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Research Article

A Research of the Relationship between Periodontal Disease, and Pancreatic Cancer: A Case-Control Study in Greek Adults

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Abstract

Introduction: The association between Periodontal Disease (PD) and Pancreatic Cancer (PC) has been investigated in many epidemiological studies.

Objective: The aim of the current research was to investigate the association between PD indices and PC risk in Greek adults.

Methods: A sample of 36 individuals who suffered from PC and 72 non-cancer individuals were enrolled in the study. PC diagnosis was confirmed by histopathological examinations of the patients. The associations between PD indices and PC risk was assessed using univariate and multivariate logistic regression analysis.

Results: According to multivariate analysis smoking [OR = 3,51, 95% CI = 1,19 - 6,39], higher socio-economic status [OR = 3,04, 95% CI = 0,99-5,76], PC family history [OR = 2,62, 95% CI = 0,95 - 5,23], chronic pancreatitis [OR = 2,31 95% CI = 0,89 - 5,96], and the presence of bleeding on probing [OR = 2,83, 95% CI = 1,12 - 6,14] were statistically significantly associated with the risk of developing PC. After performance of Cohran's and Mantel-Haenszel's, statistical method bleeding on probing remained to be significantly associated with PC risk after adjusting for con-founders, such as smoking, socio-economic status, PC family history and chronic pancreatitis.

Conclusion: Bleeding on probing as an index for PD was statistically significantly associated with the risk of developing PC.

Keywords: *Pancreatic Cancer; Periodontal Disease; Risk Factors; Adults*

Introduction

Pancreatic Cancer (PC) consists the fourth leading cause of cancer death in the United States, characterized by a rapidly development and poor prognosis for both genders [1]. Etiological and risk factors of PC is cigarette smoking which is considered as an established modifiable risk factor, whereas chronic pancreatitis, diabetes mellitus (DM) [2], obesity and insulin resistance [3], heavy alcohol drinking, metabolic syndrome, *H. pylori* infection, inflammation [4], DNA damage, immunity and genetic susceptibility [5] have been associated with PC risk. However, those factors can explain only a fraction of all PC cases [6].

A low proportion of individuals, less than 2% of all PC patients are still alive 5 years after the initial diagnosis and the main reason is that the majority of PC patients are presented with advanced stages at the time of initial diagnosis, whereas if the initial diagnosis has been made at localized early stage, TNM I and II, increases the 5-year survival rate significantly. The main causes for the mentioned high mortality are the lack of reliable bio-markers that could lead to early diagnosis and treatment [7].

The link between chronic inflammation and cancer development has been proved according to previous reports [8]. Chronic pancreatitis may be involved in the initiation and/or promotion of PC, as may enhance cellular proliferation and mutagenesis, reduce adaptation to oxidative stress, promote angiogenesis, inhibit apoptosis, and increase secretion of inflammatory mediators [9].

PD and especially periodontitis is a main cause of tooth loss in adults with dental caries and develops over many years as a result of bacterial infection and inflammation of the gingiva that spreads to one or more of periodontal tissue structures [10].

Serum levels of C-reactive protein (C-RP) and of other biomarkers of systemic inflammation are consistently higher in individuals with PD than in those who do not suffer from PD [11].

Periodontal infection in the mouth has systemic implications, as individuals with periodontal infections have elevated concentrations of circulating inflammatory markers [11], severity of disease directly correlates with serum concentrations of those markers [12] and treatment of periodontal infection can lower markers of systemic inflammatory and endothelial dysfunction within 2 - 6 months [13]. However, differing opinions remain on the relative role of confounding and biases and the causal component of those associations [14].

PD and alterations in the oral microbiome, which are responsible for its development, have been linked to several systemic diseases, including cardiovascular disease (CVD), DM, and preterm birth, possibly mediated through markers of systemic infection and inflammation [15].

Associations with respiratory diseases, and systemic infections have also been observed [15,16]. In addition, the results of several epidemiological studies have suggested a possible positive association between PD and cancer risk in different tissues, most notably in the mouth [17], upper gastrointestinal system [18,19], lung and pancreas [20-23].

Positive associations between tooth loss and PC have also been reported [24], whereas a significant association was observed in a prospective cohort study of men health professionals [22]. Other studies reported similar findings between PD [24,25] and PC.

However, similar researches which have explored the possible associations between PD indices, such as PPD, CAL, BOP, GI, etc. and PC risk have not been carried out.

