768	,931	3,359
	alcoh.consum	,631	,328	3,692	1	**,035***	1,880	,987	3,579
	toothbr.frequency	-1,122	,328	11,713	1	**,001***	,326	,171	,619
	Constant	1,708	,407	17,581	1	,000	,181		

* p-value statistically significant

DISCUSSION

The association between PD indices and cancer risk has been explored for more than 50 years, however, findings to date have little practical value as indices for prevention policies. Recently, an increasing interest exists in exploring the mentioned association, as there is evidence that PD patients were at increased risk of cancers in the head and neck location, upper gastrointestinal system, pancreas and lung. [5,12,15,69-72]

Esophageal cancer (EC) is the sixth leading cause of cancer death worldwide, in most cases concerns the squamous epithelia of the middle and lower thirds of the esophagus and therefore named ESCC, whereas Esophageal Adenocarcinoma (EAC), derived from islands of columnar cells near the gastro-esophageal junction. The mentioned histological types of EC are apparently caused by different etiological factors.[73]

As mentioned the most important risk factors for SCEC are male gender, age over 50, tobacco smoking and drinking of alcoholic beverages, low intake of fruits and vegetables and associated marginal deficiencies in vitamins, thermal irritation from consumption of hot beverages, and food, physical irritation due to loss of teeth (poor oral hygiene), carcinogens, e.g., nitrosamines, polyaromatic hydrocarbons, HPV 16 and 18 infection in some cases [22-27], and genetic susceptibility, e.g., loci at PLCE1, C20orf54, ADH1B and ALDH2. [28-30]

The current study showed that low Socio-economic Status (SES), smoking, moderate and heavy alcohol consumption, and irregular tooth brushing frequency were significantly associated with risk of developing SCEC.

Epidemiological variables such as male gender, and lower educational level increase the risk of SCEC. [22,24,74-78] The current report and a nationwide Swedish case-control study [79] did not confirm the association between lower education level and SCEC risk, as non-significant associations were recorded. Moreover, no association was found between male gender and risk of developing SCEC in the present report.

Individuals of higher SES have been associated with a lower risk for developing SCEC [24,74-79], finding that was in line with the outcomes of the current research. Smoking is a known carcinogenesis risk factor and can affect SCEC risk. [22-26] The current research showed a marginally significant association between smoking and SCEC risk. Moreover, smoking is a major risk factor for PD [80], and the bacterial microbiota in PD patients differs between smokers and non-smokers. [81,82] Smokers' microbiomes have less diversity, and

higher prevalence of species that associated with periodontal pathogenesis.[81,83] Moreover, lower humoral immune response in both current and former smokers compared to never smokers has been recorded. [84]

Alcohol consumption is associated with a modest increase in SCEC risk. This association has been consistently found in case-control and cohort studies, reducing the probability that it could be attributed to selection or information biases. Extensive epidemiological studies have found such an association [22-24,26] , finding that is in accordance with the results of the current study.

The association between PD and cancer risk has been investigated over the years. [5,7,85] Moreover, useful aspects have been provided on the role of PD treatment in reducing the risk of different types of cancers. [86]

Accumulating evidence suggests an hypothesized role of immune-inflammatory mechanisms and the potential role of inflammation in both periodontitis and cancer. [7] The periodontal bacteria and their by-products associated with chronic periodontitis can result in chronic systemic inflammation [17,18] not only at the oral tissue but even at distant regions. [19]

Previous and recent reports have observed an increased risk of SCEC among individuals with PD however, notable limitations of those included inadequate sample sizes and inadequate adjustment for potential confounders. [32-34]

Poor periodontal conditions and tooth loss are also associated with an increased risk of SCEC.[5,33,35-38] Poor oral health, indicated by PD and tooth loss/decay, is a potentially important and preventable risk factor that implicates alterations in the oral microbiome that may contribute to esophagus carcinogenesis. Poor oral hygiene has been also identified as one of the factors suggested for examination, with high priority for an upcoming IARC Monographs on the identification of carcinogenic hazards to humans. [31]

Oral health evaluated by tooth loss, DMFT score, periodontal health, and oral hygiene practices as tooth brushing, has been examined as a SCEC risk factor in many epidemiologic studies. A positive association between tooth loss and SCEC risk has been found frequently in previous case-control and large-scale prospective cohort studies. [33,35,36,39-46]

Regular tooth brushing has been shown to have a protective effect against SCEC in various studies [35,41-43] , finding that confirmed by the current research.

