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Periodontal Disease Indices, Tooth Loss and Risk of Ovarian Cancer: A Case - Control Study in Greek Females

Nikolaos Andreas Chrysanthakopoulos[1]*, Argiro Roumelioti[2]

[1] *-Dental Surgeon (DDSc),*
-Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece
-Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece
-PhD in Oncology (cand)
-Registrar in Dentistry - NHS of Greece

[2]*Registered Nurse (RN) - Health Center of Athens, NHS of Greece.*

***Corresponding Author:** Dr. Nikolaos Andreas Chrysanthakopoulos, 35, Zaimi Street, PC 26 223, Patra, Greece.

Abstract

Background/Aim: Ovarian cancer (OC) is the 5th most common cancer deaths cause in females, and has also the worst prognosis. Periodontal Disease (PD) has been associated with several diseases, such as cardiovascular diseases (CVD), diabetes mellitus (DM), and several types of cancer, such as esophageal, gastric, lung, colorectal, oral, pancreatic, head and neck, and ovarian cancers. The study was conducted to assess the possible relationsgip between PD indices, and missing teeth number and the risk of developing OC in a sample of Greek adults females.

Materials and Methods: The study was conducted between March 2021 and March 2024 and consisted of 348 females,ages 50 to 83 years. 116 were suffered from epithelial OC and 232 were healthy individuals. The examined PD indices, concerned depth of Periodontal Pockets (PPD), Gingival inflammation index (GI), Attachment Loss (CAL), Bleeding on Probing (BOP), and missing teeth number by a self-administered questionnaire and a clinical examination of oral and dental status. Data analysis was carried out using univariate and logistic regression models.

Results: Statistical analysis showed that low socio-economic status ($p< 0.001$), presence of a OC family history ($p<0,001$), increased body mass index (BMI) ($p= 0.01$), incessant ovulation ($p<0.001$), early age of menarche ($p=0.001$), GI ($p=0.003$), and BOP ($p=0.06$) were significantly associated with the risk of OC developing.

Conclusion: Females with a lower socio-economic status, a OC family history, increased body mass index (BMI), incessant ovulation, early age of menarche, and presence of BOP were significantly associated with the risk of OC developing.

Keywords: Ovarian cancer, periodontal disease, risk factors, females.

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Introduction

Ovarian cancer (OC) is the 5th most common cancer deaths cause in females,it is the 3rd after uterine and cervical cancer,it has also the worst prognosis, and the highest mortality ratio [1]. Although OC has been extensively investigated, its etiology still remains controversial and several hypotheses have been suggested. OC increased incidence is more remarkable in females over 65 years of age [2,3], whereas the median age at diagnosis is 50-79 years [2,4]. A reverse association between ovulation cycles and the risk of OC developing has been suggested [5,6]. Regarding the role of early onset of menarche and risk of OC it was found to be controversial [7-10]. Inflammation and pelvic inflammatory disease (PID) in OC development is also controverversial [11,12]. The association between endometriosis and OC has been also confirmed [13,14].

The factor that seems to be responsible for OC development is an OC or Breast cancer family history [15,16]. BRCA gene mutations (BRCA1 and BRCA2) are also one of the main causes of OC. Loss of p53 gene, at umor suppressor gene may also lead to an increase in OC risk [17]. Obesity, increases the risk of OC [17,18]. Although some researchers supported that cigarette smoking does not alter the risk of OC in females before and after menopause [19], other studies suggested that smoking increases the risk of OC development [20-22]. SES is one of the predictors of incidence and survival of OC [23,24],whereas another study reported a negative associaciation between educational status and the risk of OC developing [25].

PD and mainly the severe type, periodontitis is a chronic inflammatory disease that affects supporting tissues of tooth, affecting 47% of adults 30 years and older in the United States, resulting in more severe and aggressive cases (5-10%) [26,27]. PD is responsible for bacterial infection of gingival tissue and surrounding bone structure tissues of teeth [28]. PD as a chronic inflammatory response to pathogenic bacteria of the dental plaque [29] might result in systemic inflammation, by increased several inflammatory biomarkers blood levels, such as IL-6, C-reactive protein (CRP) [30] among patients with periodontitis.