Aim of the Study

The aim of the present retrospective case-control study was to examine the possible association between PD indices such as PPD, CAL, PlI and BOP and the PC risk in a population of Greek adults.

Methods

Sample of the study

The study sample consisted of 108 individuals, 66 males and 42 females, aged 45 - 73 years. Thirty-six individuals, 20 males and 16 females suffered from PC, were patients of two private medical practices and referred to a private dental practice for periodontal treatment, completed a medical and a dental health questionnaire and underwent a dental and periodontal clinical examination. The study was carried out from December 2015 to September 2018.

Selection criteria

PC patients-cases and non-PC patients- controls included in the study if they met the following inclusion criteria: at least a mean of 20 natural teeth-in an effort to minimize the influence of tooth number on the total number of periodontal pockets, ought not to be received

any treatment for any type of PD during a period of the previous six months and not to be received antibiotics, anti-inflammatory medication, or other systemic medication for a period of the previous six weeks. Exclusion criteria also included CVD, rheumatoid arthritis, liver cirrhosis, immuno-suppressive treatment or medication for the mentioned conditions or glucocorticoids. Cases should meet additional exclusion criteria such as: any type of treatment after PC initial diagnosis, advanced PC stage under chemotherapy, distant or recurrent disease, metastases due to a different initial location. The mentioned conditions could have potential effects on the periodontal tissues and excluded in an effort to minimize potential effects by known and unknown confounders.

Cases included patients diagnosed with PC in stages I and II (resectable stages of PC) according to clinical and histopathological examinations.

Oral clinical examination and questionnaire

All periodontal measurements (PPD, CAL, BOP) except for PlI recorded on all teeth surfaces in all quadrants and the worst values of the indices recorded. All measurements were performed with a periodontal probe (PCP 10-SE, Hu-Friedy) and the readings were recorded to the nearest 1.0 mm. Remaining roots and 3rd molars were excluded. In case a tooth cervix was destructed by lesions such as erosion, abrasion, or decay, or the cement-enamel junction (CEJ) was covered by a filling or prosthetic restoration or calculus its location was recorded by extrapolating the CEJ location from the adjacent teeth, whereas if its location could not be determined, the sites were not measured.

From the medical and dental questionnaire, the following variables were recorded: age, gender, smoking status (current/previous smokers and never smokers), socio-economic status (≤ 1,000 and > 1,000 €/month), educational level (elementary level, graduated from University/College), history of chronic pancreatitis and family history of PC and data that concerned their medical history with reference to the mentioned conditions and medication.

Familial PC is defined as an inherited predisposition based on family clustering in families in which there are multiple first and second degree relatives with ductal pancreatic adenocarcinoma in the absence of a known genetic susceptibility syndrome. A family history of PC is seen in between 5 - 10% of individuals with PC [26].

The attempt was to choose control group in such a way they can be the representatives of the population from which the cases were collected. Thus, cases and controls, were selected from the same city population in an effort to avoid or eliminate possible selection biases. Thus, the selection of controls was based on cases' environment, such as friends, colleagues, etc. According to that method, eligible control group was drawn from those, who were subjected to routine health examinations at the mentioned practices, between 2015 and 2018. Cases and controls, were matched 2 to 1 with cancer patients for age (± 3 yr) and gender in an effort to control potential confounders.

Statistical analysis

In the analysis, the variables female gender, smoking status for non-smokers or former smokers, lower educational and socio-economic status, absence of PC family history and DM history were coded 0, as dichotomous variables.

The presence of PPD was classified as follows [27]: 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 [28]: score 0: mild/moderate 1 - 4.0 mm of attachment loss, and score 1: severe ≥ 5.0 mm of attachment loss.

The record for PPD and CAL measurements concerned the immediate full millimeter.

Plaque Index (PlI) was determined by the examination and recording both soft debris and mineralized deposits on 4 surfaces of the following teeth: 16, 12, 24, 36, 32, 44, whereas missing teeth are not substituted. PlI score was coded as 0: no plaque/moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye, and as 1: abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin [29].

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

Descriptive statistics and statistical analysis were carried out with SPSS statistical package (SPSS PC19.0, SPSS, Inc., Chicago, IL, USA).

A randomly selected sample of 22 individuals (~20%), 14 noncancer individuals and 8 cancer patients were re-examined clinically by the same dentist during a period of four weeks after the first examination to assess the intra-examiner variance and no differences were recorded between 1st and 2nd clinical examinations (Cohen's Kappa = 0.96).

