

## CORRELATION BETWEEN PERIODONTAL DISEASE INDICES AND LUNG CANCER IN GREEK ADULTS: A CASE – CONTROL STUDY

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**Aim:** The aim of the present case – control study was to examine the possible associations between periodontal disease indices and the risk of lung cancer development in a sample of Greek out-patients referred to a medical and a dental private practice. **Materials and Methods:** A total of 200 individuals were interviewed and underwent an oral clinical examination, and 64 of them were suffered from several histological types of lung cancer. The estimation of the possible associations between lung cancer as a dependent variable and periodontal disease indices as independent ones was carried out by using a multiple regression analysis model. **Results:** Probing pocket depth (odds ratio (OR) = 2.72, 95% confidence interval (CI) 1.05–7.06), clinical attachment loss (OR = 3.51, 95% CI 1.30–9.47) bleeding on probing (OR = 1.93, 95% CI 0.98–3.81) were significantly associated with the risk of developing lung cancer. Smoking (OR = 2.49, 95% CI 1.20–5.17) was significantly associated with the mentioned risk, whereas it was consisted as a confounder regarding the estimated associations between moderate/severe clinical attachment loss and presence of bleeding on probing with the risk of developing lung cancer. **Conclusion:** Probing pocket depth as an index for periodontal disease severity was statistically significantly associated with the risk of developing lung cancer.

**Key Words:** periodontal disease, lung cancer, adults, chronic inflammation, risk factor.

Lung cancer (LC) is one of the most deadly of all types of cancer, and the 5<sup>th</sup> cause of mortality nowadays in industrialized countries and occurs as a result of genetic, environmental and behavioral risk factors [1, 2]. Common genetic factors are age, male gender, genetic predisposition, enzymes polymorphism and other unknown factors. The environmental and behavioral risk factors include smoking, exhibition in inhaled gases/polluted air and previous pulmonary diseases such as chronic obstructive pulmonary disease, tuberculosis (TBC) and lung fibrosis.

The last suggestion led to the hypothesis that systemic chronic inflammation could play an essential role in development and/or disease progression. Chronic inflammation may enhance mutagenesis and cell proliferation, inhibit apoptosis, reduce the adaptation to oxidative stress, promote angiogenesis, and increase the secretion of inflammatory mediators [2].

Periodontal disease (PD) and especially periodontitis is a common and destructive disease of the oral cavity, leads to tooth loss, its development is a complex process that occurs over a long period of time, as a result of bacterial infection and inflammation which spreads in periodontal fibers and alveolar bone, the supporting structures of teeth [3]. Periodontal tissues infection leads to systemic effects and an increase in circulating levels of inflammatory biomarkers, that correlate directly with the severity of disease, such as C-reactive protein, interleukin-1 and -6. The

biological mechanisms of those associations remain unknown although various inflammatory biomarkers, such as the mentioned may be involved as mediators of systemic inflammation [4, 5]. To be more specific, it remains unknown whether systemic inflammation, invasion of pathogenic bacteria in systemic circulation or immune response to periodontal infection may affect the risk for various systemic diseases development, including cancer [4].

Recent epidemiologic reports has linked periodontal pathogens to several systemic diseases, such as cardiovascular disease, diabetes mellitus, respiratory disease, and systemic infections. Those associations possibly mediated through biomarkers of systemic infection and inflammation [6, 7].

A possible correlation between PD and cancer risk in different locations, most notably in the oral cavity, upper gastrointestinal system, lung, pancreas, and other organs has also been proposed [8–14]. In two of those prospective studies [9, 10] a correlation between tooth loss, as another PD indicator, and the risk of cancer was recorded, however such correlations regarding LC remain unclear [10]. Tooth loss is caused by dental caries and PD, however the distribution of all causes depends on age and other variables. Chronic periodontitis is responsible for tooth loss in older individuals, whereas in younger ages the main cause is dental caries. Therefore, although tooth loss could be an indicator of PD, its correlation is not always strong [15].