Moreover, females with increased levels of CRP showed a 53% raise in OC risk compared with those with decreased levels [31]. PD has also been linked with various diseases, such as diabetes mellitus (DM) [32], cardiovascular diseases (CVD) [33],rheumatoid arthritis [34],and several types of cancer [35-38,39], because of possible shared factors [32,36,39,40]. In the last few years, it has become growingly essential to explore the association between PD and diverse types of cancer, as it has been associated with a total cancer and certain location-specific cancers elevated risk [40,41]. The mechanism for the mentioned association remains unclear, however, potential mechanisms by which periodontitis enhances the cancer risk are inflammation mediators that enter the blood circulation, pathogen invasion into the blood circulation, and immuno-suppression [41,42]. Periodontal bacteria could potentially translocate extra-orally in saliva via ingestion, and could infect esophagus [35] or colonic tissues [37], or by aspiration could translocate into the respiratory tract [43]. Periodontal bacteria have been detected in lymph nodes [44], arteries [45], lung aspirates [43], pre-cancerous colon [46], and gastric [47] lesions [46], and colorectal [48] and esophageal cancers [49], and may promote a proper micro-environment that can facilitate cancer progression [37,46, 50].

In Greece, no previous epidemiological studies have been conducted for exploring the possible relationship between PD indices, number of missing teeth and risk of OC developing. The aim of the present case-control survey was to explore the possible relationship between PD variables, number of missing teeth and risk of developing OC in a sample of Greek female adults.

Materials and Methods

Study Design and Sample Size Determination

A case - control research was carried out between March 2021 and March 2024. The sample size determination was assessed based on the OC prevalence and the EPITOOLS guidelines [51] considering with 95% Confidence Interval (CI) and desired power 0.8. The World Health Organization (WHO) recommendations for evaluating periodontal condition incidence were used for estimating age group [52]. The mentioned procedure led to a sample size of 116 cases individuals suffered from OC-and 232 controls-healthy ones, ages 50 to 82 years.Patients and healthy individuals were recruited from four private practices, one Dental and three Medical ones.

Cases and Controls Eligibility Criteria

OC patients and healthy individuals who underwent any type of treatment conservative or surgical in periodontal tissues within the previous six months or received systemic glucocorticoids, antibiotics, or immunosuppression drugs within the previous six months were excluded from the study protocol. Moreover, the participants should not have less than 15 teeth and should suffer from periodontitis, stage I to IV[53]. Cases and controls that suffered from CVD, DM, acute lung diseases, rheumatoid arthritis, or any other type of malignant diseases, and patients with advanced OC under surgery or chemotherapy, and those

with metastases in ovary of a primary focus at a different location, e.g. gastric cancer, were also not included into the study protocol, as the mentioned conditions could possibly influence oral and periodontal tissues [54] and may act as confounders and lead to biased secondary associations. Individuals whose the primary diagnosis of OC was based on their medical files, and abnormal physical examination defined the case group. As there is no standard screening test to identify OC , in case an OC is suspected based on an abnormal physical examination and/or symptoms/clinical signs, imaging tests of the pelvis and abdomen are usually recommended, and include trans-vaginal ultrasound, CT or MRI. The mentioned imaging tests do not afford enough data by themselves to definitively diagnose OC, however they may provide important clinical data about the position and/or expanse of a possible cancer.The only process to diagnose OC with certainty is through surgery.In some cases,if surgery is not possible or if the patient is a candidate for chemotherapy prior to surgery, a nonsurgical procedure may be performed instead. That is the fluid or tissue removal from the chest or abdomen with a needle, biopsy, for testing.A blood biomarker, known as CA 125, a tumor marker that is often elevated in the blood of females with OC can not definitely diagnose OC, however, may be done when OC is suspected. Its role in evaluating for OC is limited because the level may be elevated for many other reasons that are not OC, especially before the onset of menopause. In addition, it may be negative even when a patient has OC. However, if CA125 is elevated after menopause, or very elevated prior tomenopause, this observation increases suspicion for OC and may support a decision to proceed with surgery to make a diagnosis. An exploratory laparotomy is typically recommended when OC is suspected [55,56]. The definite diagnosis of cases in the current report was based on the trans-vaginal ultrasound in combination with CT or MRI examination [56].