The current retrospective study has not been reviewed and approved by authorized Greek committees (Greek Dental Associations, Ministry of Health, etc.), as was not an experimental one. The performance of the study was in full accordance with the World Medical Association Declaration of Helsinki. Individuals who accepted the invitation to participate in the study protocol signed an informed consent form.

Results

The study sample included 66 males and 42 females ranging in age from 45 to 73 years old and mean age 64 ± 3 years. According to univariate analysis smoking, DM history, deep periodontal pockets and BOP were found to be significantly associated with PC risk (Table 1).

Variables	Cases (no) (%)	Controls (no) (%)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)
Gender					
Males	46 (71.9)	80 (58.8)			
Females	18 (28.1)	56 (41.2)	0.075	1.79	0.94 - 3.40
Age (years)					
45 - 49	4 (6.3)	10 (7.4)			
50 - 59	11 (17.2)	32 (23.5)			
60 - 69	41 (64.0)	73 (53.7)	0.578	-	-
70+	8 (12.5)	21 (15.4)			
Socio-economic level					
Low	38 (59.4)	91 (66.9)			
High	26 (40.6)	45 (33.1)	0.300	1.38	0.75 - 2.56
Educational level					
Low	52 (81.3)	97 (71.3)			
High	12 (18.7	39 (28.7)	0.133	0.57	0.28 - 1.19
Smoking status					
No	14 (21.9)	59 (43.4)			
Yes	50 (78.1)	77 (56.6)	0.003*	2.74	1.38 - 5.42
PC family history					
No	50 (78.1)	117 (86.0)			
Yes	14 (21.9)	19 (14.0)	0.160	1.72	0.80 - 3.71
Chronic pancreas					
No	33 (51.6)	99 (72.8)			
Yes	31 (48.4)	37 (27.2)	0.003*	2.51	1.35 - 4.67
Periodontal pockets					
Depth 4,0-6,0 mm	46 (71.9)	116 (85.3)	0.024*	2.27	1.10 - 4.68
Depth >6,0 mm	18 (28.1)	20 (14.7)			
Clinical Attachment Loss					
Mild 1 - 2,0 mm	46 (71.9)	29 (21.3)	0.290	1.44	0.73 - 2.86
Moderate/Severe ≥ 3,0 mm	107 (78.7)	18 (28.1)			
Bleeding on Probing					
No	22 (47.8)	74 (54.4)	0.008*	2.28	1.23 - 4.22
Yes	42 (52.2)	62 (45.6)			
Gingival Index					
No plaque/Moderate acc.	44 (68.8)	90 (66.2)	0.718	1.12	0.60 - 2.13
Abundance of soft matter	20 (31.2)	46 (33.8)			

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

** p-value: statist. Significant.*

The Enter method (1[a] step) showed that socioeconomic status (p = 0.028) and family PC history (p = 0.054, marginally) were significantly associated with PC risk (Table 2). The same table shows adjusted OR's and 95% CI.

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp (B) Lower	95% C.I. for EXP (B) Upper	
Step 1[a]	Gender	,362	,507	,510	1	,475	,696	,258	1,880
	Age	,246	,277	,791	1	,374	,782	,454	1,345
	Socioecstat	1,093	,498	4,811	1	,028	2,982	1,123	7,916
	Educlev	,619	,500	1,531	1	,216	1,857	,697	4,951
	Smokstat	,848	,502	2,852	1	,061	2,335	,873	6,248
	Fampchist	1,071	,555	3,727	1	,054	2,919	,984	8,661
	Chronpancreat	,761	,509	2,235	1	,105	2,140	,789	5,800
	cal	,648	,529	1,497	1	,221	1,911	,677	5,395
	pd	,019	,543	,001	1	,972	1,019	,351	2,955
	bop	,678	,602	1,269	1	,106	1,970	,605	6,411
	Gingindex	,306	,542	,319	1	,572	1,358	,469	3,931
	Constant	3,022	,914	10,922	1	,001	,049		
Step 7[a]	Socioecstat	1,011	,479	5,385	1	,033	3,036	,988	5,758
	Smokstat	1,221	,477	3,734	1	,020	3,512	1,187	6,392
	Fampcthist	,964	,517	3,473	1	,042	2,623	,951	5,231
	Chronpancreat	,836	,484	2,978	1	,044	2,307	,893	5,962
	bop	1,041	,472	4,860	1	,027	2,831	1,122	6,142
	Constant	3,007	,661	22,110	1	,000	,045		

Table 2: *Presentation of correlation between independent variables and pancreatic cancer according to Enter (first step) and Wald (final step) method of multivariate logistic regression analysis model.*

a: Variable(s) entered on step 1: gender, age, socioecstat, educlev, smokstat, fampchist, chronpancreat, cal, pd, bop, gingindex.

