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Association Between Periodontal Disease and Risk of Prostate Cancer in a Greek Adult Population : A Case - Control Study

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ABSTRACT

Objective: Periodontal Disease has been associated with the risk of various systemic diseases, including several types of cancer. However, the association with Prostate Cancer remains inconclusive. The purpose of the current research was to explore the possible association of Periodontal Disease indices with the risk of Prostate Cancer. **Methods:** A total of 499 males,166 who suffered from Prostate Cancer and 333 healthy individuals, were consecutively recruited from three medical and one dental practice. Data on periodontal status was collected, through a dental and oral examination and concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI), Bleeding on Probing (BOP) and risk factors of Prostate Cancer. Univariate and logistic regression models were carried out to test the association between PD indices and Prostate Cancer risk. **Results:** Logistic regression analysis model showed that a Prostate Cancer family history (p= 0.000), increased alcohol consumption (p= 0.051), smoking (p= 0.000), chronic prostate inflammation (p= 0.054), and CAL (p= 0.039) were statistically significantly associated with risk for Prostate Cancer development. **Conclusions:** Individuals with a prostate cancer family history, chronic prostate infection, increased alcohol consumption, smoking, and CAL were at significantly higher risk for developing Prostate Cancer.

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Introduction

Prostate cancer (PC) is the most frequent type of cancer in males, the leading cause of cancer-related deaths worldwide, and the second leading cause of cancer-related death in males, behind lung cancer in the United States [1]. Although PC is an extremely common cancer in elderly males, the primary causes are still controversial. Epidemiological studies have linked the risk of PC to various factors like age, ethnicity, family history, insulin-like growth factors, lifestyle, diet, environmental and occupational exposures. Some of those such as age, Family history and race, limit its prevention [2,3].

Recent observations suggest that PC is associated with chronic inflammation [4], as plays a vital role in tumor initiation, promotion, malignant transformation, invasion and metastasis [5]. In addition to inherited genetic factors, chronic inflammation, smoking, and excess body weight are risk factors, yet these only partially explain risk for this disease [2].

Periodontal disease (PD), gingivitis and mainly periodontitis, is a chronic infectious disease caused by bacterial infection which invades gingiva and periodontal supporting tissues [6]. Periodontitis is a process in which periodontal bacteria [7] and viruses [8] lead to a host immunoinflammatory response in periodontal tissues that causes periodontal pocket formation, attachment loss and bone loss. It affects 47 % of adults aged 30 and older in the United States, and leads to gradual loss of periodontal tissues including periodontal bone, and in aggressive and severe cases to tooth loss [9]. Moreover, severe PD has affected 743 million people worldwide, its prevalence is reportedly as high as 90% and the prevalence and severity of periodontitis, increase with age [10]. Several risk factors might be responsible for chronic PD, especially smoking, obesity, and diabetes mellitus, which are also major risk factors or risk indicators for PC occurrence [11].

Oral health may influence systemic health [12] and an association between PD and systemic conditions such as cardiovascular disease [12,13], type 2 diabetes mellitus [12], osteoporosis [12], rheumatoid arthritis [14], respiratory diseases [15], and several types of human cancers, have been observed [16]. Chronic inflammation caused by bacterial infection has been reported as one of the main factors underlying the development of cancer. Periodontal infection induces inflammation that may increase the risk of tumor-promoting effects [17]. Pathogenic microorganisms such as *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* lead to chronic inflammation and destruction of periodontal tissues [18]. The spread of bacteria and inflammatory mediators from the oral cavity can cause and maintain systemic inflammatory conditions and damage to various organs [19]. The inflammatory reaction directly or indirectly induces cell proliferation and the release of reactive oxygen species (ROS) and other metabolites that can promote cancer initiation [19,20]. To be more specific, oral pathologic bacteria such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Treponema denticola*, and *Porphyromonas gingivalis* were found to be significantly positively associated with oral, pancreatic, and gastro- Intestinal cancers [21]. Oral pathologic bacteria can either up- or down-regulate pro-inflammatory cytokines and chemokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein, resulting in oral pathologic bacteria being able to affect the oral and systemic immune systems of the body and also induce oncogenic responses [22].