Poor oral health or hygiene, as indicators of PD, are possible risk factors for cancer in different organs according to recent epidemiological studies [8, 9, 16, 17]. It has been hypothesized that PD increases the risk of LC through bacterial load and subsequent chronic systemic inflammation [9, 10]. However to our knowledge previous studies have not objectively evaluated the role of PD in LC or precancerous lesions. Several reasons

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**Abbreviations used:** AC – adenocarcinoma; BOP – bleeding on probing; CAL – clinical attachment loss; LC – lung cancer; LCC – large cell carcinoma; PD – periodontal disease; PPD – probing pocket depth; SCC – squamous cell carcinoma; SCLC – small cell lung carcinoma; TBC – tuberculosis.

could explain a possible link between periodontitis and cancer. Both diseases have several risk factors in common, while smoking, advanced age and low socio-economic status have been implicated in cancer and periodontitis [18].

The present retrospective case – control study was carried out to examine the possible correlation between PD indices such as probing pocket depth (PPD), clinical attachment loss (CAL) and bleeding on probing (BOP) and the LC risk in a sample of Greek adults.

## MATERIALS AND METHODS

**Study sample.** The material consisted of 200 subjects, 126 males and 74 females. Cases and controls were selected from a private medical and dental practice, completed a health questionnaire and underwent an oral clinical examination.

**Patients selection criteria.** Patients and controls was necessary to have a mean of 20 natural teeth, since large numbers of missing teeth could lead to over- or underestimate the dental variables and the possible associations that were under consideration and the criteria of established periodontitis [19], which referred to at least 2 teeth with CAL  $\geq$  6 mm and more that one site with PPD  $\geq$  5 mm.

None of the participants had received scaling and root planning procedures or periodontal treatment during the previous 6 months or prescription of anti-inflammatory or systemic antibiotics or other systemic drugs the previous 6 weeks [20]. In order to avoid as much as possible, potential confounding influences on the study parameters, individuals with acute infections, cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, immuno-suppressed patients because of haematological malignancy or recent transplantation and those who received treatment for the mentioned diseases, liver cirrhosis and concurrent medication with general glucocorticoids were excluded from the study. They also excluded patients with advanced LC under medical treatment, patients with lung metastases of a primary focus at a different location, patients diagnosed with mesothelioma or other focuses in the region of head-neck-thorax (carcinogenesis field theory [21]). These criteria were applied because of potential effects on the oral tissues. Hospital patients did not include or patients with several location of cancer in which smoking is considered as a proven risk factor such as larynx cancer, nasopharyngeal cancer, etc.

The patients' group was consisted of individuals in which the diagnosis of LC was set initially by histological examination during the endoscopic procedure and they had been given instructions regarding their oral hygiene after diagnosis and before the application of any treatment method, such as surgery, radiotherapy or chemotherapy.

Controls group selection was carried out by the friendly and collegial environment of cases group in an effort to control potential confounders such as socio-economic level.

**Oral clinical examination.** One well trained and calibrated dentist performed the examinations at the mentioned private practices. The clinical measurements concerned the following variables: For each tooth, except for the 3<sup>rd</sup> molars and the remaining roots PPD, CAL and BOP were measured by a William's 12 PCP probe (PCP 10-SE, Hu-Friedy Mfg. Co. Inc., Chicago, IL, USA) at six sites (facial, lingual, disto-facial, mesio-facial, disto-lingual and mesio-lingual).

The presence of PPD was classified as follows [22]: score 0: moderate periodontal pockets, 4–6.0 mm, and score 1: advanced periodontal pockets,  $>$  6.0 mm.

The severity of CAL classified as follows [23]: score 0: mild, 1–2.0 mm of attachment loss, and score 1: moderate/severe,  $\geq$  3.0 mm of attachment loss. The record for PPD and CAL measurements concerned the immediate full millimeter.

The presence/absence of BOP was classified as follows: score 0: absence of BOP, and score 1: presence of BOP and deemed positive if it occurred within 15 s of probing.

**Questionnaire.** All participants were filled in a self-administered questionnaire that included variables such as age, gender, smoking status (active, former/no-smokers), socio-economic and educational level and data regarding their general medical history with reference to medication, several chronic systemic disorders and the dental follow-up frequency.

