ORIGINAL ARTICLE

Periodontal Disease Indices and Risk of Hepatocellular Cancer in A Greek Adult Population: A Case - Control Study

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ABSTRACT

Introduction: Epidemiological researches have recorded positive associations between perio-dontal disease (PD) and risk of cancer at various locations. The aim of the current study was to assess the possible association between Periodontal Disease indices and risk of developing Hepatocellular Cancer in Greek adults. **Materials and Methods:** The study sample examined 120 cases diagnosed with the main histological type of liver carcinoma, and 235 age and socio-economic status matched controls. Data on periodontal status was collected through dental and Oral examination and a questionnaire including data of their medical and dental history, and concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Gingival Index (GI) and the known risk factors for development of hepatocellular cancer. Odds ratios (OR's) and 95% Confidence Intervals (CI's), unadjusted and adjusted, were assessed using univariate and logistic regression models adjusted for possible confounders. **Results:** The final model of multivariate regression analysis application showed that previous infection with Hepatitis B or C Virus (p=0.001,OR= 2.251, 95% CI=1.366-3.708), liver cirrhosis (p= 0.000, OR= 4.275, 95% CI= 2.561-7.137), increased alcohol consumption (p= 0.010, OR= 1.963,95% CI= 1.173-3.283), smoking (p=0.048,OR=1.621, 95% CI=1.247-2.776), and Clinical Attachment Loss (p=0.031, OR= 1.746, 95% CI=1.053-2.896) were statistically significantly associated with risk for hepatocellular cancer development. **Conclusion:** Individuals with previous infection with Hepatitis B or C Virus, liver cirrhosis, increased alcohol consumption, smoking, and Clinical Attachment Loss were at significantly higher risk for developing hepatocellular cancer.

Key words: Periodontal disease, Hepatocellular Cancer, Risk factors

INTRODUCTION

Liver cancer (HCC) is the sixth most common cancer and the second leading cause of cancer mortality worldwide, and it is responsible for an estimated 841,000 new cases and 782,000 deaths annually.[1,2] The majority of HCC cases are observed in either Africa or Asia, with China alone accounting for half of all cases worldwide.[3]

The factors that increase the risk of HCC are male gender, race/ethnicity, chronic (long-term) infection with hepatitis

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DOI: 10.33309/2639-8230.040105

B virus (HBV) or hepatitis C virus (HCV), liver cirrhosis, inherited metabolic diseases, heavy alcohol consumption, smoking, increased body mass index (BMI), Diabetes Mellitus type 2, aflatoxin-contaminated foods, exposure to Vinyl Chloride, thorium dioxide (Thorotrast), anabolic steroids, and rare diseases such as Tyrosinemia, Alpha1-antitrypsin deficiency, Porphyria cutaneatarda, Glycogen storage diseases, and Wilson disease.[2,4]

All major HCC risk factors are responsible for chronic inflammation which can progress to fatty liver disease, fibrosis, cirrhosis, and eventually, HCC.[4] The most severe form of liver disease, cirrhosis, is itself a major risk factor of cancer and mortality.[5]

Based on the fact that effectiveness of HCC screening is low [6] and prognosis is poor[7], it is essential to identify modifiable risk factors and develop preventive health policies to reduce the burden of HCC.

Periodontal disease (PD), gingivitis and mainly periodontitis, a highly prevalent disease worldwide, is defined as any inherited or acquired chronic, destructive, inflammatory disease of the teeth-supporting tissues including gingiva, alveolar bone and periodontal ligament in response to the bacterial dental plaque.[8-10] SeverePD is characterized by immunological breakdown of the bone and soft tissues, and in untreated cases, periodontitis can progress, leading to destruction of the tooth-supporting structures and ultimately tooth loss.[8,9]

Periodontitis may be associated with several systemic diseases such as cardiovascular disease[10,11], stroke[12], rheumatoid arthritis[13], pneumonia[14] and fatty liver disease.[15,16] Moreover, epidemiologic studies suggested an association between periodontitis, tooth loss and the risk of cancers including oral cavity, lung, esophageal, gastric, colorectal, pancreatic and liver cancer.[17-28]