Recent meta-analyses suggest an odds ratio (OR) of 1.3 to 1.5 comparing the highest versus lowest number of teeth lost [47-49] and an OR of around 0.60 when comparing high- versus low frequency of tooth brushing [47,50] for overall EC risk. The assessments were slightly weaker for tooth loss [47,48] and slightly stronger for tooth brushing [47] when the analysis was restricted to ESCC. PD has also been associated with an increase in overall EC risk, without histological discrimination. [51,52]

In contrast, prospective studies carried out in several countries [34,53-57], and one among male health professionals in the US [7], have reported no associations between poor oral health and SCEC risk. Only in one study the researchers distinguished the histological types [53], SCEC and EAC, and this may lead to suspension of detecting risk associations since poor oral health may have definite effects on the mentioned histologic subtypes.

The reasons for the mentioned inconsistent findings remain unclear, however it is possible that the relative significance of poor oral health as a potential risk factor for EC, especially SCEC, may vary between high-incidence and lower incidence regions.

It is important to highlight that no significant associations were observed between PD indices, PPD/CAL and tooth loss as an indirect index, and the risk of SCEC development. In addition the current study was the first that directly examined the mentioned indices with the SCEC risk.

Several potential mechanisms have been suggested to explain the association between PD andSCEC. It is possible that periopathogens directly implicated in carcinogenesis. Periodontal bacteria from the oral cavity enter the blood circulation following activities including tooth brushing, flossing and chewing, particularly among PD patients.[87] Despite the fact that circulating oral bacteria are rapidly cleared, a considerable cumulative exposure to tissues has been detected. [88]

Another potential mechanism is inflammation that could be attributed to the PD influencing systemic processes including esophageal carcinogenesis. [89] PD is responsible for triggering a chronic systemic inflammation that is characterized by increased levels of C-reactive protein (C-rp) [90], IL-1β, IL-6, TNF-α, matrix metalloproteinase (MMP) and other biomarkers in blood circulation [19] with a potential impact on carcinogenesis. [91] In addition, bacterial metabolites produced in oral cavity containing nitrosamines and acetaldehyde could have a systemic impact on carcinogenesis. [92] Poor oral health could produce in higher concentrations drastic carcinogens, nitrosamines [53] which are driven by nitrate-reducing bacteria, in the oral cavity. [93]

Oral bacteria could have adverse effects on human health, by producing bacterial toxins which could disrupt the normal

cell cycle and cell growth. [94] It is possible that common risk factors such as smoking, alcohol, inflammation, oxidative stress or shared genetic factors may contribute to host susceptibility to both SCEC and PD. [95-97]

Despite the fact that oral bacteria are directly implicated in PD development, which often leads to tooth loss, and dental caries and that the existing epidemiologic data indicates that there may be an association between oral health and EC, the underlying mechanism for this association is still not understood. Consequently, it has been hypothesized that the human oral microbiome may also be implicated in SCEC etiology. [98]

Study strengths and limitations should be taken into account in interpretation of the observed outcomes. Strengths of the study are the completeness of follow-up, the well-characterized cohort that it was possible to examine both confounding and interaction by known risk factors, in order to avoid secondary biased associations. Another crucial issue is PD determination by oral clinical examination and not by self-report, thus no possible misclassification of exposure to PD exists. Such misclassification based on self-reported information may lead to the under estimation of the association examined.

A potential limitation is the possibility of confounding in estimates of risk caused by additional unknown confounders.

CONCLUSION

Individuals with lower socio-economic status, smoking, moderate and heavy alcohol consumption, and irregular tooth brushing frequency were significantly associated with Squamous Cell Esophageal Cancer.

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