A randomly chosen sample of 40 (20%) individuals was re-examined clinically by the same dentist after 3 weeks in order to establish the intra-examiner variance. After consideration of the code numbers of the double examined individuals no differences were recorded between the 1<sup>st</sup> and the 2<sup>nd</sup> clinical assessment (Cohen's Kappa = 0.98) whereas for the mentioned time period no oral hygiene instructions were given to the participants.

**Ethical consideration.** The present study was not an experimental one. In Greece only experimental studies must be reviewed and approved by authorized committees (Dental Schools, Greek Dental Associations, Ministry of Health, etc). Individuals who agreed to participate in the present study signed an informed consent form.

**Statistical analysis.** For each individual, case and control the worst values of PPD and CAL at the six sites per tooth and the presence/absence of BOP were recorded and coded as dichotomous variables. Current and former smokers were coded as 1, individuals with a high socio-economic (income/monthly  $\geq$  1000 €) and educational (graduated from University/College) level were coded as 0, males participants were coded as 1, individuals that reported genetic predisposition for LC, history of previous chronic pulmonary disease and a regular dental follow-up were coded as 1. Age groups distribution was coded as 0, 1, 2 and 3 for ages 48–49, 50–59, 60–69 and 70+, respectively.

Univariate analysis was carried out to test the relationship between the independent variables examined and the LC risk, separately, by using  $\chi^2$  test. Multivariate regression analysis was carried out to model the associations between the dependent variable, LC, and

independent ones that were determined by the enter method. Adjusted odds ratios (OR's) and 95% confidence interval (CI) were also calculated. Finally, the independent variables were included to stepwise method in order to estimate gradually the variables that showed significant correlations with the dependent one. The statistical method Cochran's and Mantel – Haenszel's was applied, in an effort to control possible con-founders, in order to avoid biased secondary associations. Statistical analysis was performed using the statistical package of SPSS ver. 17.0. A p value less than 5% ( $p < 0.05$ ) was considered to be statistically significant.

## RESULTS

The mean age of the sample was  $61.4 \pm 4.2$  years.

The most frequent histological type in males was squamous cell carcinoma (SCC) (47.8%), followed by small cell lung carcinoma (SCLC) (30.4%), adenocarcinoma (AC) (13.0%) and large cell carcinoma (LCC) (8.8%), whereas in females AC (44.4%) followed by SCC (33.3%), SCLC (16.7%) and LCC (5.6%).

Table 1 presents univariate analysis of cases and controls regarding the examined variables. PPD, BOP, history of previous chronic pulmonary disease, smoking and irregular dental follow-up were statistically significantly associated with LC risk. Table 1 also presents unadjusted OR's and 95% CI.

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

Variables	Cases, n (%)	Controls, n (%)	p value	OR	95% CI
Gender:					
Males	46 (71.9)	80 (58.8)	0.075	1.79	0.94–3.40
Females	18 (28.1)	56 (41.2)			
Age (years):					
45–49	4 (6.3)	10 (7.4)	0.578	–	–
50–59	11 (17.2)	32 (23.5)			
60–69	41 (64.0)	73 (53.7)			
70+	8 (12.5)	21 (15.4)			
Socio-economic level:					
Low	38 (59.4)	91 (66.9)	0.300	1.38	0.75–2.56
High	26 (40.6)	45 (33.1)			
Educational level:					
Low	52 (81.3)	97 (71.3)	0.133	0.57	0.28–1.19
High	12 (18.7)	39 (28.7)			
Smoking:					
No	14 (21.9)	59 (43.4)	0.003*	2.74	1.38–5.42
Yes	50 (78.1)	77 (56.6)			
Cancer family history:					
No	50 (78.1)	117 (86.0)			
Yes	14 (21.9)	19 (14.0)	0.160	1.72	0.80–3.71
History of previous pulmonary disease:					
No	33 (51.6)	99 (72.8)	0.003*	2.51	1.35–4.67
Yes	31 (48.4)	37 (27.2)			
Annual dental follow-up:					
< 2 times or no/year	27 (42.2)	38 (27.9)			
2 times/year	37 (57.8)	98 (72.1)	0.045*	0.53	0.29–0.99
Periodontal pockets:					
Depth 4.0–6.0 mm	46 (71.9)	116 (85.3)			
Depth > 6.0 mm	18 (28.1)	20 (14.7)	0.024*	2.27	1.10–4.68
CAL:					
Mild 1–2.0 mm	46 (71.9)	107 (78.7)			
Moderate/severe > 3.0 mm	18 (28.1)	29 (21.3)	0.290	1.44	0.73–2.86
BOP:					
No	22 (47.8)	74 (54.4)	0.008*	2.28	1.23–4.22
Yes	42 (52.2)	62 (45.6)			