According to the final model (stepwise/step 7[a]), smoking (p = 0.02, OR = 3,51 95% CI = 1,19 - 6,39), higher socio-economic status (p = 0.033, OR = 3,04 95% CI = 0,99 - 5,76), PC family history (p = 0.042, OR = 2,62, 95% CI = 0,95 - 5,23), chronic pancreatitis history (p = 0.044, OR = 2,31 95% CI = 0,89 - 5,96) and the presence of bleeding on probing (p = 0.027, OR = 2,83, 95% CI = 1,12 - 6,14) were statistically significantly associated with the risk of PC.

BOP was also significantly associated with PC risk after adjusting for confounders, such as smoking, socio-economic status, family PC history and chronic pancreatitis history (Table 3).

Variables	Exp (B)	95% CI
Bleeding on probing		
Non-smokers	1.144	0.281 - 2.007
Smokers	3.140	1.325 - 7.443
Bleeding on probing		
Socioeconomic status: Low	1.090	0.229 - 1.952
High	2.976	1.257 - 7.044
Bleeding on probing		
PC family history: Yes	2.854	1.204 - 6.763
No	1.049	0.186 - 1.911
Bleeding on probing		
Chronic Pancreatitis history: Yes	2.574	1.104 - 6.002
No	0.945	0.099 - 1.792

Table 3: *Application of Cohran's and Mantel-Haenszel's, statistical method for controlling possible confounders.*

Discussion

There has been a substantial interest in PD and risk of several types of cancer including PC risk over the past decade, and the associations reported have been remarkably consistent. However, the majority of those studies were based on indices such as number of missing teeth or gingivitis as direct or indirect PD indices, were prospective and were based on questionnaires and self-reported data.

The present case-control research showed that BOP was associated with an increased PC risk, after controlling for possible confounders such as smoking, socio-economic status, chronic pancreatitis history and PC family history. Despite the fact that more investigation is required in order to confirm such findings, the current findings suggest that smoking cessation could be an effective preventive measure against PC development as smoking is a known and modifiable PC risk factor.

Gender is a common cancer risk factor [30], however today there is no longer any evident gender-related difference. In the current study no association was recorded between both genders and PC risk, whereas in general, gender is considered as a confounder. That observation was in agreement with those from previous reports [31,32].

Similarly, age is also considered as a confounder, although older individuals are in a higher risk for total cancer and PC [33,34]. No association was observed between age and PC risk in the present study.

Another crucial confounder is socio-economic level, and it has been proven its possible role as a PC risk factor. Its role maybe is indirect in cases of chronic pancreatitis which caused by alcohol over-consumption as alcohol is a proven risk factor for PC development [4]. In the current report a significant association was observed between those variables examined, finding that was in accordance with those from a previous report [35].

The possible role of educational level as a risk factor for PC development has been investigated in a limited amount in previous reports. No association was recorded between educational level and PC risk in the current study. Previous studies confirmed that finding [36,37], whereas it has been suggested that, high-educated individuals take care of their own oral hygiene more than low-educated ones and could prevent diseases that are associated with PD [38].

A strong evidence has been suggested regarding a genetic predisposition for PC. Familial PC is defined, as already has stated, as an inherited predisposition based on family clustering in families in which there are multiple first and second degree relatives with ductal pancreatic adenocarcinoma in the absence of a known genetic susceptibility syndrome. A family history of PC is seen in between 5 - 10% of PC patients [26], finding that was in accordance with the findings of the current report.

Tobacco smoking seems to be the only established modifiable risk factor [34]. It is still remaining unknown the reasons why only a low proportion of smokers develop PC. 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 [39] and a proven confounder as well. Based on the mentioned suggestions the statistical method of adjustment-Cohran'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 not a confounder of the association between PC risk and BOP.

Chronic pancreatitis [40] is another causative factor of PC development. The results of the present study confirmed such an association. Several mechanisms could potentially explain that association. In general, inflammation appears to play an important role in PC pathogenesis [41], although the inflammatory biomarkers and mediators which lead to the development of PC still remain unclear.