In particular, individuals with PD have a greater risk of cancer overall [18,23-28] and site-precise malignancies including prostate[24,29,30-32]. Recent studies report an association between PC and tooth loss [23,24]. However, the results of similar studies regarding the association between PD and PC were conflicting. Considering that a single epidemiological study may not be sufficient to determine the effect of PD on PC risk, prospective and retrospective studies are required to further elucidate the association between PD and PC risk. The current study is the first in Greece that assessed the possible association, as no previous epidemiological researches have been carried out. The aim of the present retrospective case control study was to assess the possible association between PD indices and risk of PC in a sample of male adults in Greece.

Methodology

Study Design and Study Population Sample

A retrospective case-control study of 499 participants who recruited from three private medical and a dental practice was carried out between May 2020 and October 2021. The study sample size was estimated according to PC prevalence [33] and determined by "Hyman et al." [34], with 95% Confidence Level and relative precision 25.0%, whereas the age group was based on the World Health Organization recommendations [35,36] for assessing PD prevalence.

The mentioned procedure resulted in a study sample of 499 individuals [34], 166 with PC - cases and 333 healthy individuals - control, aged 45 to 78.

Cases and Controls Selection Criteria

Individuals with less than 20 natural teeth, those who were undergone a conservative or surgical PD treatment within the previous six months and those who had prescribed systemic anti-inflammatory or antibiotics or other systemic drugs, such as glucocorticoids the previous six weeks were excluded from the study protocol as those conditions could influence the oral tissues status.

Moreover, advanced PC patients under medical treatment, and hospital patients were also excluded. The mentioned criteria could lead to biased secondary associations [37].

PC patients - case group consisted of individuals whose the primary diagnosis of PC was based on their medical files and included the traditional methods, namely digital rectal examination (DRE) and prostate-specific antigen (PSA) blood test, followed by transrectal ultrasound (TRUS) guided biopsy [38].

Healthy individuals - control group selection consisted of individuals derived from the friendly and collegial environment of cases in an effort to control potential confounders such as age, gender, socioeconomic and smoking status.

Research Questionnaire

PC patients and healthy individuals completed a modified Minnesota Dental School Medical Questionnaire [39], that contained epidemiological variables such as age, smoking status, alcohol intake, current diseases and disorders, and information regarding their medical/dental history.

Intra-examiner variance was established by a randomly selected sample of 71 (20%) individuals were re-examined clinically by the same Dentist after three weeks, and no differences were observed between the 1st and the 2nd clinical assessment (Cohen's Kappa = 0.92). During this time period no oral hygiene instructions were given to the participants.

Periodontal status examination

All periodontal examinations were conducted in a private dental practice. The measurements concerned the following PD indices: Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI) and Bleeding on Probing (BOP) , and were made at six sites per tooth (mesio-, mid-, and disto-buccal; mesio-, mid-, and disto-lingual) for all teeth, excluding third molars and remaining roots using a manual periodontal probe (UNC-15; Hu Friedy Mfg. Co. Inc., Chicago, IL USA).For each individual, case and control, the worst values of PPD, CAL, and GI on six sites per tooth were recorded and coded as dichotomous variables.PPD was classified as 0-3.00 mm and ≥ 4.0 mm for absence of disease/mild disease, and mode-rate/severe disease, respectively, for mean PPD [40]. CAL severity was classified as mild, 1-2.0 mm and moderate/severe, ≥ 3.0 mm of attachment loss [41].The severity of gingivitis classified as follows:-score 0: normal situation of gingival tissue/mild inflammation, insignificant change in colour and oedema, absence of bleeding on probing, which corresponds to Löe [42] classification as score 0 and 1, and –score 1: moderate inflammatory reaction with presence of redness, oedema, glazing and bleeding on probing/severe inflammatory reaction with presence of significant redness, oedema, ulceration and tendency to spontaneous bleeding, which corresponds to Löe [42] classification as score 2 and 3.The presence/absence of BOP was coded as - score 0: absence of BOP, and-score 1: presence of BOP and deemed positive if it occurred within 15 seconds of probing.

Ethical Consideration

The current case - control study was not approved by authorized committees (Ministry of Health, etc.), as in Greece only experimental studies must be approved by the mentioned Authorities. An informed consent form was obtained by the individuals who agreed to take part in the present research.