Control group selection was not based on the familial, but the collegial and friendly environment of OC. Healthy individuals were also habitants of the same city, and visited the mentioned practices for their routine health follow-up. Moreover, healthy individuals were matched for age and smoking habits, as those variables [57,58] are essential risk factors for periodontitis, and may act as co-variates [59]. The mentioned preconditions were established in an effort to eliminate potential selection biases.

Study Research Questionnaire

Patients and healthy individuals completed a standardized Medical and Dental questionnaire [54] which comprised epidemiological variables such as age, smoking status, educational and SE status, BMI, OC and breast cancer family history, presence or absence of incessant ovulation, early or later age of menarche occurrence, endometriosis, previous pelvic inflammatory disease, current diseases, and their medical/dental history.

Participants' age was categorized as 50-59, 60-69, 70-79, 80+, educational status as lower (elementary) level and higher (graduated from University/College) level, SES as equal or less than 1,000 and more than1,000 €/ month, and cigarette smoking habits was categorized as never smokers (those who smoked <100 cigarettes during their life-time), and former smokers (those who smoked at least 100 cigarettes in their lifetime and stated that they now smoke "not at all")/current smokers (those who smoked at least 100 cigarettes in their life-time and stated they now smoke "every day"or "some days").BMI expresses obesity and was coded as normal(<30 Kg/m^2) and high (≥30 Kg/m^2) [60]. Assessment of lifetime ovulatory (or menstrual) cycles are estimated by multiplying ovulatory years by cycles per year, approximately 13, for a "normal"cycle length of 28 days. More ovulatory cycles and greater cancer risk were first linked with OC and later extended to breast and endometrial cancers [61]. Regarding the definition of "early menarche", it is usually defined as menarche before the age of 12 years, although some authors determined it at equal or less than 10 or 11 years[62].

For establishment of the intra-examiner variance the same Dentist examined a randomly elected sample of 70 (20%) patients and healthy individuals, after three weeks, and no differences were observed after the clinical examination (Cohen's Kappa = 0.95).

No oral hygiene instructions were given to the participants during the period of three weeks.

Examination of Periodontal Status

The clinical examination of periodontal tissues concerned measurement of pocket depth (PPD),attachment loss (CAL), gingival inflammation (GI),bleeding on probing (BOP),and missing teeth number. All PD measurements were concerned four sites per tooth (mesio-buccal, mesio-lingual, disto-buccal, and disto-lingual) in four quadrants. The worst measurements of the variables examined assessed to the nearest 1.0 mm, and classified as dichotomous variables, excluding third molars, and remaining roots using a Williams (with a controlled force of 0.2N DB764R,Aesculap AG &Co. KG,) periodontal probe, dental mirror, tissue forceps, and dental light source. PPD was coded as 0-3.00 mm (absence or mild disease) and ≥ 4.0 mm (moderate or severe disease) for mean PPD [63],attachment loss (CAL) severity was coded as mild attachment loss,1-2.0 mm and moderate/ severe attachment loss, ≥3.0 mm [64],and missing teeth number as none,1-

4,5-10, >10 missing teeth [65]. Gingival inflammation severity was classified as : -score 0: gingival tissue normal status and/or mild gingival tissue inflammation, that corresponds to Löe and Silness [66] classification as score 0 and 1, respectively, and -score 1: moderate/ severe gingival tissue inflammation that corresponds to the mentioned classification as score 2 and 3, respectively. BOP presence/absence was classified as- score 0: BOP absence, and-score 1: BOP presence and regarded positive if it observed within 15 seconds of probing.