The link between the mentioned associations may be attributed to systemic infection and inflammation, and the special role of circulating biomarkers, such as cytokines and chemokines. [29] It has also suggested an hypothesized role of immunity mechanisms that may be common to both diseases, PD and cancer.[19,30] The potential mechanism that links periodontitis and cancers indistant locationsis probably associated with the persistent periodontal infection and inflammation that are able to induce systemic chronic inflammation, and eventually cancer. Periodontal pathogens especially Porphyromonas gingivalis, and Fusobacterium nucleatum have been detected from some orodigestive cancer tissues, indicating that these pathogens may play a role in carcinogenesis and tumor multiplicity at distant locations.[31,32] *P.gingivalis*is an oral microorganism that is responsible for infection of periodontal tissue.[33] Oral administration of *P.gingivalis* in mice led to increased spreading of enter obacteriato the liver[34], which could be potentially hepatocarcinogenic.[35] There is also evidence that *Helicobacter pylori* infection may be associated with poor periodontal health[36] as well as increased risk of HCC[37], thus making it a potential confounder; however, confounding by *H. pylori* infection has not been assessed in previous studies.

In this context, epidemiological studies have assessed the association between periodontitis/tooth loss and the risk of HCC[17,26-28,32,38], however the findings were inconsistent. Notably, insome of those studies[17,32] the authors did not assess potential confounding by HBV or HCV infection, that are major risk factors for HCC.[4]

No previous prospective or retrospective epidemiological researches have been carried out for estimating the possible association between PD and risk of HCC in Greece. The purpose of the current retrospective case-control study was to assess the possible association between PD indices and risk of HCC in a sample of adults in Greece.

MATERIALS AND METHODS

Study Design and Study Population Sample

The current case-control study was carried out between May 2019 and June 2021. The study size was assessed based on the HCC prevalence[39], determined by Hyman et al.[40], with 95% Confidence Level and relative precision 50.0%, whereas the age group was based on the World Health Organization recommendations[41,42] for assessing PD prevalence. The mentioned procedure led to a study sample of 355 individuals[40]120 with HCC–cases and 235 healthy individuals-control, aged 55 to 80.

Cases and Controls Selection Criteria

Exclusion criteria concerned individuals with less than 20 natural teeth, those who were treated by a conservative or surgical PD procedure within the previous six months and those who had prescribed systemic antibiotics or anti-inflammatory or other systemic drugs, such as glucocorticoids the previous six weeks as those conditions could influence the oral tissues status, and could lead to biased secondary associations[43]. Advanced HCC patients under medical treatment, patients with liver metastases of a primary focus at a different location were excluded from the study protocol. Hospital patients were also not included.

The case group consisted of individuals whose the primary

diagnosis of HCC was based on patients' medical files and included Computed Tomography(CT) findings, however in a low rate of HCC patients (n= 12 or 10%) definitive diagnosis was confirmed by histopathological examination after a core needle biopsy.

The control group selection consisted of individuals derived from the friendly and collegial environment of HCC patients in an effort to control potential confounders such as age, gender and smoking status.

Research Questionnaire

Cases and controls completed a modified Minnesota Dental School Medical Questionnaire[44], that included epidemiological indices such as age, gender, smoking status, alcohol intake, BMI, current diseases and disorders, and medical/dental history.

For establishment of the intra examiner variance a randomly chosen 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

Periodontal condition indices were measured at six sites in all teeth (disto-buccal, mid-buccal, mesio-buccal, disto-lingual, mesio-lingual, and mid-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, case and control, the worst values of Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), and Gingival Index (GI) on six sites per tooth were recorded and coded as dichotomous variables.

PPD was classified as 0-3.00 mm (absence of disease/mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [45], attachment loss(CAL) severity was classified as mild, 1-2.0 mm and moderate/severe, ≥3.0 mm of attachment loss [46], and the presence or absence of gingival inflammation was classified as normal situation of gingival tissue and/or mild gingival inflammation, that corresponds to Loe and Silness[47] classification.

Ethical Consideration

The present retrospective case-control study was not reviewed and 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.