Measurement of covariates

Socio-demographic information, general and oral health examinations, and a self-reported questionnaire was used to collect data at the time of enrolment for the following potential variables regarded as risk factors or indicators for PC and included as covariates in the univariate and multivariable analyses. Education was categorized as elementary level and graduated from University/College. Socio-economic status was categorized as ≤ 1,000 and >1,000 €/month. Cigarette smoking was categorized as never (males who smoked fewer than 100 cigarettes during their lifetime), and former (males who smoked at least 100 cigarettes in their lifetime and reported that they now smoke "not at all") / current smokers (males who smoked at least 100 cigarettes in their lifetime and reported they now smoke "every day" or "some days"). Alcohol consumption was categorized at the level of daily alcohol consumption in grams of ethanol as less than10 g/drink and equal or more than 10g/ drink. Body Mass Index (BMI) was categorized as normal (less than 30 Kg/m^2) and high (equal or more than 30 Kg/m^2) [43].

Statistical Analysis

The worst values of PPD, CAL, GI and presence of BOP on six sites per tooth were recorded and coded as dichotomous variables for each individual, case and control, and coded as 1. Never smokers, individuals without PC family history/chronic prostate inflammation, normal BMI and low alcohol consumption were coded as 0. Age groups distribution was coded as 0,1,2 and 3 for ages 45-50, 51-60, 61-70, 71-78 respectively.

Categorical data were shown as frequencies and percentages. Cohort-related variables, including socio-demographic factors (age, income, education), comorbidities (PC family history, increased BMI, prostate inflammation), self-reported questionnaire (smoking status, alcohol intake habits), were analyzed using the univariate model. Multivariate regression model was carried out to investigate the associations between the dependent variable, PC, and independent ones. Unadjusted and Adjusted Odds Ratios (OR's) and 95% Confidence Interval (CI) were also estimated. The independent variables were included to stepwise method in order to assess gradually the variables that showed significant associations with the dependent one. Statistical analysis was applied using the SPSS ver.22.0 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 64.5 ± 2.5 years.

Univariate analysis is presented in Table 1, and showed that presence of PC family history (p= 0.000), increased alcohol consumption (p= 0.008), increased CAL (p= 0.007), moderate/severe gingival inflammation (GI) (p= 0.012), and BOP (p= 0.01) were statistically significantly associated with risk for PC development. **Table 1** also shows Unadjusted OR's and 95% CI for each variable examined.

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

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Age				
45-50	27 (16.3)	60 (18.0)		
51-60	65 (39.2)	127 (38.1)		
61-70	44 (26.5)	80 (24.0)	0.879	_____
71+	30 (18.0)	66 (19.9)		
PC family history				
Absence	68 (41.0)	194 (58.3)	**0.000***	0.497 (0.341-0.726)
Presence	98 (59.0)	139 (41.7)		
Previous PC chronic infection				
No	68 (41.0)	165 (49.5)	0.070	0.706 (0.485-1.030)
Yes	98 (59.0)	168 (50.5)		
Education level				
Low	81 (48.8)	164 (49.2)	0.924	0.982 (0.677-1.425)
High	85 (51.2)	169 (50.8)		
Socio-economic status				
Low	73 (44.0)	149 (44.7)	0.871	0.969 (0.666-1.410)
High	93 (56.0)	184 (55.3)		
Alcohol consumption				
<10 grams/drink	59 (35.5)	160 (48.0)	**0.008***	0.596 (0.406-0.875)
≥10 grams/drink	107 (64.5)	173 (52.0)		
Smoking				
No	65 (39.2)	155 (46.5)	0.117	0.739 (0.506-1.079)
Yes	101 (60.8)	178 (53.5)		
Body Mass Index				
<30 kg/m^2	78 (47.0)	152 (45.6)	0.777	1.055 (0.727-1.533)
≥30 kg/m^2	88 (53.0)	181 (54.4)		