Ethical Consideration

In Greece only experimental studies, such as clinical trials, etc. must be approved by Authorities, such as Health Ministry,Health Organizations, etc. The present research was a retrospective casecontrol study and was not reviewed and approved by the mentioned Authorities.The individuals who agreed to take part in the present research study obtained an informed consent form.

Statistical Analysis

For assessing the relationship between the independent variables investigated and the OC risk, a univariate model was carried out. Categorical data were presented as frequencies and percentages. Socio-demographic factors (age,SE and educational status), comorbidities (family history of OC and Breast Ca, pelvic inflammation, increased BMI), self-reported variables (smoking habits, incessant ovulation,menarche age,endometriosis, etc.),were analyzed using the mentioned model.

For assessing the relationships between OC as the dependent variable, and independent ones a multivariate logistic regression model was carried out applying the Enter step, whereas the Stepwise step was carried out to assess the possible relationships among the indices investigated. Odds Ratios (OR's), unadjusted and adjusted, and 95% (Confidence Interval) CI were also assessed. Statistical analysis was performed using SPSS statistical package (SPSS PC20.0, SPSS, Inc., Chicago,IL,USA),and a p value less than 5% ($p< 0.05$) was deemed to be statistically significant.

Results

Study sample mean age was 62.3 ± 4.3 years. The main histological types concerned epithelial type and were serous (87.3%), clear-cell (9.5%),mucinous (2.1%),and enometrioid (1.1%), as the infrequent histological types of OC were not included in the study protocol. Table 1 presents the epidemiological parameters of patients and healthy individuals after performing the univariate analysis. Low SES (p<0.001), low educational level (p=0.010), increased BMI (p<0.001), presence of family OC (p<0.001) and Breast cancer history (p=0.019), incessant ovulation (p< 0.001), endometriosis history (p<0.001), PID history (p=0.004), and gingival inflammation (GI) (p=0.009), were statistically significantly associated with risk OC developing.

Table 1 also presents Unadjusted Odds Ratio and 95% Confidence Interval (CI) for each parameter examined. After carrying out the 1st step (Enter) of the logistic regression model it was observed that low SES (p<0.001), presence of family OC (p<0.001), increased BMI (p=0.014), incessant ovulation (p=0.001), early menarche age (p=0.002), and gingival inflammation (GI) (p=0.003), were significantly associated with OC risk (Table 2).

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

Variables		Cases (116)	Controls (232)	p-value	Odds Ratio and 95% Confidence Interval
Age					
	50-59	18 (15.5)	41 (17.7)		
	60-69	38 (32.8)	74 (31.9)		
	70-79	45 (38.8)	84 (36.2)	0.927	_____
	80+	15 (12.9)	33 (14.2)		
Socio-economic status					
	Low	68 (58.6)	87 (37.5)	**0.000***	2.361 (1.498-3.722)
	High	48 (41.4)	145 (62.5)		
Education level					
	Low	63 (54.3)	92 (39.6)	**0.010***	1.809 (1.153-2.837)
	High	53 (45.7)	140 (60.4)		
Body Mass Index					
	<30 kg/m^2	47 (40.5)	144 (62.1)	**0.000***	0.416 (0.264-0.657)
	≥30 kg/m^2	69 (59.5)	88 (37.9)		