Note: \*p value: statistically significant.

After performance of the first method (step 1a) of the regression model it was found that all the examined variables except for dental follow-up and age were significantly associated with LC risk, according to the OR's. Statistically significant associations were recorded between moderate/severe CAL, BOP and risk of developing LC (Table 2). Table 2 also presents adjusted OR's with 95% CI. The final method (stepwise/step 7a) showed that smoking, PPD, CAL and BOP were significantly associated with LC risk. PPD was also significantly associated with LC risk after adjusting for confounders, such as smoking and dental follow-up (Table 3).

**Table 2.** Presentation of correlation between independent variables and LC according to Enter (first step) and Wald method (backward) of multiple logistic regression analysis model

Step	Variables	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
								Lower	Upper
1a	Gender	0.548	0.373	2.158	1	0.142	1.730	0.833	3.596
	Smoking	0.618	0.416	2.201	1	0.138	1.854	0.820	4.193
	Socio-economic level	0.448	0.400	1.256	1	0.262	1.565	0.715	3.427
	Educational level	-0.238	0.486	0.240	1	0.624	0.788	0.304	2.041
	Age	0.031	0.025	1.540	1	0.215	1.032	0.982	1.084
	Cancer family history	0.011	0.477	0.001	1	0.981	1.011	0.397	2.576
	History of previous pulmonary disease	0.558	0.384	2.109	1	0.146	1.747	0.823	3.711
	Annual dental follow-up	-0.688	0.369	3.474	1	0.062	0.502	0.244	1.036
	BOP	0.760	0.366	4.310	1	0.038	2.139	1.043	4.385
	Periodontal pockets	0.817	0.510	2.563	1	0.109	2.264	0.833	6.156
7a	CAL	1.162	0.524	4.912	1	0.027	3.197	1.144	8.937
	Constant	5.364	1.754	9.358	1	0.002	0.005		
	Smoking	0.913	0.373	6.008	1	0.014	2.492	1.201	5.173
	Annual dental follow-up	-0.588	0.351	2.803	1	0.094	0.555	0.279	1.106
	BOP	0.656	0.347	3.575	1	0.059	1.927	0.976	3.805
	Periodontal pockets	1.002	0.486	4.259	1	0.039	2.724	1.052	7.056
	CAL	1.256	0.506	6.163	1	0.013	3.513	1.303	9.474
	Constant	3.134	0.653	23.001	1	0.000	0.044		

**Table 3.** Application of Cochran's and Mantel – Haenszel's, statistical method for controlling possible confounders

Variables	Exp (B)	95% CI
Periodontal pockets		
Non-smokers	2.279	0.574–9.047
Smokers	6.708	2.182–20.622
CAL		
Non-smokers	2.138	0.652–7.006
Smokers	2.205	1.051–4.627
BOP		
Non-smokers	2.514	0.778–8.121
Smokers	2.416	1.143–5.106
Periodontal pockets		
Regular dental follow-up annually	2.745	1.043–7.227
Irregular dental follow-up annually	21.048	2.585–171.392
CAL		
Regular dental follow-up annually	3.639	1.298–10.205
Irregular dental follow-up annually	13.520	1.644–111.154
BOP		
Regular dental follow-up annually	2.041	0.921–4.520
Irregular dental follow-up annually	4.000	1.413–11.327

## DISCUSSION

The present case – control research showed that deep periodontal pockets were associated with an increased LC risk, after controlling for possible

confounders such as smoking and dental follow-up. Despite the fact that more investigation is required in order to confirm such findings, the current observations suggest that improvement of oral hygiene and smoking cessation could be an effective preventive measure against LC development.