Probing pocket depth				
0-3.00 mm	75 (45.2)	160 (48.0)	0.545	0.891 (0.613-1.295)
≥ 4.0 mm	91 (54.8)	173 (52.0)		
Clinical Attachment Loss				
1.00-2.00 mm	70 (42.2)	183 (55.0)	**0.007***	0.548 (0.410-0.871)
≥ 3.0 mm	96 (57.8)	150 (45.0)		
Gingival Index				
Absence/Mild	65 (39.2)	170 (51.1)	**0.012***	0.617 (0.423-0.901)
Moderate/Severe	101 (60.8)	163 (48.9)		
Bleeding on probing				
Absence	59 (35.5)	159 (47.7)	**0.010***	0.603 (0.411-0.886)
Presence	107 (64.5)	174 (52.3)		
* p-value statistically significant				

After performance of the first method (step 1a) of the regression model it was found that PC family history (p= 0.001), smoking (p= 0.000), and previous prostate chronic inflammation (p= 0.051), were significantly associated with PC risk (**Table 2**). Table 2 also shows Adjusted OR's and 95% CI for each parameter examined. The final step of multivariate regression analysis model (Wald method) is presented in Table 2, in which PC family history (p= 0.000), smoking (p= 0.000), increased alcohol consumption (p= 0.051), previous prostate chronic inflammation (p=0.054), and CAL(p= 0.039) were statistically significantly associated with risk for developing PC.

Table 2: Presentation of association between potentially risk factors and LC according to Enter (first step-1[a]) and Wald (last step 5[a]) method of multivariate logistic regression analysis model.

Variables in the Equation

Variables		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	age	,054	,104	,267	1	,605	1,055	,861	1,294
	fam.history	,792	,206	14,799	1	**,000***	2,208	1,475	3,306
	smoking	,902	,213	17,873	1	**,000***	2,465	1,622	3,745
	alcoh.consum	,391	,217	3,257	1	,071	1,479	,967	2,261
	body.mass.ind	,107	,204	,273	1	,601	,899	,602	1,341
	educ.level	-,024	,203	,014	1	,905	1,025	,688	1,525
	socioec.status	-,048	,207	,054	1	,817	1,049	,699	1,575
	prev.chron.pros	,408	,209	3,816	1	**,051***	1,504	,999	2,265
	period.pocket	,236	,225	1,101	1	,294	,790	,509	1,227
	clin.att.loss	,340	,229	2,207	1	,137	1,404	,897	2,198
	ging.index	,220	,218	1,017	1	,313	1,246	,813	1,909
	bleed.on.prob	,319	,217	2,153	1	,162	1,376	,898	2,107
	Constant	2,412	,398	36,643	1	,000	,090		
Step 8[a]	fam.history	,800	,204	15,346	1	**,000***	2,225	1,491	3,319
	smoking	,923	,206	20,142	1	**,000***	2,517	1,682	3,768
	alcoh.consum	,380	,211	4,248	1	**,051***	1,462	,967	2,211
	prev.chron.pros	,374	,202	4,422	1	**,054***	1,453	,978	2,159
	clin.att.loss	,428	,207	4,261	1	**,039***	1,534	1,022	2,303
	Constant	2,234	,278	64,737	1	,000	,107		

a. Variable(s) entered on step 1: age, fam.history, smoking, alcoh.consum, body.mass.ind, educ.level, socioec.status, prev.chron.pros, period.pocket, clin.att.loss, ging.index, bleed.on.prob.

* p-value statistically significant

Discussion

The outcomes of the current study showed that individuals with a PC family history, chronic prostate infection, increased alcohol consumption, smoking, and CAL were at significantly higher risk for developing PC.The exact etiology of PC remains elusive, however various modifiable and unmodifiable risk factors have been suggested as contributing factors, such as age, ethnicity, family history, genetics, obesity, diet, hormones, smoking, alcohol consumption, and certain medications, however, ethnicity and age, seem to be definite etiological factors for PC [2,3].

Age is a well-established PC risk factor as incidence of PC increases with age, whereas the disease is not frequent below the age of 40 [44,45]. The current study did not confirm that association. The current research recorded no association between educational and socioeconomic status (SES) and the risk of PC. On the contrary, previous reports have revealed such an association, and to be more specific these reports showed that PC was significantly elevated among males of higher SES compared to those with lower SES [46,47].

The possible explanation for the positive association between SES and PC incidence is a higher frequency of regular prostate-specific antigen (PSA) screening among higher-SES males compared to those with lower SES [48,49].