Family history of Ovarian Ca				
Absence	43 (37.1)	158 (68.1)	**0.000***	0.276 (0.173-0.440)
Presence	73 (62.9)	74 (31.9)		
Family history of Breast Ca				
Absence	51 (44.0)	133 (57.3)	**0.019***	0.584 (0.373-0.916)
Presence	65 (56.0)	99 (42.7)		
Smoking				
Never	57 (49.1)	118 (50.9)	0.762	0.933 (0.598-1.458)
Previous/Current	59 (50.9)	114 (49.1)		
Incessant ovulation (Ovulatory Years X Cycles per Year)				
CpY≤13	38 (32.8)	163 (70.3)	**0.000***	0.206 (0.128-0.333)
CpY>14	78 (67.2)	69 (29.7)		
History of Endometriosis				
Absence	44 (37.9)	148 (63.8)	**0.000***	0.347 (0.219-0.550)
Presence	72 (62.1)	84 (36.2)		
Menarche age				
> 13 year	55 (47.4)	102 (44.0)	0.542	1.149 (0.735-1.797)
≤ 12 year	61 (52.6)	130 (56.0)		
History of Pelvic inflam.disease				
Absence	50 (43.1)	138 (59.5)	**0.004***	0.516 (0.329-0.850)
Presence	66 (56.9)	94 (40.5)		
Probing pocket depth				
≤ 4.00 mm	48 (41.4)	99 (42.7)	0.818	0.948 (0.604-1.490)
> 4.00 mm	68 (58.6)	133 (57.3)		
Clinical Attachment Loss				
Absence/Mild: 1.00-2.00 mm	43 (37.1)	107 (46.1)	0.108	0.688 (0.436-1.086)
Moderate/Severe: ≥ 3.0 mm	73 (62.9)	125 (53.9)		
Gingival Index				
Absence/Mild Inflammation	39 (33.6)	112 (48.3)	**0.009***	0.543 (0.341-0.863)
Moderate/Severe Inflammation	77 (66.4)	120 (51.7)		
Bleeding on probing				
Absence	51 (44.0)	108 (46.6)	0.648	0.901 (0.575-1.410)
Presence	65 (56.0)	124 (53.4)		
Number of missing teeth				
None	15 (12.9)	36 (15.5)		
1-4 Teeth	24 (20.7)	52 (22.4)		
5-10 Teeth	50 (43.1)	101 (43.5)	0.723	_____
> 10 Teeth	27 (23.3)	43 (18.6)		

* p-value : statistically significant

Table 2 also presents Unadjusted Odds Ratio and 95% CI for each parameter investigated. The final step (Wald) of the model is shown in Table 2, and stated that low SES (p<0.001),family history of OC (p< 0.001), increased BMI (p= 0.010), incessant ovulation (p=0.001), early menarche age (p=0.001), and gingival inflammation (GI) (p=0.002), were statistically significantly associated with risk for developing OC, whereas bleeding on probing was marginally statistically significantly associated with risk for OC (p=0.060).

Table 2. *Multivariate logistic regression analysis model regarding the association between potentially risk factors and OC risk (Enter and Wald steps).*

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	age	,129	,158	,661	1	,416	1,137	,834	1,551
	socioec.stat	-1,244	,310	16,078	1	**,000***	,288	,157	,529
	educ.status	-,470	,299	2,473	1	,116	,625	,348	1,123
	fam.hist.ovar.ca	1,950	,327	35,560	1	**,000***	7,030	3,703	13,345
	fam.hist.br.ca	,186	,315	,349	1	,555	1,205	,649	2,235
	smok.status	,293	,197	,775	1	,323	,746	,417	1,335
	bmi	,799	,326	6,020	1	**,014***	2,223	1,174	4,209
	inces.ovulation	1,147	,332	11,966	1	**,001***	3,148	1,644	6,028
	endometriosis	,213	,333	,443	1	,311	1,144	,383	1,351
	age.menarh	1,108	,352	9,897	1	**,002***	1,830	,766	2 ,059
	pelvic.inflamm	,262	,316	,689	1	,247	1,100	,640	1,415
	prob.pock.dep	,327	,343	,512	1	,340	1,221	,568	1,411
	clin.att.loss	,420	,426	,770	1	,325	1,057	,485	1,215
	ging.index	1,365	,459	8,856	1	**,003***	2,915	1,193	5,618
	bleed.on.prob	,416	,320	,938	1	,087	1,240	,567	1,592
	tooth.loss	,100	,162	,379	1	,538	1,105	,358	1,244
	Constant	1,715	,547	9,838	1	,002	,180		
Step 9[a]	socioec.stat	-1,188	,296	16,165	1	**,000***	,305	,171	,544
	fam.hist.ovar.ca	2,010	,309	42,325	1	**,000***	7,466	4,074	13,681
	bmi	,810	,315	6,616	1	**,010***	2,248	1,213	4,166
	inces.ovulation	1,049	,309	11,535	1	**,001***	2,854	1,558	5,226
	age.menarh	1,103	,331	11,244	1	**,001***	1,330	,672	2,631
	ging.index	1,039	,349	8,881	1	**,002***	2,826	1,427	5,596
	bleed.on.prob	,735	,337	2,550	1	**,060***	1,530	,674	1,826
	Constant	2,106	,351	35,997	1	,000	,122		