Statistical Analysis

The worst values of PPD, CAL and GI on six sites per tooth were recorded and coded as dichotomous variables for each individual, case and control, and coded as 1. Males, previous/current smokers, individuals with previous HBV/HCV infection, suffering from DM type 2 and liver cirrhosis, increased BMI and alcohol consumption were coded as 1. Age groups distribution was coded as 0,1,2 and 3 for ages 55-60, 61-70, 71-80, respectively.

Univariate model was applied to examine the association between the independent variables examined and HCC risk, separately. Multivariate regression model was carried out to investigate the associations between the dependent variable, HCC, 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 62.4 ± 4.5 years. Cases with the classical histomorphologic features of HCC were included in the study protocol and consisted of well vascularized tumors with wide trabeculae (more than 3 cells), prominent acinar pattern, small cell changes, mitotic activity cytologic atypia, vascular invasion, Kupffer cells absence, and the loss ofthe reticulin network.[48]

Univariate analysis is shown in Table 1, and showed that presence of liver cirrhosis (p=0.000), increased alcohol consumption (p=0.000), smoking (p=0.002), DM type 2 (p=0.005), increased CAL (p=0.001)and moderate/severe gingivitis (GI) (p=0.048) were statistically significantly associated with risk for HCC development. Table 1 also shows Unadjusted OR's and 95% CI for each variable examined. After performance of the first method (step1a) of the regression model it was found that previous HBV/HCV infection (p=0.001), liver cirrhosis (p=0.000), increased alcohol consumption (p=0.012), and CAL (p=0.035) were significantly associated with HCC risk (Table 2). Table 2 also shows Adjusted OR's and 95% CI for each parameter examined. The final step of multi-variate regression analysis model (Wald method) is presented in Table 2, in which previous HBV/HCV infection (p= 0.001), liverirrhosis (p= 0.000), increased alcohol consumption (p= 0.010), smoking (p=0.048), and CAL (p= 0.031) were statistically significantly associated with risk for developing HCC.

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

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Age				
55-60	26 (21.7)	48 (20.4)	0.238	_____
61-70	64 (53.3)	108 (46.0)		
71-80	30 (25.0)	77 (33.6)		
Gender				
Male	74 (61.7)	134 (57.0)	0.401	1.213 (0.773-1.901)
Female	46 (38.3)	101 (43.0)		
Previous HBV/HCV infection				
No	42 (35.0)	80 (34.0)	0.857	1.043(0.657-1.656)
Yes	78 (65.0)	155 (66.0)		
Cirrhosis				
No	55 (45.8)	51 (21.7)	**0.000***	3.053 (1.899-4.906)
Yes	65 (54.2)	184 (78.3)		
Alcohol consumption				
<45 grams/day	50 (41.7)	152 (64.7)	**0.000***	0.390 (0.248-0.612)
>45 grams/day	70 (58.3)	83 (35.3)		
Smoking				
No	39 (32.5)	116 (49.4)	**0.002***	0.494 (0.312-0.782)
Yes	81 (67.5)	119 (50.6)		
Body Mass Index				
<25 kg/m^2	44 (36.7)	111 (47.2)	0.058	0.647 (0.412-1.015)
>25 kg/m^2	76 (63.3)	151 (52.8)		
Diabetes Mellitus type II				
No	40 (33.3)	115 (48.9)	**0.005***	0.522 (0.330-0.825)
Yes	80 (66.7)	120 (51.1)		
Probing pocket depth				
0-3.00 mm	54 (45.0)	116 (49.4)	0.436	0.839 (0.540-1.305)
≥ 4.0 mm	66 (55.0)	119 (50.6)		
Clinical Attachment Loss				
1.00-2.00 mm	46 (38.3)	132 (56.2)	**0.001***	0.485 (0.310-0.760)
≥ 3.0 mm	74 (61.7)	103 (43.8)		
Gingival Index				
Absence/Mild	48 (40.0)	120 (51.1)	**0.048***	0.639 (0.409-0.998)
Moderate/Severe	72 (60.0)	115 (48.9)		