Previous researchers have recorded that inflammation plays a critical role in tumorigenesis and some of the underlying molecular mechanisms have been elucidated. It is estimated that under-lying infections and inflammatory reactions are associated with a rate of 25% of all cancer cases [8]. Cancer, and more specifically, PC, is linked to chronic inflammatory processes [9,42].

PD and especially periodontitis is a chronic infectious and inflammatory disease of the periodontal supporting tissues, and results in constant low-grade systemic inflammation. PD is characterized by increased levels of circulating inflammatory bio-markers, its overall prevalence varies from 10 to 90% in adults [43] and is the main cause of tooth extraction in adults aged ≥ 40 years [44].

According to the results BOP was associated with an increased PC risk after controlling for certain confounders such as smoking, socio-economic status, chronic pancreatitis history and PC family history.

The bleeding index (BOP) reflects the host's vascular response in terms of hyperemia, the capillaries' dilation and increased blood flow in the inflammation region. PD and CAL refer to the long-term stages of chronic inflammation including destructive processes signs of a chronic inflammatory response [45]. BOP is a widely used criterion to diagnose gingival inflammation, however it has been shown that periodontal pockets with a probing depth of greater than or equal to 5 mm showed a significantly higher incidence of BOP [46].

The measurement of the state of oral hygiene by Silness-Löe plaque index is based on recording both soft debris and mineralized deposits on the following teeth and does not reflect the bacterial burden [31].

Identified inflammatory markers produced in the immune response to PD include pro-inflammatory cytokines, chemokines, peripheral leukocytes, prostanoids, proteases such as matrix metallo-proteinases (MMP), and acute-phase proteins, bio-markers of systemic inflammation including C-reactive protein (C-RP), IL-1β, IL-6, TNF-α, etc [9,11,47].

A link between PD and systemic inflammation has been suggested using biomarkers such as C-RP [11], whereas its plasma levels were assessed 30% higher in individuals who suffered from PD than in the healthy ones. It is also possible that the chronic inflammation induced by PD pathogens serves to promote already initiated cells, can lead to the breakdown of normal cell growth control, and potential carcinogenesis. Periodontal pathogens may also play a more direct role through local inflammatory and immunity responses and carcinogenic transformations [9].

Indirect mechanisms for a link between periodontitis and cancer is that periodontitis may induce a significant increase in inflammatory bio-markers and molecules that enhances the inflammatory reactions and it can lead to the release of reactive oxygen species (ROS) and other DNA toxic metabolites that could promote cancer initiation. In addition, the stimulation of the inflammatory process and the presence of cell-stimulating signal pathways may contribute to a proper environment for cell proliferation and differentiation. Such mechanisms are able to express their actions both locally and at a distance region [9,48].

It has been suggested that the oral microbial environment and PD are associated with other forms of cancer in locations such as in lungs and pancreas [17,20,23,24,49]. The possible mechanisms by which the oral microbiota might contribute to the PC development have not been determined.

The oral cavity consists a gateway for pathogens, which could then enter the blood circulation or the gastrointestinal system and are able to affect distant organs [50]. Oral pathogens are increasingly being implicated in chronic, inflammatory-based systemic diseases [51], that may lead to cancer development. *P. gingivalis* and *F. nucleatum* periodontal pathogens can stimulate tumorigenesis and human oral tumor proliferation [52]. One possible pathway is its ability to convert ethanol to acetaldehyde, which is a carcinogen and they also activate tobacco smoke and nutritional items carcinogenic N-nitroso compounds, and are able to catalyse their endogenous formation from those sources [18,53,54].

Oral nitrate-reducing bacteria are involved in the production of carcinogenic N-nitroso compounds in the stomach [53]. The endogenous production of nitrosamines has been found to be substantially higher among individuals with poor oral hygiene than among those with good oral hygiene [55]. Both N-nitroso and acetaldehyde compounds are associated with PC development [56]. Another possible pathway is its activation by innate immune signaling via Toll-like receptors (TLRs) which inhibit cellular apoptosis and stimulate tumor development [57]. Based on those observations, it has been hypothesized that PD may promote pancreatic carcinogenesis through chronic inflammation, whereas it has also been suggested that PD could influence pancreatic carcinogenesis through increased levels of carcinogens, such as nitrosamines. Individuals with PD and poor oral hygiene have increased levels of oral pathogens and nitrosamine in their oral cavity due to nitrate-reducing bacteria [53]. Nitrosamines and gastric acidity maybe play an important role in PC initiation and previous reports support this suggestion [53,54].