a. Variable(s) entered on step 1: age, socioec.stat, educ.status, fam.hist.ovar.ca, fam.hist.br.ca, smok.sta- tus, bmi, inces.ovulation, endometriosis, age.menarh, pelvic.inflamm, prob.pock.dep, clin.att.loss, ging. index, bleed.on.prob, tooth.loss.

* p-value : statistically significant

Discussion

PD, and periodontitis mainly is a chronic inflammatory disease, and because of its inflammatory nature has been associated with several systemic diseases and disorders, as already mentioned. For more than 50 years the association between PD and increased cancer risk has been examined, however, findings to date have limited practical significance as prevention indices of cancer, despite the fact that useful knowledge have been acquired regarding the role of PD treatment in reducing the risk of different cancer types [67]. The last decades, an increasing interest exists in investigating the potent relationship between PD variables, missing teeth number and cancer risk, in several organs and systems such as upper gastro-intestinal system, pancreas, lungs, head and neck region, etc.[38,68-74].

The outcomes of the present report showed that low SES, a family history of OC, an increased BMI, the presence of incessant ovulation, and early menarche age were statistically significantly associated with risk of OC development. Regarding the PD indices GI was statistically significanly associated with risk for OC

developing, whereas BOP was marginally significantly associated with the risk examined.

OC development, as already mentioned has been linked with various genetic and environmental factors. No associations were recorded in the current study between variables such as advanced age, low educational status, a previous family history of Breast cancer, cigarette smoking, and endometriosis.

Individuals with a higher SES have been linked with a lower risk of OC development, probably because they have a intense possibility of obtaining OC screening, suggestion that could result in a decreased OC risk. The present study recorded a significant relationship between low SES and risk of OC. On the other hand, SES and educational level are considered as crucial confounders, nevertheless their potent role in diverse cancer types has been confirmed. SES patterns and cancer mortality have been altered gravely over time. Individuals with a lower education and income status had elevated mortality and incidence ratios compared with the more well off ones, with a great risk being notably considerable for lung, gastric, liver, colorectal and cervical cancer [75].

An important factor that seems to be responsible for OC development is a OCor Breast cancer family history, as already mentioned. The outcomes of the present study confirmed the mentioned observations. Regarding the role of obesity and the risk of OC, diverse studies showed that obesity increase the risk of OC [17,18]. The present research confirmed the association examined. A reverse association between ovulation cycles and the risk of OC has been suggested [6], and the current article confirmed the "incessant ovulation" theory, that has already mentioned.

Although some studies have shown an association between the early menarche onset and risk of OC [7,8], outcomes that were in agreement with those of the present study, other reports showed that menarche and menopause age had no effect on the OC risk [9,10]. GI was found to be statistically significant associated with the risk of OC development among the PD indices investigated. GI reverberates gingival inflammation severity, nevertheless that index is not used regularly in epidemiological surveys regardless of that estimates the inflammatory load of gingngival tissues. A particular role has been suggested for gingival inflammation as a risk factor for various cancer types [76], whereas other researhes observed no relationships [77, 78].