* p-value statistically significant

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									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	age	,122	,238	,236	1	,625	1,112	,702	1,632
	gender	,086	,262	,108	1	,743	1,090	,653	1,820
	hbv.hcv.inf	,838	,257	10,633	1	**,001***	2,311	1,397	3,824
	cirrhosis	1,468	,266	30,552	1	**,000***	4,340	2,579	7,303
	alcohol.cons	,666	,264	6,362	1	**,012***	1,947	1,160	3,267
	smoking	,579	,277	4,992	1	,054	1,615	,938	2,780
	body mass ind	,139	,276	,255	1	,613	1,150	,670	1,974
	diab.mell.II	,472	,286	2,724	1	,099	1,603	,915	2,808
	prob.pock.dep	.296	,273	1,174	1	,279	,744	,435	1,271
	clin.attach.los	,592	,280	4,467	1	**,035***	1,807	1,044	3,129
	ging.index	,150	,269	,310	1	,578	1,161	,686	1,966
	Constant	2,844	,399	50,829	1	,000	,058		

Step 5[a]	hbv.hcv.inf	,811	,255	10,146	1	**,001***	2,251	1,366	3,708
	cirrhosis	1,453	,261	30,863	1	**,000***	4,275	2,561	7,137
	alcohol.cons	,674	,263	6,599	1	**,010***	1,963	1,373	3,283
	smoking	,583	,274	5,097	1	**,048***	1,621	1,247	2,776
	clin.attach.los	,557	,258	4,660	1	**,031***	1,746	1,053	2,896
	Constant	2,769	,342	65,676	1	,000	,063		
a. Variable(s) entered on step 1: age, gender, hbv.hcv.inf, cirrhosis, alcohol.cons, smoking, obesity, diab.mell.II, prob.pock. dep, clin.attach.los, ging.index.									

DISCUSSION

PD is a chronic infectious diseases[49], may be associated with several systemic diseases as already mentioned above.[10-16] Moreover, epidemiologic studies suggested an association between periodontitis, tooth loss and the risk of cancers in several organs. The mentioned association has been researched for more than 50 years, however, findings to date have little practical value as prevention indices[50], whereas useful aspects have been provided on the role of PD treatment in reducing the risk of different types of cancers.[51]

Recently, exists an increasing interest inexploring the mentioned, especially for cancers in the head and neck location, upper gastrointestinal system, pancreas and lung[20-22,52], as there is evidence that PD patients were at increased risk of those types of cancers.[17-28,32,50,53]

HCC is the sixth most common cancer, the second leading cause of cancer mortality worldwide[1,2], the prevalence of HCC is estimated to be about 180 million people and the incidence continues to rise, especially in the U.S.[53,54]

The outcomes of the current study showed that previous liver HBV/HCV infection, liver cirrhosis, increased alcohol consumption, smoking and CAL, were statistically significantly associated with risk for developing HCC.

The main factors that can increase the risk of HCC are male gender, chronic (long-term) infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), liver cirrhosis, heavy alcohol consumption, smoking, increased body mass index (BMI), and Diabetes Mellitus type 2.[2,4]

Host factors that are implicated in HCC development are male gender and age above 50 years old.[54,55] There are several possible explanations for this finding. Experimental studies in transgenic mice showed that the transcription of HBV genes was increased by the androgen pathway.[56,57] Moreover, increased test oster one level shave been associated with increased risk of HCC.[58] The current study showed no association between gender and risk for developing HCC. The majority of HCC cases arises from HBV/HCV infection.

In the U.S., 16% of HCC cases are attributed to HBV and 48% to HCV infection.[53] The lifetime risk of HCC is 10-25% in chronically infected HBV patients. HCV patients, on the other hand, develop HCC at an annual rate of 1-4%.[59] HCV is responsible for a 17-fold increase in the risk for HCC. Similar to HBV-related HCC most HCV-related HCC cases also tend to occur 25-30 years after chronic infection.[53] The development of HCC usually starts with injury to the liver. Both HBV and HCV infection can cause HCC due to promotion of inflammatory reactions and oxidative stress in the liver, though HCV infection is thought to contribute to greater oxidative DNA damage than HBV.[55] Under those conditions liver damage occurs, and sequentially followed by fibrosis, cirrhosis, and HCC development.[60] The current study confirmed the role of liver HBV/HCV infection in HCC etiology.