Michaud., *et al.* [58] observed higher levels of antibodies formed against *P. gingivalis* in PC patients than in healthy individuals. In the same multicenter study was also recorded a 2-fold increase in PC among individuals who had high levels of antibodies to the periodontal pathogen *P. gingivalis* ATTC 53978 compared with those with lower levels. Those observations suggest that individuals who have high levels of antibodies to *P. gingivalis* ATTC 53978 were at higher risk of PC. *P. gingivalis* as a PD specific pathogen, after invading the epithelium, was found to prevent, cell apoptosis, thus is implicated in cancer initiation [57-59]. *P. gingivalis* and other periodontal pathogens, such as *H. pylori*, have been found in carcinomas of the gingiva and are also associated with distant tumor development [60]. A recent cohort study recorded positive associations between two periodontal pathogens, *P. gingivalis* and *A. actinomycetemcomitans* and PC using direct bacterial DNA measurement from saliva of individuals collected years prior to diagnosis [61].

Oral bacteria maybe play a role in triggering chronic pancreatitis [62] and it is possible that the systemic spreading of those pathogens and their toxins may trigger systemic inflammatory and immune responses that could lead to PC development [11,50].

Previous reports have recorded an increased risk for PC in individuals with periodontitis, however the authors were based on indirect PD indices, such as number of tooth loss, or were based on questionnaires and self-reported data, whereas some of those studies were prospective.

In a study by Hujoel., *et al.* [24] was recorded an increased risk for PC in individuals with periodontitis in the NHANES I population. Positive associations were suggested for individuals with periodontitis, gingivitis, and edentulism with PC, but those associations were attenuated after adjustment for potential confounders except for smoking status.

A recently prospective study in male health professionals found a 64% increase in the risk of PC for those reporting a history of PD at baseline [20]. The association between PD and PC was stronger among those who were never-smokers, minimizing the possibility of residual confounding by smoking. Number of teeth at baseline was not related to risk of PC.

Tooth loss is an indirect PD index, as has already mentioned. Previous studies confirmed that a history of PD and tooth loss are associated prospectively with increased risk of PC [20,24].

Tooth loss occurs through poor oral and dental hygiene may be a marker for more deleterious gastrointestinal flora and, consequently, greater endogenous nitrosation. Nitrosamines are able to induce pancreatic carcinogenesis in animals and are considered potential human pancreatic carcinogens, as already mentioned [63]. However, more researches are needed to examine oral hygiene and gastrointestinal bacteria to quantify nitrosamine formation in the small intestine in smokers and nonsmokers.

Several limitations exist in the current retrospective study, as those studies do not have the reliability of the prospective ones, because of the presence of selection, random, recall, referral biases and the effect of known and unknown con-founders which are able to lead to biased secondary correlations regarding the indices examined. Moreover, possible confounders which are related with an increased risk of PC such as alcohol consumption were not included.

A potential limitation was the small sample of the current study, however the PC incidence was 7,3/100,000 according to WHO [64]. Another limitation was that the individuals could not respond or could give no reliable responses, or could over- or under-estimate the data which concerned the variables examined. The main limitation is that both diseases, PD and PC share some common risk factors such as smoking and socio-economic status. Thus, a correlation between both diseases would be expected even if a causal link did not exist.

Some strengths of the current study were that it was a matched case-control study, and used randomly selected population-based controls. Controls was selected from non-cancer individuals derived from cases environment, it is reasonable to assume that control group represented the same base population as that from which the cases were selected, warranting internal validity.

Thus, the demographic and epidemiologic factors distributions, including age, gender, and smoking, differed between cases and controls. The effects of residual confounders may not affect the main outcomes because all potential confounders, such as cancer family history or smoking, were adjusted for in this study.

A retrospective design of a study cannot avoid recall or selection bias, thus prospective cohort studies with larger number of patients are necessary to define the mechanisms by which PD may influence PC risk. Another reason is the relatively limited number of cases which also indicates that those findings need replication in a larger study.

In addition, it is essential to be mentioned 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 current study was a first attempt to approach that possible correlation in Greece. More studies are needed to confirm those findings and explore potential biological mechanisms. In conclusion, PD parameters such as BOP was associated with an increased risk of developing PC.

Conclusion

Bleeding on probing as an index for PD was statistically significantly associated with the risk of developing PC after adjusting for confounders, such as smoking, socio-economic status, PC family history and chronic pancreatitis.

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Volume 18 Issue 2 February 2019