PPD is used for assessing severity of PD [27], and the current research showed that PPD was not statistically significantly associated with the risk of OCdeveloping, findings that were confirmed by previous studies [39,79]. CAL is a critical index for assessing cumulative periodontal tissue destruction, including previous PD attacks,whereas PPD is a current disease inflammation status indicator [80]. The mentioned indices concern the long-term stages of chronic inflammation including the chronic inflammatory response destructive signs [81].The results of the present study recorded no relationship between CAL and the risk of OC developing, however,previous reports have revealed associations between CAL and other types of cancer [82,83].

BOP is another crucial index of periodontal examination and diagnosis, and the most valid indicator of PD activity [84]. It assesses the vascular response of the host as regards to hyperemia, the expansion of capillaries and the increased blood flow in the inflammation area, and it is a extensively used criterion for diagnosing inflammation of gingival tissues. A marginally statistically significantly association was recorded concerning BOP between patients and healthy females, however that index has not been also used in previous studies which examined the possible link.

Tooth loss is the advanced periodontitis final result. Previous prospective studies have stated an relationship between number of missing teeth and the cancer risk in diverse regions [41,78,85]. Similar case-control surveys, have recorded powerful links between tooth loss and upper gastrointestinal [86], lung [87], gastric [88], esophageal[89],oral [87], pancreatic [38], and ovarian [71] [HR=0.18, 95% CI=0.02-1.55] cancers.

The responsible mechanisms for cancer development among PD patients are not completely elucidated. A possible explanation could be the characteristics of local and systemic inflammation linked with bacteremia and elevated myelopoietic activity [90], as it is well known that inflammation is a critical hallmark for malignant transformation [91]. Periodontitis is responsible for an increased systemic inflammatory response because of elevated bacterial infection, oral pathogenic bacteria hematogenous spread, increased levels of inflammatory mediators and biomarkers, such as C-rp, fibrinogen, Il-1, Il-6, and increased levels of neutrophil multinucleated cells in the blood circulation [42,92].

Chronic systemic inflammatory response leads to cellular stress, DNA damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNI) production. Other inflammatory mediators such as STAT3 and NF-kB are responsible for genetic instability [93]. Inflammatory cytokines genetic polymorphisms seems to contribute to susceptibility to carcinogenesis. Patients who suffer from chronic periodontitis are also characterized by an inherent deficiency in their immune system, remarkably in regards to bacterial clearance and immune surveillance of the

tumor, that may enhance their susceptibility to malignant neoplasms [94].

Oral bacteria is another possible explanation for the mentioned association [92].Persistent periodontal infection can result in the spread of periodontal bacteria to many body locations, and the oral bacteria colonization seems to be closely associated with the occurrence and growth of can in many organs and systems such as the urogenital Cancer [95,96]. Previous studies indicated that there may be a relationship between PD and urogenital cancer risk, however the outcomes of similar epidemiological reports were inconsistent [39,41,79]. Gram-negative anaerobic bacteria are responsible for releasing virulence factors to intervene the host's defense system, and destroy host's immune system and periodontal tissue [97].In periodontitis patients the periodontal pocket biofilms act as Gram-negative anaerobic bacteria reserveoirs of *A.actinomycetemcomitans* and *P. gingivalis* [98], that secrete enzymes and are able to invade to gingival epithelial cells and connective tissues [99].Those secreted enzymes and other bacterial byproducts such as endotoxins, and metabolic components that are poisonous to gingival tissues, are responsible for instant damage to surrounding epithelial cells DNA, or may result in mutations in proto-oncogenes and tumor suppressor genes, or intervene to the molecular signaling pathways involved in cellular functions such as survival and/or proliferation [100].

Moreover, periodontal bacteria may contribute to carcinogenesis by influencing cell proliferation and activation of nuclear factor NF-κB and inhibiting apoptosis [101], and may release carcinogen agents [102]. PD plaque is in many instances not under rational control, driving periodontal bacteria to intersperse and accumulate in some locations of the human body through the digestive or respiratory tract, or endocrine system, contributing to cancer occurrence [95, 103,104].