Environmental risk factors for HCC are heavy alcohol use, cirrhosis, and tobacco smoking a known carcinogen. [55]

Worldwide, alcohol consumption accounts for around 33.3% of global incident cases of HCC with marked variations between countries and regions. [61,62] Alcohol consumption has been associated with an increased risk of several malignancies. The mentioned risk starts at doses as low as 10 g/1unit/day.[63] It is an independent risk factor for the development of HCC, with a relative risk of 2.07 for heavy drinkers compared to non-drinkers. There lative risk is also slightly increased in occasional drinkers.[63,64] A meta-analysis of 10 studies suggests that significant increased risk of HCC was associated with an ethanol intake of 25 g per day or the equivalent of two drinks per day, which was the lowest dose of alcohol considered.[65] The current report confirmed the mentioned association.

The association between smoking and HCC risk remains controversial. Two cohorts recorded positive does response associations between smoking and HCC risk [66,67], however, another cohort study did not find the increased risk of LC in smokers to remain significant after adjusting for age and gender.[68] Other cohort studies that have observed an association between smoking and HCC risk also either only studied males[69,70] or did not find this association among females. [71,72]

On the other hand, experimental data supports a causal link between tobacco smoking and HCC development. The liver is a major organ for the metabolism and transformation of more than 40 tobacco-related active compounds, several of which are well accepted carcinogens such as polycyclicaromatic hydrocarbons, nitrosamines, and aromatic amines.[73,74] Several tobacco-related carcinogens, such as *N*-nitrosodimethylamine and 4-aminobiphenyl, have been directly implicated in the development of liver tumors inanima studies.[64,75] The present report confirmed such findings.

In developed countries, the prevalence of obesity, as measured by body mass index (BMI) ≥30 kg/m^2, has been increased markedly over the past two decades. Epidemiological studies have suggested that excess weight is associated with increased several cancer risks, particularly HCC risk. A recent meta-analysis of 11 cohort studies showed increased HCC risks of 17% for over-weight people (BMI 25–30 kg/m^2) and 90%for obese (≥30 kg/m^2) people compared to those with normal weight. The authors, however, did not carried out adjusting for possible con-founders, in particular, chronic HBV and HCV infections and alcohol abuse, as potential limitations. [76]

According to the World Cancer Research Fund/American Institute for Cancer Research, there is limited and inconsistent evidence suggesting that excess body weight may increase HCC risk.[77] In addition, the exact shape of the dose-risk relationship between BMI and HCC has not been clearly defined. Other relevant studies on this association have been published with inconsistent results [78-87], whereas the current study recorded no significant association between the parameters examined.

DM is a proven risk factor of various kinds of malignancies, is strongly associated with non-alcoholic fatty-liver disease and many other metabolic processes.[88,89] Insulin resistance[90] was believed to play an important role in hepatocarcinogenesis in HBV patients with type 2 DM or even prediabetes.[91] The association between DM and HCC risk was indicated to be independent of cirrhosis, though most HCC cases presented with cirrhosis.[92] A recent systematic review demonstrated that concurrent DM is strongly associated with increased HCC risk among chronic HCV patients.[93] There are mixed results of the few studies on the association between DM and the risk of HCC in patients with HBV.[78,94-97] No significant association was observed between both diseases in the current research.

Liver cirrhosis is a known risk factor for HCC development, as its biology is characterized by a constant stimulus for hepatocellular regeneration in a micro environment characterized by chronic inflammation and tissue fibrosis, thus representing an ideal condition predisposing to the development of HCC [2,4,5,92], findings that are in accordance with those of the current study.

Positive associations of periodontal infection, including studies using tooth loss as a PD index with several cancer outcomes have been recorded, as previously stated. Tooth loss is a devastating final result of untreated bacterial infections, mainly periodontitis[8,9], and could be used as an indirect PD index.

HCC has been investigated in studies that examined all-cancer incidence or mortality, however, it has been rarely examined as an individual outcome. To the best of our knowledge, this is the first study that investigated the potential association between HCC and periodontal status parameters.