The possible influence of gender as a cancer risk factor is known, however it is considered as a confounder. The results showed no association between gender and LC risk, finding that was in accordance with those from previous reports [9, 10].

Similarly, age is also considered as a confounder, although older individuals are in a higher risk for total cancer, LC [24, 25], initiation and progression of PD [26]. No association was found between age and LC risk in the present study.

Another crucial confounder is socio-economic level, however, it has not been proven its possible role as a LC risk factor. Its role is indirect in cases of previous pulmonary diseases such as TBC that is associated with a lower socio-economic level and LC development [27, 28]. No association was observed in the current study between those variables examined.

The possible role of educational level as a risk factor of developing LC has not been investigated according to previous reports. However, it is supposed that high-educated individuals take care of their own oral hygiene more than low-educated ones [29, 30]. No association was recorded between educational level and LC risk in the current study. There is strong evidence suggesting a genetic predisposition for LC. Studies of familial aggregation have shown familial risk on the same order of that reported for breast and colon cancer [31, 32]. The results of the present study did not confirm such an association.

Smoking is considered as a causal risk factor of total cancer and LC [33]. It has been shown that smoking is associated with SCC and SCLC, mainly, and in less cases with lung AC. It is still remaining unknown the reasons why only 15% of smokers develop LC [34]. The current study confirmed its role as a causal risk factor. On the other hand smoking is considered as a risk factor for PD development and progression [35, 36] and a proven confounder as well. Based on the mentioned suggestions the statistical method of adjustment — Cochran's and Mantel — Haenszel's was carried out to assess if possible significant correlations between both diseases could be attributed to smoking status or not. It was found that smoking was a confounder of CAL and BOP.

According to the results PPD was associated with an increased LC risk after controlling for certain confounders such as smoking and socio-economic status. Similar reports that have investigated the possible associations between PD indices and LC risk, or total cancer have not been carried out, whereas the majority of the available studies are prospective and have based on questionnaires and self-reported data.

Arora et al. [37] were found that individuals with PD showed an increased LC risk however after con-

trolling for certain confounders such as gender, age, socio-economic and educational status the mentioned association was not found to be statistically significant. That research was based on a questionnaire and self-reported information regarding periodontal tissues condition examined and different PD indices were used.

In another prospective study among health professionals in which a self-reported questionnaire was used for estimation of periodontal tissues status [9], PD was significantly associated with LC risk after controlling for smoking and several risk factors. The main finding was that a limited number of remaining teeth (0–16 vs 32) was associated with an increased LC risk.

Hujoel et al. [8] based on Russel Index for PD definition were found that individuals with PD had an increased risk of total cancer and a significantly increased LC risk, finding that was not confirmed in never smokers.

A similar research in Japan [38] reported that a small number of remaining teeth was associated with an increased LC risk.

An important factor that may be taken into account during the design process of such studies, is the epidemiological phenomenon of "confounding". Both diseases, PD and cancer share some common risk factors such as smoking and socio-economic status. Consequently, a correlation between both diseases would be expected even if a causal link did not exist. Confounding may also occur through unknown factors, for example a genetic predisposition, or mutual risk factors. However, the question still remains whether the association between PD and cancer is causal or is con-founded by unmeasured factors.

Another practical problem is the accuracy definition of PD which is essential to establish on reliable and reproductive indices [39]. Data of such studies have carried out based on prospective or retrospective methodology in an attempt to control possible systematic biases, 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 decision on including older individuals who have at least 20 remaining natural teeth, may lead to an under-estimation of older individuals with previous PD and who may have had teeth extracted for periodontal reasons. In addition, it is essential to be noted that there was not any chance of benchmarking between the findings of the current study with those of similar previous studies, whereas on the other hand the present study was a first attempt to approach that possible correlation in Greece.

In conclusion, PD parameters such as deep periodontal pockets were associated with an increased risk of developing LC.

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