Similarly, more educated males are more likely than their peers with less education to use regular PC screening [48,49]. The PSA test can detect PC at early asymptomatic stages and, consequently, increase the incidence of PC among well-educated males exposed to more frequent screening [50].

PC is associated with an increased heritability, suggestion that is in accordance with the results of the current study. [51] recorded that males with a father or brother diagnosed with PC showed a two to four-fold risk of developing PC, and the risk was higher if a brother was diagnosed with the disease. The risk attributed to genetic factors increases further in a case in which more relatives being affected and in an earlier age at diagnoses [52]. Moreover, the variation of PC risk among twins attributed to genetic factors was 57%, finding that confirms that PC is one of the most heritable cancers [53].Genome Wide Association Studies (GWAS) have provided greater emphasis to the genetic predisposition for PC risk. More than 180 independent single nucleotide polymorphisms (SNPs) have been detected to be associated with PC risk, which account for a third of familial PC heritability risk [54]. A similar review showed that PC genetic susceptibility variants can explain 37.5% of the familial relative risk of PC, with approximately 6% accounting for infrequent variants, including two rare SNPs on 8q24 and HOXB13 and 31.5% for commonly occurring SNPs [55].

Smoking is modifiable risk factors for PC and is associated with PC incidence and mortality [3]. "Huncharek et al."[56] in a meta-analysis of 24 cohort studies recorded that there was no increased risk or incidence of PC among current smokers, but the risk increased with increasing amount of smoke consumption. It also showed that former smokers showed

Increased risk of PC and heavy smokers had a 24-30% increase risk of PC related deaths [56]. The current research confirmed that association.

Alcohol intake is another modifiable risk factors for PC [3]. Previous reports were not convincing regarding alcohol consumption and PC risk. A systematic review and meta-analysis that consisted of 340 studies showed that there was a significant dose-response association between alcohol consumption and PC risk. The risk increases with increasing volume of alcohol consumption when compared to non-drinkers. [57] The outcomes of the current research confirmed the mentioned associations between smnoking/alcohol consumption and PC risk.

Obesity and increased BMI have been linked with many types of cancer including PC, with increased adiposity resulting in increased mortality risk of PC [58]. It has been recorded that an increase in 5 kg/m^2 in BMI resulted in a 20% higher risk of PC mortality [59]. Three possible factors are responsible for that association, insulin like growth factor 1 (IGF-1), sex hormones, and adipokines, in an effort to explain the underlying mechanisms [60].

As mentioned chronic inflammation has been associated with cancer development [61]. The pathway of cancer-related inflammation is the recruitment of leukocytes, production of cytokines and chemokines, and subsequent progression, angiogenesis, epithelial-mesenchymal transition (EMT), migration, and metastasis [62]. Chemokines are chemotactic cytokines that influence immune responses and inflammation. Chronic infections, irritation and inflammation increase the risk of cancer. The invasion of oral pathological bacteria, especially *Porphyromonas gingivalis*, may induce traumatic injury and irritation of the oral epithelium and mucosa, and play a role in subsequent cancer progression [31]. However, it remains unclear whether PD directly increases cancer risk or shared genetic and/or environmental etiological factors are also involved. Dysbiosis of the oral microbiota, bacteria induced immune evasion and dysregulation, formation of various Signalling pathways, and subsequent inhibition of apoptosis and activation of cell proliferation in patients with chronic PD have been suggested as pro-tumorigenic mechanisms [63]. Some of the genes consistently associated with aggressive periodontitis, such as COX2 and CDKN2B are also associated with cancer, observation that suggests shared genetic susceptibility between PD and cancer [24].

Activated inflammatory cells, such as neutrophils, macrophages, and dendritic cells, secrete pro-inflammatory and pro-growth substances, such as TNF-α, cytokines, chemokines, matrix metallo-proteases, pro-angiogenic molecules, reactive oxygen (ROS) and nitrogen (RNI) species that produced from the mentioned cells can induce DNA damage in epithelial cells and produce an environment for both initiation and promotion of carcinogenesis at local and distant sites [64].