The current research recorded no significant association between two PD indices examined, PPD and GI, and the risk of HCC. On the contrary, a significant association was observed between CAL and the mentioned risk. CAL is an indicator of cumulative tissue destruction, including past PD, whereas PPD is an indicator of current disease status inflammation.[98]

Previous and recent epidemiological studies have investigated the potential association between tooth loss and/or periodontal health status and the risk of HCC[17,26-28,32,38,99-101], however the findings were inconsistent. Moreover, a prospective study based on NHANES III reported higher mortality rate for HCC for individuals with periodontitis, but it is unclear whether this association was due to confounding as this comparison was not based on adjusting for covariates.[32]

Tooth loss is the final result of bacterial infections, mainly periodontitis as already mentioned. The accurate mechanism that is responsible for the potential association between PD/tooth loss with distant cancers is not yet entirely clear. However, a number of pathways have been suggested. The first is that persistent periodontitis is able to induce systemic inflammation through activating inflammatory mediators and biomarkers such as cytokines and chemokines.[102] Another potential pathway involves the role of oral pathogens [103-105], as it has been detected that oral microbiome is implicated in initiation and progression of orodigestive cancers.[31,32,103,106] Oral pathogens especially periodontal pathogens may to contribute to carcinogenesis pathways through producing carcinogenic metabolic byproducts, with subsequent anti-apoptotic and oncogenic effects.[31,104,105,107] PD and poor oral hygiene have been reported to elevate oral bacteria

levels, and influence carcinogenesis through the increased production of carcinogens, specifically nitrosamines[17], as higher nitrosamine levels have been detected in the oral cavity due to the presence of nitrate-reducing bacteria.[17,108] Periodontal pathogens such as *P. gingivalis* and *F.nucleatum* have been involved in cancer progression and were detected from various oro-digestivecancers. [31,32,104,107]

Moreover, periodontal infection has been involved in chronic liver inflammation, cirrhosis and none-alcoholic fatty liver disease, both of which are precursor conditions of HCC.[16,109-111] Alakhali et al.[15], inarecent systematic review reported a strong association between PD and non-alcoholic fatty liver disease. Similar findings, especially for the role of *P. gingivalis* and non-alcoholic fatty liver disease development and progression have been reported by previous researchers.[112,113] Experimental animal studies found that oral administration of *P.gingivalis* caused deteriorate dintestine barrier function, increased serum endotoxin levels, and spreading of enter obacteria to the liver[34] which could have a hepatocarcinogenic effect.[35]

Helicobacter pylori is the main pathogen causing gastritis and gastric cancer.[114] *H pylori* is able to co-aggregate with *F.nucleatum* and *F.periodonticum*, in the oral cavity[115], where as it is known that dental plaque serves as a reservoir for *H. pylori*. Periodontitis patients showed a significantly higherrate of *H. pylori*intheir dental plaque (79% vs 43%; $P<0.05$) and the stomach (60% vs33%; $P<0.05$) than patients with no periodontitis. Additionally, a positive association was reported between *H. pylori*infection and periodontal pathogens.[116] *H. pylori* infection could influence the chronic periodontitis by the change of microecology and inflammation, and induce the severe progress of this disease. [116] The positive detection rate of *H. pylori* was previously reported to be markedly higher in patients with moderate and severe periodontitis than in those with mild periodontitis.[117]

However, the potential role of *H. pylori* in pathogenesis of HCC has not been yet investigated. Study strengths and limitations should be taken into account in interpretation of the recorded findings. Strengths, include 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 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 HCC 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.

CONCLUSION

Individuals with previous infection with Hepatitis B or C Virus, liver cirrhosis, increased alcohol consumption, smoking, and Clinical Attachment Loss were at significantly higher risk for develping HCC.

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How to cite this article: Chrysanthakopoulos NA, Vryzaki E, Karkoulias K. Periodontal Disease Indices and Risk of Hepatocellular Cancer in A Greek Adult Population: A Case - Control Study. J Clin Res Oncol 2021;4(1):28-38. DOI: 10.33309/2639-8230.040105