Fusobacterium and *Porphyromonas* species, as anaerobic bacteria,are not only PD pathogens but are also urinary system pathogens [105]. It has been found that some periodontal pathogens such those mentioned and *Treponema* species, have been isolated in PD patients urogenital fluid who suffer from chronic prostatitis and benign urogenital hypeplasia [106]. The inflammatory condition caused by chronic inflammation of prostate and urinary tract infection has been suggested to be strictly associated with urogenital cancer [107]. Moreover, *Fusobacterium,* was detected in the tumors of patients with urogenital cancer [102]. It could be concluded that oral pathogens invasion after mucosal or epithelial cells traumatic damage may result in urogenital disease development and then have an effect on the subsequent cancer development, although it does not incur a direct evidence of the relationship between PD and urogenital cancer, however, all suggestions intimate that PD and oral pathogens are completely linked with urogenital cancer. It has been found that periodontitis patients have elevated MUC1 salivary levels [108], a high molecular weight, membrane-bound, protein released at low levels by various normal epithelial cell types, whereas in epithelial cancers, such as ovarian and breast cancer released at high levels [109]. In addition, *A.actinomycetemcomitans, P.gingivalis* and *Candida albicans*, are able to increase IL-6 and IFN-γ production, resulting in MUC1 up-regulation in oral epithelial cells [110].

Conditions that implicate MUC1 elevated expression such as pregnancy and breast feeding, are linked with circulating anti-MUC1 antibodies reduced levels [111], which have been suggestively linked with a reduced risk of OC developing [112], probably because they could be eradicating OC cells that express MUC1[110].It is possible that the salivary increase in MUC1 caused by periodontitis could result in anti-MUC1 antibodies elevated levels, which may affect OC risk. Epigenetic mechanisms are used by the cell to regulate gene expression and involved in normal cellular growth, however, epigenetic process disruption seems to play a critical role in oncogenesis. Epigenetic alterations in carcinogenesis concern methylation of DNA, noncoding RNAs, histone modifications, and nucleosome positioning [113]. The role of epigenetics has not been considerably investigated in periodontitis, however it has been suggested that epigenetic alterations play a critical role in periodontitis occurrence [114]. An increase in E-cadherin and cyclooxygenase-2 gene hypermethylation is involved in tumor development and metastasis [115]. In a similar way, *P.gingivalis* is able to induce DNA methylation in normal gingival epithelial cells, observation confirmed in mice infected with *P.gingivalis* and in human periodontal tissues derived from periodontitis patients [116].

The current study has certain strengths and limitations. Strengths of the study concern the follow-up completeness, the well-structured cohort design which controlled confounding and possible interactions by known risk factors. Another important issue was that PD condition was determined by oral clinical examination and not by non-standardized, or self-report questionnaires. Therefore, no potent mis-classification of exposure to PD incurs, as such a misclassification may lead to underestimation of the link between PD and OC risk. This study was limited to females suffered from epithelial OC, thus indings can only be generalized with confidence to the examined groups, and further researhes could investigate the link between diverse PD severity and different OC subtypes. Other interfering factors concern that such surveys have

used different criteria for the definition of PD clinical measurement.The vast majority of studies has used the common PD variables,such as CAL, BOP, PPD, GI, ABL, missing teeth number and others based on self-reported questionnaires patient history, and radiographic data as criteria for PD patients [117].

Another potential limitation, is the possibility of confounding in assessment of risk caused by unknown confounders. In addition, among those studies, some environmental parameters also seem to act as confounders, such as age, gender, educational and SES, genetic factors, as have been regarded as risk factors for the diseases examined. Indeed, surveys which are adjusted for the mentioned indices can be used for PD assessment as a cancer independent risk factor [71].

Conclusion

In conclusion, low socio-economic status, presence of an OC family history, increased BMI, incessant ovulation, early age of menarche, gingival inflammation, and bleeding on probing were significantly associated with the risk of OC developing. Those associations remained after controlling for certain confounders such as smoking status and SES.

Conflict of Interest and Source of Funding Statement

The authors declare that they have no conflict of interests

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