Periodontal pathogens might promote cancer development through invasion of blood vessels, bacteremia, and subclinical infection in distant sites[31]. Carcinogenic by-products of oral bacteria metabolism are suggested to be important in the link between PD and cancer. Periodontal pathogens also seem to play roles in the carcinogenesis of distant organs, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* [65, 66]. However, the etiological relationships between PD and PC remain controversial, and little is known about their underlying mechanisms. As the etiology of PC develops, increasing evidence suggests that chronic or recurrent inflammation may also be associated with PC risk [4].

Epidemiological, histopathological, and *in vivo* investigations have suggested an association between chronic inflammation and an increased risk of PC [4,67]. However, the contribution of the prostate gland inflammation, and the mechanisms that result in the development of PC remain unclear.

Previous meta-analysis and case-control studies have shown that males with prostatitis have a considerable increase risk of developing PC [68,69]. It has been shown the role of chemokines produced by cancer cells and PC-related chronic inflammation pathway [62]. The findings of the present research confirmed such an association.

The current report showed that among the PD indices examined, CAL was found to be associated with risk of PC development. Several studies have investigated the association between PD and PC risk, however the results were conflicting [23,30,70] demonstrated that PD was associated with the excess risk of PC. "Lee et al."[30], focused on the influence of smoking status on PC risk amongst individuals with PD and found that current smokers with PD had a significantly increased risk of PC, that is,1.68 times (HR= 1.68, 95%CI= 1.52-1.85) greater than that for non-smokers. '' Corbella et al. '' [19], also revealed a statistically significant association between periodontitis and risk of PC development (1.25; CI 95%: 1.04, 1.51), whereas ''Dizdar et al." [31], reported a positive associations between PC and chronic PD. ''Arora et al." [24], in a longitudinal study, suggested a positive association between incidence of PC and periodontitis classified by self-report after adjusting for potential confounders (OR=1.47, 95% CI:1.04-2.07).

On the contrary, ''Hujoel et al. '' [23], in a prospective cohort reported a negative Association between periodontitis and PC risk (OR=1.81, 95% CI: 0.76-4.34) and gingivitis (OR=1.48, 95% CI: 0.56-3.94). ''Michaud et al.'' [25, 29] based on a similar population from the same database. Both studies revealed that PD was not significantly associated with the increased risk of PC (HR= 1.17, 95% CI: 0.94-1.47) and (HR= 0.90, 95% CI: 0.73-1.12), respectively. The same study also showed [29] an inverse association between tooth loss and PC but did not include non-aggressive PC cases in the analyses. ''Hiraki et al. '' [71], in a case-control study, used tooth loss as a PD indicator, and found that a decreased number of teeth remaining was associated with a lower OR for PC of 0.49 after adjusting for potential confounders.

Additionally, major clinical parameters of PD, especially CAL, were significantly worse in individuals with moderate-to-severe prostatitis [72, 73]. Considering the similarity in the etiopathogenesis of prostatitis and PD, it is possible that a pathological link exists between them, however, further studies are necessary to draw a conclusion.

PD and PC are responsible for generalized inflammation and infection in the body, and especially chronic PD has been shown to increase the level of prostate-specific antigen (PSA) that is produced primarily by epithelial prostate cells and is used to diagnose PC [72].

The PSA level is significantly higher in chronic prostatitis patients with PD characterized by a gingival clinical attachment level of $\geq$ 2.7 mm (10.8±7.0 ng/ml) than in those without such PD (5.6±3.7 ng/ml, P = 0.05) (75). There is accumulating evidence of pro-inflammatory cytokines such as IL-6, IL-8, IL-18, TNF-α, and C-reactive protein being associated with the pathogenesis of PC [24]. These observations may indicate the similarity of the etiopathogenesis of PD and PC. Study strengths and limitations should be taken into account in interpretation of the recorded findings. Strengths, concern 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. An important issue is the determination of PD status by oral clinical examination and not by self-report, thus no possible misclassification of exposure to PD exists. Such misclassification based on self-reported data may lead to the underestimation of the association between PD and PC risk. A potential limitation is the possibility of confounding in estimates of risk caused by additional unknown confounders. Smoking status may play another role as it is a known confounder.

In conclusion, individuals with a prostate cancer family history, chronic prostate infection, increased alcohol consumption, smoking, and CAL were at significantly higher risk for developing prostate cancer.

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